17 October 2024
EMA/CHMP/514389/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Masitinib AB Science

International non-proprietary name: masitinib

Procedure No. EMEA/H/C/005897/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
(s)(f)ALS	(spontaneous) (familial) amyotrophic lateral sclerosis
ALSAQ-40	Amyotrophic Lateral Sclerosis Specific Assessment Questionnaire
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
$AUC_{0\text{-}24h}$	Area under the concentration-time curve from time zero to 24 hours
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time zero to time t
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time zero to infinity
BID	Twice daily
CSF-1R	Colony-stimulating factor 1 receptor
BCRP	Breast cancer resistance protein
BMI	Body mass index
$BMDL_{10}$	BMDCL associated with a benchmark response of 10%
CAFS	Combined assessment of function and survival
CMA	Conditional marketing authorisation
C_{max}	Maximum concentration observed
CI	Confidence interval
CIR	Copy increments from reference
CL(/F)	(Apparent) clearance
CNS	Central nervous system
DDI	Drug to drug interaction
DRESS	Drug rash with eosinophilia and systemic symptoms
ECG	Electrocardiogram
EMG	Electromyography
ERA	Environmental risk assessment
FVC	Forced vital capacity
HED	Human equivalent dose
HPLC	High performance liquid chromatography
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration
IDMC	Independent Data Monitoring Committee
J2R, JTR	Jump to reference
(m)ITT	(modified) Intent-to-treat
MI	Multiple imputation
IWRS	Interactive Web Response System
LMN	Low motor neuron
(m)LOCF	(modified) Last observation carried forward
MAR	Missing at random
MOE	Margin of exposure
MTA	Major therapeutic advantage
NOAEL	No-observed-adverse-effect-level
NPP	Named patient programme
OAT(1)(3)	Organic anion transporter (1)(3)
OATP1B1	Organic anion transporting polypeptide 1B1
OCT2	Organic cation transporter 2

OS	Overall survival
PBPK	Physiologically based pharmacokinetic
PBT	Persistence, bioaccumulation and toxicity
PDGFR	Platelet derived growth factor receptor
PFS	Progression free survival
PK	Pharmacokinetic
PNS	Peripheral nervous systems
popPK	Population PK
PP	Per protocol
QD	Once daily
SA	Scientific advice
SEM	Standard error of the mean
SD	Standard deviation
SmPC	Summary of product information
SOC	System organ class
SOD1	Superoxide Dismutase type 1
TKI	Tyrosine kinase inhibitors
t_{max}	Time of maximum concentration observed
$t_{1/2}$	Apparent half-life
UMN	Upper motor neuron
Vd/F	apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AB Science submitted on 29 July 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Masitinib AB Science, through the centralised procedure falling within Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 March 2021.

Masitinib AB Science was designated as an orphan medicinal product EU/3/16/1722 on 29 August 2016 in the following condition: treatment of amyotrophic lateral sclerosis (ALS).

The applicant applied for the following indication: Masitinib AB Science in combination with riluzole is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS)

During the procedure, the applicant amended the indication to: Masitinib AB Science in combination with riluzole is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS) *prior to any loss of function.*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicant's own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0001/2020 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation (CMA) in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active Substance status

The applicant requested the active substance Masitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
20 September 2018	EMEA/H/SA/573/16/2018/PA/SME/II	*Dr. Susan Morgan* *Dr. Mario Miguel Rosa*
13 December 2018	EMEA/H/SA/573/16/FU/1/2018/PA/SME/II	*Dr. Susan Morgan* *Dr. Mario Miguel Rosa*

The protocol assistance pertained to the following clinical aspects:

- Study run-in period and definition of the study population, overall, 3-arm study design, proposed dosing scheme for masitinib, the proposed PK protocols and PK model, choice of primary endpoint, proposed estimand, statistical analysis, randomisation approach and study size.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Larisa Gorobets Co-Rapporteur: Elita Poplavska

The application was received by the EMA on	29 July 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 November 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	22 November 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	25 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	02 May 2023

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 May 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 May 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 January 2024
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 January 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	30 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	28 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Masitinib AB Science on	27 June 2024
The CHMP adopted a report on similarity of Masitinib AB Science with Qalsody on (see Appendix on similarity)	27 June 2024
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	27 June 2024

1.8. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Margareta Bego

The applicant submitted written notice to the EMA, to request a re-examination of Masitinib AB Science CHMP opinion of 27 June 2024 on	16 July 2024
The CHMP appointed Daniela Philadelphy as Rapporteur and Margareta Bego as Co-Rapporteur on	26 August 2024
The applicant submitted the detailed grounds for the re-examination on	02 September 2024
The re-examination procedure started on	03 September 2024
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP and PRAC members on	01 October 2024
SAG group experts were convened to address questions raised by the	10 October 2024

CHMP on The CHMP considered the views of the SAG experts as presented in the minutes of this meeting	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the detailed grounds for re-examination to all CHMP and PRAC members on	11 October 2024
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	16 October 2024
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the conditional marketing authorisation on	17 October 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

ALS is a neurodegenerative disorder affecting upper (UMN) and lower motor neurons (LMN) causing progressive muscle weakness and wasting. ALS often has a focal onset but subsequently spreads to different body regions, where failure of respiratory muscles typically limits survival to 2–5 years after disease onset.

1. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020 Oct;27(10):1918-1929.
2. Brotman RG, Moreno-Escobar MC, Joseph J, et al. Amyotrophic Lateral Sclerosis. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.

2.1.2. Epidemiology

Of the two forms of ALS, 90-95% of cases are sporadic (sALS), with the remainder being familial (fALS). ALS has an estimated incidence of 1.75–3 per 100 000 persons per year and a prevalence of 10–12 per 100 000 in Europe, but significant geographical differences exist. The incidence amounts to 4–8 per 100 000 persons per year in the age group with the highest risk of developing ALS (45–75 years). The estimated number of 2020 ALS cases across the 22 countries is 121,028 prevalent. Mean age at onset of symptoms is variable: 58–63 years for sALS and 40–60 years for fALS. An estimation of the cumulative lifetime risk for developing ALS is 1:350 in men and 1:400 in women. Men have a higher risk of developing limb onset sALS compared to women; the global sex ratio is 1.2–1.5. Globally, a higher incidence is associated with White ethnicity. The only established risk factors for ALS are age and family history.

2.1.3. Aetiology and pathogenesis

ALS is thought to be caused by a combination of genetic factors, environmental factors and aging-related dysfunction. At the genetic level, more than 20 genes have been linked with the disease to date, and it is anticipated that more genetic factors will be discovered. The genetic architecture of ALS appears complex, where monogenetic mutations with high effect size currently explain about 15% of patients, but where common and rare genetic variants with low and moderate effect size seem to contribute to the risk of developing ALS as well. The overall heritability of ALS is high; in patients with sALS the heritability is estimated to be 30%–60%. The risk of developing ALS doubles in first degree relatives of ALS patients.

Although many potential mechanisms have been proposed, a precise, single aetiology of sporadic ALS is yet unproven. These mechanisms include altered RNA processing leading to prion-like self-aggregation, superoxide dismutase type 1 (SOD1) mutations leading to free radical toxicity, cascading inflammatory responses, and excessive concentrations of glutamate, among others. The rarer entity of fALS has numerous genetic mechanisms, most frequently repeat expansion of the C9ORF72 gene and various mutations of the SOD1 gene. Mutated SOD1 protein misfolds and forms aggregates, leading to cellular injury and eventually apoptosis. Both genetic aberrations are inherited in a mainly autosomal dominant pattern. Ultimately, rather than a single unifying cause, ALS is an etiologically diverse clinical entity, which is the result of a multitude of separate potential preceding aberrations.

In 1993, the first ALS-related gene was discovered: SOD1, responsible for 20% of fALS and 1%–2% of sALS. Mutations in this gene do not cause ALS by loss of SOD1 function but rather by rendering the protein prone to aggregation, which disturbs multiple important cellular functions.

In 2008 and 2009, mutations in TARDBP and FUS, the genes encoding the RNA-binding proteins TDP-43 and FUS, were discovered. These mutations are responsible for 3%–5% of fALS and for <1% of sALS. In 2011, C9orf72 was discovered, responsible for 30%–50% of fALS and for 7%–10% of sALS. Patients with hexanucleotide repeat expansions in C9orf72 are more likely to get bulbar onset ALS and to have cognitive and behavioural impairment as well.

Mutations in TBK1 are most probably the fifth most common cause of autosomal dominant ALS, responsible for about 1% of patients, but up to 10% of patients with amyotrophic lateral sclerosis with frontotemporal dementia.

Although most SOD1 mutations have a high penetrance, the other genes mentioned are known to have a reduced penetrance, which complicates genetic counselling. Rarely, patients carry mutations in more than one of these genes, suggesting that ALS can be oligogenic in origin.

Using next-generation sequencing, several rare variants in additional genes have been identified. Whilst mutations in many of these genes are rarely identified as the cause of ALS, they appear to cluster in some emerging disease pathways.

Apart from genetic factors, age and male sex increase the risk for ALS. Several studies have suggested environmental risk factors for ALS, such as smoking, body mass index, physical exercise, occupational and environmental exposures to metals, pesticides, β-methylamino-l-alanine, head injury and viral infections. However, the causal relationship of these factors with ALS remains to be established.

2.1.4. Clinical presentation, diagnosis and prognosis

The hallmark of ALS is progressive muscle weakness, accompanied by muscle atrophy, fasciculations, muscle cramps and slowness of movements with muscle stiffness. The onset of muscle weakness in ALS is usually focal and typically spreads to adjacent body regions. This pattern is compatible with spreading of disease pathology within the motor system, with neuroanatomic propagation within the spinal cord segments and the motor cortex.

The disease usually presents with unilateral distal muscle weakness and atrophy in upper or lower limb muscles (spinal ALS, roughly in two-thirds of patients) or in bulbar muscles (bulbar ALS, in about one-third of patients). Upper limb onset is most commonly in the dominant hand, with thenar muscles being more affected than hypothenar muscles (which is referred to as the split-hand syndrome), with early involvement of the first interosseous muscle and finger extensors more affected than finger flexors. In the lower limb the anterior tibial muscle is typically affected earlier in the disease course than the gastrocnemius muscle, the hamstrings before the quadriceps muscles.

Bulbar onset ALS presents most commonly with dysarthria or dysphagia, less commonly with dysphonia, or reduced mouth closure or chewing problems. Axial muscle weakness with head drop and problems with posture are common in later stages of the disease, but rarely can be the presenting symptom. In about one-third of patients, there can be bouts of uncontrolled laughing or crying (referred to as a pseudobulbar affect).

In some patients, the muscle weakness is preceded by a period in which fasciculations, muscle cramps or mild weight loss has been noted.

On neurological examination, a combination of signs of UMN and LMN involvement is found in patients with classic ALS. Signs of LMN involvement include muscle weakness, atrophy, fasciculations and reduced

muscle tone. Signs of UMN involvement to look for include hyperreflexia (or retained reflexes in atrophic muscles), increased muscle tone (especially in upper limb flexors and lower limb extensors) and slowness of movements (e.g. of tongue movement).

Although the majority of patients can be labelled as having a classic ALS phenotype with spinal or bulbar onset, it is increasingly recognised that ALS is clinically a heterogeneous syndrome with distinct motor and extra-motor manifestations. There is considerable heterogeneity within the motor manifestations of the disease itself and the motor manifestations can be accompanied by variable degrees of frontotemporal involvement. This results in different phenotypic presentations of the disease which have different disease trajectories. Although no widely accepted clinical criteria for the different ALS phenotypes exist, there is a growing need for a new classification system using universally accepted terms to account for the disease heterogeneity in ALS.

The diagnosis of ALS remains a clinical diagnosis and is based on the presence of both UMN and LMN signs, in patients with progressive muscle weakness in whom no alternative explanation can be found. Most clinicians do not rely on the available revised El Escorial criteria or the Awaji algorithm, as these criteria lack sensitivity, especially in patients with bulbar-onset ALS (Brooks, 2000) and importance to electromyography (EMG) signs, particularly the fasciculation potentials recorded during EMG examination, rather capturing disease progression and only indirectly diagnostic certainty. Moreover, these criteria have been developed for research purposes to select patients for participation in clinical trials. There is a high need for clinical diagnostic criteria of ALS and related subtypes of motor neuron disease, to reduce the diagnostic delay, which is unfortunately still often up to a year after disease onset. Recently, new simplified diagnostic criteria for ALS have been proposed, requiring only combined UMN and LMN dysfunction in one body region, or LMN dysfunction in at least two regions. Whether this will reduce the diagnostic delay requires further study.

The diagnosis of ALS relies on the medical history, physical examination, electrodiagnostic testing (with needle EMG) and neuroimaging. EMG remains a very useful diagnostic tool to confirm LMN involvement in clinically affected and non-affected muscles (with fibrillation potentials, sharp waves, fasciculation potentials in relaxed muscles and chronic neurogenic changes upon contraction).

Biomarkers can play a crucial role in diagnostic, prognostic or predictive research studies. They could potentially become important for stratification of patients and monitoring treatment effects in clinical trials. Although not yet integrated into standard clinical practice, several biomarkers such as cerebrospinal fluid neurofilament levels (especially phosphorylated neurofilament heavy subunit) are useful in supporting the diagnosis, particularly in patients with very recent onset of muscle weakness, without clear signs of UMN involvement, or with concomitant neuropathy/plexopathy/cervical myelopathy.

Brain and spinal cord magnetic resonance imaging are often performed to exclude structural lesions affecting the motor system. Furthermore, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography, if readily available, can reveal a typical pattern of hypometabolism in Rolandic brain regions and frontotemporal involvement.

Genetic testing of the five most prevalent genes found to be mutated in ALS is routinely offered to patients with a positive family history (C9orf72, SOD1, TDP-43, FUS, TBK-1). Although there is no consensus on genetic testing for patients with sALS, there is a trend to offer it to all patients. However, genetic testing should only be performed if genetic counselling can be provided in the event that a pathogenic gene mutation is identified. Gene panels also including rarer ALS-related genes are emerging, but the diagnostic yield on top of the five most prevalently mutated genes remains low.

Life expectancy in ALS is extremely variable. Many different clinical features, already present at first disease presentation, are known to be associated with a shorter survival. They include a bulbar onset, a

short diagnostic delay, a fast functional decline [e.g. as measured by the revised ALS Functional Rating Scale (ALSFRS-R) decline], a pronounced loss of weight (or body mass index (BMI)), the presence of frontotemporal dementia, an older age at the onset of symptoms and a low forced vital capacity. Moreover, genetic factors also influence survival. Some monogenetic causes are associated with a shorter survival (Ala5Val mutation in SOD1, C9orf72 repeat expansion, P525L mutation in FUS), but common and rare variants with effects on survival have been described as well. For example, homozygosity for the C allele of rs12608932 in UNC13a is associated with a shorter survival.

2.1.5. Management

There are two medicinal products authorised for ALS in the EU. Riluzole is an antiglutamatergic medicinal product authorised for the treatment of ALS. Riluzole 50 mg twice daily prolongs the mean patient survival by 3–6 months. The most common side effects include nausea, diarrhoea, fatigue, dizziness, and liver problems.

Qalsody (tofersen) has been recently authorised for the treatment of SOD1-ALS.

On top of the above, ALS treatment benefits from a multidisciplinary symptomatic management including pharmacological and non-pharmacological interventions

2.2. About the product

Masitinib AB Science (also referred to as AB1010, the mesilate salt of AB1003) is a non-cytotoxic new chemical entity that belongs to the pharmacological class of drug known as tyrosine kinase inhibitors (TKI). Masitinib AB Science is a small molecule drug that selectively inhibits specific tyrosine kinases such as colony-stimulating factor 1 receptor (CSF-1R), c-Kit, LYN, FYN, and platelet derived growth factor receptor (PDGFR) α and β, in the sub micromolar range [Dubreuil 2009; Davis 2011]. At the cellular level, Masitinib AB Science is a potent inhibitor of CSF1R-dependent cell proliferation, of wild-type c-Kit-dependent cell proliferation, of LYN- and FYN-dependent cell proliferation, and of PDGFR dependent cell proliferation. Two independent studies have demonstrated masitinib mesilate to be one of the most highly selective protein kinase inhibitors developed (circa 2011) [Anastassiadis 2011; Davis 2011].

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a CMA in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive. The applicant's position is that considering the impact of ALS on the life prognosis of patients suffering from the disease, the urgent need for developing more efficacious ALS therapeutic alternatives, and based on the study results from AB10015, as well on long term survival data, the benefit associated with Masitinib AB Science outweigh the known and potential risks of Masitinib AB Science in treating patients with ALS.
- It is likely that the applicant will be able to provide comprehensive data. The applicant committed to continue the ongoing pivotal Phase 3 randomised, placebo-controlled study AB19001 to evaluate the efficacy and safety of masitinib in ALS patients. The applicant initially claimed that the completion of the Phase 3 AB19001 study would lead to comprehensive data on the efficacy and safety of masitinib in ALS patients and that the granting of a CMA will not affect the ability to complete this study. In order to minimise the impact on the recruitment and conduction of AB19001 study in case the CMA is granted, the applicant proposed to amend the protocol to replace these patients with patients from other geographies and to activate non-EU sites as a substitution to sites

in the EU. During the procedure, the applicant stated that the enrolment in study AB19001 has been slow due to the restrictive design features of that study. Consequently, the applicant proposed a new confirmatory study - AB23005 study- and presented the previously proposed confirmatory AB19001 study as an exploratory one. The new confirmatory AB23005 study is expected to enrol 408 patients. The applicant presented a feasibility analysis and concluded that a total of 855 patients could be enrolled over a 12-month period including 583 patients in non-EU countries and US. The applicant claimed that Study AB23005 can be completed within 2.5 years with involvement of site from USA and other non-EU countries or within 3 years with involvement of site only from other non-EU countries. Thus, the applicant position is that confirmatory study AB23005 is feasible outside of the EU and further facilitated since Relyvrio (tradename of the fixed combination medicinal product including sodium phenylbutyrate and ursodoxicoltaurine, known as Albrioza in EU) is withdrawn from market in USA and Canada. Upon the withdrawal, edaravone and riluzole will be the only medicinal products specifically authorised for all ALS patients except those with SOD1-ALS who can also benefit from treatment with tofersen. The applicant's position is that the willingness to participate in a trial assessing efficacy and safety of a new medicinal product for ALS is expected to be increased among the patients with ALS upon Relyvrio withdrawal.

- Unmet medical needs will be addressed, as ALS is a severely debilitating and life-threatening disease that leads to a progressive inability to move, respiratory function insufficiency, and poor prospects of long-term survival. Currently, there is no cure for ALS. The applicant position is that no treatment can halt the course of the disease and no authorised medicinal treatments generate clinically significant prolongation of survival. At the time of submission of this application, riluzole was the only medicinal product authorised in the EU for the treatment of ALS. Riluzole, a glutamate antagonist, has been the standard treatment approach for people with ALS for over 25 years, even though it is associated with a very modest increase in survival and with little improvement in quality-of-life or slowing of functional loss. Riluzole is still required to be used along with any new drug candidates by all/most regulatory agencies. During the procedure, Qalsody was authorised for the treatment of SOD1-ALS. The applicant claimed that Masitinib AB science has a different mechanism of action and that SOD1 represents approximately 2% of people living with ALS. The applicant claimed that Masitinib AB Science makes a major contribution to patient care with a benefit on ALSFRS-R, quality of life, progression free survival (PFS), overall survival (OS) (+12 months).
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The applicant position is that benefit associated with the immediate availability of Masitinib AB Science based on number of deaths avoided and total gain in life-years as estimated based on AB10015 study (pivotal study for this CMA) outweighs the risk of adverse events (AEs).

2.4. Quality aspects

2.4.1. Introduction

The finished product was proposed as film-coated tablets containing 100 mg and 200 mg of masitinib (as mesilate) as active substance.

Other ingredients were: microcrystalline cellulose, povidone, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol, talc and sunset yellow lake (E110).

The proposed packaging was HDPE bottle, closed with a sealed film and a child-resistant (polypropylene) PP cap.

2.4.2. Active Substance

An ASMF for masitinib mesilate was submitted. A letter of access to the ASMF in relation to the application for the proposed 100 mg and 200 mg film-coated tablets was provided. The discussion below refers to this source alone, as it is the only proposed for marketing. Masitinib mesilate is considered by the applicant to be a new active substance.

2.4.2.1. General information

The chemical name of masitinib mesilate is 4-[(4-methyl-piperazin-1-yl)methyl]-*N*-(4-methyl-3-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}-phenyl)benzamide, methane sulphonic acid salt and has the following structure:

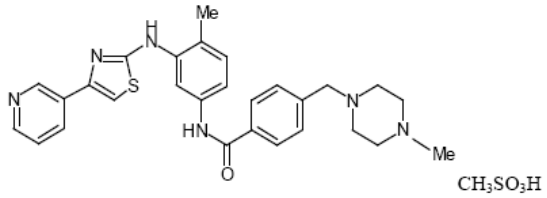


Figure 1: Structure of masitinib mesilate

The molecular structure of masitinib mesilate has been confirmed by elemental analysis, UV spectroscopy, IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and LC-MS using a reference batch of active substance.

Masitinib mesilate is a white to pale yellow powder, slightly hygroscopic, practically insoluble in acetone, slightly soluble in ethanol, sparingly soluble in methanol. It exhibits pH-dependent aqueous solubility. It is freely soluble in 0.1 N HCl and soluble in water.

The molecular structure does not contain asymmetric carbon atoms.

Three polymorphic forms of masitinib mesilate were identified by differential scanning calorimetry and x-ray spectrometry. It has been demonstrated that masitinib mesilate consistently manufactured by the proposed manufacturer is the polymorphic Form DRX1, anhydrous which is the most stable form. The polymorphic forms can be differentiated by melting point/range. Melting point is included in the active substance specification.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is synthesised in a convergent synthesis consisting of several chemical steps, purification, salt formation followed by drying and sieving. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The synthesis is comprised of 6 steps (with step 4 being divided into 3 sub-steps). Steps 1 to 4.1 are synthetic steps (bond breaking/formation), steps 4.2 to 6 comprise purification and salt formation. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The proposed starting materials comply with the general principles for selection of the starting materials as outlined in ICH Q11 and its Q&A document and were found to be acceptable. The information provided on the route of synthesis of the starting materials allows for an adequate assessment of the impurities arising from their synthesis.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Comprehensive details and discussion are provided on impurities. Potential and actual impurities were well discussed with regards to their origin. Specified impurities are controlled in compliance to the ICH Q3A guideline. Several mutagenic impurities were identified and control strategies in accordance with ICH M7 guideline have been proposed for.

The active substance is packed in double LDPE bags which comply with EC 10/2011 and with the Ph. Eur. monograph 3.1.4.

2.4.2.3. Specification

The active substance specification includes tests for appearance (colour), identity masitinib (IR, UPLC/UV) identity mesilate ion (^{1}H-NMR), melting point (DSC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), related substances (UPLC/UV), residual solvents (GC), microbiological purity (Ph. Eur.), particle size distribution (laser diffraction), assay masitinib (UPLC/UV) and methanesulfonic acid (titration).

In addition, tests for the metal impurities palladium and vanadium (ICP OES), test for the alkyl mesilates (GC) and tests for a number of potential mutagenic impurities (UPLC/MS) are included.

The analytical methods used have been adequately described and the non-compendial methods appropriately validated in accordance with the ICH guidelines.

The specifications and their limits are considered to be acceptable and have been appropriately justified. The potential formation of genotoxic impurities has been investigated and appropriate specifications have been set.

Batch analysis data on 3 production scale batches of the active substance (manufactured in 2015 according to the process described in the current version of the ASMF) were provided. The batches were all analysed according to the analytical methods presented in the dossier. The results were within the proposed specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data on 3 production scale batches of the active substance stored for up to 12 months under long term conditions at 25ºC / 60% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH were provided. These batches were tested according to the specifications and with the analytical methods presented in the current version of the ASMF.

A statistically significant trend is observed for increasing a certain impurity content and for an unidentified impurity. An OOS result was observed. It is claimed that for one of batches this is due to the fact that batch was placed on stability studies more than 1 year after manufacturing date, besides it was stored at room temperature. However, the same is observed for another batch as well. Only one batch stored at 5ºC complies with all parameters tested for 24 months, whereas 12 months' compliant data is available for another batch. Therefore, based on results of these two batches, a 12-month re-test period if stored at 5ºC can be granted.

A forced degradation study was conducted on masitinib mesilate in the solid state and in aqueous solution. In aqueous solution, degradation was observed under all conditions, except alkaline with the

formation of an impurity (for which formation mechanism is unexplained) and unknown degradation products. The impurity is due to masitinib hydrolysis occurring under the stressed conditions. In the solid state, no significant change was observed.

Two batches of masitinib mesilate were exposed to light for about 24 h (1.2 MioLux/h), according to ICH guideline Q1B. This photostability study revealed no significant changes due to the UV-light exposure; masitinib mesilate appears not to be photosensitive.

Historical stability data was submitted for information only. Primary (batches manufactured from 2015 to 2017) and supportive stability data were presented to support the initially claimed 18 months retest period and storage (at 5ºC) and transport conditions (no specific condition). The stability data was obtained under the ICH Q1A(R2) conditions: 5ºC for long term conditions, 25ºC±2ºC / 60%±5% RH for accelerated conditions and 40ºC±2ºC / 75%±5% RH for stress conditions. Stability studies on six batches of the drug substance manufactured in 2009 and 2010 (before changes to the manufacturing process of the drug substance were implemented) were provided. These batches were tested as per the specifications and using the analytical methods in force at the time of the studies. The results from long-term stability studies (3 batches x 60 months and 3 batches x 48 months) as well as from the accelerated stability studies (6 batches x 6 months) show that the drug substance is stable as all parameters comply with the established specification limits; no trend and no significant differences between room temperature and accelerated conditions were observed.

Overall, the batch data provided justify the retest period of 12 months for the masitinib mesilate active substance.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product was proposed as 100 mg film-coated tablets that are light orange coloured, capsule shaped, embossed with "100" on one side and "C" on the other side, and 200 mg film-coated tablets that are light orange coloured, capsule shaped, embossed with "200" on one side and "C" on the other side. mesilate The strengths are distinguished by size and number marking which is acceptable. The 100 mg & 200 mg strengths are manufactured fully dose proportional.

The excipients are microcrystalline cellulose (Avicel pH101 and pH200), povidone, crospovidone type A and magnesium stearate. The film coat contains polyvinyl alcohol, titanium dioxide, macrogol, talc and sunset yellow lake (E110). Opadry II orange 85F23318 contains hydrolysed polyvinyl alcohol, titanium dioxide, talc, macrogol and sunset yellow lake (E110).

The two strengths of the formulation are manufactured from one common blend.

The proposed container closure system was HDPE bottle, closed with a sealed film and a child-resistant (polypropylene) PP cap.

The applicant has not defined the quality target product profile (QTPP), has not identified potential critical quality attributes (CQAs) of the finished product and has not defined a control strategy, which according to ICH guideline Q8 (R2) on pharmaceutical development (EMA/ CHMP/ICH/167068/2004) requirements. It is acknowledged the applicant's position regarding the quality target product profile (QTPP) which was not requirement in 2004 when product development began. Since manufacturing process of film-coated tablets is considered a standard process and critical/non-critical aspects of process and product quality were considered during product development and implemented in the updated process validation protocol, this can be considered acceptable.

Masitinib mesilate exists in three polymorphic forms. Polymorphic form DRX 1, the most stable form, is used to manufacture the finished product. This form exhibits a pH-dependant solubility profile across the physiological pH range with highest solubility at low pH (34 g/l at pH 1.3). The particle size of the drug substance is reduced by impact milling and is controlled in the active substance specification.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The compatibility of the active substance and excipients was investigated. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

In early clinical development masitinib 50 mg capsules were used. Later on, an immediate release tablet was developed as the commercial formulation. Bioequivalence has been demonstrated between the phase 1 capsule formulation (2 x 50 mg) and the tablet formulation (1 x 100 mg). The applicant provided detailed information on the selection of dissolution method to bridge between the clinical tablet formulation and the proposed commercial tablet formulation. Since the tablets used during phase 2 and phase 3 studies have the same composition and are manufactured by a simple manufacturing process, the bridging between clinical formulations and the proposed commercial formulation, supported by relevant dissolution data, was considered acceptable.

The proposed dissolution method uses the Ph. Eur. paddle apparatus with 0.01 N HCl as dissolution medium, 900 ml volume, 37.0 ± 0.5ºC temperature. The applicant initially proposed the dissolution method with a paddle speed of 100 rpm. However, this was not considered sufficiently discriminatory resulting in a major objection. The applicant proposed to reduce paddle speed to 75 rpm based on similar dissolution results at 20 minutes time points to increase the discriminatory power of the method this way. However, several deficiencies and the lack of a reasonable explanation for the significant differences of dissolution data between the 100 mg strength and the 200 mg strength, as well as differences of dissolution data between different batches of 200 mg strength were identified. The suitability of the dissolution method to ensure proper control of the medicinal product, especially for 200 mg strength has not been demonstrated. The applicant has been repeatedly asked to explain and justify the differences in dissolution results between the 100 mg batches and the 200 mg batches, given that both strengths are homothetic, qualitative and quantitative composition is proportional and the same manufacturing process is used. It is not obviously demonstrated that tablet mass, hardness and film-coating or the differences observed between the two strengths are the root causes for the differences in dissolution results observed between 100 mg and 200 mg tablets. The dissolution of two 100 mg tablets could have been compared with the dissolution of one 200 mg tablet to obtain data that could potentially reveal the causes of the different and variable dissolution results (according to Guideline on the Investigation of Bioequivalence; CPMP/EWP/QWP/1401/98), however this data has not been provided. Potential reasons for different dissolution results between 200 mg batches (intra-batch and inter-batch) have not been discussed and justified in order to ensure that, e.g., the manufacturing process is adequate to obtain a high-quality product. For finished product batches of 200 mg strength where results of dissolution do not exceed 85% in 15 minutes and high RSD% values have been observed, similarity with 100 mg strength should have been confirmed by statistical methods other than F2 calculation (e.g., bootstrap method etc), which was also not done. Therefore, the major objection regarding the dissolution method has not been resolved.

2.4.3.2. Manufacture of the product and process controls

The film-coated tablets are manufactured from a quantitatively identical common granule formulation using conventional mixing, wet granulation, fluid bed drying, final blending (3 granulation sub-lots) compression and film-coating. Differentiation of the tablet strengths is applied at the compression stage,

where both target tablet core weight and compression tooling are different. The manufacturing process is considered a standard manufacturing process.

Based on the submitted batch data, the batch size ranges are considered approvable.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Process validation for three production scale batches has been carried out on the granulation steps only. The process validation protocol and approach to validation are considered acceptable.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form, such as appearance (visual assessment), identification (HPLC, UV), uniformity of dosage units by mass variation (Ph. Eur.), average weight, dissolution (Ph. Eur.), moisture content (Ph. Eur.), degradants (HPLC), microbiological quality (Ph. Eur.), assay (HPLC) and a specific impurity.

The specifications have been justified in accordance with relevant guidelines and pharmacopoeial requirements.

A risk-based approach to assess the potential presence of elemental impurities in the drug product is provided and complies with the ICH Q3D Guideline for Elemental Impurities Option 2b.

A risk evaluation of the manufacturing process in terms of risk of formation and contamination of N-nitrosamines in active substance and finished product is presented from the finished product manufacturer. A risk of presence of nitrosamines impurities has been identified due to amine-containing functional groups in the active substance and nitrites/nitrates in the excipients, and according to the results of confirmatory testing, the finished product must be controlled for nitrosamines. The major objection raised in the previous round is considered resolved.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, a limit for an impurity was proposed for the specifications of the finished product and this was considered acceptable. The acceptable intake (AI) has been adopted by the CHMP after consulting the Nitrosamines Safety Operational Expert Group (NSOEG).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 16 batches of 100 mg tablets and 33 batches of 200 mg tablets manufactured at the proposed commercial manufacturing site and clinical site, at various scales, confirming the consistency of the manufacturing process.

2.4.3.4. Stability of the product

Stability data from five batches of the 100 mg tablets and ten batches of the 200 mg tablets (all manufactured at commercial scale) stored under long term conditions at 25ºC / 60% RH for up to 36 months and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided. Samples were tested for appearance, moisture content, hardness, assay,

impurity content, dissolution and microbial testing. During the assessment procedure, both release and shelf-life specifications of the finished product have been updated to include an acceptable limit for N-nitroso-masitinib, thereby ensuring control of the impurity throughout shelf-life.

The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The stability data presented do not show degradation in any of the batches presented under any condition.

Force degradation was carried out under various stress conditions as part of the analytical validation. Degradation was observed under acidic, alkaline and oxidative conditions. Satisfactory mass balance data showed that the analytical procedure for impurities is stability indicating.

In addition, a photostability study as per ICH Q1B conducted on one batch of tablets from each strength showed a slight fading of the colour of film-coating, however the proposed HDPE primary packaging offers sufficient protection from light exposure. No change was observed in any of the other parameters tested.

A holding time study was conducted for each dosage strength on one batch of core tablets and one batch of film-coated tablets packaged and stored in bulk in PE bags. The holding time of 1 month before coating step and 6 months as coated tablet was confirmed.

Based on available stability data, the shelf-life of 36 months when stored in the original container to protect from light is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used. It is confirmed that the raw materials used for the production of magnesium stearate are of synthetic or plant origin.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The major objection, raised during the procedure, on the suitability of the proposed dissolution method to ensure proper control of the medicinal products during the lifecycle of the medicinal product, especially for the 200 mg strength, and therefore to ensure batch to batch consistency has not been sufficiently demonstrated and therefore not resolved. Several deficiencies and the lack of an acceptable explanation for the significant differences of dissolution data between the 100 mg strength and the 200 mg strength, as well as differences in dissolution profiles between different batches of the 200 mg strength remain at the time of opinion. The applicant has not convincingly demonstrated that tablet hardness and film-coating are the main issues for differences in dissolution results between 100 mg and 200 mg tablets as dissolution results do not correlate with these parameters. Moreover, the potential reasons for different dissolution results between 200 mg batches (intra-batch and inter-batches) were not discussed in order to ensure that, e.g., the manufacturing process is adequate to obtain a product with the intended high quality.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is not considered acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product were not demonstrated.

The suitability of the proposed dissolution method, raised as a major objection during the procedure,

has not been sufficiently demonstrated. It can not be assured that the medicinal products during the lifecycle of the medicinal product will be controlled in a satisfactory manner, especially for the 200 mg strength, and therefore batch to batch consistency cannot be ensured.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Within this application, Masitinib AB Science, in combination with riluzole, is proposed for the treatment of adults with ALS.

The nonclinical development strategy followed for Masitinib AB Science is compliant with ICH guidance as laid out in ICH M3 (R2). The nonclinical package addresses all of the principal nonclinical issues, including pharmacokinetics, general toxicity, reproductive toxicity (segment III study), carcinogenicity, genotoxicity, mutagenicity, and safety pharmacology. Individual studies are compliant with detailed ICH safety guidance documents.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Masitinib AB Science (mesilate salt of AB1003 also referred to as AB1010) is a non-cytotoxic new chemical entity that belongs to the pharmacological class of drug known as TKI [Dubreuil 2009]. Masitinib AB Science is a small molecule drug that selectively inhibits specific tyrosine kinases such as CSF1R, c-Kit, LYN, FYN, and PDGFR α and β, in the submicromolar range [Dubreuil 2009; Davis 2011]. Two independent studies showed masitinib mesilate to have a very high level of selectivity from a wide range of protein kinase inhibitors [Anastassiadis 2011; Davis 2011]. At the cellular level, masitinib mesilate is a potent inhibitor of CSF1R-dependent cell proliferation (half maximal Inhibitory Concentration (IC_{50}) 90 nM), of wild-type c-Kit-dependent cell proliferation (IC_{50} 100-300 nM), of LYN- and FYN-dependent cell proliferation (IC_{50} 225-240 nM), and of PDGFR-dependent cell proliferation (IC_{50} 0.25-20 nM).

There is a growing body of evidence indicating that immune dysfunction and neuroinflammation may be pathological characteristics of ALS [Vahsen 2021; Clarke 2020; Skaper 2018; Iyer 2018; Crisafulli 2018; Skaper 2014]. Microglia are the immune cells of the central nervous system (CNS) that play a well-known pathogenic role during ALS progression [Brites 2014]. Mast cells are effector immune cells and key in chronic neuroinflammatory processes, constituting an important source of inflammatory mediators, sustaining the neuroinflammatory network and modulating the blood-brain barrier permeability. Moreover, evidence suggests that ALS is a neurodegenerative disorder in which crosstalk between mast cells, microglia and astrocytes results in motor neuron damage.

Within this application, Masitinib AB Science is intended for the treatment of adult patients with ALS. The exact molecular pathways causing motor neuron degeneration in ALS remain unknown, but as with other neurodegenerative diseases, it is likely to involve a complex interplay between multiple pathogenic cellular mechanisms.

Hence, because of its potent and selective activity against CSF1R, masitinib mesilate is able to inhibit the CSF1/CSF1R signalling pathway thereby regulating CSF1R-dependent cells such as microglia, the immune cells of the CNS that play a well-known pathogenic role during ALS progression [Brites 2014]. Likewise, by merit of its activity against c-Kit, LYN and FYN, masitinib mesilate is able to inhibit mast cells, an effector immune cell that is key in chronic inflammatory processes. The development of Masitinib AB Science in ALS is therefore based on its pharmacological action in microglia and mast cells, among others, an approach that has been shown to slow microglial-related disease progression, reduce neuro-inflammation, and modulate the degenerative neuronal microenvironment in both central and peripheral (PNS) nervous systems [Kovacs 2021; Harrison 202; Trias 2016, Trias 2020; Trias 2018; Trias 2017].

Mast cells orchestrate inflammatory processes and contribute to the neuroinflammatory cascade by merit of the wide array of pro-inflammatory mediators they release. Indeed, mast cells represent one of the main CNS sources of cytokines and chemokines [Stassen 2002; Kinet 2007]. In both the CNS and PNS, as in other tissues, activated mast cells may undergo explosive degranulation or may steadily release granules into their microenvironment. Following activation, mast cells remain intact and viable to resynthesise their granules. Secretory granules store a wide variety of mediators, which when released into the CNS can alter the function of both neural and vascular elements. The importance of c-Kit, LYN and FYN for mast cell function and activation is well-known. Krystel-Whittemore 2016; Reber 2014

Microglia play a fundamental pathogenic role during ALS disease progression. It is now well established in the literature that proliferation and accumulation of microglial cells (microgliosis), which also promotes the emergence of aberrant glial cells, is a major neuropathological feature of SOD1G93A ALS animal models [Trias 2013; Díaz-Amarilla 2011]. Microglial cells are regulated by the CSF1/CSF1R signalling pathway. Additionally, evidence suggests that ALS is a neurodegenerative disorder in which crosstalk between mast cells, microglia and astrocytes may result in motor neuron damage [Sandhu 2021; Skaper 2014].

Thus, while microglial and mast cells individually play important roles in sustaining the inflammatory network of the PNS and CNS, the existence of mast cell-microglia crosstalk is likely to further contribute to the exacerbation of neurodegenerative disease and to accelerate disease progression. Microglia and mast cells therefore represent potential therapeutic targets in ALS for a pharmacological agent capable of simultaneously modulating their pathogenic roles.

2.5.2.2. Secondary pharmacodynamic studies

Secondary PD studies were not performed.

2.5.2.3. Safety pharmacology programme

From a safety pharmacology perspective, Masitinib AB Science after single dose administration did not induce significant effects on the central nervous and respiratory system in rats, and no modifications of cardiovascular function or electrophysiological parameters in telemetered dogs were observed. Results from chronic toxicology studies in dogs demonstrated that Masitinib AB Science had no significant effect on the cardiovascular function and the cardiac electrophysiology. Moreover, the clinical experience did not evidence any sign of cardiotoxicity with Masitinib AB Science. However, when the effects of AB1010 were tested on hERG channel stably expressed in HEK-293, there was a significant concentration-dependent reduction (IC_{50}: 8.3 ± 1.1 µmol/L) in hERG tail current amplitude in presence of AB1010 from 0.1 to 30 µmol/L. This effect was only partially reversed after the washout period and was significant compared to the spontaneous run-down observed in the control group.

2.5.2.4. Pharmacodynamic drug interactions

No PD drug to drug interaction (DDI) studies were performed for Masitinib AB Science. All studies are pharmacokinetic (PK) drug interactions.

2.5.3. Pharmacokinetics

Preclinical PK and toxicokinetic investigations have been conducted in mice, rats, and dogs in order to characterise the PK behaviour of Masitinib AB Science.

Absorption

Masitinib AB Science is well absorbed after oral administration. Oral bioavailability following gavage administration of radiolabelled AB1010 (labelled on the phenylpiperazine moiety) to rats or dogs at 10 mg/kg was:

- 69.5% and 74.8% as plasma radioactivity in male and female rats, respectively
- 64.3% and 66.2% as whole blood radioactivity in male and female rats, respectively
- 84.6% and 81.4% as plasma radioactivity in male and female dogs, respectively
- 79.8% 78.0% as whole blood radioactivity in male and female dogs, respectively

In mice, the time of maximum concentration observed (t_{max}) was reached 1 or 2 hours after oral (gavage) administration. Systemic exposure [as measured by the maximum concentration observed (C_{max}) and area under the concentration-time curve from time zero to 24 hours (AUC_{0-24h})] increased with dose-level in an approximately dose proportional manner. There was no gender effect on systemic exposure to AB1010, but plasma levels of AB3280 tended to be approximately 2-fold higher in females than males. Systemic exposure to AB3280 represented between 6 and 23% (approximately) of the AB1010 exposure in terms of AUC.

In rats, following single oral administration of AB1010 the maximum concentration was reached at 4 hours (t_{max}) with an apparent half-life $t_{1/2}$ of 3 hours. A supra-linear increase in systemic test item exposure expressed as area under the concentration-time curve from time zero to time t (AUC_{0-t}) or area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) was noted in males and females and this was more marked between 10 and 30 mg/kg/day. A gender effect was also noted after single and repeated administration, as test item exposure was about 2-fold higher in females than in males. After repeated daily administration, comparison of $AUC_{0-\infty}$ values obtained on days 1 and 28 showed increased systemic AB1010 exposure at all dose-levels in both sexes. Exposure to the plasma metabolite AB3280 was higher in males than in females.

In dogs, in a 4-week study by daily oral administration at 3, 10 and 30 mg/kg/day AB1010 was rapidly absorbed with a t_{max} at 1 or 2 hours after administration. A supra-linear increase in systemic exposure was noted between 3 and 30 mg/kg/day in males and females after single and repeated administration. Systemic exposure to AB1010 and AB3280 was similar in males and females. Systemic exposure to AB1010 and AB3280 was broadly similar after single administration or repeated administration for 4 weeks.

Overall, masitinib mesilate appeared to be well absorbed after oral administration in the different animal models (mice, rats, cats and dogs). Bioavailability (in terms of measured radioactivity) varies from 65% in rats to around 80% in dogs. Absorption was reasonably rapid with t_{max} values between 0.5 and 4 hours in all species and (apparent half-life $t_{1/2}$) values in the range 1-4 hours in the rat and 2 -5 hours in the dog.

In mice there was no effect of sex on systemic exposure to Masitinib AB Science, but plasma levels of AB3280 were approximately 2-fold higher in females than males. In rats a sex effect on systemic

exposure to masitinib was noted after single and repeated administration, with consistently an approximate 2-fold higher exposure in female rats than males. In dogs there was no evidence of any sex effect on systemic exposure to Masitinib AB Science.

Absorption was broadly dose-proportional with a tendency to increase in a supralinear fashion; this was more marked at lower dose-levels. There was evidence of increased systemic exposure after repeated daily administration in the rat but not in the dog.

Distribution

Binding of AB1010 to the cellular fraction of whole blood was studied by partitioning and protein binding of AB1010 was studied by equilibrium dialysis. Binding to blood cells was high when suspended in buffer (>90% for human, rat, mouse, and dog blood cells) and reduced in the presence of plasma (63% for human, 45% for rat, 78% for mouse, and 56% for dog blood cells). Plasma protein binding of AB1010 was also high for human (93%), rat (92%), mouse (86%), dog (93%) and rabbit (98%) at therapeutic plasma concentrations.

AB3280 metabolite plasma protein binding was determined by a blood partitioning method. Binding was high in all species: more than 90% in human plasma and more than 85% in dog, mouse and rat plasma. It is interesting to notice that human plasma has a total binding capacity for AB3280 twice as high (NKp =14.0) as in animal plasma (NKp =5.77, 6.56 and 7.23 respectively for dog, mouse and rat) implying a lower free fraction in human plasma.

Tissue distribution of ^{14}C-AB1010 was studied in the rat. Following oral gavage at 10 mg/kg, quantifiable levels of radioactivity were found in most tissues at 24 hours, the highest levels being found in the adrenals, kidneys, spleen and intestines (in the range 3000 to 16 000 ngeq/g tissue at 24 hours). The high values for volume of distribution (6.7 L/kg at 5 mg/kg, *i.v.*; 11.7 L/kg at 10 mg/kg, oral) indicate extensive distribution of AB1010 to the tissues. Radioactivity was rapidly eliminated and only trace levels remained at 7 days post administration. There was no data suggesting that AB1010 crosses the blood-brain barrier under normal circumstances.

Metabolism

Several *in vitro* and *in vivo* studies allowed identification of four main metabolic pathways for AB1010: N-demethylation, hydrolysis of amide bond, N-oxidation, Hydroxylation.

Below table summarises the results of these *in vitro* and *in vivo* studies, according to the species used for toxicity testing and in humans.

Table 1: Overview of metabolic pathways in species used for toxicity testing and in humans

Metabolic pathways		**Mouse**	**Rat**	**Dog**	**Human**
N-demethylation (AB3280)	*in vitro*	+	+	-	+
	in vivo	+	+	+	+
Hydrolysis (AB1187.3+AB2436)	*in vitro*	+	+	-	-
	in vivo	**+**	**+**	+	+
N-oxidation (AB1010 N-oxide)	*in vitro*	+	+	+	+
	in vivo	ND	+	+	ND
Hydroxylation (mono-hydroxyAB1010)	*in vitro*	ND	ND	ND	ND
	in vivo	ND	+	+	ND

ND: not determined. '+' = present in one of the studies. '–' = not present in any studies

N-demethylation

When the N-methyl piperazine group is removed, the N-demethyl derivative (AB3280) of masitinib mesilate (AB1010) is formed.

The N-demethylation pathway leading to the formation of AB3280 is, by far, the major route of metabolism of AB1010. This reaction was observed *in vitro* in all species except dogs. *In vivo* N-demethylation has been identified as the main pathway of metabolism since AB3280 was the main metabolite found in plasma as well as in feces. In urine, however, AB3280 was present only in small quantities, a logical consequence of its poorly soluble in aqueous media, with it therefore being expected to be mainly excreted in feces.

Hydrolysis

When the amide group of AB1010 is hydrolysed by drug metabolizing enzymes, in particular in mice and rats, two hydrolysis products are formed:

- A carboxylic acid moiety (internal code: AB1187.3) containing the phenylpiperazine moiety that then undergoes conjugation with glucuronic acid.
- An aniline part (internal code: AB2436) containing the thiazole heterocycle, which is subject to oxidation to a further metabolite (internal code: AB5235).

The hydrolysis of the central amide bond leading to the formation of AB236 and AB1187.3 takes place in all species but there are some conflicting results between *in vitro* and *in vivo* data.

In vitro, AB2436 was present as a major metabolite in mouse and rat but not in human (<1%). Cleavage of the amide bond to give AB1187.3 and AB2436 was detected by LC-MS/MS in human; however, it was not determined to be a major route of metabolism in human.

AB1187.3 was found in non-negligible amounts in human plasma. AB1187.3 was identified as the major urinary metabolite in rats and dogs. It was also found in significant quantities in human urine but was not looked for in mouse urine.

AB2436 could be detected in human plasma and AUC values of AB2436 at steady-state represented less than 3% of AUCs of AB1010. It was found in rat plasma albeit in low concentrations i.e. at AUCs 200 times lower than the plasmatic AUC_t measured for AB1010; in mouse plasma it was detected at high concentrations i.e. at an AUC_t 4 times higher than the plasmatic AUC_t measured for AB1010. AB2436 was found in urine of mice, rats and humans. An oxidised form of AB2436, the pyridone AB5235 has been found but only in mouse urine, which is in agreement with the large quantities of AB2436 found in this biological fluid.

AB2436 was not detected in dogs' urine although AB1187.3 was present. In feces, there was no evidence of the presence of either AB1187.3 or AB2436.

N-oxidation

The N-oxidation was identified as a minor metabolic pathway whatever the species, including humans. This pathway was evidenced *in vitro* and confirmed *in vivo* with the formation of N-oxide metabolites in urine and feces of rats and dogs.

Hydroxylation

The other minor metabolic pathway was the hydroxylation pathway identified in rats and dogs with the formation of mono-hydroxylated derivatives of the parent compound in urine and feces and conjugates such as sulfates. It was not determined in mice and humans.

Role of cytochromes in the AB1010 metabolism

An *in vitro* metabolism study with pooled human liver microsomes was performed to identify which *human* cytochrome P450 isotype(s) contribute to the metabolism of AB1010. The results indicated that that CYP3A4 catalyses the metabolism of AB1010 (and the formation of metabolites named MET 1-4) in human liver, with a possible minor contribution by CYP2C8 in the formation of AB3280.

An *in vitro* study with human liver microsomes confirmed the involvement of CYP2C8 in the formation of AB3280 (AB3280 formation ratio = 7.0% at 5 µM). However, when CYP2C8 specific inhibitor montelukast was incubated with microsomes, the inhibition of AB3280 formation was partial and was only about 52%. These results seem to indicate the involvement of another enzyme in AB3280 formation. The additional data submitted by the applicant supports the conclusion that CYP3A4 and CYP2C8 are the main enzymes involved in AB3280 formation. This information was included in the SmPC.

Excretion/Elimination

The principal route of elimination of masitinib mesilate appeared to be biliary excretion. After oral or intravenous administration of radiolabelled masitinib mesilate (AB1010) to rats or dogs, approximately 90% of radioactivity was excreted in the feces, mainly as parent compound. Less than 10% of the administered dose was found in urine with a moderately rapid elimination within 48 hours. Excretion was almost complete within 7 days, regardless of administration route, dose, and species. There was no evidence of hepatobiliary cycling, and no evidence of sex differences in excretion.

AB3280 is the main metabolite in feces (the principal route of elimination). The second major metabolite in dog feces corresponds to a sulfate conjugate of a mono-hydroxylated form of masitinib. The major metabolite in urine is AB1187.3, the carboxylic acid fragment arising from the hydrolysis of the central amide linkage present in masitinib. Apart from the parent compound up to 12 metabolites were detected in urine and 8 metabolites were identified in the feces.

The analysis of urine samples of male Sprague Dawley rats having received masitinib mesilate at oral doses of 30, 125, 250 and 500 mg/kg demonstrated a low concentration of masitinib mesilate in urine, confirming that urinary excretion is not the main route of excretion, whatever the masitinib dose tested. Only one metabolite, AB2436 was found in rat urine in concentrations similar to those of AB1010. No AB6465 was detected, which was expected since this acetylated-aniline is most probably cleaved into the parent aniline (AB2436) before being excreted.

Conversely, in male Swiss mice, analysis of urine samples demonstrated the presence of AB1010 and two metabolites, AB2436 and AB5235, whatever the masitinib dose tested. Except for one sample at the 500 mg/kg dose, AB6465 was not detectable in mouse urine.

Pharmacokinetic Drug Interactions

Medicinal products That may decrease masitinib plasma concentrations

Concomitant administration of masitinib with inducers of CYP3A4 may decrease masitinib plasma concentrations. The extent has not been elucidated *in vivo*. However, as demonstrated in the clinical trial AB14004, masitinib plasma exposure was poorly altered by a strong inhibitor of both CYP3A4 and P-gp (itraconazole). It may thus be estimated that masitinib will be weakly sensitive to CYP3A4 or P-gp inducers.

Medicinal products that may increase masitinib plasma concentrations

Concomitant administration of masitinib with CYP3A4 inhibitors or P-gp inhibitors may increase masitinib plasma concentrations. As demonstrated in the clinical trial AB14004, masitinib plasma exposure was poorly altered by a strong inhibitor of both CYP3A4 and P-gp (itraconazole). CYP2C8 is partially responsible for masitinib *in vitro* biotransformation. Because of the lack of *in vivo* DDI investigations, the co-administration of masitinib with CYP2C8 inhibitors should be used with caution.

Effect of masitinib on other medicinal products

Masitinib is an inhibitor of CYP3A4 *in vitro* with an IC_{50} ≥ 14µM. However, this concentration is unlikely to be reached for masitinib dose up to 6.0mg/kg.

Masitinib is an inhibitor of P-gp at concentrations higher than 10µM. This concentration is unlikely to be reached in case of masitinib treatment at 6.0mg/kg/day. However, coadministration by oral route of masitinib with narrow therapeutic index P-gp substrates should be avoided.

There is a risk of DDI with medicinal products which are Breast Cancer Resistance Protein (BCRP) substrates. The extent has not been investigated *in vivo*. Co-administration of masitinib with narrow therapeutic index BCRP substrates should be avoided.

No data are available concerning masitinib inhibitory potential on CYP2B6. Caution should be taken when administering masitinib with CYP2B6 substrates.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single dose toxicity studies comprised three GLP-compliant studies in Sprague-Dawley rats, two with administration by oral gavage (0 or 2000 mg/kg) and one with administration by intravenous injection (0 or 100 mg/kg). Clinical signs of toxicity were observed in all studies, including, after oral administration, hypoactivity or sedation, piloerection and dyspnoea and, after intravenous administration, hypoactivity. Mortality (2 out of 10 animals) was observed in one of the studies with oral administration. The approximately lethal doses in rats were, therefore, 2000 mg/kg, following oral administration, and higher than 100 mg/kg, following intravenous administration. Results of the studies showed that masitinib mesilate has low acute toxicity.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies were conducted in mice, rats and dogs, with daily administration by oral gavage, and a duration of treatment of up to 13, 26 and 39 weeks, respectively. Except for three studies, all the others were claimed to be GLP-compliant.

The main toxicity target organs identified were the bone marrow, liver, kidney, gastrointestinal tract, and reproductive organs. At higher dose-levels these findings were accompanied by bodyweight changes and mortality.

Bone marrow toxicity observed in mice, rats and dogs was characterised by a reduction in red blood cell parameters (reductions in red blood cells, haemoglobin and packed cell volume), a reduction in white blood cells (leucocytes, lymphocytes and neutrophils), bone marrow hypocellularity in rats and dogs as well as clinical signs in the form of pallor and abnormal breathing in the dog. Haematological effects were observed at doses ≥ 10 mg/kg/day in rats and dogs.

Liver weight increase and hepatocellular hypertrophy was noted in mice, rats and dogs. This finding was accompanied by a moderate (≥ 2-fold) increase in liver enzymes (alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)) at doses ≥100 and ≥ 150 mg/kg/day in rats and dogs, respectively. Moreover, reversible bile canalicular plugs were noted in dogs treated with 50 mg/kg masitinib for 4 weeks.

Renal toxicity was observed in rats (protein in the urine, increased urine volume and pH, increased kidney weight, increases in plasma creatinine and urea as well as degenerative/necrotic tubular nephropathy) and in dogs (blood, bilirubin, proteins in urine) at the highest dose in the 4-week study.

In the mouse there was urinary bladder urothelial hyperplasia in male mice which was not fully reversible during a recovery period. Similar results were found in a 13-week follow-up study in male mice to further investigate the neoplastic findings in bladders of mice in the carcinogenicity study.

Gastro-intestinal toxicity was recorded in dogs and was mostly characterised by clinical observations. These clinical observations included vomiting, regurgitation, and soft feces.

Female genital organs showed morphological changes indicative of oestrous cycle disturbance in rats from 10 mg/kg/day. At 100 mg/kg/day, the ovaries had moderate to large number of luteal and/or follicular haemocysts, no or few corpora lutea, and very few or few follicular development. Depending on ovarian stage, this was associated with endometrial cell atrophy or hypertrophy together with vaginal epithelial cell hyperplasia, hyperkeratinisation or mucification. Ovary weight was increased and on the macroscopic level, discoloured and enlarged ovaries were observed. Partial reversibility was noted in the 4-week toxicity in rats, although not confirmed in the 13-week toxicity in rats.

Following 39-weeks treatment with 30 mg/kg/day masitinib, vacuolation of the epithelium in the seminiferous tubules and oligospermia in the epididymides were observed in dogs. Most male Beagle dogs are sexually mature by eight to nine months of age and since the animals applied in the 39-week dog study were 6 to 7 months at study initiation the majority were sexually mature at sacrifice (1 male out of 4 was pubertal).

Additional effects identified included hyperostosis - slight to moderate hyperostosis were observed in the bones of rats administered 100 mg/kg/day for 6 months – and cardiac changes.

The repeated dose toxicity studies revealed myocardial degeneration and fibrosis in the rat 26-week study at doses 30 and 100 mg/kg/day and pericardial oedema in 1/4 female dogs at the 30 mg/kg/day dose in the 39-week study.

Regarding toxicokinetic data and safety margins, following a routine GLP compliance inspection in June 2007 by the French National Authorities, the bioanalytical (and dosage form) analysis activity for studies performed in the period 25 March 2005 to 06 June 2007, are not to be claimed GLP-compliant. The toxicokinetics data for such studies, which include the chronic toxicity studies in rats and dogs, can be considered to have indicative value only. For this reason, the repeated dose toxicity studies were complemented by two 4-weeks toxicokinetic studies conducted in rats and dogs using the same dose levels as in the chronic toxicity studies.

Systemic exposures in rats and dogs increased with dose levels; in rats, but not in dogs, there was a gender effect, with relatively higher systemic exposures in females; there was no marked accumulation with treatment duration. On a few occasions, masitinib was detected in the plasma samples collected from control animals. However, it is considered that these minor deviations have not impacted on the validity of the affected studies.

2.5.4.3. Genotoxicity

In vitro and *in vivo* studies were performed with masitinib mesilate to determine potential genotoxicity.

Masitinib was non-genotoxic in a test battery comprising the following assays: Ames test, human lymphocytes, L5178Y TK+/- mouse lymphoma cells, *in vivo* mouse bone morrow micronucleus test and Comet assays of mouse and rat liver and bladder tissues.

2.5.4.4. Carcinogenicity

An overview of the carcinogenicity studies performed is presented in the below table. The vehicle consisted of a sterile, isotonic saline solution.

Table 2: Carcinogenicity studies

Study ID /GLP	**Dose (mg/kg/day)**	**Species/ No. of animals/ Route**	**NOAEL (mg/kg/ day)**	**Major findings**
SR-1-29400-tcs/ In vivo phase: GLP Dosage form analysis: partly GLP	Group 1: Vehicle (isotonic saline) Group 2: 30/20 Group 3: 150/100/40 Group 4: 500/300/80	CD-1 mice/ 50/sex/group/ p.o. (gavage)	30/20	Urinary bladder neoplasms
SR-2-29402-tcd GLP	Group 1: vehicle (isotonic saline) Group 2: 10 Group 3: 30 Group 4: 75/60	Sprague-Dawley rats /50/sex/group	10	Uterine adenocarcinomas Pulmonary cystic keratinizing epitheliomas Thyroid follicular adenomas

Long-term carcinogenicity study in CD-1 mice (SR-1-29400-tcs)

Toxicology

- Clinical signs

Treatment with AB1010 caused reflux at dosing in all treated groups, hard abdomen in all test item-treated males and in all females, increase in size of the abdomen for males from groups 3 and 4 and in all females. Limited cases of loud breathing from groups 3 and 4 and few animals showed dyspnoea in all groups.

- Palpable masses

The frequency, time of onset, location, size, and morphological type of the palpable masses recorded were similar in the controls and treated groups.

- Body weight and food consumption

The mean body weight of males and females given 500/300/80 mg/kg/day was statistically significantly lower than that of controls from week 1, but differences were 10 to 14% lower between weeks 38 and 77 (males) or -1 to -8% lower between weeks 42 and 77 (females). The overall body weight gain of males in this group was -20% lower than that of controls. In both sexes, these effects were not observed after the reduction of the dose to 80 mg/kg/day. There were no remarkable and/or consistent differences from control in the body weight gain of males and females in the other test item-treated groups. Generally, the mean food consumption of males and females given 500/300/80 mg/kg/day groups was affected from week 9 and until the dose reduction to 80 mg/kg/day from week 77. Food intake in the other test item- treated groups was not affected throughout the study.

- Haematology and blood biochemistry

There were no treatment-related differences of toxicological importance in any of the haematological or blood biochemical parameters investigated at the end of the dosing scheduled or premature period.

Neoplastic findings

After repeated administration of Masitinib AB Science for 2 years, urinary bladder transitional carcinomas and papillomas were seen in five high-dose males, while transitional papillomas were observed in the

intermediate dose group. Urinary bladder transitional cell hyperplasia was also seen in group 3 and 4 males and females with a greater incidence than in controls and low-dose mice. As the tumours were seen only in treated animals, with a clear dose-relationship, in association with pre-neoplastic finding in males and females, in incidences far outside from historical control data and with statistically positive trend, they were attributed to treatment with Masitinib AB Science.

Malignant lymphoma

A slight decrease in malignant lymphoma was observed in males and females treated at 30/20, 150/100/40 and 500/300/80 mg/kg/day. This was likely related with shorter survival of treated animals. However, an effect of AB1010 could have contributed to this lower incidence.

- Non-neoplastic findings in the liver and pigments

The following findings were observed in the liver:

- Hepatocellular centrilobular hypertrophy from 150/100/40 mg/kg/day in males and at 500/300/80 mg/kg/day in females,
- Marginally increased incidence of hepatocellular necrosis from 150/100/40 mg/kg/day in males and females,
- Hepatocellular enlargement/microvacuolation in occasional animals from 150/100/40 mg/kg/day in males and at 500/300/80 mg/kg/day in females.

  Two types of pigments were noted in treated animals:
- Renal dark grey pigment at 500/300/80 mg/kg/day in both sexes,
- Brown pigment in multiple organs from 20/30 mg/kg/day in both sexes (kidneys, heart, brain, liver, adrenals, adipose tissue, skeletal muscle, tongue, spleen, lymph nodes, thyroid glands).

Results suggest:

- There were no treatment-related neoplastic findings in female mice.

- In males, administration of AB1010 at the dose-levels of 500/300/80 mg/kg/day for 2 years initially resulted in treatment-related urinary bladder transitional carcinoma and papilloma. At the intermediate dose-level, only papillomas were observed.

Treatment-related urinary bladder transitional carcinomas and papillomas were observed in male mice treated at the high dose-level of AB1010, while transitional papillomas were observed in the mid-dose group of male mice. Noteworthy, in subsequent *in vivo* Comet assays performed in accordance with OECD Test Guideline No. 489, AB1010 induced no significant increase in DNA strand breaks either in the liver or in the bladder of male mice and rats and was thus considered as having no *in vivo* genotoxic activity in both these organs.

The lack of genotoxicity in the bladder of mice receiving high doses of masitinib mesilate appears in contradiction with the formation of bladder carcinomas during the carcinogenicity study during which mice were administered lower doses. Anyway, even if it is not possible to totally exclude non-genotoxic carcinogenic mechanisms of action in mice (e.g., urinary crystals, shunting of kinase activity), the hypothesis that the formation of carcinomas after administration of AB1010 to male mice is due to the high concentration of genotoxic metabolites (anilines) present in their urine cannot be excluded. In that way, a genotoxic mode of action constitutes a worst-case.

From the mouse carcinogenesis study, the calculation of the BMDCL associated with a benchmark response of 10% ($BMDL_{10}$) for an extra risk of 10% bladder carcinomas as observed in male mice was of 220 mg/kg bw/d. The level of confidence of this reference value is very high considering the choice of the critical effect and the choice of the key study (the most sensitive species and gender).

Furthermore, it was deemed useful to convert experimental doses used in mice in Human Equivalent Dose (HED) by using allometric factors and to compare the interspecies differences of urinary exposure to AB1010 and genotoxic anilines, as measures of the achieved local exposure of the carcinogenic target organ rather than to compare "administered external dose" values.

In the mouse, the urine concentration of genotoxic anilines at external dose of 125 mg/kg bw, i.e. 10 mg/kg bw in HED, was of 58,545 ng/mL. In Human, the dose of 6.7-8 mg/kg bw led to a urine concentration (0-24h) of 190 ng/mL genotoxic anilines. At equivalent dose, the ratio between the urine concentrations of genotoxic anilines in mouse and Human corresponds to 308 (table below).

Table 3: Dose and exposure in carcinogenicity studies

Species	Dose (mg/kg)			Exposure to AB1010	Exposure to **genotoxic anilines** AB2436 + AB5235 + AB6465		**Signs of bladder carcinogenicity**
	External dose	Averaged dose[2]	**HED**[1]	*Plasma* $AUC_{(0\text{-}24h)}$ *(ng.h/mL)*	***Plasma*** $AUC_{(0\text{-}24h)}$ *(ng.h/mL)*	***Urine*** $Concentration_{(0\text{-}24h)}$ *(ng/mL)*	
Human	**400**	-	**6.7 to 8***	7,024	53	**190**	None expected
Rat	30	-	4.8	2,618	51	141	None
	125	-	20	40,934	1,553	656	NA
	250	-	40	70,900	3,425	2,487	NA
	500	-	80	121,337	13,275	4,427	NA
Mouse	30	30	2.4	1,193	7,600	12,962	**None**
	150/100/40	96	7,8	12,864**	NA	NA	**Papillomas**
	125	**125**	**10**	6,816	33,000	**58,545**	NA
	250	250	20	17,342	78,601	158,490	NA
	500/300/80	281	22.5	64,998***	NA	NA	**Papillomas & carcinomas**
	500	500	40	55,075	169,605	253,294	NA
Mouse/Human				1.83 (=12,864/7,024)	622 (=33,000/53)	**308** (=58,545/190)	

*400 mg/day corresponds to weight-adjusted doses of 6.7 to 8 mg/kg for patients weighing 60 to 50 kg

[1]: Human Equivalent Dose: HED (mg/kg/day) = Animal dose (mg/kg/day) X [Animal weight (kg)/Human weight (kg)]$^{0.33}$ (Shin et al, 2010[2] ; Nair and Jacob, 2016)[3]

[2]: The averaged doses were calculated only for doses used in the carcinogenicity study (see Paragraph A.1Dose levels used in the carcinogenicity study in mice)

NA: not available

Otherwise, it is currently considered that for carcinogenic and genotoxic compounds for which a Benchmark Dose (BMDL10) has been defined, the risk can be ruled out beyond a margin of exposure (MOE) of 10,000 for a lifetime exposure. This MOE of 10,000 corresponds to an excess risk of developing cancer of 1 in 1.105. As the urinary concentration of anilines in humans is 308 times lower than that observed in mice at a comparable dose, the adjustment can be made directly to the acceptable MOE of 10,000, i.e. 10,000/308, giving an adjusted MOE of 32.5.

In terms of posology, treatment in Human is performed at a daily dose of 4.5 mg/kg bw/twice a day that reaches a very low level of urinary concentration (a dose of 6.7 to 8 mg/kg bw/day led to a urine concentration of 190 ng/mL).

Therefore, the BMDL10/32.5 would lead to an acceptable level of excess risk with the occurrence of one bladder tumour per 1.105. Therefore, a daily treatment of 6.7 mg/kg bw/day (220/32.5) for lifetime in Human is acceptable in terms of excess risk of bladder tumours with an occurrence of 1 for 1.105.

Long-term carcinogenicity study in Sprague-Dawley rats (SR-2-29402-tcr)

Neoplastic findings

Trend test statistics, conducted according to Peto et al. (1980), revealed statistically significant increases for neoplasms in several organs at the dose level of 75/60 mg/kg/day.

Incidence of selected uterine neoplastic and pre-neoplastic findings

The incidence of uterine adenocarcinomas seen at the high dose was higher than that observed in CIT control data or in the literature, therefore this neoplasm was considered to be related to the administration of the test item at 75/60 mg/kg/day. The increased incidence observed in this study may be related to the increased incidence of ovarian follicular cysts as this lesion is reported to be associated with such cysts and is thought to be the result of prolonged oestrogen stimulation (Boorman et al., 1990).

Incidence of selected thyroid neoplastic and pre-neoplastic findings

The incidence of follicular cell adenomas (benign tumours) at 75/60 mg/kg/day was higher than that noted in female Sprague-Dawley rats in CIT control data or in the literature (Charles River Laboratories, 2004), and therefore the high incidence at 75/60 mg/kg was considered to be related to the test item. The incidence recorded at 30 mg/kg/day was within the range of that recorded in CIT control data or in the literature and was not considered to be treatment related. The single occurrence of a follicular cell carcinoma (malignant tumour) noted for each dose-levels of 10, 30 and 75/60 mg/kg/day in females was within the range of that recorded in the literature in control female Sprague-Dawley rats.

Incidence of selected neoplastic and pre-neoplastic findings in the lungs

Pulmonary cystic keratinizing epithelioma was found in 4/50 high-dose females whereas it was not recorded in the CIT control data or in the compilation of spontaneous neoplasms of control Sprague-Dawley rats from Charles River Laboratories (2004) and therefore was considered to be induced by masitinib mesilate. The cystic keratinizing epithelioma appears to be a proliferative lesion limited to the rat and is rarely seen in other species (Boorman *et al.*, 1996). In the current study, it was thought to be secondary to the irritation elicited in the alveoli by the presence of foamy macrophages induced by the test item administration. Bronchoalveolar hyperplasia in the lungs and squamous metaplasia in the lungs, trachea and larynx were considered to be regenerative and secondary to the injury elicited by the presence of foamy alveolar macrophages.

Two cases of astrocytoma and a single case of oligodendroglioma was seen in the male high-dose group comprising 50 animals while a single case of astrocytoma was noted in a female control animal. While a possible relationship to treatment cannot be excluded, in view of the presence of one astrocytoma in a control female and incidences within the range of that noted in male Sprague-Dawley rats in CIT control data or in the literature (Charles River Laboratories, 2004), this was considered unlikely.

In addition, a reduced incidence of pituitary adenomas was observed in high-dose animals.

The main conclusions of this study, as described by pathologists, indicate that:

- There is no significant increase in the total number of primary tumours with masitinib.
- There were no neoplastic findings related to the test item in male rats.
- At the high dose (75/60 mg/kg/day), a statistically significant increase in malignant uterine tumours (adenocarcinomas) is observed, probably linked to endocrine imbalance.
- There is an induction of benign pulmonary tumours (cystic keratinizing epithelioma) at the high dose (75/60 mg/kg/day) in female rats. These tumours are considered to be secondary to the irritation elicited in the alveoli by the presence of foamy macrophages induced by masitinib.
- There is a statistically significant increase in benign thyroid tumours (follicular cell adenomas) in female rats at the high dose (75/60 mg/kg/day). Although the single occurrence of a follicular cell carcinoma (malignant tumour) was noted for each dose- levels of 10, 30 and 75/60 mg/kg/day in females, it was not considered as treatment related at doses of 10 and 30 mg/kg/day and its significance was thought to be equivocal at the high dose-level.
- There is a statistically significant decrease in benign tumours of the pituitary (adenomas of the pars distalis) in female rats at the high dose (75/60 mg/kg/day).

Rat uterus tumours

In female rats there was an increase in the incidence of malignant uterine adenocarcinomas at the high dose-level of 75/60 mg/kg. These tumours are proposed to result from the elevated levels of oestrogens secreted by the ovarian cysts. A histopathological profile of "persistent oestrus" was observed in female rats, characterised by uterine hyperplasia and squamous metaplasia, vaginal increased epithelial thickness (hypertrophy) and cornification. No hormonal imbalance was observed in female patients treated with masitinib. In females, the increase of uterine adenocarcinomas could be specific of the species.

Rat thyroid tumours

A single occurrence of follicular cell carcinoma was reported at each dose level in female rats. These findings were within the historical control ranged recorded by the animal supplier for female SD rats. A statistically significant increase in the incidence of benign thyroid tumours (follicular cell adenomas) was seen at the high-dose level (75/60 mg/kg) in female rats. These thyroid effects in female rats are proposed to be related to the proestrogenic effect described above, and not observed in humans.

Pulmonary cystic keratinizing epitheliomas

Pulmonary cystic keratinizing epithelioma was found in 4/50 high-dose females whereas it was not recorded in the CIT control data or in the compilation of spontaneous neoplasms of control Sprague Dawley rats from Charles River Laboratories (2004) [Charles River Laboratories 2004] and therefore was considered to be induced by the test item. The cystic keratinizing epithelioma appears to be a proliferative lesion limited to the rat and is rarely seen in other species [Boorman 1996]. Pulmonary cystic keratinizing epithelioma was described to occur in the rat lung after chronic exposure to high burdens of particulate material, and more commonly in female rats [Boorman 1996]. In the current study, it was thought to be secondary to the irritation elicited in the alveoli by the presence of foamy macrophages induced by the test item administration. Bronchoalveolar hyperplasia in the lungs and squamous metaplasia in the lungs, trachea and larynx were considered to be regenerative and secondary to the injury elicited by the presence of foamy alveolar macrophages. Foamy macrophages were not considered to be adverse at the dose-level of 10 mg/kg/day in the absence of associated hyperplastic and metaplastic changes.

No increase in malignant tumours in males

In the study 29402 TCR, in males, there is no increase in malignant tumours, regardless of the administered dose. No increase in the frequency of malignant tumours has been observed in male rats, with the exception of a slight increase in the frequency of astrocytomes and oligodendrogliomes at the high dose. No increased frequency for these tumours has been observed for the CIT control data.

2.5.4.5. Reproductive and developmental toxicity

Reproductive toxicity studies comprised studies on fertility and early embryonic development, in rats, and embryo-fetal development, in rats and rabbits. All studies used the oral route of administration and were claimed to be GLP-compliant. The lack of studies on pre-postnatal development and juvenile animals was justified by the applicant on the basis of the target patients' population and risk mitigation measures in the SmPC.

The fertility and early embryo-fetal development studies with treatment of males and females (0, 10, 30 or 100 mg/kg/day) starting before mating and continuing up to gestation day 7 showed effects in the ovaries (haemorrhagic cysts, low number of corpora lutea), reduction in pregnancy rate and implantation sites and the higher pre-implantation loss. No effects were observed in male reproductive organs or sperm parameters. The reproductive no-observed-adverse-effect-level (NOAEL) for males and females were set at 100 and 10 mg/kg/day, respectively. No effects were observed in an additional study in rats

were masitinib mesilate was administered to females only (15 or 50 mg/kg/day) which were mated with untreated males after a recovery period of two weeks.

The potential effects of masitinib (0, 10, 30 or 100 mg/kg/day) on embryo-fetal development were evaluated in rats and rabbits. The study in rats revealed, at the maximum tested dose, lower fetal body weights and statistically significant increased incidence of unossified or incompletely ossified bones. Maternal toxicity was observed in the form of a significant reduction in body weight gain at 100 mg/kg/day. Moreover, maternal macroscopic findings were made in all masitinib-treated groups. The study in rabbits showed maternal toxicity (reduced body weight and food consumption) but no adverse effects on embryo-fetal development. None of the studies revealed teratogenic effects of masitinib. The NOAEL for effects on embryo-fetal development in rats and rabbits were determined to be, respectively, 30 mg/kg/day ($AUC_{0.5\text{-}24}$ at gestation day 17 =20191 ng.h/mL) and 100 mg/kg/day ($AUC_{1\text{-}24h}$ at gestation day 18=110938 ng.h/mL).

2.5.4.6. Local tolerance

Skin sensitization potential was assessed in mice using the local lymph node assay (Study 33510 TSS). Significant lymphoproliferative responses were observed in the absence of local skin irritation at the site of administration (Study 33510 TSS). Masitinib mesilate showed skin sensitization potential and exposure may result in delayed contact hypersensitivity. Masitinib should be considered as a strong sensitiser. Masitinib mesilate was found to be a slight irritant when applied topically (Study 33511 TAL) and to be severely irritating when administered by the ocular route to rabbits (Study 33512 TAL).

2.5.4.7. Other toxicity studies

AB3280 being the major plasmatic metabolite of AB1010 found in all species including man, a 2-week toxicity study was conducted, and results are presented hereafter. Under the experimental conditions of the study and considering the slight effects on blood biochemical parameters, the NOAEL is 250 mg/kg/day. No effects on the organ weights and no macroscopic or microscopic findings were observed at any dose-levels. The test item did not induce any noteworthy increase in the number of revertants, in either experiment, in any of the six strains. Although *in vitro* studies have been carried out in the presence of S9 which is supposed to metabolise AB1010, two specific genotoxicity studies have been performed on AB3280, its main plasmatic metabolite. AB3280 did not show any mutagenic activity in the bacterial reverse mutation test with *Salmonella typhimurium* and *Escherichia coli*. Additionally, AB3280 did not induce chromosome aberrations in cultured human lymphocytes.

AB1187.3 did not show any mutagenic activity either with or without a rat liver metabolic activation system in Salmonella typhimurium TA 98 and TA 100.

AB2436 showed mutagenic activity in the bacterial reverse mutation test with metabolic activation in the TA 1537, TA 98, TA 100, and TA 102 *Salmonella typhimurium* strains.

AB2436 induced chromosome aberrations in cultured human lymphocytes in the presence of S9 mix.

AB5235, showed a mutagenic activity in the presence of S9 mix both in TA 98, TA 100, and TA 102 *Salmonella typhimurium* strains.

Among the potential reasons for the formation of tumours, the more plausible hypothesis is based on the genotoxicity of masitinib aniline metabolites. The applicant further discussed that:

- From literature, aniline compounds are well-known to be responsible for urinary bladder cancers.

- The bladder carcinogenic risk has been reported to be dose-dependent [Bolt and Huici- Montagud 2008] as it is the case with masitinib since the low dose administered during the carcinogenicity study did not induce any tumours.
- Three anilines, namely AB2436, AB5235 and AB6465, have been found to be formed after from different *in vitro* studies performed both on hepatic microsomes and freshly prepared hepatocytes and from *in vivo* studies.
- According to available studies, these three anilines AB2436, AB5235 and AB6465 were found mutagenic only in the presence of metabolic activation via the S9 mix.

Following these *in vitro* results and in order to evaluate the risk of carcinogenicity in humans, the formation of the three mutagenic anilines has been quantified *in vivo* using fully validated analytical methods in plasma and urine of mice, rats, and humans.

The estimated ratios between mice and humans are: 152 regarding plasma AUCs and 68 regarding urinary concentrations.

Thus, it is hypothesised that the high concentrations of aniline metabolites in male mice urine and plasma could be responsible for the formation of bladder cancer.

2.5.5. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) Phase I was conducted to consider the risk to the environment arising from the use of masitinib mesilate 100 mg and 200 mg, film-coated tablet. In combination with riluzole is indicated for the treatment of adult patients with ALS

According to the applicant, the ERA report was prepared in accordance with the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* EMEA/CHMP/SWP/4447/00 corr 2, 2006 and Questions and answers document on the same Guideline EMA/CHMP/SWP/44609/2010 Rev.1. 26 May 2016.

Relevant endpoints, methods and results were discussed, and study results are summarised below.

Table 4: Summary of main study results of ERA

Substance (INN/Invented Name): Masitinib mesilate			
CAS-number (if available): 790299-79-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 117	1.44	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.44	not B
	BCF		not B
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Refined PEC	0.00824 µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

For screening on persistence bioaccumulation and toxicity (PBT) an experimental Log Kow value was calculated by the High-Performance Liquid Chromatography (HPLC) method according to OECD 117. It was below the limit set in the EMA´s Guideline on the Environmental Risk Assessment of Medicinal

Product for Human Use (EMEA/CHMP/SWP/4447/00 corr 2) and study report was provided by the applicant.

Fpen was refined based on prevalence data in the EU taken from the orphan designation for masitinib (Orphanet, Amyotrophic lateral sclerosis, accessed June 2016) for the treatment of ALS. Based on prevalence data of approximately 0.5 in 10,000 Fpen was refined and used for calculation of $PEC_{surface\ water}$ resulting in a value of 0.00824 µg/L. The refined $PEC_{surfacewater}$ does not exceed the action limit of 0.01 µg/L and the provided calculation is acceptable. It is in line with Questions and answers document of the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* EMA/CHMP/SWP/44609/2010 Rev. 1, 2016.

2.5.6. Discussion on non-clinical aspects

The non-clinical pharmacology dossier consists of the combination of documents of non-clinical study reports ("original data") and bibliographical references. The *in vivo* studies all have been performed in human $SOD1^{G93A}$ transgenic rodents, which show a phenotype similar to ALS in humans. The chosen animal study has a good face validity that strengthens the translatability potential of the obtained non-clinical data into clinical setting.

None of the studies had GLP status. It is generally acceptable that proof-of principle in-house studies are performed in a non-GLP setting, nor the GLP status is required by ICH S7A guidelines. Most studies were approved by authorised animal ethics committees, one lacked the ethics statement. Randomisation were performed in most cases; however, some study documentation did not state this information and thus, in case if not applied, it might have led to the data bias. Blinding was not mentioned. Not all the studies could be fully evaluated regarding 3Rs standard compliance since in the study reports the provided information was scarce (e.g., regarding housing conditions, acclimatisation etc). Proper endpoints for the studies were chosen to minimise the suffering of animals but allowing to gain relevant scientific data on survival, which is in line with the 3Rs principle in animal research ethics.

Human dose equivalents for the animal studies were appropriately chosen. No information on the deviation from the initial study protocols was present in any of the *in vivo* study reports present in the primary PD dossier.

From a primary PD perspective, Masitinib AB Science distinguishes itself from many other ALS-developmental drugs by exerting neuroprotection in both the CNS and the PNS via selective kinase inhibition that modulates functionality of different cells implicated in ALS pathogenesis.

Non-clinical pharmacology evidenced the biological plausibility for using masitinib mesilate in ALS through its dual targeting of mast cells and microglia and also supports the hypothesis that masitinib may provide a clinical benefit if administered early stage of disease progression (i.e., prior to the point of a permanent loss of function or a severe impairment of functionality). The importance of CSF1R in microglial proliferation, and the importance of c-Kit and Lyn for mast cell activation is well-established. The potent and selective activity of masitinib against CSF1R leads to the inhibition of the CSF1/CSF1R signalling pathway, thereby regulating CSF1R-dependent cells such as microglia and aberrant glial cells. Due to its activity against c-Kit and Lyn, masitinib is also able to modulate the function of mast cells.

It is hypothesised that via this multifaceted therapeutic approach, Masitinib AB Science is capable of slowing or preventing ALS disease progression.

After evaluating *in vivo* study protocols on primary pharmacodynamics, several technical/methodological issue-related concerns raised. Namely, experimental results were not always set out clearly (the actual effect size from the drug treatment was not always expressed, also the use of standard deviation (SD) instead of standard error of the mean (SEM) would have been of higher informative value), and the

interpretation of the obtained data was not comprehensively carried out. Besides, in the study protocols, only representative examples of the obtained of histopathological microscopy results were provided, and the full dataset was not found to enable comprehensive assessment of the study results. Statistical procedures used to design the *in vivo* experiments and to analyse the obtained data were not always clearly traceable and/or meaningful and may have resulted in overoptimistic statistical significance estimations. Moreover, studies were not always properly designed to reach the necessary power for the clear demonstration of the drug effect (ALS-MICE Apr 2014, ALS RATS Jan 2013). Moreover, in the study ALS-MICE Apr 2014, the applicant concludes that "*these results are very encouraging considering that masitinib alone could improve grip strength in symptomatic mice and the combination of masitinib with riluzole could in fact improve riluzole effect on it*" – this conclusion cannot be drawn as seen from the presented study report data since sex-related differences are obviously present – in males, riluzole alone seems to outperform the combination of Masitinib AB Science and riluzole, in contrast to females. These differences were not commented or discussed elsewhere by the applicant. Besides, no proper data analyses (e.g., two-way analysis of variance (ANOVA) in case of factorial experiment design, which would be appropriate in this case) were applied to evaluate the significance of the observed sex-related differences regarding the effect of masitinib alone or in combination with riluzole. The interaction of the sex as a possible confounding factor to the combined Masitinib AB Science and riluzole treatment effect was not properly addressed and assessed.

The applicant was requested to justify the reliability of the non-clinical pharmacological results and the extrapolability to an *in vivo* ALS model and further discussed the discrepancy in the results on survival between the two ALS model animals (mice vs. rats) and its clinical relevance. First, a reasoning behind the observed discrepancies in survival data between murine and rat ALS models have been discussed emphasizing that the data from the rat ALS model should be seen as the definitive data set, which can be agreed (the sample sizes were appropriate allowing to gain robust data and draw more credible conclusions). Besides, the applicant has additionally submitted 4 full study reports (previously presented as research papers) allowing to further substantiate the mechanism of action of Masitinib AB Science in ALS – i.e., provided biological plausibility for the use of Masitinib AB Science in ALS through its dual targeting of mast cells and microglia. Furthermore, Masitinib Science is proposed for the treatment of adults with ALS in combination with Riluzole. The combination of riluzole and Masitinib AB Science was tested only in ALS mice (study ALS-MICE Apr 2014). Moreover, the study of combined masitinib and riluzole treatment lacked power (not enough animals per group were used to convincingly demonstrate the effect). Combination value of the two drugs on the therapeutic effect was not further discussed or elaborated in non-clinical setting but has been assessed in the clinical setting. Based on the summary of existing data provided by the applicant, this comparison is only relative/indicative (riluzole data coming mainly from ALS mice model exploited in a different setting), although all the available data are in favour of Masitinib AB Science's beneficial effect and use in clinical setting for ALS patients.

Secondary PD studies were not performed. It is nevertheless accepted that masitinib by itself or in combination with riluzole did not impact negatively on the global condition of treated animals, which is indicative that there were no detrimental secondary PD effects at the administered dose.

Concerning safety pharmacology, masitinib did not induce any relevant modification of the respiratory function or central nervous system activity. Masitinib mesilate, at 10 mg/kg and 50 mg/kg also did not induce modifications of cardiovascular function or electrophysiological parameters in telemetered dogs. Moreover, the clinical experience did not evidence any sign of cardiotoxicity with masitinib. However, when the effects of AB1010 were tested on hERG channel stably expressed in HEK-293, there was a significant concentration-dependent reduction (IC_{50}: 8.3 ± 1.1 µmol/L) in hERG tail current amplitude in presence of AB1010 from 0.1 to 30 µmol/L. This effect was only partially reversed after the washout period and was significant compared to the spontaneous run-down observed in the control group. The applicant was requested to provide further clarification on the mechanism involved in the effect of

masitinib in the hERG tail current and evaluate possible pharmacological interactions of masitinib with other drugs known to induce QT prolongation. Upon revision of the answers, it can be agreed that at a therapeutic dose in humans, it is unlikely that masitinib inhibit hERG channel. This is reinforced by the fact that in the clinical trial AB14004 masitinib did not induce QT prolongation.

No PD drug interaction studies were performed for masitinib. All studies are PK drug interactions. Masitinib is indicated for the treatment of adult patients with ALS in combination with riluzole, which have different targets *in vivo*. Thus, not performing the DDI in the non-clinical setting is acceptable.

Preclinical PK and toxicokinetic investigations have been conducted in mice, rats, and dogs in order to characterise the PK behaviour of masitinib.

Masitinib mesilate appeared to be well absorbed after oral administration in the different animal models (mice, rats, cats and dogs). Bioavailability (in terms of measured radioactivity) varies from 65% in rats to around 80% in dogs. Absorption was reasonably rapid with t_{max} values between 0.5 and 4 hours in all species and apparent $t_{1/2}$ values in the range 1-4 hours in the rat and 2 -5 hours in the dog. In mice there was no effect of sex on systemic exposure to masitinib, but plasma levels of AB3280 were approximately 2-fold higher in females than males. In rats a sex effect on systemic exposure to masitinib was noted after single and repeated administration, with consistently an approximate 2-fold higher exposure in female rats than males. In dogs there was no evidence of any sex effect on systemic exposure to masitinib. Absorption was broadly dose-proportional with a tendency to increase in a supralinear fashion; this was more marked at lower dose-levels. There was evidence of increased systemic exposure after repeated daily administration in the rat but not in the dog.

Binding to blood cells was reduced in the presence of plasma (63% for human, 45% for rat, 78% for mouse, and 56% for dog blood cells). Plasma protein binding of AB1010 was also high for human (93%), rat (92%), mouse (86%), dog (93%) and rabbit (98%) at therapeutic plasma concentrations. AB3280 metabolite plasma protein binding was high in all species: more than 90% in human plasma and more than 85% in dog, mouse, and rat plasma. Tissue distribution of ^{14}C-AB1010 indicate extensive distribution of AB1010 to the tissues. Radioactivity was rapidly eliminated and only trace levels remained at 7 days post-administration. There was no data suggesting that AB1010 crosses the blood-brain barrier under normal circumstances.

AB2436 could be detected in human plasma and AUC values of AB2436 at steady-state represented less than 3% of AUCs of AB1010. It was found in rat plasma albeit in low concentrations i.e. at AUCs 200 times lower than the plasmatic AUC_t measured for AB1010; in mouse plasma it was detected at high concentrations i.e. at an AUC_t 4 times higher than the plasmatic AUC_t measured for AB1010. AB2436 was found in urine of mice, rats and humans. An oxidised form of AB2436, the pyridone AB5235 has been found but only in mouse urine, which is in agreement with the large quantities of AB2436 found in this biological fluid. Upon request, the pharmacological and toxicological implications related to the observed metabolic differences between humans and mice have been discussed. The applicant suggests that the hypothesis of the contribution of aniline derivatives of the bladder tumour in mouse is plausible. An estimation of threshold in human was made which shows that bladder tumour is unlikely to occur in human at the estimated therapeutic dose of masitinib mesilate.

An *in vitro* study with human liver microsomes (Study DC15041/AB1010-2C8) confirmed the involvement of CYP2C8 in the formation of AB3280 (AB3280 formation ratio = 7.0% at 5 µM). However, when CYP2C8 specific inhibitor montelukast was incubated with microsomes, the inhibition of AB3280 formation was partial and was only about 52%. These results seem to indicate the involvement of another enzyme in AB3280 formation. The additional data submitted by the applicant during the procedure supports the conclusion that CYP3A4 and CYP2C8 are the main enzymes involved in AB3280 formation. This information was included in the SmPC.

After oral administration to rats and dogs, the majority of administered masitinib is excreted in bile as parent (AB1010) or as desmethylated (AB3280). Overall, AB1010 is cleared via metabolism and via biliary (and to a lesser degree, urinary) excretion.

Concerning PK interactions, co-administration of masitinib mesilate with BCRP substrates, P-gp substrates with narrow therapeutic index and BCRP inhibitors or inducers should be avoided. Coadministration of masitinib mesilate with CYP2B6 substrates, CYP3A4 substrates with narrow therapeutic index, CYP2C8 inhibitors, CYP3A4 inhibitors and strong inducers and P-gp strong inducers should be given with caution.

Potential PK interactions are adequately addressed in the SmPC, considering the available data.

Focusing on interactions with drugs that are potentially going to be co-administered as per the requested indication, (treatment of adults with ALS in combination with riluzole), the applicant was requested to justify the absence of PK PD DDI studies. It was shown in a clinical study, by co-administering Riluzole and Masitinib at therapeutic range – 3.0 mg/kg/day (7 patients) and 4.5 mg/kg/day (11 patients) – the PK parameters of Riluzole were not significantly different when comparing both arms. It is important to note that low patient number in this study and considerably high inter-individual variability in the riluzole's main metabolising enzyme CYP1A2 obviously leads to low power of the study to convincingly demonstrate the putative impact of Masitinib's PK. However, the fact that Riluzole and Masitinib AB Science have different main metabolising pathways strengthens the conclusion made by the applicant, that Masitinib AB Science, regardless of the dose, does not significantly modify the AUC of Riluzole in humans.

Results of single dose toxicity studies showed that masitinib mesilate has low acute toxicity. The approximately lethal dose in rats is 2000 mg/kg following oral administration and higher than 100 mg/kg following intravenous dosing. Clinical signs of toxicity after oral administration included hypoactivity or sedation, piloerection, and dyspnoea and, after intravenous administration, hypoactivity. Repeat-dose toxicity studies were conducted in mice, rats, and dogs, with daily administration by oral gavage, and a duration of treatment up to 13, 26 and 39 weeks, respectively. Among these, the studies in rats and dogs may be considered as the main repeated dose toxicity studies; the studies in mice were mostly related to the carcinogenicity studies, aiming either at selecting doses levels for such studies or at investigating mechanisms of carcinogenicity.

In repeated dose toxicity studies, the main toxicity target organs identified were the bone marrow, the liver and the kidney in dogs and rats, gastrointestinal tract intolerance in dogs, the female genital tract in rats and the male genital tract in dogs. At higher dose-levels these findings were accompanied by bodyweight changes and mortality. Additional effects identified included hyperostosis and cardiac changes.

Considering the important role of c-Kit during haematopoiesis, the bone marrow toxicity represents an expected finding. The applicant hypothesised that the renal disorders observed in rats and dogs may be explained by the mechanism of action of masitinib which induces some permeability dysfunctions through inhibition of PDGFR or other kinases involved in podocyte function and renal leakage. The urinary bladder urothelial hyperplasia in male mice, an effect not observed in other species, was attributed to a much higher production of the aniline metabolite AB2436 in mice as compared with other species. As requested, the applicant discussed the findings of the ovarian dysfunction observed in rats and the cardiac effects observed in the chronic toxicity studies - myocardial degeneration and fibrosis in rats and pericardial oedema in 1/4 female dogs at the top dose. According to the applicant, the pericardial oedema observed in one dog was part of a generalised oedema and was attributed to severe anaemia. Masitinib did not directly caused the pericardial oedema. For the ovary findings according to the applicant, these are attributed to inhibition of c-kit by masitinib. c-kit plays a key role in the development of ovarian primordial follicles and is involved in the release of prolactin in rat. The discussion regarding cardiac

effects in rats suggests that the applicant considers that the findings have not been caused by masitinib. It may not be concluded that the ovarian disfunction and cardiac findings observed in rats are not of relevance to humans.

The available data on pharmaco/toxicokinetics suggest low to no safety margins for bone marrow toxicity, renal toxicity, reproductive toxicity in male dogs and oestrous cycle disturbances in female rats, and small to moderate safety margins for liver toxicity, ovarian toxicity, hyperostosis, and myocardial toxicity.

Masitinib mesilate is not genotoxic. Negative results were obtained with masitinib in all *in vitro* assays. Moreover, no genotoxic activity of masitinib was reported *in vivo* in the mouse micronucleus test or in the comet test performed on the liver and the bladder of mice and rats. No genotoxicity was found for the main plasma masitinib metabolite AB3280, whatever the species. No genotoxicity was found for the metabolite AB1187.3 in the Ames test either with or without a rat liver metabolic activation system. In contrast, the metabolites AB2436, AB5235 and AB6465 showed some evidence of mutagenicity in the Ames test, only in the presence of rat live S9 metabolic activation.

The applicant has submitted long-term carcinogenicity studies conducted with masitinib in CD-1 mice and Sprague-Dawley rats. masitinib-treatment was associated with mortality in the mice. Hence, the overall survival rates ranged from 26-38% in the treated animals versus 40% in the control group. Due to high mortality rates, the study treatment period and the administered doses were reduced. Urinary bladder transitional carcinomas and papillomas were seen in, respectively, 5/52 and 3/52 male CD-1 administered 500/300/80 mg/kg/day masitinib for 80 weeks, while transitional papillomas (2/52) were observed in the intermediate dose group (150/100/40 mg/kg/day). Urinary bladder transitional cell hyperplasia was also seen in 150/100/40 and 500/300/80 mg/kg/day males and females with a greater incidence than in controls and mice administered with 30/20 mg/kg/day mice. As the tumours were seen only in treated animals, with a clear dose-relationship, in association with pre-neoplastic finding in males and females, in incidences far outside from historical control data and with statistically positive trend, they were attributed to treatment with masitinib. A NOAEL for the urinary bladder transitional carcinomas was established at 30/20 mg/kg/day.

The applicant hypothesised that the increase in urinary bladder carcinomas and papillomas and urothelial papillomas were mouse-specific findings based on the production of two aniline metabolites in mouse hepatocytes *in vitro* and not in hepatocytes from other species including humans. This hypothesis appears incorrect since the genotoxic metabolite AB2436 was also formed in rat hepatocytes *in vitro* and urinary bladder carcinomas and papillomas were not observed in the rat carcinogenicity study.

While Masitinib AB Science treatment was not associated with significant mortality in the long-term rat carcinogenicity study, it induced uterine adenocarcinomas and atypical uterine hyperplasia with a NOAEL of 30 mg/kg/day. Thyroid follicular cell adenomas were observed in 1/50 and 5/50 female rats administered 30 and 75/60 mg/kg/day, respectively. These findings were accompanied by follicular cell hyperplasia hence the overall NOAEL is considered 10 mg/kg/day.

For the rat uterine and thyroid tumours, the applicant proposes a proestrogenic effect of masitinib in female rats, which is not observed in humans. Upon request, the applicant has presented additional data that sufficiently supports the view that masitinib leads to hypoprolactinaemia and this is reflected in the tumour findings in the rat carcinogenicity study. It is agreed that due to markedly different mechanism in female reproductive hormonal regulation between humans and rats, these rat tumours are generally considered to have no significance to humans. The lack of clinical relevance is further supported by the absence of estrous cycle disturbances in clinical studies.

Pulmonary cystic keratinising epithelioma was found in 4/50 high-dose females whereas it was not recorded in the CIT control data or in the compilation of spontaneous neoplasms of control Sprague-Dawley rats from Charles River Laboratories (2004) and therefore was induced by masitinib.

The applicant further addressed whether there is a carcinogenic risk for patients under the presumption that bladder tumours in mice are caused by the aniline metabolites and taking into consideration the ADME data on differences in exposure to aniline metabolites in mice versus humans.

The way the applicant has taken to apply the principles of ICH M7 for this case is agreed. However, there is some uncertainty about parameters taken into the calculation.

The principle for deriving at a dose resulting in a less than $1/10^5$ cancer risk is to take the dose resulting in a 50% tumour incidence (TD_{50}) and divide by 50000. As an alternative one may use the benchmark dose lower confidence limit 10% ($BMDL_{10}$, an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodent). The applicant has chosen this approach, which is understandable since tumour incidence was clearly below 50%. While the data do not allow a clear calculation of $BMDL_{10}$, the applicant has presented a value of 220 mg/kg bw/d which may be agreed. However, calculations need to consider both transitional carcinomas and papillomas, and not separately, given that these tumours are likely to be related in terms of mechanism. Nevertheless, even if this approach was not considered in the calculations, the $BMDL_{10}$ would still fall in the interval between the mid dose and high dose.

The dose was lowered at two occasions during the mouse carcinogenicity due to toxicity and high levels of mortality. The applicant has made a calculation of an average lifetime daily dose. This is considered acceptable as a conservative dose estimate.

To make a risk estimate based on exposure to the aniline metabolites, the applicant refers to data showing about 622 times higher plasma exposure and about 308 times higher urine exposure in mice versus humans when comparing at a human equivalent dose. These factors are based on PK data.

As the urinary concentration of anilines in humans is 308 times lower than that observed in mice at a comparable dose, the adjustment may be made directly to the acceptable MOE of 10,000, i.e. 10,000/308, giving an adjusted MOE of 32.5. In terms of posology, treatment in Human is performed at a daily dose of 4.5 mg/kg bw/twice a day that reaches a very low level of urinary concentration (a dose of 6.7 to 8 mg/kg bw/day led to a urine concentration of 190 ng/mL).

As calculated by the applicant, the $BMDL_{10}/32.5$ would lead to an acceptable level of excess risk with the occurrence of one bladder tumour per 1.105. Therefore, a daily treatment of 6.7 mg/kg bw/day (220/32.5) for lifetime in Human may be acceptable in the setting of the proposed therapeutic indication in terms of excess risk of bladder tumours with an occurrence of 1 for 1.105.

Overall, given the conservative nature of the AI calculation it is concluded that the presence of aniline metabolites is not considered a carcinogenic threat in patients. However, based on uncertainties related to the performance of the carcinogenicity study and the lack of a full characterisation of metabolic pattern in humans, a carcinogenic risk of masitinib for patients, based on the bladder tumour findings in mice cannot be fully excluded. It is not anticipated that further nonclinical evaluation will clarify this risk. These findings should be mentioned in the product information and be taken care of in the risk management programme (as proposed by the applicant).

The lack of studies on pre-postnatal development and juvenile animals was justified by the applicant on the basis of the target patients' population and risk mitigation measures in the SmPC, mentioning that masitinib is contraindicated in pregnant women or in women of childbearing potential. The lack of such studies is accepted based on the target patient's population.

Altogether, results from fertility and early embryonic development studies indicate reversible adverse effects on female fertility. This is consistent with the results from the repeated dose toxicity studies where the ovaries were identified as one of the target organs of toxicity.

Skin sensitization potential was assessed in mice using the local lymph node assay (Study 33510 TSS). Significant lymphoproliferative responses were observed in the absence of local skin irritation at the site of administration (Study 33510 TSS). Masitinib mesilate showed skin sensitisation potential and exposure may result in delayed contact hypersensitivity. Masitinib should be considered as a strong sensitiser. Masitinib mesilate was found to be a slight irritant when applied topically (Study 33511 TAL) and to be severely irritating when administered by the ocular route to rabbits (Study 33512 TAL).

The provided value for log Kow determined by OECD 117 HPLC method is not acceptable for ERA. The n-octanol /water distribution coefficient (logD) is a key parameter in environmental risk assessment as they are used to estimate environmental fate and bioconcentration and thus exposure and toxicity. Since masitinib is an ionisable substance (pKa =7.5) for which the solubility is pH dependent, an ion-corrected log Dow should be performed, covering the environmentally relevant pH range. The applicant was requested to submit log Dow values at environmental relevant pHs (5,7 and 9) to guarantee that the assay was performed at different ionization stages, and the respective study report. According to the applicant, the Log D of masitinib varies from 0.53 (cationic form at pH 4.70) to 3.75 (neutral form at pH 11). As Log D values are well below the trigger value, at all environmentally relevant pHs, screening for Persistence, Bioaccumulation and Toxicity (PBT) is not required, in line with the Questions and answers document on "Guideline on the environmental risk assessment of medicinal products for human use" (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016). Therefore, an ERA phase II assessment is not necessary.

It was concluded that this medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.5.7. Conclusion on the non-clinical aspects

The CHMP considers that the non-clinical data could be sufficient for a marketing authorisation application.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The applicant claims that the Clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 5: Clinical pharmacology programme

Type of study	Study number	Location in eCTD	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	No. of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
BA (food-effect)	AB1010-PIHV05031	5.3.1.1	evaluate the food intake influence on pharmacokinetic profiles	Cross over	Masitinib, Tablet, 200mg, oral	12	healthy volunteers	Single dose	Complete, Full
Comparative BE	AB1010-PIHV04015	5.3.1.2	compare the relative BA of AB1010 from two different formulations (capsule or tablet)	Cross over	Masitinib, Tablet, Capsules, 100mg, oral	12	healthy volunteers	Single dose	Complete, Full
PK (HV)	AB1010-PIHV03001	5.3.3.1	determine safety / tolerability and PK parameters of AB1010	Double blind, placebo-controlled	Masitinib, powder for solution, ascending doses (40, 100, 200, 400 and 800 mg), oral	40	healthy volunteers	Dose escalations, single dose	Complete, Full
PK (HV)	AB1010-PIHV03003	5.3.3.1	determine safety / tolerability and PK parameters of AB1010	Double blind, placebo-controlled	Masitinib, Capsule, ascending doses (100, 200, 400 and 800 mg), oral	30	healthy volunteers	7 days	Complete, Full
PK (patients)	AB03002	5.3.3.2	Assess safety ,tolerability and determine the MTD, Assess PK parameters of AB1003, assess clinical activity of masitinib	open-label, dose escalating study	Masitinib, doses ranging from 40 to 1,000 mg/day, oral	40 (with 19 GIST patients)	patients with advanced and/or metastatic solid tumours	12 weeks + extension phase	Complete, Full
Extrinsic PK (HV)	18-169	5.3.3.4	Determination of Riluzole concentration and pharmacokinetic parameters in human plasma samples.	Samples coming from the pivotal study AB AB10015	-masitinib (AB1010) at 4.5 mg/kg/day + riluzole -masitinib (AB1010) at 3 mg/kg/day + + riluzole - Placebo + + riluzole	18	Patients with ALS	48 weeks	Complete, full
Extrinsic PK (HV)	AB14004 (DDI part)	5.3.3.4	Evaluate the pharmacokinetics (PK) of a single dose masitinib and its metabolites after CYP3A4 and P-Gp inhibition using itraconazole.	single-center, open-label, active-controlled, 4-sequence study	Masitinib, tablet, 3 mg/kg/day at day 1, oral Masitinib, tablet, 3 mg/kg/day from day 17 to 24, oral moxifloxacin 400 mg at Day 1 Itraconazole 200 mg once daily (QD) from Day 9 to Day 13	15	healthy volunteers	28 days	Complete, Full
Population PK	AB010015	5.3.3.5	To evaluate pK of masitinib in ALS patients. -To validate POP PK model population	This study was part of a double blind, placebo-controlled, parallel groups, randomised study for which the primary objective is efficacy and safety	Each subject received masitinib or placebo at the dose of either 3 mg/kg or 4.5 mg/kg per day.	18	Patients with amyotrophic lateral sclerosis	48 weeks	Complete Full
Population PK	AB14004	5.3.3.5	To evaluate pK of masitinib in ALS patients. -To validate POP PK model population	This study was part of a double blind, placebo-controlled, parallel groups, randomised study for which the primary objective is efficacy and safety	3.0 mg/kg/day (single dose) 6.0 mg/kg/day (repeated doses – 5 days).	15	Patients with amyotrophic lateral sclerosis	48 weeks	Complete Full

Mass-balance (HV)	AB17001/QCL118054	5.3.3.1	To assess the mass balance recovery after a single oral dose of ^{14}C-AB1010 (masitinib)	Open Label, Non-Randomised, Single-Dose, Single-Period Study	single dose, ^{14}C-AB1010 oral solution 4 mg/ml (free base)	4	healthy volunteers	Single oral regimen administration on a single occasion.	Complete, Full
Mass balance	AB17001/ ABS06	5.3.3.1	Identification of the metabolites of AB1010 (Masitinib) in plasma, urine and faeces from Clinical Study AB17001-QCL118054.	See AB17001	See AB17001	See AB 17001	See AB17001	See AB17001	Complete, full
Mass balance	AB/17001/TNO 2018 R10121	5.3.3.1	Investigation of metabolite profiles in plasma, urine and homogenized faeces samples collected during study AB17001	See AB 17001	See AB 17001	See AB 17001	See AB17001	See AB17001	Complete, full

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

The absorption profile of Masitinib AB Science demonstrates a relatively slow absorption with t_{max} median values between 1.5 to 5.0 hours at the proposed clinical doses.

No data on absolute bioavailability in healthy subjects or the target population has been presented.

Bioequivalence has been adequately demonstrated *in vivo* for the tablet formulation intended for the market versus the formulation used in phase I. In the study No AB1010-PIHV04015, twelve healthy male volunteers received a single oral dose of AB1010 base (100 mg) on day 1 of each of both treatment periods. The two administrations were separated by at least a one-week interval where no AB1010 was taken in order to prevent any carry over effect. The aim of the study was to compare the relative bioavailability of AB1010 from two different formulations (capsule or tablet) in 12 healthy male volunteers after a 100 mg AB1010 base single oral administration.

The PK results obtained for AB1010 base are provided in the Figure 2 and Table 6.

Figure 2: Mean and SD plasma concentration versus time profiles of AB1010 base following single oral administration of 100 mg of AB1010 base as one tablet (Treat A) or as two capsules (Treat B)

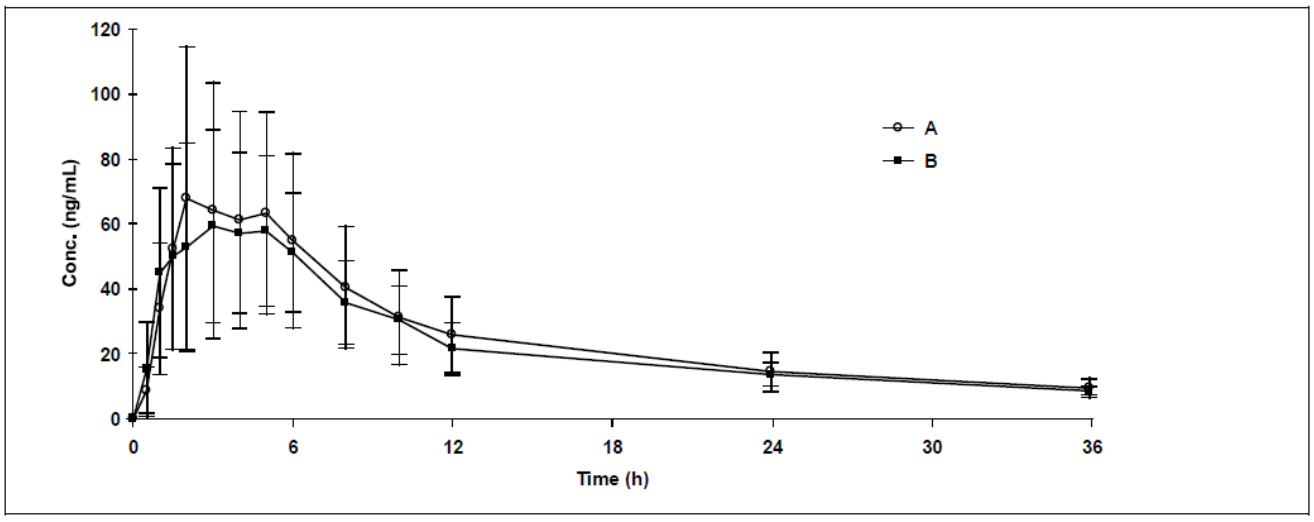


Table 6: Geometric mean and CV% PK parameters of AB1010 base following single oral administration of 100 mg of AB1010 base as one tablet (Treat A) or as two capsules (Treat B)

	N=12	C_{max} (ng/mL)	$t_{max}^{\#}$ (h)	$t_{lag}^{\#}$ (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	$t_{1/2}$ (h)	F_{rel}
Treat A (Tablet)	Geom. Mean	67.00	3.50	0.00	791	977	13.7	1.00
	CV%	57	[1.50;6.00]	[0.00;1.00]	49	44	17	27
Treat B (Capsule)	Geom. Mean	65.88	4.00	0.00	748	977	15.5	-
	CV%	41	[1.50;6.00]	[0.00;0.50]	39	29	27	-
Analysis of variance		NS	NS	NS	NS	NS	-	-
Point estimate [90% confidence interval]		1.02 [0.84;1.23]	-	-	1.06 [0.92;1.22]	1.00 [0.87;1.15]	-	-

median and [min-max]
NS: Not Significant (p>0.05)

The effect of food (a high-fat meal) on the PKs of Masitinib AB Science was determined in a single centre, open, randomised, two-way crossover study No AB1010-PIHV05031/ AB05031. According to the study results, following a high fat meal, Masitinib AB Science C_{max} and $AUC_{0-\infty}$ increased by 19% and 23%, respectively.

Distribution

Masitinib AB Science is extensively bound to plasma proteins; the major binding protein appears to be albumin. No information is provided on protein binding *ex/in vivo*. The blood: plasma ratio is around 1. The distribution kinetics of Masitinib AB Science in healthy subjects is non-linear. The apparent volume of distribution (Vd/F) is high, indicating an extensive tissue distribution.

In vitro

Study PR6592-1-CC2099: binding to human serum albumin was high, 91.44 %. A lower binding occurred on α1-acid-glycoprotein and on gamma-globulin, 74.26% and 45.95%, respectively. According to the ^{14}C-AB1010 concentration used, 100-3000 ng/mL the binding to human, rat, mouse, dog, and rabbit plasma proteins is high 93.93%, 92.15%, 86.12%, 93.33% and 97.50%, respectively and constant within the tested concentration range.

Study AB3280-PB: The plasma protein binding was high in all species: more than 90% in human plasma and more than 85% in dog, mouse, and rat plasma. It is interesting to notice that human plasma has a total binding capacity for AB3280 twice as high (NKp =14.0) as in animal plasma (NKp =5.77, 6.56 and 7.23 respectively for dog, mouse, and rat) implying a lower free fraction in human plasma.

Studies in humans

Study AB17001: plasma concentrations ratios were found close to 1.

Study AB03001: The Vd/F of Masitinib AB Science decreased with increasing doses: from 2144 L at 40 mg dose to 1052 L at 800 mg dose.

Elimination

Steady state apparent total clearance and renal clearance were 0.7-1.4 L/min and 9-18 ml/min, respectively. Apparent clearance (CL/F) decreased with increasing dose indicating a saturation of enzymes responsible for metabolism and/or increased bioavailability (potentially due to inhibition of intestinal P-pg). Elimination half-life after single-dose and repeated dose Masitinib AB Science were approximately 13 h and 17 h, respectively. Urinary recovery rates were low with less than 2% recovery for Masitinib AB Science and metabolite AB3280. A mass-balance study has additionally been conducted. A mean of 69% (range 55% to 83%) of radioactivity administered was recovered by the end of the

sampling period (168 h) and the majority of radioactivity was recovered in faeces, up to 59% of the administered dose. The urinary recovery was low, approximately 10% of the dose. It can be concluded that the main excretion pathway for AB1010 and its related metabolites is the faeces.

The PK of plasma Masitinib AB Science was described by a two-compartment open model with linear elimination. The main covariate effects were related to body weight, which influenced all PK parameters, and to albumin. The model showed that clearance (CL) was not affected by dose, and that AUC thus, behaves in a dose-proportional manner. AUC-based accumulation ratios for Masitinib AB Science in healthy subjects was 1.8-2.3 at therapeutic doses.

The applicant's position is that PK in adult patients with probable or definitive ALS was similar to healthy subjects. However, Masitinib AB Science is administered concomitantly with riluzole and no DDI study was presented.

Study AB03001 (AB1010-PIHV03001)

This was a double blind, placebo-controlled, single dose study, with parallel groups of ascending doses (40, 100, 200, 400 and 800 mg); there was a minimum of 6 days between dose escalations. A total of 40 subjects were studied in 5 successive groups, each group consisting of 8 subjects (6 received active drug, AB1010 and 2 subjects received placebo).

Figure 3: Mean plasma concentrations versus time profiles of Masitinib AB Science following single oral doses of 40, 100, 200, 400 and 800 mg of AB1010 (linear scale)

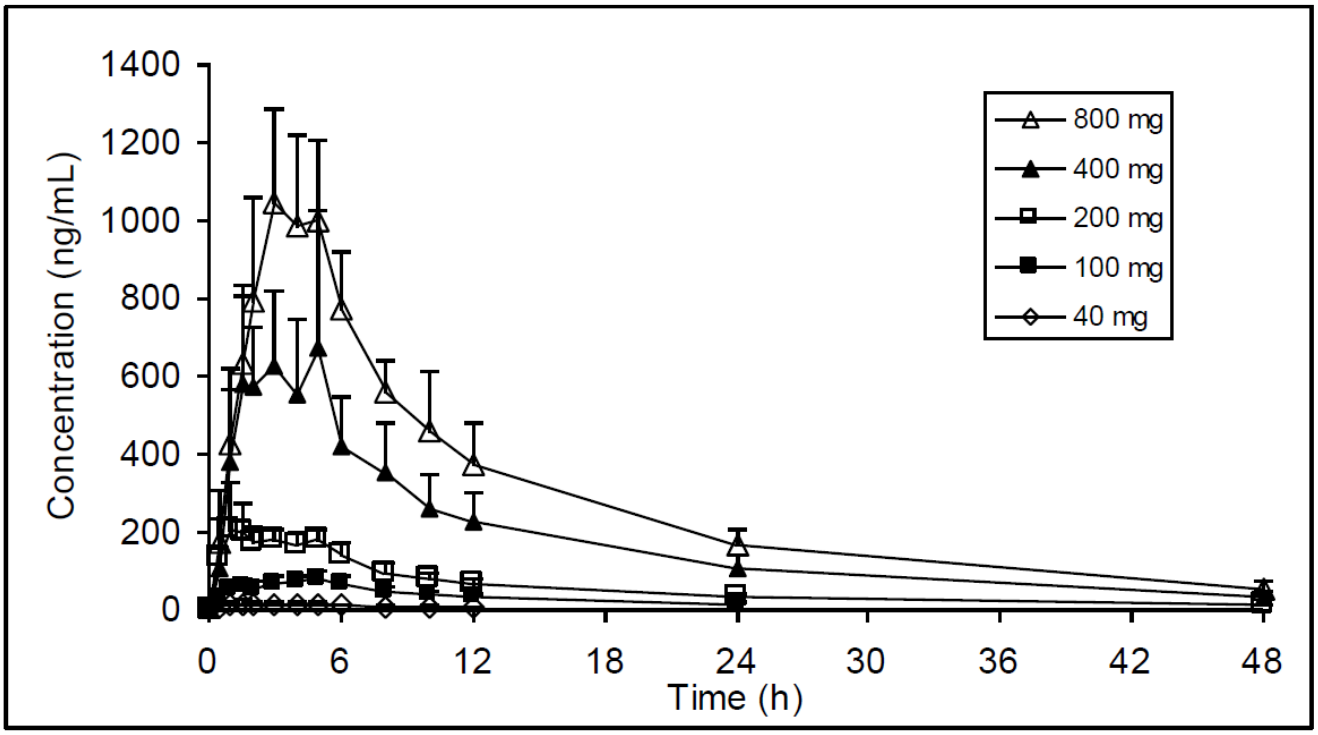


Table 7: Mean and CV% PK parameters of Masitinib AB Science following single oral doses of 40, 100, 200, 400 and 800 mg of Masitinib AB Science

Treatment (N=6)		C_{max}[(1)] (ng/mL)	t_{max}[(2)] (h)	$t_{1/2}$ (h)	AUC_{0-t} [(1)] (h*ng/mL)	$AUC_{0-\infty}$[(1)] (h*ng/mL)	Cl/F (L/min)	Vd/F (L)
40 mg	Mean	14.51	2.0	11.8*	103	269	2.71*	2144*
	CV%	59	[1.0-5.0]	76	96	56	41	19
100 mg	Mean	82.43	5.0	12.6	981	1201	1.41	1547
	CV%	23	[1.5-5.0]	22	27	19	18	30
200 mg	Mean	238.77	1.5	13.3	2557	2823	1.20	1367
	CV%	32	[1.0-5.0]	18	23	21	21	20
400 mg	Mean	711.10	3.5	13.9	8244	8951	0.77	937
	CV%	35	[1.5-5.0]	13	31	30	26	34
800 mg	Mean	1121.54	3.5	13.0	13471	14456	0.94	1052
	CV%	21	[3.0-5.0]	9	21	22	23	20

(1): geometric mean and CV calculated from logarithmic values; (2): median and [min-max]; *:N=4

Study AB14004

This was a single-centre, open-label, active-controlled, 4-sequence study in 15 healthy subjects. Each subject received in sequence the 4 following treatments:

1. Treatment Sequence 1: single dose oral administration of moxifloxacin 400 mg on Day 1.
2. Treatment Sequence 2: single dose oral administration of Masitinib AB Science 3 mg/kg according to the subject's weight at screening on the morning of Day 3
3. Treatment Sequence 3: repeated dose oral administration of itraconazole 200 mg once daily (QD) from Day 9 to Day 13. On the morning of Day 12, a single dose of Masitinib AB Science 3 mg/kg was administered 1h after the administration of itraconazole 200 mg.
4. Treatment Sequence 4: repeated dose twice daily (BID) oral administration of Masitinib AB Science 6 mg/kg/day according to according to the subject's weight at screening from the evening of Day 17 to the morning of Day 24. The evening dose had to be taken in a range time from 30 min before to 30 min after dinner. The morning dose had to be taken in a range time from 30 min before to 30 min after breakfast. Masitinib AB Science had to be administered in a sitting position. All study drugs were administered with a large glass of water (250 mL or 8 oz). Masitinib AB Science and moxifloxacin were administered after breakfast; itraconazole was administered in fasting condition.

Table 8: Plasma PK Parameters of Moxifloxacin After Oral Administration of Moxifloxacin at 400 mg to Healthy Volunteers (Treatment Sequence 1)

Dose (mg)	Subject	Cmax (ng/mL)	Tmax (h)	AUCt (ng/mL*h)	%AUCextra	AUCinf (ng/mL*h)	Kel (1/h)	t1/2 (h)
Moxifloxacin	N	15	15	15	15	15	15	15
	Mean	2429.1	3.4	29453.4	26.496	*40181.2*	*0.059590*	*12.214*
	Stdev	387.02	1.5	3938.0	7.3134	*4402.4*	*0.013535*	*2.8698*
	%CV	15.93	44.88	13.37	27.60	*10.96*	*22.71*	*23.50*

Table 9: Mean Plasma PK Parameters of AB1010 and AB3280 After Oral Administration of AB1010 at 3 mg/kg to Healthy Volunteers (Treatment Sequence 2)

Analyte	Subject	Cmax (ng/mL)	Tmax (h)	AUCt (ng/mL*h)	%AUCextra	AUCinf (ng/mL*h)	Kel (1/h)	$t_{1/2}$ (h)
AB1010	N	15	15	15	15	15	15	15
	Mean	198.11	4.5	3065.7	6.4773	3244.9	0.044918	16.268
	Stdev	89.777	2.1	1375.7	3.1273	1378.2	0.0098632	4.172
	%CV	45.32	45.37	44.87	48.28	42.47	21.96	25.65
AB3280	N	15	15	15	14	14	14	14
	Mean	47.795	4.8	566.19	32.730	*862.48*	*0.060063*	*14.500*
	Stdev	23.820	1.4	385.33	13.239	*461.64*	*0.027568*	*8.3031*
	%CV	49.84	29.67	68.06	40.45	*53.52*	*45.90*	*57.26*

Table 10: Mean Plasma PK Parameters of AB1010 and AB3280 After Oral Administration of AB1010 at 3 mg/kg and Itraconazole at 200 mg Daily to Healthy Volunteers (Treatment Sequence 3)

Analyte	Subject	Cmax (ng/mL)	Tmax (h)	AUCt (ng/mL*h)	%AUCextra	AUCinf (ng/mL*h)	Kel (1/h)	$t_{1/2}$ (h)
AB1010	N	14	14	14	14	14	14	14
	Mean	250.93	5.0	4341.8	7.0771	4653.1	0.034303	21.239
	Stdev	90.284	1.4	1372.2	3.2004	1413.2	0.0078441	4.9931
	%CV	35.98	27.17	31.60	45.22	30.37	22.87	23.51
AB3280	N	14	14	14	13	13	13	13
	Mean	53.269	4.9	763.30	37.098	*1301.0*	*0.035345*	*28.637*
	Stdev	27.181	1.0	449.39	13.232	*557.73*	*0.026028*	*16.715*
	%CV	51.03	20.23	58.87	35.67	*42.87*	*73.64*	*58.37*

Table 11: Mean Plasma PK Parameters of AB1010 and AB2436 Plasma Concentration Measured After Oral Administration of AB1010 at 3 mg/kg Twice Daily to Healthy Volunteers (Treatment Sequence 4)

Analyte	Subject	Cmax,ss (ng/mL)	Tmax,ss (h)	AUCt,ss (ng/mL*h)	AUC0-12,ss (ng/mL*h)	AUC0-24,ss (ng/mL*h)	%AUCextra	AUCinf,ss (ng/mL*h)	Kel (1/h)	$t_{1/2}$ (h)
AB1010	N	12	12	12	12	12	12	12	12	12
	Mean	471.63	5.6	10802.7	4499.1	7024.3	3.8326	11211.0	0.033494	21.543
	Stdev	160.30	1.6	3633.8	1557.6	2397.6	1.9425	3688.9	0.0070266	4.5408
	%CV	33.99	29.04	33.64	34.62	34.13	50.68	32.90	20.98	21.08
AB2436	N	12	12	12	12	12	5	12	12	12
	Mean	3.5311	10.1	52.955	28.406	49.242	54.935	NC	NC	NC
	Stdev	1.3471	5.6	40.378	14.093	30.407	9.3890	NC	NC	NC
	%CV	38.15	55.85	76.25	49.61	61.75	17.09	NC	NC	NC

NC: Not calcutated

In Treatment Sequence 4, AB1010, AB2436, AB5235 and AB6465 concentrations in plasma were measured and PK parameters were calculated for AB1010 and AB2436 (all concentrations for AB5235 and AB6465 were below the limit of quantification). Mean C_{max} at steady state was 471.63 ng/mL for AB1010 and 3.5311 ng/mL for AB2436. Ratios of AUCs between AB2436 and AB1010 were calculated. AUCs of AB2436 at steady state were lower than 3% of AUCs of AB1010. All PK urine samples were below the limit of quantification for AB5235 and AB6465. At steady state, the mean amount of AB1010 excreted in urine was 6.697 mg and of AB2436 was 0.340 mg (about 5% of AB1010 amount). The mean excreted fraction was 1.44% of administered dose for AB1010 and 0.128% of administered dose (equivalent AB1010) for AB2436.

Study AB17001 (ABS/06)

This was an open label, non-randomised, single-dose, single-period study designed to assess the mass balance recovery, metabolite profile and metabolite identification of 14C-AB1010 in healthy male subjects (n=4). Each volunteer entered into this study received a single dose of the Investigational Medicinal Product, 14C-AB1010 oral solution 4 mg/ml (free base) provided as 50mL oral solution containing NMT 37 kBq (1000nCi) 14C in the fasted state. Blood, plasma, urine and faeces samples were collected for all 4 volunteers until 168h (Day8).

Following a single 200 mg (50 ml of 4mg/ml) oral dose of [14C] AB1010 a mean of 69% (range 55% to 83%) of radioactivity administered was recovered by the end of the sampling period (168 h). The majority of radioactivity was recovered in faeces, up to 59% of the administered dose. Urinary recovery was low (approximately 10% of the dose). The percentage of the mean cumulated radioactivity in faeces compared to the mean cumulated radioactivity in excreta (urine + faeces) is about 85%. For all subjects, this ratio is higher than 80%. So, the main excretion pathway for AB1010 and its related metabolites is the faeces.

Blood: plasma concentrations ratios were found close to 1.

AB1010 was rapidly absorbed with t_{max} values between 0.5 and 2 h then declined with a mean geometric half-life of 29 h, longer than the 13 to 17 h previously reported. The PK parameters determined following dosing at 200 mg were also considered similar to those observed in previous studies. AB1010 contributed to 12 % of the total circulating radioactivity in plasma when comparing $AUC_{0\text{-last}}$ values of AB1010 and total radioactivity. Plasma concentrations of the major and active N-desmethylated metabolite AB3280 peaked approximately 1.5h after dosing. The geometric mean C_{max} of AB3280 was approximately 28% of that for AB1010, with a similar terminal elimination phase (geometric mean t1/2 of 29h). Total exposure ($_{AUC0\text{-}\infty}$) to AB3280 was approximately 3.4-fold lower than the parent AB1010. The aniline metabolite AB2436 was quantifiable in plasma at low concentrations (geometric C_{max} 0.985 ng/mL) from 0.5h up to between 12 and 48 h after dosing. Geometric mean C_{max} and $AUC_{0\text{-last}}$ of AB2436 were both 0.4% of those for parent AB1010. Due to the low levels of AB2436, an accurate characterisation of the terminal elimination was not possible. Plasma concentrations of metabolites AB6465 and AB5235 were below the limit of quantification (0.2 ng/mL) throughout, therefore no PK parameters could be derived. Total radioactivity was detectable in plasma shortly after dosing, consistent with the appearance of AB1010 and its metabolites. t_{max} ranged between 2 and 6h, and total radioactivity remained quantifiable until the final sampling time point of 168 h in all subjects. Overall geometric mean exposure ($AUC_{0\text{-last}}$) of parent AB1010, AB3280 and AB2436, accounted for approximately 12%, 3.1% and 0.05% of the total circulating radioactivity measured in plasma, respectively. The geometric mean apparent terminal half-life for total radioactivity was 94.7 h which was longer than that observed in parent AB1010 or quantifiable metabolites AB3280 and AB2436. Supporting the presence of uncharacterised metabolites with considerably longer terminal eliminations. Safety 2 out of 4 subjects experienced adverse events. One subject had 1 AE (blister). One other subject had 3 AEs namely headache, decreased white blood cell count and neutropenia. All the AEs were analysed and not considered to be related to the study treatment.

Study AB03003

This was a phase I, randomised, double blind, placebo-controlled study to determine the safety, tolerability and PK profiles of ascending, multiple oral doses of AB1010 in healthy, young male subjects. Plasma concentrations of Masitinib AB Science observed about 2-fold greater than after single oral dose. CL/F and Vd/F of Masitinib AB Science decreased with increasing doses and the mean half-life was about 17 h. Elimination route of Masitinib AB Science almost extra-renal. Exposure to Masitinib AB Science more than dose proportional over the 100-400 mg dose range. Increase of AB3280 concentrations concomitant with the increase of Masitinib AB Science concentrations. Concentrations of AB3280 about 4-fold lower than Masitinib AB Science concentrations. The mean half-life of AB3280 ranged from 25 to

38 h. At steady-state about 1% of the dose recovered in urine as AB3280 over the dosing interval. Increase of C_{max} and $AUC_{0\text{-}Tau.}$ of AB3280 over the 100-400 mg range at steady-state was proportional. The safety and tolerability good up to 400 mg per day defined as MLT.

Study AB1010-PIHV03003

This was a phase I, randomised, double blind, placebo-controlled study to determine the safety, tolerability and PK profiles of ascending, multiple oral doses of AB1010 in healthy, young male subjects.

Thirty-two subjects were studied in 4 successive groups (Groups 1, 2, 3 and 4), each group consisting of 8 subjects. In each group, 6 subjects received active drug (AB1010) and 2 subjects received placebo. Each subject received either AB1010base or placebo once daily for 7 days. Doses were administered in an escalating manner following satisfactory review of safety data and PK data from the lower doses. Four dose levels of AB1010base (100 mg, 200 mg, 400 mg, 800 mg) were planned to be studied.

Figure 4: AB1010base - Day 1 Mean and SD plasma concentration versus time profiles of AB1010base following the first oral administration of 100, 200, 400 and 800 mg of AB1010base

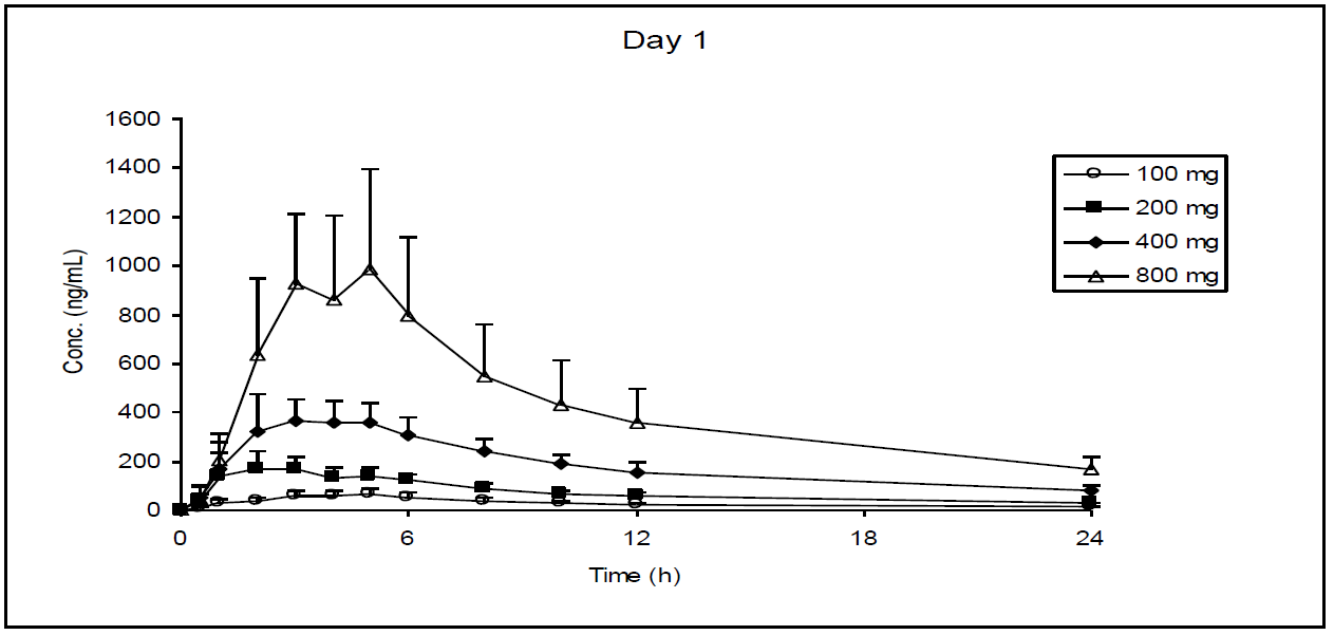


Table 12: Mean and CV% PK parameters of AB1010base following the first administration with 100, 200, 400 and 800 mg of AB1010base

Treatment		C_{max} (ng/mL)	t_{max}# (h)	t_{lag}# (h)	$AUC_{0-\tau}$ (h*ng/mL)	C_{trough}* (ng/mL)	$fe_{(0-24)}$* (%)	CLr* (mL/min)
100 mg	Mean	63.16	5.00	0.00	675	11.92	0.70	17.20
(N=6)	CV%	33	[3.00 - 6.00]	[0.00 – 0.50]	33	32	23	17
200 mg	Mean	175.92	2.50	0.00	1772	26.74	0.52	9.98
(N=6)	CV%	39	[1.00 - 5.00]	[0.00 - 0.00]	23	20	26	36
400 mg	Mean	379.59	3.00	0.00	4317	81.49	0.98	14.99
(N=6)	CV%	26	[2.00 - 4.00]	[0.00 - 0.50]	26	26	63	60
800 mg	Mean	1063.24	4.00	0.00	9724	168.08	0.89	12.66
(N=4)	CV%	38	[3.00 - 5.00]	[0.00 - 0.50]	43	29	31	39

#. median and [min-max]; *: Arithmetic mean and CV from natural data

Figure 5: Mean and SD plasma concentration versus time profiles of AB1010base following the last oral administration of 100, 200 and 400 mg of AB1010base once daily for 7 days

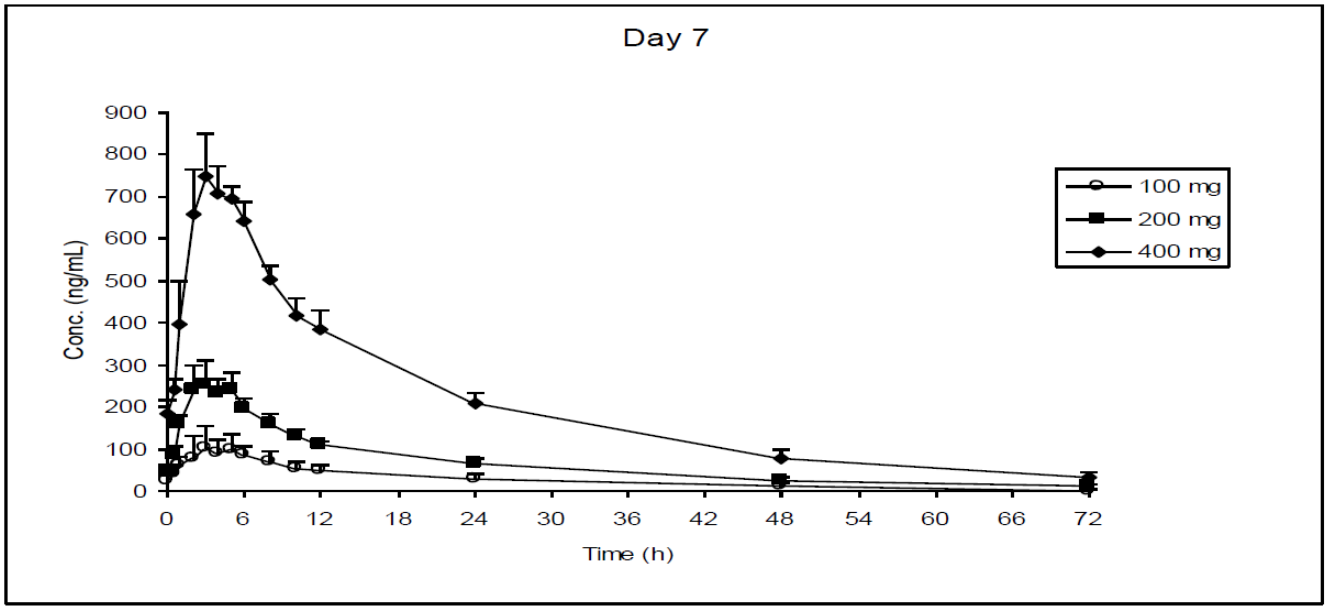


Table 13: Mean and CV% PK parameters of AB1010base following the last administration with 100, 200 and 400 mg of AB1010base once daily for 7 days

Dose		C_{max} (ng/mL)	t_{max}# (h)	AUC_{0-t} (h*ng/mL)	$AUC_{0-\tau}$ (h*ng/mL)	$t_{1/2}$* (h)	CL/F* (L/min)	Vd/F* (L)	$fe_{(0-48)}$* (%)	CLr* (mL/min)
100 mg	Mean	99.98	4.00	1706	1249	16.3	1.43	1935	1.74	17.97
(N=6)	CV%	43	[2.00 ; 5.00]	57	40	27	41	37	28	20
200 mg	Mean	264.46	4.00	4638	3179	17.5	1.06	1578	1.22	9.79
(N=6)	CV%	17	[3.00 ; 5.00]	19	13	19	13	17	60	53
400 mg	Mean	764.27	3.00	14759	10000	18.0	0.67	1043	1.71	8.99
(N=6)	CV%	11	[3.00 ; 5.00]	9	8	14	7	17	16	28

Dose		C_{trough}* (ng/mL)	$fe_{(0-24)}$* (%)	Ratio C_{max}* Day 7/Day 1	Ratio C_{trough}* Day 7/Day 1	Theoretical* ratio
100 mg	Mean	27.54	1.37	1.60	2.31	1.57
(N=6)	CV%	45	27	17	29	15
200 mg	Mean	66.99	0.96	1.54	2.54	1.63
(N=6)	CV%	18	53	24	17	11
400 mg	Mean	210.13	1.34	2.09	2.71	1.66
(N=6)	CV%	11	22	33	25	9

#. median and [min-max]; *: Arithmetic mean and CV from natural data

In this study Blood Sampling for the Analysis was conducted not only for the AB1010base but also for Masitinib AB Science metabolite - AB3280.

After multiple oral dosing with AB1010 in healthy volunteers it was shown that the safety and tolerability were good up to the dose of 400 mg per day which was found to be the maximum tolerated dose. The plasma concentrations of AB1010base observed were about 2-fold greater than after single oral dose. CL/F and Vd/F of AB1010base decreased with increasing doses and the mean half-life was about 17h. The elimination route of AB1010base was almost entirely extra-renal. The exposure to AB1010base was

more than dose proportional over the 100-400 mg dose range and it seems it would be confirmed at 800 mg. The increase of AB3280 concentrations was concomitant with the increase of AB1010base concentrations. Concentrations of AB3280 were about 4-folds lower than AB1010base concentrations. The mean half-life of AB3280 ranged from 25 to 38 h. At steady-state about 1% of the dose was recovered in urine as AB3280 over the dosing interval.

Study AB03002

This was a multicentre, non-randomised, open-label, sequential cohort, dose-escalation phase I study of oral Masitinib AB Science in adults with advanced and/or metastatic cancer. Patients with advanced solid tumours were included in subsequent cohorts of escalating treatment dose as follows: The first dose levels were administered as initially planned in the protocol. Successive cohorts of one patient each received escalating doses of oral Masitinib AB Science daily for up to three months or until unacceptable toxicity or documentation of disease progression or any other reason for patient's withdrawal. Masitinib was administered.

PK parameters after the first administration of masitinib were as follows:

- The C_{max} increased with the dose at day 1 from 54.96 ng/mL with 40 mg to 1303.47 ng/mL with 1000mg. In the dose range 250, 500 and 1000 mg, mean C_{max} increased in a ratio of 1.39 and 2.44 when dose increased in a ratio of 2 and 4.
- The t_{max} was found between 1.7 and 4.1 hours.
- Extrapolated AUC_{0-24} increased with the dose at day 1 from 249 h*ng/mL with 40 mg to 12945 h*ng/mL with 1000mg. In the dose range 250, 500 and 1000 mg, the mean AUC_{0-24} increased in a ratio of 2.02 and 3.66.
- The CL/F and Vd/F were high, decreasing from 153.23 L/h to 62.27 L/h and from 1330 L to 1059 L respectively when dose increased from 100 mg to 1000 mg.
- The half-life of AB1003 was between 6 and 14 hours.
- The inter-individual variability was high with heterogeneous with coefficient of variation varying between 15% and 96% depending on parameters.

PK parameters after repeated administration of Masitinib AB Science were as follows:

- The C_{max} increased with the dose at day 14 from 157.62 ng/ml with 100 mg to 1563.26 ng/mL with 1000mg. In the dose range 250, 500 and 1000 mg, mean C_{max} increased in a ratio of 1.56 and 2.24 when dose increased in a ratio of 2 and 4.
- The t_{max} was found between 1.7 and 4.7 hours.
- Extrapolated AUC_{0-24} increased with the dose at day 1 from 1483 h*ng/mL with 100 mg to 20871 h*ng/mL with 1000mg. In the dose range 250, 500 and 1000 mg, the mean AUC_{0-24} increased in a ratio of 1.71 and 3.21.
- The half-life of AB1003 was relatively long (from 10 to 40 hours).
- The CL/F and Vd/F of AB1003 were high, decreasing from 82.05 L/h to 23.91 L/h and from 1870 L to 859 L respectively when dose increased from 100 mg to 1000 mg.
- The inter-individual variability was high with heterogeneous with coefficient of variation varying between 25% and 60% depending on parameters.

CYP3A4 catalyses the metabolism of Masitinib AB Science and the formation of metabolites in human liver, with a minor contribution by CYP2C8 in the formation of AB3280, which is considered to be the

primary metabolite. The PK profile for the metabolite AB3280 is similar to its parent compound Masitinib AB Science. AB3280 steady state plasma concentration in healthy subjects corresponded to roughly 20-30% of the steady state Masitinib AB Science plasma concentration. The transformation of masitinib mesilate to AB3280 appears to be rapid, indicating that Masitinib AB Science undergoes first-pass conversion to AB3280. Several Masitinib AB Science metabolites have been identified. It is unclear in which extent metabolites have been identified in humans. In addition to this, under the mass-balance study, the plasma PK for parent, AB1010, known metabolites i.e. AB3280, AB2436, AB5235 and AB6465 and total radioactivity were also determined. Overall geometric mean exposure ($AUC_{0\text{-last}}$) of parent AB1010, AB3280 and AB2436, accounted for approximately 12%, 3.1% and 0.05% of the total circulating radioactivity measured in plasma, respectively. The geometric mean apparent terminal half-life for total radioactivity was 94.7 h which was longer than that observed in parent AB1010 or quantifiable metabolites AB3280 and AB2436. These are strong indications that there are yet to be identified major metabolites involved in the masitinib elimination.

Pharmacokinetics of metabolites

In vitro studies identified AB3280, an N-desmethylated compound, as the main metabolite of Masitinib AB Science after incubation with human hepatocytes. AB3280 is the product of the metabolization of AB1010 by CYP3A4 with minor contribution of CYP2C8.

Plasma concentrations of AB3280 are approximately equivalent to 20-25% of the Masitinib AB Science plasma concentrations.

Aniline-derivatives metabolites were identified (AB2436, AB5235 and AB6465). PK of these metabolites were found in low concentration in human. They were genotoxic in *in vitro* studies after undergoing metabolization.

Concentrations of Masitinib AB Science and its metabolites (AB2436, AB5235 and AB6465) were evaluated in human plasma and urine (Study AB14004). They were determined at steady state following 7 days of dosing at 3.0 mg/kg/day bid:

- Plasma C_{max} at steady state were 471.63 ng/mL for Masitinib AB Science and 3.53 ng/mL for AB2436. C_{max} was below the limit of quantification for AB5235 and AB6465.
- Ratios of $AUC_{0\text{-t}}$ between AB2436 and AB1010 was <3%, meaning that the AUC of AB2436 at steady-state was lower than 3% of AUC of AB1010.
- Urine C_{max} at steady state were between 59.89 ng/mL and 338.16 ng/mL for AB2436 (mean: 187.79 ng/mL) and between 1,064.4 and 6,249.3 ng/mL for AB1010 (mean: 3792.3 ng/mL). Thus, in human urine, AB2436 concentration was lower than 5% of AB1010 concentration.

Dose proportionality and time dependencies

Study AB1010-PIHV03003

Table 14: Dose proportionality of AB1010base C_{max} and $AUC_{0\text{-t}}$ within the dose range 100-400 mg after the first oral administration of AB1010base

Parameters	Proportionality constant, α	Shape parameter, β - [90% CI]
C_{max} (ng/mL)	0.17	1.29 - [1.06; 1.52]
$AUC_{0\text{-}\tau}$ (h*ng/mL)	1.43	1.34 - [1.15; 1.53]

Dose proportionality seems to be nonlinear.

Table 15: Dose proportionality of AB1010base C_{max} and AUC_{0-t} within the dose range 100-400 mg after the last administration with 100, 200 and 400 mg of AB1010base once daily for 7 days

Parameters	Proportionality constant, α	Shape parameter, β - [90% CI]
C_{max} (ng/mL)	0.11	1.47 - [1.28; 1.65]
$AUC_{0-\tau}$ (h*ng/mL)	1.20	1.50 - [1.33; 1.67]

Dose proportionality seems to be nonlinear.

Systemic exposure after (single and) multiple dose administration of the therapeutic dose and evaluation of time dependency was evaluated in study AB1010-PIHV03003. Concentrations were greater on Day 7 than on Day 1. The mean ratio of C_{max} observed between Day 7 and Day 1 was 1.60, 1.54 and 2.09 following treatment with Masitinib AB Science 100, 200 and 400 mg respectively. In addition, the mean ratio of Ctrough was 2.31, 2.54 and 2.71 over this dose range. AUC-based accumulation was calculated using AUC values obtained on day 1 and day 7.

*Table 16: AUC(0-tau) (h*ng/mL) at day 1 and 14 and resulting accumulation ratios for Masitinib AB Science in healthy volunteers*

	100 mg	200 mg	400 mg	800 mg
AUC_{0-tau} (day 1) [h*ng/mL]	675	1772	4317	9724
AUC_{0-tau} (day 7) [h*ng/mL]	1249	3179	10000	na
Accumulation	1.9	1.8	2.3	na

For the doses of 100, 200, and 400 mg, the AUC-based accumulation ratios were 1.8, 1.8, and 2.3, respectively.

Special populations

Study AB010015 population PK

The PK of Masitinib AB Science in healthy volunteers and oncology patients was satisfactorily described by a two-compartment open model with linear elimination. The main covariate effects were related to body weight. A central volume higher than the circulating blood volume and a large volume of deep compartment suggest that masitinib has large tissue diffusion. No significant gender effect on PK parameters of Masitinib AB Science was observed. However, a tendency was observed for sex effect on central volume of distribution of Masitinib AB Science. The V1 is higher in male than female which is not consistent with lipophilic characteristic of masitinib.

Pharmacokinetic interaction studies

In Silico: Quantitative prediction of the systemic exposure of AB1010 using prior in vitro and in vivo data: potential for CYP3A4 mediated drug-drug interactions with AB1010 as a perpetrator (Quantitative Prediction Report)

The primary aim of this study was to use physiologically based pharmacokinetic (PBPK) modelling and prior *in vitro* and clinical PK data for AB1010 to predict the *in vivo* drug interaction potential of the drug as a perpetrator of CYP3A4 mediated interactions. As the relative contributions of CYP3A4, CYP2C8 and P-gp could not be elucidated using the available data, a non-mechanistic "fit for purpose" model was developed using the PK data to drive the model. The objective of the modelling was to evaluate the likely impact of co-administration of AB1010 on the exposure (C_{max} and AUC) of the CYP3A4 substrates midazolam (high extraction) and alprazolam (relatively low extraction) in healthy subjects.

Following the incorporation of the *in vitro* CYP3A4 Ki,u of 1.79 µM, the "fit for purpose" PBPK model was used prospectively to predict the extent of drug interaction with the CYP3A4 substrates midazolam (sensitive substrate) and alprazolam (moderate sensitive substrate) following co-administration of the

victim drugs on the 7th day of 10 or 14 days of dosing of AB1010 at 400 mg QD and 6 mg/kg/day BID. Simulations indicated increases of 1.01-and 1.02- fold and 1.00-and 1.01-fold in the C_{max} and AUC for midazolam and alprazolam, respectively, following co-administration of 6 mg/kg/day BID AB1010. Corresponding C_{max} and AUC ratios following co-administration of AB1010 400 mg QD were 1.10 and 1.12 and 1.10 and 1.03, respectively.

In vivo: AB14004 (DDI part)

AB1010 and its main metabolite AB3280 concentrations in plasma were measured and PK parameters were calculated. As detailed above, all the calculated PK parameter were significantly increased after the inhibition of CYP 3A4 by itraconazole. There was a significant increase in exposure to Masitinib AB Science (the mean C_{max} and AUCt of Masitinib AB Science rose by 26% and 41.6%, respectively) in healthy subjects when it was co-administered with itraconazole (a CYP3A4 inhibitor and P-gp inhibitor). The exposure to the main active metabolite of masitinib (AB3280) was significant increased but less than the exposure to Masitinib AB Science (the mean C_{max} and AUCt of Masitinib AB Science rose by 11% and 34.8%, respectively).

Pharmacokinetics using human biomaterials

The potential for DDI has mainly been investigated *in vitro*. The applicant has provided several CYPP450 metabolism and transporter studies that suggest that there may be several clinically relevant DDI interactions. Concomitant administration of masitinib with CYP3A4 or P-gp inducers may decrease its plasma concentrations. Clinical trial AB14004 showed that masitinib exposure was minimally affected by a strong inhibitor of both CYP3A4 and P-gp (itraconazole), suggesting weak sensitivity to these inhibitors. While the Masitinib inhibits CYP3A4 and P-gp in vitro, but likely not at clinical doses, so caution is advised with narrow therapeutic index substrates. Co-administration with narrow therapeutic index BCRP substrates should be avoided or given with caution due to potential drug-drug interactions. A number of questions were raised during the procedure that require further discussion and additional studies. The potential for inhibition of the transporter bile salt export pump have not been investigated as recommended in the DDI guideline CPMP/EWP/560/95/Rev.1 Corr.**. The clinical relevance of the *in vitro* findings needs to be further clarified and the commitment of *in vivo* studies must be justified based on the relevance of the data acquired through in vitro studies. Since the solubility of Masitinib AB Science is pH dependent in the physiological pH range, there is a potential for an interaction with medicinal products that moderate pH in the gut. The caution has been included in the SmPC (section 4.5) to minimise risk: H2 antagonists and PPIs should be taken 2 hours after Masitinib AB Science, and antacids 2 hours before or after masitinib; if not possible, avoid co-administration with pH-modifying drugs. Overall, at the current time, additional *in vitro* and, if necessary, *in vivo* studies were requested for elucidating the PK of Masitinib AB Science in special populations and its DDI potential:

The applicant proposed to conduct following studies as a post-authorization commitments:

1) *In vitro* study investigating Masitinib AB Science inhibition activity on BSEP using inside-out vesicles expressing BSEP and taurocholic acid as probe substrate (with Ketoconazole as a positive control inhibitor).

2) *In vitro* study investigating Masitinib AB Science inhibition activity on CYP2B6.

3) *In vitro* study to assess Masitinib AB Science as an inhibitor of BCRP substrate.

4) A study to evaluate the consequences of DDI interaction between Masitinib AB Science and CYP3A4/5 inducers.

2.6.2.2. Pharmacodynamics

Mechanism of action

Masitinib mesilate is claimed to target independent pathological mechanisms in different cell types of the brain, spinal cord, and peripheral nervous system components, such as sciatic nerve and neuromuscular junctions In particular, masitinib is claimed to be able to inhibit the CSF1/ CSF1R signalling pathway thereby regulating CSF1R-dependent cells such as microglia, the immune cells of the central nervous system that play a well-known pathogenic role during ALS progression. Likewise, by merit of its activity against c-Kit, LYN and FYN, masitinib is claimed to be able to inhibit mast cells, an effector immune cell that is key in chronic inflammatory processes. Of significance, recent data provide a direct link between SOD1 model-derived evidence and human ALS pathology (with data being derived from ALS patient autopsied quadriceps femoris muscles). This implies that cell targets identified in masitinib preclinical studies might also be implicated in ALS human pathology.

In vitro experiments have demonstrated that masitinib inhibited purified recombinant CSF1R kinase activity at nanomolar concentrations (IC_{50} 90 nM) and prevented M-CSF induced proliferation and migration in cultured microglia [Trias 2016]. Therefore, it has been concluded that the concentrations needed to inhibit CSF-induced microglia proliferation is around 0.1 µM.

In a recombinant enzymatic assay, masitinib mesilate exhibited inhibitory activity against c-Kit-mediated phosphorylation (IC_{50} 20 ± 2 nM) and Lyn and Fyn-mediated phosphorylation (IC^{50} 225 ± 40 nM and IC_{50} 240 ± 130 nM, respectively). In Ba/F3 cells expressing human or mouse wild-type KIT, masitinib inhibited stem cell factor-induced proliferation and KIT tyrosine phosphorylation with an IC_{50} of 150 ± 80nM. Hence, it was concluded that the concentration needed to inhibit these kinase targets is around 0.2 µM.

Primary and Secondary pharmacology

No PK/PD clinical data is currently available in ALS patients. No primary pharmacology studies were conducted.

Masitinib AB Science at therapeutic doses of 6 mg/kg/day is unlikely to induce clinically relevant increases in QTc interval or provoke any proarrhythmia. The issue of a drug effect on QTc interval is intricately linked to the potential of the drug for interactions with comedications or comorbidities (Study AB14004).

The applicant also reports the Analysis of gastrointestinal toxicities by dose level did not show a clear dose-dependence of gastro-intestinal disorders, except for a trend of increased frequency at dose levels above 12mg/kg/day (Table 17).

Table 17: Frequency of gastrointestinal disorders by weight-adjusted dose in study AB03002

	Weight-adjusted initial dose (mg/kg/day)			
	<3 (N=7)	[3; 6] (N=4)	]6; 12] (N=18)	>12 (N=11)
Nausea	2 (28.6%)	2 (50.0%)	8 (44.4%)	10 (90.9%)
Vomiting	5 (71.4%)	2 (50.0%)	7 (38.9%)	7 (63.6%)
Diarrhoea	5 (71.4%)	1 (25.0%)	8 (44.4%)	7 (63.6%)

Table 18: Dose limiting toxicity in study AB03002

	All	#1 40 mg	#2 100 mg	#3 150 mg	#4 250 mg	#5 500 mg	#6 1,000 mg	#7 800 mg b.i.d.
N	26	1	3	3	4	3	6	6
Number (%) of patients with at least one DLT	2 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (16.7%)

Table 19: Brief summary of adverse events by weight-adjusted initial dose (mg/kg/day)

Number of patients with	All (N=40)	<3 (N=7)	[3; 6] (N=4)	]6; 12] (N=18)	>12 (N=11)
At least one AE					
All	40 (100%)	7 (100%)	4 (100%)	18 (100%)	11 (100%)
Suspected	38 (95.0%)	7 (100%)	3 (75.0%)	17 (94.4%)	11 (100%)
At least one SAE (non fatal)					
All	15 (37.5%)	4 (57.1%)	2 (50.0%)	4 (22.2%)	5 (45.5%)
Suspected	7 (17.5%)	-	-	3 (16.7%)	4 (36.4%)
Death					
All	4 (10.0%)	-	1 (25.0%)	-	3 (27.3%)
Suspected	1 (2.5%)	-	-	-	1 (9.1%)
At least one suspected AE leading to discontinuation	8 (20.0%)	-	1 (25.0%)	2 (11.1%)	5 (45.5%)
At least one suspected AE leading to interruption	8 (20.0%)	-	-	5 (27.8%)	3 (27.3%)
At least one suspected AE leading to dose reduction	7 (17.5%)	-	-	3 (16.7%)	4 (36.4%)
At least one severe AE (grade ≥3)					
All	29 (72.5%)	6 (85.7%)	3 (75.0%)	11 (61.1%)	9 (81.8%)
Suspected	16 (40.0%)	2 (28.6%)	-	6 (33.3%)	8 (72.7%)
At least one AE grade 4/5 or non-hematological G3					
All	29 (72.5%)	6 (85.7%)	3 (75.0%)	11 (61.1%)	9 (81.8%)
Suspected	15 (37.5%)	2 (28.6%)	-	6 (33.3%)	7 (63.6%)
At least one DLT*	7 (17.5%)	-	-	3 (16.7%)	4 (36.4%)

***Dose Limiting Toxicity**

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The clinical pharmacology programme was based on several clinical studies examining single-dose and multiple-dose PK, and in addition, a population PK (popPK) model was used to estimate population PK parameters as well as to characteriseise explore possible covariates, and PBPK study was conducted to predict the extent of possible DDI. The applicant has investigated PK of Masitinib AB Science in four phase 1 studies (AB03001, AB03003, AB14004 and AB17001), all of which were conducted in healthy volunteers.

The provided popPK analysis utilised pooled PK data collected from 7 studies and included a total of 144 subjects (111 males, 33 females) with 1807 concentration records. The parameter estimates of the final model were determined with a reasonable precision. The model showed that CL was not affected by dose, and that AUC thus behaves in a dose-proportional manner. However, observations in the patient population are sparse.

ADME

The PK characteristics of Masitinib AB Science after a single dose of Masitinib AB Science from 40 mg to 800 mg in 40 healthy volunteers were determined in the study AB03001 and are as follows: single dose at 200 mg: mean C_{max} = 238.8 ng/mL and AUC_{0-t} = 2,557 ng.h/mL; single dose at 400 mg: mean C_{max} = 711.1 ng/mL and AUC_{0-t} = 8,244 ng.h/mL; mean t_{max} obtained after 1.5 to 5 hours; Mean half-life of plasma Masitinib AB Science between 13 to 17 hours; mean half-life of plasma AB3280 (main metabolite) between 15 to 38 hours.

The PK characteristics of Masitinib AB Science after repeated doses of Masitinib AB Science at 200 mg and 400 mg are as follows (based on Study AB1010-PIHV03003 data): Steady state reached at 4 to 5

days; Plasma level at steady state increased to up 1.5-fold; Repeated doses at 200 mg: mean C_{max} = 264.5 ng/mL and AUC_{0-t} = 3,179 ng.h/mL; Repeated doses at 400 mg: mean C_{max} = 764.3 ng/mL and AUC_{0-t} = 10,000 ng.h/mL. Following a high fat meal, Masitinib AB Science C_{max} and $AUC_{0-\infty}$ increased by 19% and 23%, respectively. As no clinically meaningful food effect seems to be evident in terms of overall exposure, the omission of precautions with respect to concomitant food intake is considered acceptable. However, the contribution of biliary excretion to drug elimination is unclear. The applicant proposed performing an absolute bioavailability clinical trial to provide further evidence that could enable conclusions regarding the contribution of different elimination routes to Masitinib AB Science clearance and quantify the contribution of biliary excretion.

Steady state plasma concentration for Masitinib AB Science (200 mg and 400 mg) was reached on or prior to day 5 in healthy subjects. The Vd/F is high, indicating an extensive tissue distribution. Masitinib AB Science extensively bound to plasma proteins (approximately 93%); the major binding protein appears to be albumin. The blood: plasma ratio is around 1. The distribution PK of Masitinib AB Science in healthy subjects is non-linear.

At clinically significant concentrations of Masitinib AB Science, binding to human plasma proteins was approximately 93% based on *in vitro* experiments, mostly to albumin and alpha-acid-glycoprotein, with little binding to gamma-globulin (Study PR6592-1-CC2099).

The study AB05031 data shows that simultaneous administration of 200 mg of AB1010 with a high fat breakfast increase the exposure to AB1010base by about 23%. Hence, the extent of formation of the metabolite AB3280 also increase by about 17%. In the clinical pharmacology programme, the studies AB1010-PIHV05031 and AB0503 seem to be the same study. This was clarified by the applicant upon request.

In vitro studies identified AB3280, an N-desmethylated compound, as the main metabolite of Masitinib AB Science after incubation with human hepatocytes. AB3280 is the product of the metabolization of AB1010 by CYP3A4 with minor contribution of CYP2C8. Plasma concentrations of AB3280 are approximately equivalent to 20-25% of the Masitinib AB Science plasma concentrations. Aniline-derivatives metabolites were identified (AB2436, AB5235 and AB6465). PK of these metabolites were found in low concentration in human. Concentrations of masitinib and its metabolites (AB2436, AB5235 and AB6465) were evaluated in human plasma and urine (Study AB14004). They were determined at steady state following 7 days of dosing at 3.0 mg/kg/day bid: Plasma C_{max} at steady state were 471.63 ng/mL for Masitinib AB Science and 3.53 ng/mL for AB2436. C_{max} was below the limit of quantification for AB5235 and AB6465. Ratios of $AUC_{0-\tau}$ between AB2436 and AB1010 was <3%, meaning that the AUC of AB2436 at steady-state was lower than 3% of AUC of AB1010. Urine C_{max} at steady state were between 59.89 ng/mL and 338.16 ng/mL for AB2436 (mean 187.79 ng/mL) and between 1,064.4 and 6,249.3 ng/mL for AB1010 (mean: 3792.3 ng/mL) Thus, in human urine, AB2436 concentration was lower than 5% of AB1010 concentration.

PK analysis in healthy volunteers showed that the elimination route of masitinib was mainly extra-renal. The renal clearance was slow (about 9 to 18 mL/min) compared with total clearance (about 1000 mL/min). The elimination of Masitinib AB Science and its major metabolites was further investigated in a mass balance study (Study AB17001). In this study, a single 200 mg oral solution dose of [14C]-AB1010 (radiolabelled Masitinib AB Science) was administrated in 4 healthy volunteers and the following results were found: Overall, 69% (range 55% to 83%) of radioactivity administered was recovered by the end of the sampling period (168 h). Up to 59% of the radioactivity was recovered in feces. Approximately 10% of the radioactivity was recovered in urine (low urinary recovery). The main compounds (accounting for more than 10%) found in faeces were AB1010 followed by AB3280 co-elating with a mono-hydroxy, desaturated (or keto) metabolite of AB1010. In plasma, about 60% of radioactivity were related to unextractable compounds which might be a pool of metabolites covalently bound to

plasma proteins. Total recovery of 69% of radioactivity administered is considered insufficient However, it is considered that the covalent binding of some metabolites to plasma proteins is the basis for this phenomenon. The recovery of radioactivity increases very slowly after 168 hours, as the 7-day stay of volunteers was not sufficient to recover more than 69% of the total radioactivity. This is in accordance with the very long half-life of plasma proteins (3 weeks for the most abundant of them, albumin), indicating that the rate of elimination of radioactivity is very low after 120 hours.

While it can be agreed that the present data support that faeces is the main excretion pathway for Masitinib AB Science and its related metabolites, it is noted that the overall geometric mean exposure ($AUC_{0\text{-last}}$) of parent masitinib (AB1010) and its respective metabolites AB3280 and AB2436 accounted for approximately 12%, 3.1% and 0.05% of the total circulating radioactivity measured in plasma. In single- and repeated-dose PK studies, elimination half-life after single-dose and repeated dose Masitinib AB Science were approximately 13 h and 17 h, respectively, which is not in line with the results obtained in the human mass-balance study, where the plasma half-life time for Masitinib AB Science and its main metabolite AB3280 was found to be at about 29 h.

PK in special populations

No study was conducted in special populations. The potential impact of some intrinsic factors, including age, bodyweight, human serum albumin and impact of hepatic activity described by ASAT and ALAT populations have been examined by the use of popPK analyses. No studies were performed in patients with impaired renal function. No studies in patients with hepatic impairment were performed, and no information is available on how race may affect the PK of masitinib. A contraindication of Masitinib AB Science use with hepatic impairment was requested to be included in the SmPC. No significant gender effect on PK parameters of Masitinib AB Science was observed. The PK data on elderly were not initially provided, however during the procedure the applicant clarified that there were 6 ALS patients over 70 years of age, of whom one was in the target population (age = 75). In this patient, PK parameters of Masitinib AB Science mesilate were in accordance with his age and body weight.

Interactions

The AB14004 (DDI part) study showed that there is a risk of DDI between Masitinib AB Science and CYP 3A4 and P-gp inhibitors.

In vitro studies demonstrated CYP3A4 to be the primary CYP enzyme responsible for Masitinib AB Science metabolism, with a minor contribution by CYP2C8. As Masitinib AB Science is administered concomitantly with riluzole, the DDI study of Masitinib AB Science and riluzole has been provided. In study AB10015, riluzole PK parameters (C_{max}, t_{max} and $AUC_{0\text{-}t}$) were analysed in 18 patients. Together with *in vitro* studies it could be agreed that Masitinib AB Science did not significantly modify the AUC of riluzole.

In vitro data suggested that Masitinib AB Science was mainly metabolised by CYP3A4 but a DDI study with the strong CYP3A4 inhibitor itraconazole increased masitinib $AUC_{0\text{-}\infty}$ with 43%. Therefore, the elimination pathways are not clear. Masitinib AB Science is a substrate and an inhibitor of P-gp, a weak inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1) (IC_{50} not reached) and a slight inhibitor towards organic anion transporting polypeptide 1B3 OATP1B3 (IC_{50} of 130 µM). Masitinib AB Science is a strong inhibitor of human BCRP with a calculated IC_{50} of 0.7 µM. Masitinib AB Science is a substrate of BCRP-mediated transport.

Further studies were proposed by the applicant as post-authorization measures to investigate the potential for clinically relevant DDI with Masitinib AB Science: *in vitro* study investigating Masitinib AB Science inhibition activity on BSEP using inside-out vesicles expressing BSEP and taurocholic acid as probe substrate (with Ketoconazole as a positive control inhibitor), *in vitro* study investigating Masitinib AB Science inhibition activity on CYP2B6, *in vitro* study to assess Masitinib AB Science as an inhibitor of

BCRP substrate, and a study to evaluate the consequences of DDI between Masitinib AB Science and CYP3A4/5 inducers.

Studies in target population

In study AB010015 a model for the popPK of Masitinib AB Science was validated. The PK of masitinib in healthy volunteers and oncology patients was satisfactorily described by a two-compartment open model with linear elimination. The main covariate effects were related to body weight. However, the decision to use an unequal splitting in the dosing scheme e.g. 100mg in the morning and 200 mg in the evening could not be based on PK data. This decision to use this dosing scheme, could be justified by the tolerability (PD) parameters. The visual predictive check and prediction-corrected visual predictive check showed some outlier areas but are given the current data acceptable. This is probably due to the lack of exact information about sampling times or dosing time of subsequent cycles of treatment or residual sampling. The applicant provided explanations that no such data is available: the sampling times were not recorded in the studies. It was also shown that a change in AUC values (drug exposition) is expected when the body weight changes as the CL is affected by body weight.

No PK studies were performed in adult patients with probable or definitive ALS. The applicant tried to overcome the respective limitation through popPK modelling approach because the applicant´s position is that PK of Masitinib AB Science does not depend on the indication. The Masitinib AB Science plasma concentrations from 18 ALS patients who had PK samples in Study AB10015 were added to the previously established popPK model. The initial popPK modelling has been performed using data from 5 different studies (AB03001, AB03003, AB05031, AB04015, and AB03002). Variations in clearance between healthy individuals and those with ALS were observed. The applicant has not provided expected PK differences between the healthy and ALS populations at least in terms of $T_{1/2}$ and AUC_{0-t} and/or $AUC_{0-\infty}$.

The existing sample size of ALS patients in the popPK analysis is deemed inadequate. The limited number of ALS patients included in the popPK analysis (18 patients) was acknowledged by the applicant. Given the current evidence, the applicant did not provide any acceptable evidence to support posology in ALS. PK in target population remains not to be clearly established which hampers the establishment of optimal posology. Given the small sample size, only tentative data shows that there might be a relationship between C_{max}, AUC and PD. However, it is unclear whether higher exposure is not associated with occurrence of adverse events.

The applicant did not provide PK/PD clinical data in ALS patients. The applicant suggests that Masitinib AB Science downregulates secondary damage mediated by chronically activated glial and immune cells in the CNS and PNS, based on provided non-clinical data for PD. However, the potential effect of Masitinib AB Science on the underlying mechanisms of disease in ALS is not considered fully demonstrated and provided evidence by preclinical data are fragmented, limiting possibility to establish further conclusions on possible therapeutic utility of a treatment in clinical practice.

While currently provided *in vitro* data and data from literature in general support proposed PD concept, further demonstration of proof-of-concept was expected and was requested because it is considered that studies in rodent models aimed to demonstrate replication of effect would be beneficiary in support of proposed effect of masitinib on the underlying mechanisms of disease. The applicant is apparently unable to provide any clinical PD or PK/PD data in patients despite the current scientific progress provide possibilities to use a relatively wide array of different blood-based biomarkers. It is agreed that the data presented can be considered feasible and might support the claimed mechanism of action of masitinib AB Science in ALS patients, although certain limitations exist, e.g. associated with the animal model limitations, doses administered to experimental animals etc. Thus, it is still considered that primary PD effect of masitinib AB Science is not adequately described and confirmed with any human PD data; however, non-clinical data provided could support the claimed mechanism of action although certain limitations exist.

In terms of safety, there is no specific discussion on possible secondary PD except the phase I study on possible QT/QTc effects of masitinib and it(s) metabolite(s) Thorough QT/QTc Study with positive control of moxifloxacin was conducted to evaluate possible secondary pharmacology. Exposure-response modelling by the PK/PD analysis was performed separately for masitinib and moxifloxacin by matching individual values of changes in QTcF with the corresponding concentrations measured at the same time points. After a single dose of 3 mg/kg the bootstrap predicted mean effect was a QTc shortening of -3.10 msec (90% CI: -5.01; -0.810) and after a repeated dose of 6 mg/kg the mean predicted effect was -1.8 msec (90% CI: -4.7, 1.4 msec). Overall, it is considered justified that masitinib holds a limited and clinically non-significant potential on QTc interval change. However, besides the potential QT/QTc effects, secondary pharmacology aspects were not addressed by the applicant.

2.6.4. Conclusions on clinical pharmacology

The PK in the target population and PK/PD relationship are not clearly established which may have hampered the establishment of optimal posology for ALS in the clinical studies. The pharmacological mechanism of Masitinib AB Science on the underlying pathophysiology of disease in ALS is not considered fully demonstrated and provided evidence could not be considered supportive for efficacy studies. There is insufficient knowledge of the concentration-response.

The CHMP considers the following measures would have been necessary to further address the issues related to pharmacology:

- *In vitro* study investigating Masitinib AB Science inhibition activity on BSEP using inside-out vesicles expressing BSEP and taurocholic acid as probe substrate (with Ketoconazole as a positive control inhibitor).
- *In vitro* study investigating Masitinib AB Science inhibition activity on CYP2B6.
- *In vitro* study to assess Masitinib AB Science as an inhibitor of BCRP substrate.
- A study to evaluate the consequences of DDI between Masitinib AB Science and CYP3A4/5 inducers.
- A study to evaluate Masitinib AB Science PK profile in patients with impaired hepatic function.

It is possible that further studies may be needed to investigate possible DDI interactions with newly characterised metabolites.

The CHMP considers that the above uncertainties would have not prevented a positive recommendation for a CMA.

2.6.5. Clinical efficacy

Table 20: The main efficacy study performed with Masitinib AB Science

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
AB10015	34 sites from 9 countries (Spain, Argentina, Slovakia, Portugal, Mexico, Italy, Greece, Netherlands, and Canada) enrolled at least 1 patient.	A prospective, multicentre, randomised, double-blind, placebo-controlled, parallel groups, phase II/III study to compare the efficacy and safety of masitinib versus placebo in ALS patients.	masitinib at 3 or 4.5 mg/kg/day + riluzole or placebo +riluzole	efficacy and safety of two doses of masitinib as add-on therapy to Riluzole	394 patients were enrolled (active control, N=133; masitinib 4.5, N=130; masitinib 3.0, N=131).	08 April 2013 - 05 December 2016; follow-up phase: November 2017- 14 June 2020	The mean age at screening was 56 y (range 22-75), 62,4% of patients were male.	Laboratory supported probable, clinically probable or definite ALS according to the World Federation of Neurology revised El Escorial criteria with disease duration from diagnosis no longer than 36 months at the screening visit; treated with a stable dose of riluzole (100 mg/day) for at least 30 days prior to screening; FVC ≥60 %	Change from baseline to week 48 in the ALSFRS-R

2.6.5.1. Dose response study(ies)

During the clinical Phase 3 studies in patients with ALS that were designed for the evaluation of the efficacy and safety of Masitinib AB Science a dose escalation part is an integral part of this study. Separate dose response studies were not performed. Dose response PK/PD is discussed in clinical pharmacology section.

2.6.5.2. Main study(ies)

Phase IIb/III AB10015 prospective, multicentre, randomised, double-blind, placebo-controlled, parallel groups, phase 2/3 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from ALS.

Methods

- **Study Design**

After the visit week 48, patients could enter a protocol extension phase on an optional basis depending only if the benefit/risk was assessed as positive by the investigator after discussion with the patient. During this protocol extension period, the double-blind was maintained. The study periods are presented below according to Supplemental clinical study report, version 3.1.

Long-term assessment for study AB10015 encompassed five distinct periods:

- #1: The double-blind main protocol period, which incorporated the prospectively declared 48-week treatment period of all patients (with date of first enrolment in April 2013 and date of last completed W48 visit in December 2016). This period is part of the planned blinded, prospective part of the study.

- #2: The double-blind first extension period, which incorporated the prospectively declared blinded extension period after week 48 visit for all patients, until week 48 last patient last visit was completed

in December 2016. This period defines the data cut-off date (December 5, 2016) for the clinical study report.

- #3: The double-blind second extension period, a double-blinded period commencing at the date of data readout in December 2016 until April 2017.

- #4: The open label third extension period, an open-label period from April 2017 until November 2017. During this period all patients remained in their assigned treatment groups and no switching between arms was permitted.

- #5: The open label post study follow-up period from November 2017 until June 2020, during which patients were followed for overall survival. At the start of this period, an optional, open-label, early access, Named Patient Programme (NPP) was initiated. This allowed those patients still receiving Masitinib AB Science to continue treatment, while also allowing patients from the AB10015 placebo arm to begin Masitinib AB Science treatment.

For analysis of long-term overall survival, the vital status (i.e., survival status of alive or dead, including date of death) of all patients originally randomised to study AB10015 was collected from each participating investigational site. As such, three patient groups were defined: long-term high-dose (4.5 mg/kg/day) Masitinib AB Science, long-term low-dose (3.0 mg/kg/day) Masitinib AB Science, and long-term placebo.

Long-term assessment for study AB10015 encompassed the prospectively declared 48-week treatment period with associated double-blind extension (commencing in April 2013 until data readout), and a post study follow-up period (from November 2017 until June 2020). Following data readout for the main protocol period of study AB10015, treatment assignment was unblinded and an optional, open-label, early access NPP was initiated. This allowed those patients still receiving Masitinib AB Science to continue treatment (23% (30/131) of patients from the Masitinib AB Science 3.0 mg/kg/day treatment arm, and 22% (29/130) of patients from Masitinib AB Science 4.5 mg/kg/day treatment arm), while also allowing patients from the AB10015 placebo arm to enter Masitinib AB Science treatment arm (19% (25/133) of patients from the placebo arm switched to Masitinib AB Science arm). During the assessment, the applicant clarified that 5 patients from placebo arm started Masitinib AB Science treatment - 3 patients started the treatment with 6 mg/kg/d dose, 1 – with 4 mg/kg/d, 1 – with 3 mg/kg/d. Patients still alive at the time of analysis were censored at the date of last contact.

Methods

- **Study Participants**

Patients enrolled in study AB10015 diagnosed with "probable" or "definite" ALS according to the World Federation of Neurology revised El Escorial criteria. The study population included ALS patients without restriction on the baseline ALSFRS-R score, with up to 3 years of disease history, and excluded patients on gastrostomy. Patients had to be aged between 18 aged between 18 and 75 years old with a weight > 50 kg and a BMI between 18 and 35 kg/m^2. Patients must present with FVC (Forced Vital Capacity) equal or more than 60 % predicted normal value for gender, height, and age at the screening visit.

Patient with various conditions, including but not limited to significant sensory abnormalities, dementia, other neurologic diseases, uncompensated medical illness, and psychiatric illness were also not eligible. Patient who underwent tracheotomy and /or gastrostomy were also excluded.

- **Treatments**

Patients were to be enrolled into one of three groups:

- Group 1: patients on Masitinib AB Science at 4.5 mg/kg/day and riluzole

- Group 2: patients on Masitinib AB Science at 3 mg/kg/day and riluzole
- Group 3: patients on placebo and riluzole

Subjects enrolled were to receive a total daily dose of 4.5 or 3 mg/kg masitinib AB Science, or a matching placebo, to be taken orally during meals in two daily doses over 48 weeks with a possibility of double-blind extension period.

Irrespective of the treatment allocated, active or placebo in combination with riluzole, them adaptation of the total dose to the weight followed the same procedure. The following table was used to determine the number of tablets to take at each administration and their dosage. Study treatment daily dose of 3 mg/kg was administered in divided doses as indicated below.

Table 21: Dose of study treatment (mg) according to patient's weight (3 mg/kg/day; 4,5 mg/kg/day

		3 mg/kg/day		
Patient's weight in kg		**Daily dose (mg)**	**Morning* (mg)**	**Evening** (mg)**
	≤49.9	NOT POSSIBLE		
> 49.9	83.3	200	100	100
> 83.3		300	100	200

		4.5 mg/kg/day		
Patient's weight in kg		**Daily dose (mg)**	**Morning* (mg)**	**Evening** (mg)**
	≤55.5	200	100	100
> 55.5	77.7	300	100	200
> 77.7	99.9	400	200	200
> 99.9		500	200	200+100

*Morning: the tablets were to be taken during breakfast. In case of nausea, the administration could be taken place during lunch. **Evening: the tablets were to be taken during dinner.

Riluzole was not considered as investigational medical product in this study and as such was not provided by the Sponsor. The product was prepared, handled, used, and stored according to standard practices and the Summary of Product Information (SmPC).

Prohibited concomitant treatments included live attenuated vaccines, phenytoin prescribed as prophylactic anticonvulsive agent, benzodiazepine, amiodarone, chemotherapies, any hepatotoxic agent (e.g. allopurinol, methyldopa, sulfasalazine), any investigational treatment related or not to ALS, drugs known to be at high risk of Stevens-Johnson syndrome: allopurinol, lamotrigine, carbamazepine, phenytoin, phenobarbital, sulfasalazine, sulfamide, oxicam and nevirapine; or to be at high risk of drug rash with eosinophilia and systemic symptom syndrome: minocycline, modafinil, dapsone.

- **Objectives**

Main study period:

- The primary objective of the study was to evaluate the efficacy of Masitinib AB Science in combination with riluzole based on the change in the ALSFRS-R from baseline to week 48.
- The secondary objectives of the study were to evaluate efficacy of Masitinib AB Science in combination with riluzole based on other efficacy endpoints (see below endpoints section)

Open-label follow up period:

- To test whether a signal in OS based on the long-term follow-up dataset from study AB10015 is evident in an enriched patient population - excluding very severe and/or severe patients.

- To test whether any survival benefit detected in the aforementioned enriched patient population is also evident at the earlier cut-off corresponding to the end of the prospectively blinded protocol study period.
- To test the consistency of any detected survival treatment effect with the clinical endpoints of ΔALSFRS at week 48 and PFS, thereby testing whether these endpoints are appropriate surrogates of OS.
- To analyse long-term safety.

- **Outcomes/endpoints**

Primary Efficacy Endpoint

• Change from baseline to week 48 in the ALSFRS-R

The ALSFRS-R is a score from 0-48 assessing disability. The ALSFRS-R includes 12 questions, each task is rated on a five-point scale from 0 = can't do, to 4 = normal ability. Individual item scores are summed to produce a reported score of between 0=worst and 48=best. ALSFRS-R scores correlate significantly with quality of life (Cedarbaum, Stambler et al. 1999).

Secondary study endpoints

Efficacy Endpoints

• Time to event analysis, defined as median Progression free survival (PFS), with progression defined death or > 9 points decline in ALSFRS-R from baseline.

• Change from baseline to week 48 in Forced Vital Capacity (FVC).

• Combined Assessment of Function and Survival (CAFS) between baseline and week 48

• OS defined as the time from randomization to the time of the documented death

• Tracheostomy free survival defined as the time from randomization to the date of documented death or first tracheostomy

Quality of Life Endpoint

• Absolute and relative change from baseline in ALSAQ-40 (Amyotrophic Lateral Sclerosis Specific Assessment Questionnaire) at week 4, 8, 12, 24, 36 and week 48

Safety Endpoints

• Occurrence AEs

• Treatment emergent changes in physical examination, vital signs (blood pressure, pulse rate and body temperature) and electrocardiogram (ECG) and clinical laboratory tests (biochemistry, haematology, urinalysis)

- **Sample size**

The objective of the study was to compare each "Masitinib AB Science + riluzole" group (i.e. Masitinib AB Science 3 mg/kg/day + riluzole and Masitinib AB Science 4.5 mg/kg/day + riluzole) to "placebo + riluzole" group. Therefore, the sample size was calculated in a 1:1 randomization ratio for the comparison of each Masitinib AB Science group to the active control group making the same hypothesis for each Masitinib AB Science group.

The original sample size estimation has been modified following three amendments of the study protocol (see conduct of the study) (changing the phase 2 to a phase 2/3) from 45 patients to 381 patients.

A distinction between Normal and Fast Progressors was introduced through an amended protocol (version 3.0). This distinction was based on ALSFRS-R progression rate from disease-onset to baseline (ΔFS). The 'Normal Progressors' were those with ΔFS <1.1 points/month before randomization while the 'Fast Progressors' were defined as having ΔFS ≥1.1 points/month before randomization.

Sample size calculation was based on absolute change from baseline to Week 48 in ALSFRSR (hypothesis for riluzole are based on data from Fornai and colleagues [Fornai et al., 2008]). ALSFRS-R change from baseline to week 48 was supposed to be higher in the full study population comprising "normal + fast progressors" (with a SD equal to 9) than in the "normal progressor" subpopulation (with a SD equal to 7.5), notably because patients have more tracheostomy and death in the full study population comprising "normal + fast progressors" than in "normal progressor" subpopulation.

Primary analysis was performed using a re-randomization test basis the estimates from the Analysis of Covariance (ANCOVA) model.

▪ "Normal Progressor" subpopulation

The parameters considered for sample size calculations in the normal progressor subpopulation as follows:

- Alpha set to 5% 2-sided test
- Power set to 80%
- Difference in mean change of ALSFRS-R between placebo control group and Masitinib AB Science group equal to 3.3
- Standard deviation of the change from baseline to week 48 from all groups equal to 7.5
- Effect size = 0.44
- Allocation ratio: 1:1
- One interim analysis planned at around 50% of information fraction
- Pocock alpha spending method approximated with Hwang, Shih and DeCani class alpha spending function.

Comparison of the 'Masitinib AB Science 4.5 mg/kg/day + riluzole' group to the 'placebo + riluzole' group

With the hypotheses described above, 186 evaluable patients (93 patients treated in Masitinib AB Science 4.5 mg/kg/day group / 93 patients treated with placebo) were necessary to detect a 3.3 (±7.5) point difference between Masitinib AB Science 4.5 mg/kg/day group and placebo control group with a power of 80% and a type-I error of 5%.

Comparison of the 'Masitinib AB Science 3 mg/kg/day + riluzole' group to the 'placebo + riluzole' group

Same calculation as for the comparison of the 'Masitinib AB Science 4.5 mg/kg/day + riluzole' group to the 'placebo + riluzole' group.

Taking into account around 5% of non-evaluable patients, 300 patients defined as "normal progressors" (100 in each Masitinib AB Science group and 100 treated in the placebo control group) were enough to detect a 3.3 (±7.5) point difference between groups (each of the Masitinib AB Science groups versus placebo control group) in order to achieve a power of 80% with a significance level for a two sided test of 5% in "normal progressor" subpopulation.

Full study population comprising "Normal + Fast Progressors".

The parameters considered for sample size calculations in the full population comprising normal + fast progressor as follows:

- Alpha set to 5% 2-sided test
- Power set to 80%
- Mean change from baseline for active control group equal to -11 (from 38 to 27)

- Mean change from baseline for Masitinib AB Science groups equal to -7.7 (from 38 to 30.3)
- Difference in mean change of ALSFRS-R between active control group and Masitinib AB Science group equal to 3.3 which is considered to reflect clinically meaningful improvement.
- Standard deviation of the change from baseline to week 48 from all groups equal to 9
- Effect size = 0.36
- Allocation ratio: 1:1

354 patients (118 in each Masitinib AB Science group and 118 in the placebo control group) should be included to detect a 3.3 (±9) point difference between groups (each of the Masitinib AB Science groups versus placebo control group) in order to achieve a power of 80% with a significance level for a two-sided test of 5%.

Considering around 5% of non-evaluable patient, 381 patients (127 in each Masitinib AB Science group and 127 in the placebo control group) were included to detect a 3.3(±9) point difference between groups (each of the Masitinib AB Science groups vs active control group) in order to achieve a power of 80% with a significance level for a two-sided test of 5%.

During the assessment, the applicant clarified that secondary endpoints (CAFS and FVC) for the normal progressor subpopulation also reached a power of 80% based on the primary sample size calculation and are therefore, also sufficiently powered for this study. PFS and OS endpoints were not powered for this study.

Table 22: Sample size in each ALS population

Population	Change of ALSFRS-R from baseline to W48				
	Difference between masitinib and active control groups	N per arm	N to detect a difference between masitinib and active control groups	N total	N total taking account of discontinuations
"Normal Progressors"	3.3 (± 7.5)	**93**	**186**	**279**	**300**
"Normal + Faster Progressors"	3.3 (± 9)	**118**	**236**	**354**	**381**

Follow-up phase

For analysis of long-term overall survival, the vital status (i.e., survival status of alive or dead, including date of death) of all patients originally randomised to study AB10015 was collected from each participating investigational site. As such, three patient groups were defined: long-term high-dose (4.5 mg/kg/day) Masitinib AB Science, long-term low-dose (3.0 mg/kg/day) Masitinib AB Science, and long-term placebo. Long-term assessment for study AB10015 encompassed the prospectively declared 48-week treatment period with associated double-blind extension (commencing in April 2013 until data readout), and a post study follow-up period (from November 2017 until June 2020).

Following data readout for the main protocol period of study AB10015, treatment assignment was unblinded and an optional, open-label, early access named patient programme was initiated. This allowed those patients still receiving Masitinib AB Science to continue treatment (23% (30/131) of patients from the Masitinib AB Science 3.0 mg/kg/day treatment arm, and 22% (29/130) of patients from the Masitinib AB Science 4.5 mg/kg/day treatment arm), while also allowing patients from the AB10015 placebo arm to begin Masitinib AB Science treatment (19% (25/133) of patients from the placebo arm switched to receive Masitinib AB Science). Patients still alive at the time of analysis were censored at the date of last contact.

- **Randomisation and Blinding (masking)**

A randomization list was generated for packaging and labelling by cardinal system (Vendor later rebranded as Venn Life Sciences).

Eligible patients were randomised by means of a computerised central randomization system called IWRS (Interactive Web Response System). The automated system assigned the appropriate investigational medicinal product for each patient. Interaction with the automated system was initiated by Sponsor. Sponsor supplied the Investigators with user guides for the automated system in the national language.

Randomization was performed with a minimization algorithm on:

- ALS patient's population ("normal progressors" (progression of ALSFRS-R score before randomization < 1.1 points/month) versus "faster Progressors" (progression of ALSFRS-R score before randomization ≥ 1.1points/month))

- Progression of ALSFRS-R score (point/month) from date of first symptom to baseline (ALSFRS-R score at date of first symptom supposed to be 48), balanced between treatment groups in each of ALS patient's subpopulation "normal progressors" and "faster progressors".

- Site of onset (bulbar versus spinal)

- ALSFRS-R score at baseline

- Age at baseline

- Region (Canada and Western Europe versus Eastern Europe versus other countries).

The study is a double-blind study. In the study AB10015, three patients were unblinded by the pharmacovigilance department due to SUSAR before the data lock of the clinical database: toxic hepatitis with jaundice, oral and pharyngeal candidiasis and Drug Rash with Eosinophilia and Systemic Symptom (DRESS) likely.

- **Statistical methods**

A. Analysis datasets and subpopulations

Intent-To-Treat (ITT) dataset: all randomised patients with probable or definite ALS, whether they have received the study treatment or not. Patients were classified according to the treatment arm to which they have been randomised, irrespective of the actual treatment received. The actual number of patients in the final analysis ITT population was 394 patients, including 330 "normal progressor" patients and 64 "fast progressors" patients.

Modified Intent-To-Treat (mITT) dataset: all ITT patients with at least one post baseline efficacy assessment who took at least one dose of study treatment (Masitinib AB Science /placebo). The actual number of patients in the final analysis mITT population was 391 patients, including 328 "normal progressor" patients and 63 "fast progressors" patients. Efficacy analyses were performed primarily in mITT set.

Per Protocol (PP) dataset: all patients of the mITT population without any major protocol deviation. This was the set of patients who participated in the study as intended. Patients terminating the study prematurely were included in the PP population provided that there was no protocol deviation. Before locking the data base, the precise reasons for excluding patients from the PP population were fully defined and documented by Data Review Committee. This population was used for certain sensitivity analyses. Protocol deviations are defined as: inclusion and non-inclusion criteria were not met, intake of forbidden medication, non-respect of visit dates, missing value for main criterion without premature termination, non-respect of protocol design, any other deviations during the course of the study.

Safety population: The safety population consists of all patients randomised and who took at least one dose of study medication (Masitinib AB Science or placebo).

A distinction between normal and fast Progressors was introduced through an amended protocol (version 3.0). As indicated above, this distinction was based on ALSFRS-R progression rate from disease onset to baseline (ΔFS). The 'normal progressors' were those with ΔFS <1.1 points/month before randomization while the 'fast progressors' were defined as having ΔFS ≥1.1 points/month before randomization.

According to the applicant, this approach selected a more homogeneous primary efficacy population (i.e., 'normal progressors'), while concurrently permitting assessment (secondary analysis) of the broader more heterogeneous population (i.e., full study population comprising 'normal and fast progressors'). According to the applicant, this split was recommended by the principal investigator and supported by literature reference [Kimura 2006; Kollewe 2008; Gordon 2006] and approved by investigators and external experts solicited.

Table 23: Number and Percent of Subjects by Treatment Group

Number of Subjects	Placebo	Masitinib 4.5	Masitinib 3.0	Total
Overall Population				
ITT population	133	130	131	394
mITT population	132 (99.2%)	128 (98.5%)	131 (100.0%)	391 (99.2%)
Normal Progressors				
ITT population (n (% overall)	114 (85.7%)	106 (81.5%)	110 (84.0%)	330 (83.8%)
mITT population (n (%ITT)	113 (99.1%)	105 (99.1%)	110 (100%)	328 (99.4%)
Fast Progressors				
ITT population (n (% overall)	19 (14.3%)	24 (18.5%)	21 (16.0%)	64 (16.2%)
mITT population (n (%ITT)	19 (100%)	23 (95.8%)	21 (100%)	63 (98.5%)

At the time of the amendment, 12% of the patients enrolled in the study could have reached the week 48 time point.

Table 24: Enrolment Status at the Time of Protocol amendment version 3.0

	Placebo	**Masitinib 3.0**	**Masitinib 4.5**	**Total**
	N = 133	N = 131	N = 130	394
Patients enrolled at the time of amendment submission	49	46	47	142 (36%)
Patients reaching week 48 at the time of amendment	18	15	13	46 (12%)

Follow up phase

For long-term survival analysis, the definitions of studied subpopulations were:

Step 1 an enriched cohort of patients having moderate (non-severe) ALS, defined as a baseline score of at least 2 on each individual component of the ALSFRS-R (i.e., prior to any complete loss or severe impairment of functionality) and a ΔFS of less than 1.1 points/month (subset of normal progressors subpopulation).

Step 2 an enriched cohort of patients having moderate and severe ALS, defined as a baseline score of at least 1 on each individual component of the ALSFRS-R (i.e., prior to any complete loss of functionality) and a ΔFS of less than 1.1 points/month (subset of normal progressors subpopulation).

Step 3 the cohort of patients having moderate, severe, and very severe ALS (i.e., any baseline ALSFRS-R score) and a ΔFS of less than 1.1 points/month (subset of normal progressors subpopulation).

B. Study treatment period and protocol extension phase

Analysis of the primary endpoint:

Control of family-wise type I error

While the study was ongoing, the applicant changed the primary efficacy population of the study through an amendment of the protocol (third amendment, dated 08 October 2014) so the efficacy of Masitinib AB Science in combination with riluzole based on the change in the ALSFRS-R from baseline to week 48 was first evaluated in the mITT "normal progressors" subpopulation and only subsequently, in the mITT full study population comprising the normal and fast progressors. The below sequence for controlling family-wise type I error was re-defined according to the change of the primary study population.

To control overall family-wise type I error rate at the study level, analyses of efficacy will be conducted in a stepwise manner (fixed sequence method) to control the global family-wise error rate.

- Sequence 1 "Normal progressors" subpopulation – Masitinib AB Science 4.5 mg/kg/day.
- Sequence 2 "Normal progressors" subpopulation - Masitinib AB Science 3 mg/kg/day.
- Sequence 3 full study population comprising "normal + fast progressors" - Masitinib AB Science 4.5 mg/kg/day.
- Sequence 4 full study population comprising "normal + fast progressors" - Masitinib AB Science 3 mg/kg/day.

Primary analysis was to be performed in mITT "normal progressors" subpopulation on patients randomised at an initial Masitinib AB Science dose of 4.5mg/kg/day (Group 1) versus placebo patients (Group 3) at a 5% alpha-level. In accordance with the fixed sequence method as above described, the first step is to demonstrate a statistically significant difference between Masitinib AB Science at a dose of 4.5 mg/kg/day + riluzole versus placebo + riluzole on ALSFRS-R after a 48-week treatment period in the normal progressor subpopulation. If this analysis is conclusive, then the next objective is to compare Masitinib AB Science 3.0 mg/kg/day + riluzole versus placebo + riluzole for change from baseline in ALSFRS score at week 48 in the normal progressor subpopulation. If this analysis is conclusive, then based on fixed sequence method, the next objective is to compare Masitinib AB Science 4.5 mg/kg/day + riluzole versus placebo + riluzole for change from baseline in ALSFRS score at week 48 in the full study population comprising normal + fast progressors. If this analysis is conclusive then based on the fixed sequence method, the last objective is to compare Masitinib AB Science 3.0 mg/kg/day + riluzole versus placebo + riluzole for change from baseline in ALSFRS score at week 48 in the full study population comprising normal + fast Progressors.

Missing data

Missing values of ALSFRS-R at study visit were to be replaced based on the modified last observation carried Forward (mLOCF) method defined as follows:

- Case 1: discontinuation before week 48 for toxicity, lack of efficacy, or unknown reason. In this case, missing data will be imputed with the LOCF method.
- Case 2: discontinuation before week 48 for a documented reason excluding toxicity or lack of efficacy. In this case, non-observed values can be considered as Missing at Random (MAR), and no imputation will be done (observed cases).
- Case 3: death for related disease progression before week 48. If patient was treated when he died, score ALSFRS-R is replaced by 0.

Primary analysis

Absolute change from baseline to week 48 in ALSFRS-R will be estimated using a model of ANCOVA adjusted on following factors: treatment (Masitinib AB Science /placebo) and stratification criteria:

- ALS patients' population ("normal progressors" versus "faster progressors") only for analyses in the full study population comprising "normal progressors + faster progressors".
- Progression of ALSFRS-R score (point/month) from date of first symptom to baseline (ALSFRS-R score at date of first symptom supposed to be 48).
- ALS patients' subpopulations ("normal progressors" versus "faster progressors")
- ALSFRS-R score at baseline
- Site of onset (bulbar versus others)
- Age at baseline
- Region (North America and West Europe versus Est Europe versus Other Countries)

Two-sided 95% confidence interval (CI) of the difference of mean change from baseline to week 48 between groups will be provided.

The primary analysis uses a re-randomization test. Re-randomization test, also called randomization test involves the reshuffling of observed data and computing the test statistic (in this case test associated with the treatment effect estimate in analysis of covariance model), with the following conditions:

- Re-running of the minimization algorithm in order to assign a treatment group for each randomised patient.
- Maintenance of the real order (=observed) of arrival of the patients (e.g. patient 00101 randomised in first)
- Maintenance of the hazard set for minimization algorithm (20% in hazard in study AB10015)
- Maintenance of the ALSFRS-R score at each visit for the statistical analysis

Step 1: Model of analysis of covariance described above will be performed on observed data, and test statistic will be provided along with p-value.

Step 2: The minimization algorithm will be run to obtain a new "randomization list" (assignment of each patient to a treatment group) for the population of randomised patients (ITT). For the population of interest (mITT), the ANCOVA model will be computed at each rerandomization.

This step (rerandomization and computation of the test statistic) will be performed 10,000 times, to obtain 10, 000 replicate datasets.

Step 3: The proportion of replicates for which the p-value of treatment factor is at least as small as the p-value of treatment factor from the original data will be calculated. In this proportion the observed p-value of treatment factor will be also accounted for one replicate in numerator and denominator.

That proportion is the p-value for the randomization test.

The hypothesis of no treatment difference will be rejected at the 5% level of significance if the observed test statistic falls outside the middle 95% of the observed distribution of the resampled statistic. This step determines how often the resampled statistic of interest is as extreme as the observed value of the same statistic.

Sensitivity Analysis

1. Absolute change from baseline to week 48 in ALSFRS-R will be estimated using a model of ANCOVA adjusted on following factors: treatment (Masitinib AB Science /placebo) and stratification criteria (no re-randomization test).

2. Multivariate sensitivity analysis: Absolute change from baseline until week 48 in ALSFRS-R will be estimated using a model of ANCOVA adjusted on the following factors: treatment (Masitinib AB Science / placebo), stratification criteria and following criteria: sex, time from date of first symptom to baseline, time from date of diagnosis to baseline, time from date of first symptom to date of diagnosis, progression of ALSFRS-R score (point/month) from date of diagnosis to baseline (ALSFRS-R score at date of diagnosis supposed to be 48), FVC at baseline, BMI, other parameters defined by the blind review committee before lock of data-base. Firstly, univariate analyses will be done at a 20% level. At a second time, only significant factors presenting less than 20% of missing data will be introduced into the multivariate model. Some interactions will be tested. Treatment factor will be included in the final model whatever its level of significance. Two-sided 95% CI of the difference of baseline change until week 48 between groups will be provided.

3. Primary analysis and sensitivity analysis 1- and 2- will be repeated using observed cases method (i.e.no imputation of missing data).

4. Primary analysis and sensitivity analysis 1- and 2- will be repeated using multiple imputation (MI) for missing data.

5. Absolute change from baseline to week 48 in ALSFRS-R will be estimated using a model of analysis of covariance (ANCOVA using SAS PROC MIXED) adjusted on following factors: treatment (Masitinib AB Science /placebo), visit as well as a treatment by visit interaction and stratification criteria. Treatment by visit interaction will be tested and study treatment effect will be given at each time (using SLICE=TIME option). LSMEANS of absolute variation from baseline at each visit with corresponding95% two-sided CI will be given with this model.

6. Primary analysis and sensitivity analysis 1-, 2-, 3-, 4- and 5- will be repeated on the ITT and PP populations.

Missing values of ALSFRS-R at study visit were replaced based on the mLOCF, referred to as Rule 1 method. Six sensitivity analyses, referred to as Rule 2 to Rule 7, were pre-specified to assess the impact of missing data based on the reasons of premature patient withdrawal from the study.

A description of censoring rules used for the primary efficacy analysis and sensitivity analyses of study AB10015 are described below [Mora 2020].

- Rule 1 was used for the primary analysis. Missing data was imputed via LOCF when patients discontinued before week-48 for documented reasons of toxicity or lack of efficacy. If patient died before week-54 (included) after randomization, ALSFRS-R score was replaced by zero (0). Patients discontinuing prematurely for the following documented reasons were not imputed (lost to follow-up, non-compliance, travel, procedure, protocol deviation, any other reason not mentioned above). LOCF sensitivity analyses.
- Rule 2 was the same as rule 1 with the exception that imputation via LOCF was also done in case of premature discontinuation due to withdrawal of consent related to study procedure.
- Rule 3 was the same as rule 1 with the exception that imputation via LOCF was also done in case of premature discontinuation due to any travel issue.
- Rule 4 was the same as rule 1 with the exception that imputation via LOCF was also done in case of premature discontinuation due to withdrawal of consent related to study procedure or due to any travel issue.

- Rule 5 imputed data via LOCF for all patients with the exception of those patients who were non-compliant after the date of non-compliance. For these patients, the week-48 ALSFRS score was imputed using the last available score before non-compliance, where non-compliance was defined as per site clinical judgement, 'patient who could and should have continued to use study treatment but did not due to different reasons as mentioned in statement signed by the investigators'.

Single imputation based on clusters

In the two imputation methods detailed below (rule 6 and rule 7), missing data for early discontinuation or death were imputed, regardless of the cause of discontinuation.

- Rule 6 used single imputation methodology, i.e., non-LOCF, copying increment from similar patients, i.e., imputation was done by clustering patients by a given prognostic factor, then using the average increment within groups.
- Rule 7 was the same as rule 6 with the exception that a penalty of 50% was applied to those patients who discontinued early due to lack of efficacy, an imputation method based on recommendations from The National Research Council Panel on Handling Missing Data in Clinical Trials [Permutt 2016].

In this analysis, no imputation was performed for three patients who had no other patient in their cluster.

Considering further the full analysis dataset methods of rules 6 and 7, these sensitivity analyses estimate ALS disease progression for similarly clustered patients, with clustering being done on the variables of: site of onset at baseline, region, and treatment group. The applicant states that this method decreases possible bias introduced by LOCF methods because it tries to identify the trend within similar patients and then imputes the missing value using this average trend.

Furthermore, to ensure that these pre-specified methods for handling missing data arising from patient withdrawals did not give rise to bias in the estimated treatment effect, the applicant performed additional sensitivity analyses based on alternative methodologies. These analyses were performed in the "normal progressor" subpopulation receiving Masitinib AB Science 4.5 mg/kg/day.

- Sensitivity analysis based on MI,

- Sensitivity analyses applying the most conservative approaches, namely multiple imputation with jump to reference (J2R).

Analysis of the secondary endpoints:

According to the Final Statistical Analysis Plan dated 16 March 2017 for secondary endpoints type I error was controlled as part of the testing sequence if primary analysis is significant.

Combined Assessment of Function and Survival (CAFS)

CAFS on rank data will be analysed with an ANCOVA model with treatment as a fixed effect adjusted on stratification criteria.

Re-randomization test using treatment effect statistic test of ANCOVA model will be performed.

Sensitivity analyses:

1. CAFS will be analysed with an ANCOVA model with treatment as a fixed effect adjusted on stratification criteria (no re-randomization test).

2. CAFS difference between groups will be analysed with a Generalised Gehan-Wilcoxon rank test.

3. Primary analysis corresponding to CAFS and sensitivity analysis 1- and 2- will be repeated on the ITT and PP populations.

Change of FVC from baseline to week 48

Absolute change from baseline to week 48 in FVC will be estimated using a ANCOVA model adjusted on following factors: treatment (Masitinib AB Science / placebo) and stratification criteria. Missing values of FVC at study visit will be replaced based on the mLOCF method.

Re-randomization test using treatment effect statistic test of ANCOVA model will be performed.

Sensitivity analyses:

1. Absolute change from baseline to week 48 in FVC will be estimated using a ANCOVA model adjusted on following factors: treatment (Masitinib AB Science / placebo) and stratification criteria (no re-randomization test). Missing values of FVC at study visit will be replaced based on the mLOCF.
2. Primary analysis corresponding to FVC and sensitivity analysis 1- will be repeated using observed cases method (i.e. no imputation of missing data).
3. Primary analysis corresponding to FVC and sensitivity analysis 1- and 2- will be repeated on the ITT and PP populations.

Time to first tracheotomy defined as the time from randomisation to the time of the first tracheotomy.

Time to first tracheotomy analysis will be analysed with a rerandomization test using stratified log-rank test as statistical test.

Sensitivity analyses:

1. Time to first tracheotomy will be analysed using stratified log-rank test (no re-randomization test).
2. Multivariate Cox proportional hazards regression model will be constructed to compare hazard rates between treatment groups if the basic assumption that hazard ratio (HR) is constant through time is verified.
3. Primary analysis corresponding to time to first tracheotomy and sensitivity analysis 1- and 2- will be repeated on the ITT and PP populations.

Survival defined as the time from randomisation to the date of documented death or first tracheotomy.

Survival analysis will be analysed with a rerandomization test using stratified log-rank test as statistical test.

Sensitivity analyses:

1. Survival analysis will be analysed using stratified log-rank test (no re-randomization test).
2. Multivariate cox proportional hazards regression model will be constructed to compare hazard rates between treatment groups if the basic assumption that HR is constant through time is verified.
3. Primary analysis corresponding to overall survival and sensitivity analysis 1- and 2- will be repeated on the ITT and PP populations.

Futility analysis

For each dose group (3mg kg/day and 4.5mg/kg/day) and each subpopulation ("normal progressors" and full study population comprising "normal progressors + faster progressors"), the independent data monitoring committee (IDMC) should review the different efficacy criteria about 48 weeks after the [60th - 75th] patient randomised.

In case of lack of efficacy, the IDMC recommends the discontinuation of the dose group for futility reason. The futility boundary will be based on conditional power.

Study could be considered as non-futile for a dose group (3mg /kg/day or 4.5mg/kg/day) if:

- Conditional power is less than a prespecified threshold for "Normal progressors" subpopulation.

OR

- Conditional power is less than a prespecified threshold for the full population comprising "normal progressors + faster progressors".

Full details were prespecified in the interim statistical analysis plan.

For planned analysis, the significance levels to be used for rejecting the null hypotheses will be directly derived from the above cumulative alpha spending function so that the type I error would be controlled at the level.

The interim analyses to be performed without any unblinding for the sponsor. An independent CRO was mandated by AB Science to perform the analysis. The results were sent directly to the IDMC members. The IDMC had to recommend either stopping or continuing the study. If the size of treatment effect seems lower than expected but still clinically relevant, the IDMC were able to recommend a sample size re-estimation, respecting an upper limit for the increase of 100% of the initial sample size, and will communicate it directly to the CRO in charge of Interactive Randomization System.

Follow-up phase

The primary endpoint is defined as the OS for participants from study AB10015 and its associated long-term follow-up until survival cut-off date. The primary endpoint OS was analysed based on the ITT population according to the treatment group patients are randomised and the strata they are assigned at randomization using a stratified log-rank test.

All investigational sites from study AB10015 were contacted with a request for an update on each patient's vital (survival) status. Overall survival was defined as the time elapsed between randomization and death from any cause. Overall survival P values were calculated via the multivariate log-rank test using the covariates of age and ALSFRS-R score at randomization, site of onset (spinal versus bulbar), geographical region, and post-onset ALSFRS-R progression rate (ΔFS). All covariates were prespecified in the AB10015 protocol as randomization stratification factors [Mora 2020]. HR and 95% CI were calculated via the Cox proportional-hazards model using the abovementioned covariates.

During the assessment, the applicant provided information the 25 patients initially randomised in the placebo arm and subsequently switched to Masitinib AB Science, were included in the long-term OS analysis. For long-term OS analysis, these patients were analysed based on their initial randomization scheme in AB10015 study, i.e., the placebo group.

Primary analysis was performed on enriched patient populations from the ITT dataset following the sequence described before and according to the full follow-up period cut-off of 14 June 2020.

Sensitivity analyses of the primary endpoint will repeat the above sequence with the following modifications:

- Using a cut-off date of 14 June 2020 as above but without restrictions placed on baseline ΔFS (i.e., cohorts including both normal and fast progressors.

- Using a cut-off date of 05 December 2016, corresponding to the planned blinded and prospective part of the study.

Results

- **Participant flow**

The mITT population has been used for the efficacy analysis (132, 131, and 128 patients in the placebo, Masitinib AB Science 3.0 mg/kg/day, and Masitinib AB Science 4.5 mg/kg/day treatment-arms, respectively).

Table 25: Subject Disposition – Number and Percent of Subjects by Treatment Group

	Placebo (N=133)	Masitinib 4.5 (N=130)	Masitinib 3 (N=131)	Total (N=394)
Number of Subjects in ITT population				
N	133	130	131	394
Number of Subjects in mITT population				
Yes	132 (99.2%)	128 (98.5%)	131 (100.0%)	391 (99.2%)
Number of Subjects in Safety population				
Yes	133 (100.0%)	129 (99.2%)	131 (100.0%)	393 (99.7%)
Number of Subjects in PP population				
Yes	130 (97.7%)	127 (97.7%)	129 (98.5%)	386 (98.0%)
Subjects status in main period W0-W48				
W48 reached	92 (69.2%)	83 (63.8%)	89 (67.9%)	264 (67.0%)
Prematurely discontinued before W48	41 (30.8%)	47 (36.2%)	42 (32.1%)	130 (33.0%)
Reason of discontinuation W0-W48 period				
N	41	47	42	130
AE Related	1 (2.4%)	12 (25.5%)	7 (16.7%)	20 (15.4%)
Lost to Follow-up	0 (0.0%)	1 (2.1%)	0 (0.0%)	1 (0.8%)
Non compliance	0 (0.0%)	3 (6.4%)	2 (4.8%)	5 (3.8%)
Lack of Efficacy	15 (36.6%)	19 (40.4%)	19 (45.2%)	53 (40.8%)
Travel	8 (19.5%)	4 (8.5%)	1 (2.4%)	13 (10.0%)
Procedure	3 (7.3%)	0 (0.0%)	0 (0.0%)	3 (2.3%)
Death	9 (22.0%)	6 (12.8%)	9 (21.4%)	24 (18.5%)
Protocol Deviation	2 (4.9%)	1 (2.1%)	2 (4.8%)	5 (3.8%)
Cancer not related	2 (4.9%)	1 (2.1%)	0 (0.0%)	3 (2.3%)
Prohibited Concomitant treatment	1 (2.4%)	0 (0.0%)	2 (4.8%)	3 (2.3%)

A total of 267 patients completed the week 48 main protocol period at week 48. Patients could enter the extension phase on an optional basis depending only if the benefit/risk was assessed as positive by the investigator after discussion with the patient.

Table 26: Number of Patients Dropping out at Initiation of Extension Period

Study Period	Placebo (N= 133)	Masitinib 4.5 mg/kg (N=130)	Masitinib 3 mg/kg (N= 131)	Total (N=394)
Reached visit week 48	92 (69.2%)	83 (63.8%)	89 (67.9%)	264 (67.0%)
Extension Period	80 (60.2%)	73 (56.2%)	80 (61.1%)	233 (59.1%)
Dropout at visit week 48	12 (9.0%)	10 (7.7%)	9 (6.9%)	31 (7.9%)

In absolute value, 12 patients in the active control arm dropped out at the visit week 48 versus 19 patients in the combined Masitinib AB Science arms. The randomization ratio between Masitinib AB

Science and placebo control being 2:1.

Table 27: Patients' disposition by treatment-arm and status – normal progressor subpopulation-[W0 – W48]

	Placebo (N=114)	Masitinib 4.5 (N=106)	Masitinib 3 (N=110)
Patients status in main period W0-W48			
N	114	106	110
W48 reached	83 (72.8%)	73 (68.9%)	76 (69.1%)
Prematurely discontinued before W48	31 (27.2%)	33 (31.1%)	34 (30.9%)
Reason of discontinuation main part			
N	31	33	34
AE Related	1 (3.2%)	11 (33.3%)	7 (20.6%)
Non compliance	0 (0.0%)	2 (6.1%)	1 (2.9%)
Lack of Efficacy	9 (29.0%)	13 (39.4%)	15 (44.1%)
Travel	7 (22.6%)	3 (9.1%)	1 (2.9%)
Procedure	2 (6.5%)	0 (0.0%)	0 (0.0%)
Death	7 (22.6%)	2 (6.1%)	7 (20.6%)
Protocol Deviation	2 (6.5%)	1 (3.0%)	2 (5.9%)
Cancer not related	2 (6.5%)	1 (3.0%)	0 (0.0%)
Prohibited Concomitant treatment	1 (3.2%)	0 (0.0%)	1 (2.9%)

Table 28: Patients' disposition by treatment-arm and status – full study population comprising normal + fast progressors –[W0 – W48]

	Placebo (N=133)	Masitinib 4.5 (N=130)	Masitinib 3 (N=131)
Patients status in main period W0-W48			
n	133	130	131
W48 reached	92 (69.2%)	83 (63.8%)	89 (67.9%)
Prematurely discontinued before W48	41 (30.8%)	47 (36.2%)	42 (32.1%)
Reason of discontinuation main part			
N	41	47	42
AE Related	1 (2.4%)	12 (25.5%)	7 (16.7%)
Lost to Follow-up	0 (0.0%)	1 (2.1%)	0 (0.0%)
Non compliance	0 (0.0%)	3 (6.4%)	2 (4.8%)
Lack of Efficacy	15 (36.6%)	19 (40.4%)	19 (45.2%)
Travel	8 (19.5%)	4 (8.5%)	1 (2.4%)
Procedure	3 (7.3%)	0 (0.0%)	0 (0.0%)
Death	9 (22.0%)	6 (12.8%)	9 (21.4%)
Protocol Deviation	2 (4.9%)	1 (2.1%)	2 (4.8%)
Cancer not related	2 (4.9%)	1 (2.1%)	0 (0.0%)
Prohibited Concomitant treatment	1 (2.4%)	0 (0.0%)	2 (4.8%)

The largest portion of the patients discontinued the study due to lack of efficacy in Masitinib AB Science 4.5 mg/kg/day (40,4%) and Masitinib AB Science 3 mg/kg/day (45,2%) groups in both study

subpopulations and more than in placebo (36,6%) group. Discontinuation due to the death is the same in placebo and Masitinib AB Science 3 mg/kg/day groups (22% and 21,4 % respectively) and lower (12,8%) in Masitinib AB Science 4.5 mg/kg/day in the full study population comprising normal + fast progressors.

A breakdown of updated survival status according to study period and patient disposition from study AB10015 is shown below.

Table 29: Survival status according to study periods

Period (Start-End)	**Main Protocol Period** (Apr 2013–Dec 2016)		**Protocol Ext. Period** (Dec 2016–Nov 2017)		**Follow-up** (Nov 2017-June 2020)
Blinding status	Blinded		Blinded up to Apr 2017 Open label from Apr 2017		Open-label
Survival status	Alive at start	Deaths during	Alive at start	Deaths during	Alive at start
M3.0	131 (100%)	45/131 (34%)	86/131 (66%)	19/86 (22%)	67/131 (51%) Entered NPP: 30 No NPP: 37
M4.5	130 (100%)	44/130 (34%)	86/130 (66%)	16/86 (19%)	70/130 (54%) Entered NPP: 29 No NPP: 41
PBO	133 (100%)	43/133 (32%)	90/133 (68%)	12/90 (13%)	78/133 (59%) Entered NPP: 25 No NPP: 53
Total	394 (100%)	132/394 (34%)	262/394 (66%)	47/262 (18%)	215/394 (54%) Entered NPP: 84 No NPP: 129

Table 30: Disposition of populations for long-term overall survival analysis of study AB10015

COHORT	PBO (n)	M4.5 (n)	M3.0 (n)	Total (n)
Overall (mITT) population	133	130	131	394
Survival status verified less than 7 months prior to cut-off [$]	128 (96.2%)	122 (93.8%)	124 (94.7%)	374 (94.9%)
Survival status older than 7 months	5 (3.8%)	8 (6.2%)	7 (5.3%)	20 (5.1%)

[$] Survival status (also referred to as vital status) verified by investigational site within 7 months prior to cut-off (June 2020) for long-term OS analysis. OS: Overall survival.

- **Recruitment**

Between April 2013 and December 2015, a total of 394 patients underwent randomization from 34 sites in 9 countries (specifically: Spain, Argentina, Italy, Slovakia, Netherlands, Canada, Greece, Portugal, and Mexico).

- **Conduct of the study**

Protocol amendments

The protocol version 1.0 dated 03 August 2012 (version 1.0 ESP) was designed as a phase II and planned to enrol 45 patients, comparing two treatment arms (pooled Masitinib AB Science 3.0 or Masitinib AB Science 4.5 mg/kg/day + riluzole versus placebo + riluzole). The study was initiated in April 2013. There were four protocol amendments while the study remained blinded. The details of these are provide below:

- Protocol version 2.0 (first amendment, dated 02 July 2013) with successful recruitment, it was decided to transform the phase 2 directly into a phase 3, without reviewing the phase 2 data. Protocol Version 2.0 incorporated the following changes for primary analysis: defined hypothesis of difference between the two treatment groups of 3.3. points, use of repeated measure from week 4 to week 48, replacement of missing data with LOFC, the modification of the sample size change from phase 2 to phase 2/3 study with 210 patients.
- Protocol version 3.0 (second amendment, dated 21 March 2014) incorporated the comparison of three treatment-arms (Masitinib AB Science 3.0 mg/kg/day versus Masitinib AB Science 4.5 mg/kg/day versus placebo), use of repeated measures at week 24, 36 and 48, replacement of missing data with observed cases, sequence of testing Masitinib AB Science 4.5 mg/kg/day then Masitinib AB Science 3.0 mg/kg/day, new stratification factors introduced, definition of treatment failure, the planning for a futility test and an interim analysis. The sample size was further modified as a result of the changes in the study design (change from 210 patients to 300 patients).
- Protocol Version 4.0 (third amendment, dated 08 October 2014) introduced a distinction between "normal progressor" patients and "fast progressor" patients. "Normal progressors" were redefined as the primary efficacy population for primary analysis. The applicant considers that this amendment was indicated to be not data driven and was made to avoid the risk of bias inherent to "fast progressor" subpopulation. A switch from repeated measures to absolute change from baseline to week 48 was also introduced in the primary analysis, with LOCF as primary method for missing data handling at week 48. Sequence of analysis was redefined as Masitinib AB Science 4.5mg/kg/day normal progressors subpopulation then Masitinib AB Science 3.0 mg/kg/day normal progressors subpopulation then Masitinib AB Science 4.5mg/kg/day in the full study population comprising normal + fast progressors then Masitinib AB Science 3mg/kg/day in the full study population comprising normal + fast progressors. The sample size was further increased taking into consideration the change from repeated measure to LOCF method (change from 300 patients to 381 patients). Interim analyses were changed from 200 to 190 patients (to represent 50% of the target population).
- Protocol Version 5.0 (fourth amendment, dated 16 March 2015) introduced minor changes, including modification in the LOCF method.

Inspections

A total of four GCP inspections of study AB10015 were conducted, by EMA, Health Canada, ANMAT (Argentina), and Infarmed (Portugal).

The following conclusions have been made by local agencies:

Argentina

Administrative and/or legal penalty against the investigator, Sponsor or CRO, after development of the pertaining disciplinary proceedings. Official Action Indicated point 12.2, Section D, ANMAT Disposition 6677/10 for PI in his role of PI to carry out the following actions: Sign a commitment letter with the Administration for the future clinical trials to be conducted. Official Action Indicated for the Sponsor LAT Research to carry out the following actions: Sign a commitment letter with the Administration for the future clinical trials to be conducted.

Canada

No observations or corrective actions required.

Portugal

The selection of participants was made by fulfilling the inclusion criteria (although with certain shortcomings in the documentation process). There were no indications of a possible relationship between the publication of results of the interim analysis that might have put into question the concealment of the trial in this centre. Critical non-compliances were not identified.

EMA coordinated inspections:

As part of a previous marketing authorisation application based on the same pivotal trial, GCP inspections were carried-out at the request of the Committee, at the two main sites which enrolled >40% of the full study population. During the inspection critical and major findings were identified. Critical findings were related to clinical trial monitoring, inadequate clinical conduct of the trial, failing to communicate relevant protocol deviations to the Spanish Medicines Agency and suboptimal management of trial at site by the Sponsor and CRO.

Major findings were related to clinical conduct of the trial, safety reporting, investigational medicinal product, source data verification, qualification and training, production, version control and content of essential documents. It was concluded that it cannot be ensured that the data are trustworthy. The integrity of data was likely impaired, and it was considered highly likely to have an impact on the final results. During the current marketing authorisation procedure, the applicant was requested to justify the use of data from AB10015 study to substantiate the current MAA. The applicant presented the implemented corrective measures and provided updated version of the CSR for study AB10015. The corrective measures the applicant implemented on the AB10015 study were assessed and, despite some improvements, were found insufficient to ensure the trustworthiness of the data (please see also section 2.6.6 Discussion on clinical efficacy below).

- **Baseline data**

Study treatment period and extension phase

Table 31: Demographics and disease characteristics of the study patients (full study population comprising normal + fast Progressors)

	Placebo (N=133)	Masitinib 4.5 (N=130)	p-value (M 4.5 vs P))	Masitinib 3 (N=131)	p-value (M 3 vs P)
Country			0.6972 (F)		0.9875 (F)
N	133	130		131	
ARGENTINA	38 (28.6%)	40 (30.8%)		41 (31.3%)	
CANADA	4 (3.0%)	1 (0.8%)		3 (2.3%)	
GREECE	2 (1.5%)	4 (3.1%)		2 (1.5%)	
ITALY	28 (21.1%)	21 (16.2%)		26 (19.8%)	
MEXICO	1 (0.8%)	1 (0.8%)		1 (0.8%)	
NETHERLANDS	3 (2.3%)	4 (3.1%)		3 (2.3%)	
PORTUGAL	0 (0.0%)	2 (1.5%)		1 (0.8%)	
SLOVAKIA	6 (4.5%)	4 (3.1%)		3 (2.3%)	
SPAIN	51 (38.3%)	53 (40.8%)		51 (38.9%)	
Gender			0.5370 (C)		0.7794 (C)
N	133	130		131	
Male	80 (60.2%)	83 (63.8%)		81 (61.8%)	
Female	53 (39.8%)	47 (36.2%)		50 (38.2%)	
Progression ALSFRS_R before randomisation (point/month)			0.7516 (A)		0.4667 (A)
n	133	130		131	
Mean +/- SD	0.7 +/- 0.7	0.7 +/- 0.6		0.7 +/- 0.5	
Median	0.5	0.6		0.5	
Range	0.1 ; 5.0	0.0 ; 3.7		0.1 ; 2.2	
Normal progressors (Progression ALSFRS_R before randomisation<1.1)			0.3599 (C)		0.6926 (C)
n	133	130		131	
Yes	114 (85.7%)	106 (81.5%)		110 (84.0%)	
Progression ALSFRS_R before randomisation (point/month)			0.7516 (A)		0.4667 (A)
n	133	130		131	
Mean +/- SD	0.71 +/- 0.69	0.73 +/- 0.63		0.65 +/- 0.48	
Median	0.53	0.55		0.53	
Range	0.05 ; 5.00	0.03 ; 3.69		0.09 ; 2.24	
ALSFRS score at baseline			0.3773 (A)		0.3119 (A)
N	133	130		131	
Mean +/- SD	38.1 +/- 5.5	37.5 +/- 5.5		37.4 +/- 5.7	
Median	39.0	38.0		38.0	
Range	21.0 ; 47.0	23.0 ; 47.0		21.0 ; 46.0	
Age (years)					
N	133	129		131	
Mean +/- SD	55.2 +/- 10.6	55.5 +/- 10.6		55.7 +/- 10.2	
Median	56.0	55.0		57.0	
Range	27.0 ; 75.0	24.0 ; 79.0		33.0 ; 75.0	
Site of onset			0.9405 (C)		0.6634 (C)
N	133	130		131	
Other_than_bulbar	109 (82.0%)	107 (82.3%)		110 (84.0%)	
Bulbar	24 (18.0%)	23 (17.7%)		21 (16.0%)	
Region			0.9206 (C)		0.6664 (C)
N	133	130		131	
North America and West Europe	86 (64.7%)	81 (62.3%)		84 (64.1%)	
Eastern Europe	8 (6.0%)	8 (6.2%)		5 (3.8%)	
Other Countries	39 (29.3%)	41 (31.5%)		42 (32.1%)	

	Placebo (N=133)	Masitinib 4.5 (N=130)	Masitinib 3 (N=131)	Total (N=394)
ALSFRS-R Baseline				
N	133	130	131	394
Mean ± SD	38.1 ± 5.5	37.7 ± 5.5	37.4 ± 5.7	37.7 ± 5.6
Median	39.0	38.0	38.0	38.0
Range	21.0 ; 47.0	23.0 ; 47.0	21.0 ; 46.0	21.0 ; 47.0
FVC Baseline				
N	133	130	131	394
Mean ± SD	89.2 ± 18.7	87.5 ± 16.9	86.8 ± 18.7	87.8 ± 18.1
Median	88.0	85.0	87.5	87.0
Range	37.0 ; 136.0	45.0 ; 131.0	51.0 ; 149.0	37.0 ; 149.0

Table 32: Demographics and disease characteristics of the study patients (normal progressors subpopulation)

	Placebo (N=114)	Masitinib 4.5 (N=106)	p-value (M 4.5 vs P)	Masitinib 3 (N=110)	p-value (M3 vs P)
Country			0.5411 (F)		0.9730 (F)
N	114	106		110	
ARGENTINA	33 (28.9%)	36 (34.0%)		36 (32.7%)	
CANADA	4 (3.5%)	1 (0.9%)		3 (2.7%)	
GREECE	2 (1.8%)	4 (3.8%)		2 (1.8%)	
ITALY	26 (22.8%)	16 (15.1%)		22 (20.0%)	
MEXICO	1 (0.9%)	1 (0.9%)		1 (0.9%)	
NETHERLANDS	3 (2.6%)	4 (3.8%)		2 (1.8%)	
PORTUGAL	0 (0.0%)	2 (1.9%)		1 (0.9%)	
SLOVAKIA	6 (5.3%)	4 (3.8%)		3 (2.7%)	
SPAIN	39 (34.2%)	38 (35.8%)		40 (36.4%)	
Gender			0.4838 (C)		0.6316 (C)
n	114	106		110	
Male	69 (60.5%)	69 (65.1%)		70 (63.6%)	
Female	45 (39.5%)	37 (34.9%)		40 (36.4%)	
Normal progressors (Progression ALSFRS_R before randomisation<1.1)			NA		NA
Yes	114 (100.0%)	106 (100.0%)		110 (100.0%)	
Progression ALSFRS_R before randomisation (point/month)			0.9986 (A)		0.7830 (A)
n	114	106		110	
Mean +/- SD	0.49 +/- 0.24	0.49 +/- 0.25		0.48 +/- 0.25	
Median	0.48	0.50		0.45	
Range	0.05 ; 1.07	0.03 ; 1.08		0.09 ; 1.07	
ALSFRS score at baseline			0.1341 (A)		0.2557 (A)
n	114	106		110	
Mean +/- SD	39.3 +/- 4.6	38.3 +/- 5.3		38.6 +/- 5.1	
Median	39.0	39.0		40.0	
Range	27.0 ; 47.0	23.0 ; 47.0		23.0 ; 46.0	
Age (years)					
n	114	105		110	
Mean +/- SD	55.4 +/- 10.5	54.8 +/- 10.8		54.9 +/- 10.3	
Median	57.0	54.0		54.5	
Range	27.0 ; 75.0	24.0 ; 79.0		33.0 ; 75.0	
Site of onset			0.8196 (C)		0.3687 (C)
n	114	106		110	
Other_than_bulbar	90 (78.9%)	85 (80.2%)		92 (83.6%)	
Bulbar	24 (21.1%)	21 (19.8%)		18 (16.4%)	
Region			0.6885 (C)		0.6498 (C)
n	114	106		110	
North America and West Europe	72 (63.2%)	61 (57.5%)		68 (61.8%)	
Eastern Europe	8 (7.0%)	8 (7.5%)		5 (4.5%)	
Other Countries	34 (29.8%)	37 (34.9%)		37 (33.6%)	

	Placebo (N=114)	Masitinib 4.5 (N=106)	Masitinib 3 (N=110)	Total (N=330)
ALSFRS_R Baseline				
n	114	106	110	330
Mean +/- SD	39.3 +/- 4.6	38.3 +/- 5.3	38.6 +/- 5.1	38.7 +/- 5.0
Median	39.0	39.0	40.0	39.0
Range	27.0 ; 47.0	23.0 ; 47.0	23.0 ; 46.0	23.0 ; 47.0
FVC Baseline				
n	114	106	110	330
Mean +/- SD	90.3 +/- 19.0	89.0 +/- 16.5	88.1 +/- 18.9	89.2 +/- 18.1
Median	87.0	92.0	88.0	89.0
Range	37.0 ; 136.0	60.0 ; 131.0	51.0 ; 149.0	37.0 ; 149.0

Table 33: Baseline characteristics for fast and normal progressors subpopulations (ITT population)

	Normal Progressors		Fast Progressors	
	Placebo (N=113)	Masitinib 4.5 (N=105)	Placebo (N=19)	Masitinib 4.5 (N=23)
Gender				
Male	69 (61.1%)	68 (64.8%)	11 (57.9%)	13 (56.5%)
Female	44 (38.9%)	37 (35.2%)	8 (42.1%)	10 (43.5%)
Progression ALSFRS-R before randomization (point/month)				
Mean +/- SD	0.49 +/- 0.24	0.49 +/- 0.25	1.98 +/- 1.06	1.76 +/- 0.75
Median	0.48	0.49	1.47	1.42
ALSFRS-R score at baseline				
Mean +/- SD	39.3 +/- 4.6	38.2 +/- 5.4	31.0 +/- 5.3	34.4 +/- 4.5
Median	39.0	39.0	32.0	34.0
Time from first symptom to randomization(months)				
Mean +/- SD	19.5 +/- 8.5	21.6 +/- 8.8	9.8 +/- 3.7	8.4 +/- 3.2
Median	19.0	22.0	10.0	8.0
Time from diagnosis to randomization (months)				
Mean +/- SD	9.8 +/- 7.3	11.1 +/- 8.6	5.0 +/- 2.4	4.1 +/- 3.0
Median	8.0	9.1	4.7	3.0
FVC (% predicted)				
Mean +/- SD	90.2 +/- 19.0	88.9 +/- 16.5	82.0 +/- 15.1	82.7 +/- 16.1
Median	87.0	92.0	88.0	79.0
Age (years)				
Mean +/- SD	55.5 +/- 10.6	54.8 +/- 10.8	53.8 +/- 11.2	59.3 +/- 9.1
Median	57.0	54.0	49.0	61.0
Site of onset				
Spinal	89 (78.8%)	84 (80.0%)	19 (100.0%)	21 (91.3%)
Bulbar	24 (21.2%)	21 (20.0%)	0 (0.0%)	2 (8.7%)
Region				
North America and West Europe	72 (63.7%)	61 (58.1%)	19 (82.6%)	49 (77.8%)
Eastern Europe	8 (7.1%)	7 (6.7%)		
Other Countries	33 (29.2%)	37 (35.2%)	4 (17.4%)	14 (22.2%)

Delta-FS before randomization for normal progressors subpopulation was comparable between treatment arms, in terms of mean (0.49 and 0.50 points/month for placebo and Masitinib AB Science 4.5 mg/kg/day, respectively, median (0.48 and 0.49 points/month, respectively and range. In the fast progressors subpopulation, median ΔFS was comparable between the treatment groups (1.47 and 1.42 points/month for placebo and Masitinib AB Science 4.5 mg/kg/day, respectively).

Follow-up phase

Table 34: Baseline characteristics for the moderate ALS enriched cohort (≥2 on each baseline ALSFRS-R item) with ΔFS<1.1 (Primary analysis - step 1)

		PBO (N=62)	M4.5 (N=45)	*Delta**
Sex; n (%)	**Male**	39 (62.9%)	31 (68.9%)	*+6.0%*
ΔFS<1.1; n (%)	**Yes**	62 (100.0%)	45 (100.0%)	*0%*
Average ΔFS (pts/month)	**Mean ± SD**	0.41 ± 0.23	0.39 ± 0.25	*-4.9%*
	Range	0.05 ; 1.07	0.03 ; 1.01	
Average ALSFRS-R	**Mean ± SD**	42.0 ± 3.2	42.2 ± 3.1	*+0.5%*
	Range	34.0 ; 47.0	36.0 ; 47.0	
Age (years)	**Mean ± SD**	55.0 ± 10.1	55.6 ± 11.5	*+1.1%*
	Range	28.0 ; 73.0	24.0 ; 78.0	
ALS diagnosis; n (%)	**Definite**	39 (62.9%)	25 (55.6%)	*-7.3%*
	Probable	19 (30.6%)	16 (35.6%)	*+5.0%*
	Probable, lab	4 (6.5%)	4 (8.9%)	*+2.4%*
Disease duration†(months)	**Mean ± SD**	7.3 ± 5.9	8.2 ± 7.6	*+12.3%*
FVC (% predicted)	**Mean ± SD**	92.9 ± 17.9	93.8 ± 17.0	*+1.0%*
Site of onset; n (%)	**Spinal**	46 (74.2%)	35 (77.8%)	*+3.6%*
	Bulbar	16 (25.8%)	10 (22.2%)	*-3.6%*
Region; n (%)	**North America and Western Europe**	35 (56.5%)	24 (53.3%)	*-3.2%*
	Eastern Europe	4 (6.5%)	4 (8.9%)	*+2.4%*
	Other Countries	23 (37.1%)	17 (37.8%)	*+0.7%*

Table 35: Baseline characteristics for the moderate/severe ALS enriched cohort (≥1 on each baseline ALSFRS-R item) with ΔFS<1.1 (Primary analysis - step 2)

		PBO (N=104)	M4.5 (N=85)	*Delta**
Sex; n (%)	**Male**	64 (61.5%)	58 (68.2%)	*+6.7%*
ΔFS<1.1; n (%)	**Yes**	104 (100%)	85 (100%)	*0%*
Average ΔFS (pts/month)	**Mean ± SD**	0.49 ± 0.25	0.45 ± 0.25	*-8.2%*
	Range	0.05 ; 1.07	0.03 ; 1.08	
Average ALSFRS-R	**Mean ± SD**	39.8 ± 4.3	39.9 ± 4.2	*+0.3%*
	Range	29.0 ; 47.0	30.0 ; 47.0	
Age (years)	**Mean ± SD**	55.4 ± 10.8	54.3 ± 10.7	*-2.0%*
	Range	27.0 ; 75.0	24.0 ; 78.0	
ALS diagnosis; n (%)	**Definite**	61 (58.7%)	50 (58.8%)	*+0.1%*
	Probable	35 (33.7%)	29 (34.1%)	*+0.4%*
	Probable, lab	8 (7.7%)	6 (7.1%)	*-0.6%*
Disease duration†(months)	**Mean ± SD**	9.4 ± 7.1	9.8 ± 7.8	*+4.3%*
FVC (% predicted)	**Mean ± SD**	90.9 ± 18.4	91.8 ± 15.9	*+1.0%*
Site of onset; n (%)	**Spinal**	81 (77.9%)	69 (81.2%)	*3.3%*
	Bulbar	23 (22.1%)	16 (18.8%)	*-3.3%*
Region; n (%)	**North America and Western Europe**	66 (63.5%)	49 (57.6%)	*-7.9%*
	Eastern Europe	7 (6.7%)	8 (9.4%)	*+2.7%*
	Other Countries	31 (29.8%)	28 (32.9%)	*+3.1%*

Table 36: Baseline characteristics for the moderate/severe/very severe ALS cohort (regardless of baseline ALSFRS-R item) with ΔFS<1.1 (Primary analysis - step 3)

		PBO (N=114)	M4.5 (N=106)	*Delta**
Sex; n (%)	**Male**	69 (60.5%)	69 (65.1%)	*4.6%*
ΔFS<1.1; n (%)	**Yes**	114 (100.0%)	106 (100.0%)	*0%*
Average ΔFS (pts/month)	**Mean ± SD**	0.49 ± 0.24	0.49 ± 0.25	*0%*
	Range	0.05 ; 1.07	0.03 ; 1.08	
Average ALSFRS-R	**Mean ± SD**	39.3 ± 4.6	38.3 ± 5.3	*-2.5%*
	Range	27.0 ; 47.0	23.0 ; 47.0	
Age (years)	**Mean ± SD**	55.4 ± 10.5	54.8 ± 10.8	*-1.1%*
	Range	27.0 ; 75.0	24.0 ; 79.0	
ALS diagnosis; n (%)	**Definite**	66 (57.9%)	64 (60.4%)	*2.5%*
	Probable	38 (33.3%)	33 (31.1%)	*-2.2%*
	Probable, lab	10 (8.8%)	9 (8.5%)	*-0.3%*
Disease duration†(months)	**Mean ± SD**	9.6 ± 7.1	11.0 ± 8.6	*14.6%*
FVC (% predicted)	**Mean ± SD**	90.3 ± 19.0	89.0 ± 16.5	*-1.4%*
Site of onset; n (%)	**Spinal**	90 (78.9%)	85 (80.2%)	*1.3%*
	Bulbar	24 (21.1%)	21 (19.8%)	*-1.3%*
Region; n (%)	**North America and Western Europe**	72 (63.2%)	61 (57.5%)	*-5.7%*
	Eastern Europe	8 (7.0%)	8 (7.5%)	*0.5%*
	Other Countries	34 (29.8%)	37 (34.9%)	*5.1%*

- **Outcomes and estimation**

Primary endpoint: Change in ALSFRS-R

The primary analysis was to test a statistically significant difference between the treatment arms of Masitinib AB Science + riluzole and placebo + riluzole on the ALSFRS-R. In accordance with the amended fixed sequence method to control the global family-wise error rate, the first step was to demonstrate a statistically significant difference between Masitinib AB Science at a dose of 4.5 mg/kg/day or 3 mg/kg/day + riluzole versus placebo + riluzole on ALSFRS-R after a 48-week treatment period in the normal progressor subpopulation. Table 37 summarises the datasets for the primary and sensitivity analyses on ALSFRS-R absolute change from baseline to week 48.

Table 37: Number of patients analysed for the primary and sensitivity analyses on ALSFRS-R – A. Masitinib AB Science 4.5 mg/kg/day; B. Masitinib AB Science 3 mg/kg/day – Normal Progressor subpopulation (mITT)

A.

	Number of patients with LOCF or Single imputation data / Number of patient						
	Primary	**Rule 2**	**Rule 3**	**Rule 4**	**Rule 5**	**Rule 6**	**Rule 7**
Placebo + riluzole	102/113	103/113	107/113	108/113	111/113	111/113	111/113
Masitinib 4.5 mg + riluzole	99/105	99/105	102/105	102/105	104/105	104/105	104/105

B.

	Number of patients with LOCF or Single imputation data / Number of patient						
	Primary	**Rule 2**	**Rule 3**	**Rule 4**	**Rule 5**	**Rule 6**	**Rule 7**
Placebo + riluzole	102/113	103/113	107/113	108/113	111/113	111/113	111/113
Masitinib 3 mg + riluzole	106/110	106/110	107/110	107/110	110/110	110/110	110/110

Table 38: Absolute change from baseline to week 48 in ALSFRS-R - Primary efficacy analysis – A. Masitinib AB Science 4.5 mg/kg/day; B. Masitinib AB Science 3 mg/kg/day – Normal Progressor subpopulation (mITT, LOCF Rule 1/Primary)

A.

Treatment group	**N**	**LS Mean**	**Difference of means [95% confidence interval]**	**p-value**	**p-value re-randomisation test**
Placebo	102	-12.63	3.39 [0.65;6.13]	0.0157	0.0158
Masitinib 4.5 mg	99	-9.24			

B.

Treatment group	**N**	**LS Mean**	**Difference of means [95% confidence interval]**	**p-value**
Placebo	102	-11.34	2.73 [-0.18;5.65]	0.0661
Masitinib 3 mg	106	-8.61		

The applicant claimed there was a statistically significant difference in the ALSFRS-R score between Masitinib AB Science 4.5 mg.kg/d and placebo (difference of least quare means=3.39; p=0.0158) but not between Masitinib AB Science 3mg/kg/d and placebo (difference of least scare means = 2.73, p=0.0661) in the normal progressor subpopulation.

Sensitivity analyses

The applicant claimed that sensitivity analyses on the primary endpoint, based on reasons of discontinuation, were all positive for Masitinib AB Science 4.5 mg/kg/day treatment arm (p-value ranging

from 0.019 to 0.029), but not for Masitinib AB Science 3 mg/kg/day treatment arm (the treatment difference estimates ranging from 2.16 to 2.61, with p-value ranging from 0.07 to 0.13) in normal progressor subpopulation.

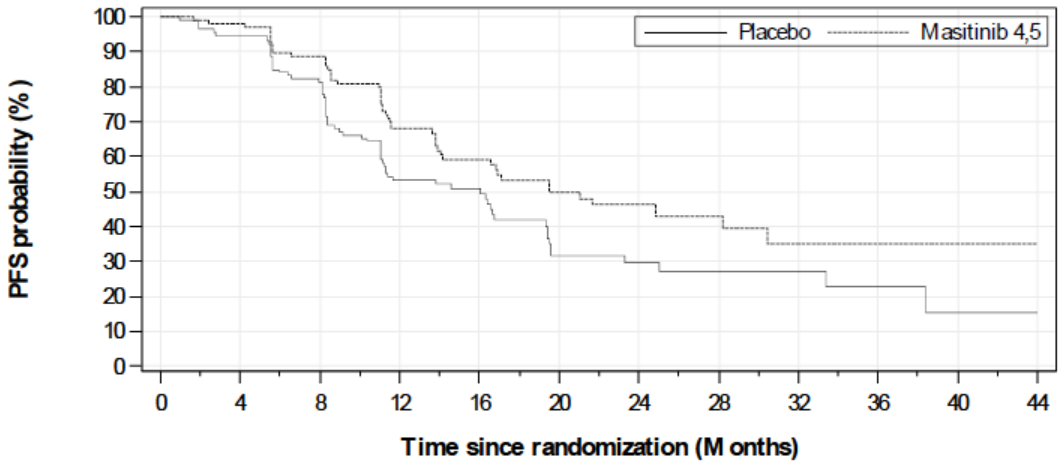
Table 39: Masitinib AB Science 4.5 mg/kg/day - Primary Analysis: Rule 2 to Rule 7

Rule	Analysis	Diff of LS means [95 % CI] (P-Value)
2	Rule 2: Same as mLOCF. In addition, imputation was also done only in case of premature discontinuation due to withdrawal of consent-related to *study procedure*.	3.28 [SE: 1.38] [0.55;6.01] **0.019**
3	Rule 3: Same as mLOCF. In addition, imputation was also done only in case of premature discontinuation due to *travel*.	3.06 [SE: 1.35] [0.39;5.73] **0.0248**
4	Rule 4: Same as mLOCF. In addition, imputation was also done only in case of premature discontinuation due to *travel* or due to withdrawal of consent related to study procedure.	2.96 [SE: 1.34] [0.31;5.62] **0.0289**
5	Rule 5: LOCF method was applied for all patients but excluded data of those patients who were non-compliant after the date of non-compliance.	2.86 [SE: 1.30] [0.29;5.43] **0.0291**
6	Cluster based imputation.	3.01 [SE: 1.26] [0.53;5.49] **0.0176**
7	Same as Rule 6 but in addition we will apply a penalty of 50% average increment in the group for those who discontinue due to ***lack of efficacy***.	3.03 [SE: 1.27] [0.52;5.54] **0.0182**

Secondary endpoint: Progression free survival (PFS)

In the normal progressor subpopulation, median PFS was increased by 4 months in the Masitinib AB Science 4.5 mg/kg/day group as compared with placebo group, and this improvement was claimed to be statistically significant (p-value=0.0159), corresponding to a 25% increase. No statistically significant difference is claimed between Masitinib AB Science 3 mg/kg/day group and placebo group. The analysis in ITT population showed consistent results with mITT population.

Figure 6: Kaplan Meier of PFS – Masitinib AB Science 4.5 mg/kg/day vs active control – Normal Progressor subpopulation (mITT, LOCF Rule 1/Primary)



Secondary endpoint: Quality of life

The applicant claimed that a statistically significant difference was observed between Masitinib AB Science 4.5 mg/kg/day (P=0.0078) group and placebo group and also between Masitinib AB Science 3

mg/kg/day (p=0.0057) group and placebo group in the ALSAQ 40 for the normal progressor subpopulation (improvement 42% - 46% and 34 respectively). The applicant claimed that the improvement was observed across all components except emotion reactions. Results were consistent in ITT population.

Table 40: ALSAQ-40 score – Masitinib AB Science 4.5 mg/kg/day A; Masitinib AB Science 3 mg/kg/day– versus placebo in the normal progressor subpopulation (mITT)

A.

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
mLOCF Rule 1				
Placebo	102	27.18	-7.76 [SE: 2.888] [-13.45;-2.06]	0.0078
Masitinib 4.5 + R	99	19.42		
mLOCF Rule 5				
Placebo	111	25.51	-6.72 [SE: 2.721] [-12.08;-1.36]	0.0143
Masitinib 4.5 + R	104	18.79		

Placebo + R = Placebo + riluzole (Active control). Masitinib 4.5 + R = Masitinib 4.5 mg/kg/day + Riluzole
Source: Statistical Table 14.2.8.1 and Table 14.2.8.7

B.

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
mLOCF Rule 1				
Placebo	102	23.65	-8.04 [SE: 2.876] [-13.71;-2.37]	0.0057
Masitinib 3.0 + R	106	15.60		

Placebo + R = Placebo + riluzole (Active control). Masitinib 3.0 + R = Masitinib 3.0 mg/kg/day + Riluzole
Source: Statistical Table 14.2.8.3 and Table 14.2.8.9

Secondary endpoint: Functional Vital Capacity (FVC)

The applicant claimed that a statistically significant difference was observed between Masitinib AB Science 4.5 mg/kg/day group and placebo group in the absolute change from baseline to week 48 in FVC for the normal progressor subpopulation (improvement between 25% and 29%). The difference observed for FVC in Masitinib AB Science 3 mg/kg/day group versus placebo group was lower. Results were consistent in ITT population.

Table 41: Absolute change from baseline to week 48 in FVC – Masitinib AB Science 4.5 mg/kg/day – versus placebo in the normal progressor subpopulation (mITT)

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
mLOCF Rule 1				
Placebo	102	-33.99	7.55 [SE: 3.439] [0.75;14.32]	0.0296
Masitinib 4.5 + R	98	-26.45		
mLOCF Rule 5				
Placebo	111	-32.02	6.40 [SE: 3.262] [-0.03;12.83]	0.0511
Masitinib 4.5 + R	103	-25.62		

Placebo + R = Placebo + riluzole (Active control). Masitinib 4.5 + R = Masitinib 4.5 mg/kg/day + Riluzole
Source: Statistical Table 14.2.13.1 and Table 14.2.13.5

Secondary endpoint: Combined assessment of function and survival (CAFS)

The applicant claims that there was a trend (p = 0.0776; difference = 14.95 and p = 0.0698; difference = 15.57) observed between Masitinib AB Science 4.5 mg/kg/day and Masitinib AB Science 3 mg/kg/day treatment groups versus placebo group for CAFS score in the normal progressor subpopulation. Results were consistent in ITT population.

Table 42: CAFS score – Masitinib AB Science 4.5 mg/kg/day A.; Masitinib AB Science 3 mg/kg/day B. – versus placebo in the normal Progressor subpopulation (mITT)

A.

Treatment group	N	Mean Score	Difference of means	p-value
Placebo	111	100.77	14.95	0.0776
Masitinib 4.5 + R	104	115.72		

Placebo + R = Placebo + riluzole (Active control). Masitinib 4.5 + R = Masitinib 4.5 mg/kg/day + Riluzole
Source: Statistical Table 14.2.12.1

B.

Treatment group	N	Mean Score	Difference of means	p-value
Placebo	111	103.25	15.57	0.0698
Masitinib 3.0 + R	110	118.82		

Placebo + R = Placebo + riluzole (Active control). Masitinib 3.0 + R = Masitinib 3.0 mg/kg/day + Riluzole
Source: Statistical Table 14.2.12.3

Secondary endpoint: Tracheostomy free survival (TFS)

No statistically significant difference (p = 0.7382) is claimed between Masitinib AB Science 4.5 mg/kg/day or Masitinib AB Science 3 mg/kg/day groups and placebo group for time to TFS in the normal progressor subpopulation.

Secondary endpoint: Overall survival (OS)

There was no benefit on OS with Masitinib AB Science 4.5 mg/kg/day or Masitinib AB Science 3 mg/kg/day as compared with placebo group in the normal progressor subpopulation.

Fast progressors

The applicant claimed that results in fast progressor subpopulation did not show statistically significant differences in primary endpoint as well as FVC and ALSAQ-40 secondary endpoints. Analyses of other secondary endpoints were not provided.

Table 43: Masitinib AB Science 4.5 mg/kg/day versus placebo in the fast progressor subpopulation (mITT)

	Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
ΔALSFRS-R mLOCF1	Active control	17	-14.18	-3.75 [-12.84;5.35]	0.4069
	Masitinib 4.5 +R	21	-17.93		
ΔALSFRS-R Imputation of all missing data by cluster (Rule 6)	Active control	19	-18.10	-3.60 [-11.09;3.90]	0.3365
	Masitinib 4.5 +R	21	-21.69		
ΔALSFRS-R Multiple imputation				-2.77 [SE:4.223]	0.5186
FVC mLOCF1	Active control	17	-42.20	-7.61 [-30.08;14.88]	0.4945
	Masitinib 4.5 +R	20	-49.81		
ALSAQ-40 mLOCF Rule 1	Active control	17	29.19	1.22 [-16.07;18.52]	0.8862
	Masitinib 4.5 +R	20	30.41		

Normal + fast progressors

The applicant claimed that results for the full study population comprising normal + fast progressors are presented only for descriptive purposes because there was no statistically significant difference between Masitinib AB Science 3 mg/kg/day and placebo group for the normal progressor subpopulation (as defined for amended fixed sequence method for statistical analysis).

The observed difference in the primary endpoint between Masitinib AB Science 4.5 mg/kg/day and placebo group was mean LS 2.09 95% CI (-0.55; 4.73), $p_{nominal}$ = 0.1202. The observed difference in the primary endpoint between Masitinib AB Science 3 mg/kg/day and placebo group was mean LS 1.80 95% CI (-0.91; 4.51), $p_{nominal}$ = 0.1918.

Table 44: Absolute change from baseline to week 48 in ALSFRS-R – Primary efficacy analysis – Masitinib AB Science 4.5 mg/kg/day versus placebo – Normal + Fast Progressor total population (mITT)

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
Active control	119	-12.97	2.09 [SE: 1.339] [-0.55;4.73]	0.1202
Masitinib 4.5 + R	120	-10.89		

Active control = placebo + riluzole. Masitinib 4.5 + R = Masitinib 4.5 mg/kg/day + Riluzole
Source: Statistical Table 14.2.1.2

Table 45: Number of patients analysed for the primary and sensitivity analyses on ALSFRS-R – Masitinib AB Science 3 mg/kg/day versus placebo Normal + Fast Progressor total population (mITT)

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
Active control	119	-12.07	1.80 [SE: 1.375] [-0.91;4.51]	0.1918
Masitinib 3.0 + R	126	-10.27		

Active control = placebo + riluzole. Masitinib 3.0 + R = Masitinib 3.0 mg/kg/day + Riluzole
Source: Statistical Table 14.2.1.4

Secondary endpoints

PFS in full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5 mg/kg/day gain versus placebo group was 3 months (17 [14; 22] versus 14 [11; 17]), $p_{nominal}$=0.1389.

ALSAQ-40 (mLOCF Rule 1) in full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5 mg the difference of means versus the placebo group was -6.59, $p_{nominal}$ =0.0148.

FVC in full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5 mg difference of means versus the placebo group was 5.63, $p_{nominal}$ =0.0914.

CAFS in full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5 mg relative benefit versus the placebo group was 11.9%, $p_{nominal}$ =0.1185.

Result for TFS in full study population comprising normal + fast progressors was not presented.

There were not enough deaths to estimate median OS during the double-blind period.

Follow-up phase

Vital status (i.e., survival status of alive or dead, including date of death, with patients still alive at the time of analysis being censored at the date of last contact) of all patients originally randomised to study AB10015 was collected from each participating investigational site. Information for 95% (374/394) of patients being verified less than 7 months prior to cut-off, while 5% (20/394) of patients had a status that dated back further than 7 months from the June 2020 cut-off.

As such, three patient groups were defined: long-term high-dose (4.5 mg/kg/day) Masitinib AB Science, long-term low-dose (3.0 mg/kg/day) Masitinib AB Science, and long-term placebo. These new long-term OS data are based on an average follow-up of 75.6 months since diagnosis and 66.1 months since randomization and included cross-over from placebo to Masitinib AB Science treatment.

The study AB10015 conducted throughout the 2013-2016 period had broad inclusion criteria in terms of disease severity at baseline. There was a study population enrichment strategy applied based on the severity of ALS at baseline used for the assessment of OS after follow-up phase of the study. The flowing cohorts were used during statistical analysis in both populations – normal progressors subpopulation and full study population comprising normal + fast progressors:

1. Moderate ALS enriched cohort (≥2 on each baseline ALSFRS-R item) with pre-randomization ΔFS<1.1 (i.e. restricted normal progressors subpopulation)
2. Moderate/severe ALS enriched cohort (≥1 on each baseline ALSFRS-R item) with pre-randomization ΔFS<1.1(i.e. restricted normal progressors subpopulation)
3. Moderate/severe/very severe ALS cohort (regardless of (any) baseline ALSFRS-R item) with pre-randomization ΔFS<1.1 (i.e. normal progressors subpopulation)
4. Moderate ALS enriched cohort (≥2 on each baseline ALSFRS-R item and any ΔFS) (i.e.. restricted full study population comprising normal and fast progressors)

5. Moderate/severe ALS enriched cohort (≥1 on each baseline ALSFRS-R item and any ΔFS) (ie. restricted full study population comprising normal and fast progressors)
6. Moderate/severe/very severe ALS cohort (regardless of (any) baseline ALSFRS-R item and any ΔFS (i.e. full study population including normal and fast progressors)

At the 14 June 2020 cut-off date (corresponding to the end of the long-term follow-up period) there has been an average follow-up from diagnosis of 75 months. A summary of long-term median OS results for various patient cohorts of the AB10015 study population is presented in the tables below.

For the moderate ALS enriched cohort of restricted normal progressors subpopulation [i.e. LT-M4.5 including ALS patients with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1 (cohort number 1)]. A median OS for Masitinib AB Science 4.5 mg/kg/day (n=45) of 69 months (95%CI [45–NE]) versus 44 months (95%CI [33-62]) for placebo (n=62). Hazard ratio analysis showed a 44% reduced risk of death (HR= 0.555 (95%CI [0.321-0.961]); $p_{nominal}$ =0.0355).

For the moderate/severe ALS enriched cohort of restricted normal progressors subpopulation [i.e. LT-M4.5 including ALS patients with ≥ 1 on each baseline ALSFRS-R item and ΔFS<1.1 (cohort number 2)] a median OS for Masitinib AB Science 4.5 mg/kg/day (n=85) of 53 months (95% CI 36; NE) versus 43 months (95% CI 31;49) for placebo (n=104). Hazard ratio analysis showed a 30% reduced risk of death (HR=0.699 95% CI (0.475-1.029) $p_{nominal}$=0.0695.

For the moderate/severe/very severe ALS enriched cohort of restricted normal progressors subpopulation [i.e. regardless of (any) baseline ALSFRS-R item) with pre-randomization ΔFS<1.10, (cohort number 3)], the between group difference in median OS was 6 months (median OS of 46 versus 40 months, respectively), hazard ratio 0.773 (95% CI [0.545–1.096])) $p_{nominal}$ =0.1489. The total included population was 106 in the Masitinib AB Science 4.5mg/kg/day and 114 in the Placebo group.

Table 46:

A Long-term overall survival analysis in enriched patient populations of study AB10015 with ΔFS ≤1.1 points/month (June 2020 cut-off; Masitinib AB Science 4.5 mg/kg/day versus placebo) - Primary analysis

COHORT	MAS (n)	PBO (n)	Deaths		Median OS [95%CI]		ΔOS (months)	P-value (Log rank)
			MAS	PBO	MAS	PBO		
Moderate ALS (≥2 each baseline ALSFRS-R item, ΔFS<1.1)	45	62	21(47%)	38 (61%)	69 [45;NE]	44 [33;62]	+25	0.0477
Moderate/severe ALS (≥1 each baseline ALSFRS-R item, ΔFS<1.1)	85	104	44 (52%)	66 (63%)	53 [36;NE]	43 [31;49]	+10	0.0395
Moderate/severe/very severe ALS (Any baseline ALSFRS-R score, ΔFS<1.1)	106	114	60 (57%)	73 (64%)	46 [33;69]	40 [30;48]	+6	0.1054

MAS: Masitinib. PBO: placebo. OS: Overall Survival. ΔOS: Between group difference in median OS (MAS minus PBO). ΔFS: ALSFRS-R progression rate calculated from disease-onset to baseline. NE: Non-estimable. P-value calculated using the Log Rank test. Source: Statistical Table 14.2.1.1d, Table 14.2.1.1e, Table 14.2.1.1f

B Long-term hazard ratio analysis in enriched patient populations of study AB10015 with ΔFS ≤1.1 points/month (June 2020 cut-off; Masitinib AB Science 4.5 mg/kg/day versus placebo) - Primary analysis

COHORT	MAS (n)	PBO (n)	Hazard Ratio	95%CI	Reduced risk of death	P-value
Moderate ALS (≥2 each baseline ALSFRS-R item, ΔFS<1.1)	45	62	0.555	0.321–0.961	44%	0.0355
Moderate/severe ALS (≥1 each baseline ALSFRS-R item, ΔFS<1.1)	85	104	0.699	0.475–1.029	30%	0.0695
Moderate/severe/very severe ALS (any baseline ALSFRS-R score, ΔFS<1.1)	106	114	0.773	0.546–1.096	23%	0.1489

MAS: Masitinib. PBO: placebo. ΔFS: ALSFRS-R progression rate calculated from disease-onset to baseline. Source: Statistical Table 14.2.1.1.2a

For the moderate ALS enriched cohort of restricted full study population comprising normal and fast progressors [i.e. ALS patients with ≥2 on each baseline ALSFRS-R item, regardless of ΔFS (cohort number 4)], a survival benefit of 15 months (median OS of 59 versus 44 months) and 43% reduced risk of death ($p_{nominal}$ =0.0407, hazard ratio 0.569 (95%CI [0.332–0.976])) was observed for patients receiving 4.5 mg/kg/day Masitinib AB Science (n=50) versus placebo (n=63).

For the moderate/severe ALS enriched cohort of restricted full study population comprising normal and fast progressors [i.e. ALS patients with ≥1 on each baseline ALSFRS-R item, regardless of ΔFS (cohort 5)], the between group difference in median OS was 7 months (median OS of 46 versus 39 months) for patients receiving 4.5 mg/kg/day Masitinib AB Science (n=97) versus placebo (n=115), corresponding to a 23% reduced risk of death ($p_{nominal}$ =0.1435, hazard ratio 0.767 (95% CI [0.538–1.094])). The between mean difference for the moderate/severe/very severe ALS enriched cohort of restricted full study population comprising normal and fast progressors [i.e. regardless of (any) baseline ALSFRS-R item) regardless of ΔFS (cohort 6)] was 1 month (median OS of 36 versus 37 months) for patients receiving Masitinib AB Science 4.5 mg/kg/day (n=130) versus placebo (n=133). This cohort corresponds to the full study population of Study AB10015 comprising normal plus fast progressor) population of study AB10015).

Table 47:

A Long-term overall survival analysis in enriched patient populations of study AB10015 regardless of baseline ΔFS (June 2020 cut-off; Masitinib AB Science 4.5 mg/kg/day versus placebo) - Sensitivity analysis

COHORT	MAS (n)	PBO (n)	Deaths		Median OS [95%CI]		ΔOS (months)	P-value (Log rank)
			MAS	PBO	MAS	PBO		
Moderate ALS (≥2 each baseline ALSFRS-R item, any ΔFS)	50	63	25 (50%)	38 (60%)	59 [44;NE]	44 [33;62]	+15	0.0477
Moderate/severe ALS (≥1 each baseline ALSFRS-R item, any ΔFS)	97	115	55 (56%)	74 (64%)	46 [30;69]	39 [30;48]	+7	0.1152
Moderate/severe/very severe ALS (regardless of baseline ALSFRS-R or ΔFS)	130	133	81 (63%)	89 (67%)	36 [28;48]	37 [28;44]	-1	0.1507

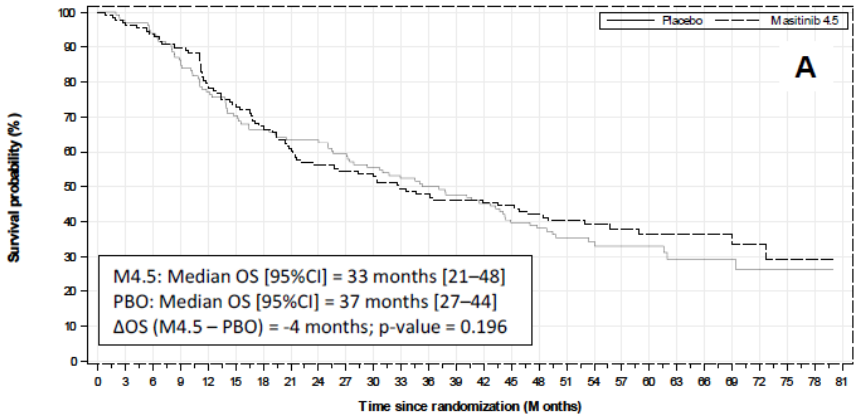
MAS: Masitinib. PBO: placebo. OS: Overall Survival. ΔOS: Between group difference in median OS (MAS minus PBO). ΔFS: ALSFRS-R progression rate calculated from disease-onset to baseline. NE: Non-estimable. P-value calculated using the Log Rank test. Source: Statistical Table 14.2.1.1a, Table 14.2.1.1b, Table 14.2.1.1c

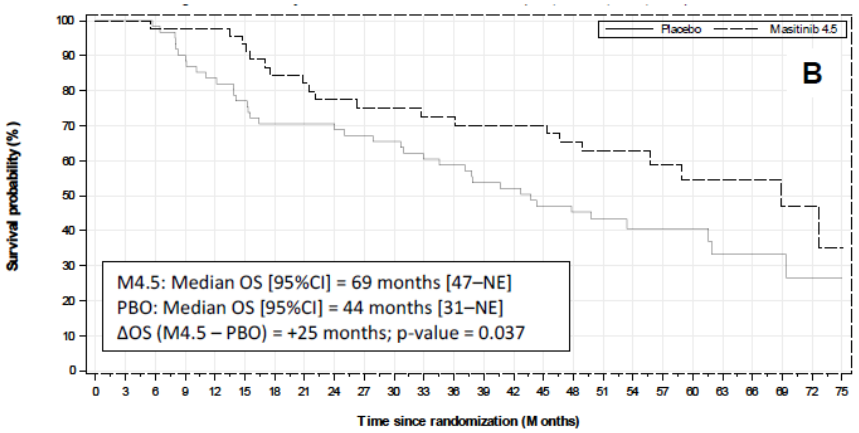
B Long-term hazard ratio analysis in enriched patient populations of study AB10015 regardless of baseline ΔFS (June 2020 cut-off; Masitinib AB science 4.5 mg/kg/day versus placebo) - Sensitivity analysis

COHORT	MAS (n)	PBO (n)	Hazard Ratio	95%CI	Reduced risk of death	P-value
Moderate ALS (≥2 each baseline ALSFRS-R item, any ΔFS)	50	63	0.569	0.332–0.976	43%	0.0407
Moderate/severe ALS (≥1 each baseline ALSFRS-R item, any ΔFS)	97	115	0.767	0.538–1.094	23%	0.1435
Moderate/severe/very severe ALS (regardless of baseline ALSFRS-R or ΔFS)	130	133	0.808	0.592–1.102	19%	0.1778

In contrast, results from the Masitinib AB Science 3 mg/kg/day arm of study AB10015 (LT-M3.0) showed that none of the enriched patient subgroups tested produced an improvement in median OS with respect to placebo.

Figure 7: Kaplan-Meier survival curves from Masitinib AB Science study AB10015 long-term survival analysis. (A) Overall Masitinib AB Science 4.5 mg/kg/day cohort versus placebo (regardless of baseline ΔFS or individual component scores). (B) Enriched Masitinib AB Science 4.5 mg/kg/day cohort versus placebo (≥2 on each baseline ALSFRS-R individual component score and post-onset ΔFS<1.1)*





* Enriched cohort (≥2 on each baseline ALSFRS-R individual component score and post-onset ΔFS<1.1), (corresponding to the population enrolled in confirmatory phase 3 AB19001). M4.5: masitinib at 4.5 mg/kg/day treatment-arm. PBO: placebo. OS: Overall Survival. ΔOS: Between group difference in median OS. ΔFS: ALSFRS-R progression rate calculated from disease-onset to baseline.

Considering the cohort most closely matched to the target population of study AB19001 (i.e. 'M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1'), ΔALSFRS-R for Masitinib AB Science 4.5 mg/kg/day was -6.36 versus -11.03 for placebo, corresponding to a significant 42% slowing in rate of decline ($P_{nominal}$=0.0176), while PFS for this cohort showed a trend improvement of 13 months in favour of Masitinib AB Science 4.5 mg/kg/day ($P_{nominal}$=0.0597).

Table 48: Summary of ΔALSFRS-R analysis at week-48, exploring impact of patient enrichment on the AB10015 study dataset

	n	ΔALSFRS-R (LSM)	ΔLSM [95%CI]	ΔEffect *	*P* value
M4.5, regardless of baseline ALSFRS-R scores or ΔFS					
PBO	119	-12.97	2.09 [-0.55; 4.73]	16%	0.1202
M4.5	120	-10.89			
M4.5 (ΔFS<1.1, any baseline ALSFRS-R scores)					
PBO	102	-12.63	3.39 [0.65; 6.13]	27%	0.0157
M4.5	99	-9.24			
M4.5 (≥2 each baseline ALSFRS-R item, any ΔFS)					
PBO	57	-11.51	4.81 [0.95; 8.67]	42%	0.0152
M4.5	48	-6.70			
M4.5 (≥2 each baseline ALSFRS-R item, ΔFS<1.1)					
PBO	56	-11.03	4.68 [0.84; 8.52]	42%	0.0176
M4.5	43	-6.36			

PBO = Placebo. M4.5 = Masitinib 4.5 mg/kg/day. Patients having a score above a given threshold value for each ALSFRS-R item (a higher threshold indicates less severe disease). ΔFS: ALSFRS-R progression rate calculated from disease-onset to baseline. ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. LSM = Least-squares means difference from baseline. ΔLSM = Between treatment-arm difference of LSM. 95% two-sided confidence intervals [95%CI]. *Treatment effect defined as slowing in the rate of decline for masitinib treatment-arm relative to placebo. Missing data was imputed via last observation carried forward (LOCF) when patients discontinued before week-48 for documented reasons of toxicity or lack of efficacy. If patient died before week-54 (included) after randomization, ALSFRS-R score was replaced by zero (0). Patients discontinuing prematurely for the following documented reasons were not imputed (lost to follow-up, non-compliance, travel, procedure, protocol deviation, any other reason not mentioned above).

Table 49: Summary of time-to-event (PFS) analysis, exploring impact of patient enrichment strategy on the AB10015 study dataset

	n	Median [95%CI] (months)	ΔMedian (M-P)	*P*-value
M4.5 (regardless of baseline ALSFRS-R scores or ΔFS)				
PBO	132	14 [11; 17]	+3	0.1389
M4.5	128	17 [14; 22]		
M4.5 (ΔFS<1.1, any baseline ALSFRS-R scores)				
PBO	113	16 [11; 19]	+4	0.0159
M4.5	105	20 [14; 30]		
M4.5 (≥2 each baseline ALSFRS-R item, any ΔFS)				
PBO	63	17 [11; 33]	+13	0.1499
M4.5	50	30 [15; NE]		
M4.5 (≥2 each baseline ALSFRS-R item, ΔFS<1.1)				
PBO	62	17 [11; 33]	+13	0.0597
M4.5	45	30 [22; NE]		

Patients having a score above a given threshold value for each ALSFRS-R item (a higher threshold indicates less severe disease). ΔFS: ALSFRS-R progression rate calculated from disease-onset to baseline. ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. Time-to-event analysis defined as time interval (months) for ALSFRS-R deterioration of 9 points from baseline or death. ΔMedian = Between treatment-arm difference of time-to-event median. 95% two-sided confidence intervals [95%CI]. PBO = Placebo. M4.5 = Masitinib 4.5 mg/kg/day. P-value calculated using the Log Rank test. NE: Non-estimable.

During the assessment, the applicant proposed new target population - ALS patients prior to any loss of function.

This enriched population is based on baseline functional score severity, i.e., baseline ALSFRS-R score>0 on each individual component of the ALSFRS-R (considering that at baseline, for each of the 12 ALSFRS-R items, patients can have a score of 4 (normal function), a score of 3 (mild impairment of function), a score of 2 (moderate impairment of function), a score of 1 (severe impairment of function) or a score of 0 (loss of function)). The ALS population prior to any loss of function, accounted for 80% (311/391) of patients from the mITT population.

The applicant claims that selection of this population is methodologically acceptable and mechanistically plausible. It exhibits a higher benefit / risk ratio, being associated with several efficacy endpoints showing a favourable direction or statistical significance for Masitinib AB Science 4.5 mg/kg/day (including the highly relevant endpoint CAFS) and is associated with an improved safety profile (patients with loss of functions tending to have more adverse events). Furthermore, it is seen as generalisable to the majority of diagnosed patients and easily applicable in clinical practice. Results for ALS patients prior to any loss of function are shown below.

Table 50: Results for ALS patients prior to any loss of function

ΔALSFRS-R mLOCF	Diff. of mean	3.27
	p-value	0.0266
ΔALSFRS-R Imputation of all missing data by cluster (Rule 6)	Diff. of mean	2.91
	p-value	0.0315
Median PFS	Gain in Median PFS	+5 months
	Median [95% CI]	20 [14; 30] vs 15 [11; 19]
	p-value log rank	0.0236
	p-value Wilcoxon	0.0183
ALSAQ-40 mLOCF Rule 1	Diff. of mean	-8.17
	p-value	0.0074
FVC	Diff. of mean	8.29
	p-value	0.0182

- **Ancillary analyses**

Validation of a population PK model for Masitinib AB Science used in patients with ALS was performed to validate a previously developed popPK model for Masitinib AB Science using internal and external techniques.

For a given patient, riluzole PK parameters was first determined at week 0 (before Masitinib AB Science /placebo intake) and week 1 visits. Up to 10 patients were planned to be enrolled in this analysis. Recruitment for the PK study could be done at any step of the study until the desired number of patients for the analysis was reached.

- **Summary of main efficacy results**

Title: A prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 2 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS)		
Study identifier	AB10015 EudraCT number: 2010-024423-24 ClinicalTrials.gov number NCT02588677	
Design	Multicentre, randomised, double-blind, placebo-controlled, parallel group, phase 2 study to compare the efficacy and safety of masitinib in combination with riluzole versus placebo in combination with riluzole in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase (OLE):	08 April 2013 - 05 December 2016 NA. November 2017 - 14 June 2020
Hypothesis	Superiority of Masitinib AB Science 4.5 mg/kg/day plus riluzole on placebo plus riluzole and Masitinib AB Science 3 mg/kg/day plus riluzole on placebo plus riluzole	
Treatments groups	Group 1: masitinib at 4.5 mg/kg/day + riluzole	Masitinib or placebo were administered orally in two daily doses.

Title: A prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 2 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS)			
Study identifier	AB10015 EudraCT number: 2010-024423-24 ClinicalTrials.gov number NCT02588677		
	Group 2: masitinib at 3 mg/kg/day + riluzole		Riluzole was prepared, handled, used and stored according to standard practices and the Summary of Product Characteristics (SPC).
	Group 3: placebo + riluzole		
Endpoints and definitions	Primary endpoint: - Absolute change from baseline to week 48 in Amyotrophic Lateral Sclerosis Functional Rating Scale	ΔALSFRS-R	Absolute change from baseline to week 48 in ALSFRS-R
	Secondary endpoint: - Progression Free Survival	PFS	Progression Free Survival, defined as a 9-point drop in ALSFRS-R score from baseline or death.
	Secondary endpoint: Overall survival	OS	Overall survival, defined as the time from randomization to the time of the documented death.
	Secondary endpoint: Quality of Life (measured by ALSAQ-40)	ALSAQ-40	Quality of life was assessed based on the absolute change from baseline to week 48 in the ALSAQ-40 score.
	Secondary endpoint: Absolute change from baseline to week 48 in FVC score	FVC	Absolute change of FVC from baseline to week 48
	Secondary endpoint: Tracheostomy-free survival	TFS	Tracheostomy-free survival defined as the time from randomization to the date of documented death or first tracheotomy.
	Secondary endpoint: CAFS on rank data	CAFS	CAFS which takes into account changes in ALSFRS-R total scores and time to death up to week 48.
Database lock	05 December 2016		

Title: A prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 2 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS)

Study identifier	AB10015 EudraCT number: 2010-024423-24 ClinicalTrials.gov number NCT02588677	
Long-Term Overall Survival Follow-up	Primary objective	Long-term OS analysis performed based on mature OS data, using the following sequential analysis in 3 steps. **Step** / **Enriched patient subpopulations analyzed** 1 — Moderate ALS — ΔFS<1.1, ≥2 each baseline ALSFRS-R item 2 — Moderate and Severe ALS — ΔFS<1.1, ≥1 each baseline ALSFRS-R item 3 — Moderate, Severe, and Very Severe ALS — ΔFS<1.1, any baseline ALSFRS-R score As a sensitivity analysis, the OS analysis was performed at the December 2016 cut-off date, corresponding to the planned blinded and prospective part of the study. As another sensitivity analysis, the criteria related to progression rate from disease-onset to baseline (ΔFS) were relaxed to include fast progressors (i.e., ΔFS≥1.1) to assess whether a significant benefit is detected in an enriched patient population.
	Secondary objectives	- to test the consistency of the treatment effect with the clinical endpoint of ΔALSFRS at week 48, ALSFRS being a surrogate endpoint of survival. - Time-to-event analysis referred to as PFS.

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Modified-Intent to treat (mITT) patients with at least one post baseline efficacy assessment who took at least one dose of study treatment (masitinib/placebo).				
Effect estimates per comparison	Treatment group Comparison groups	Normal progressors M4.5 vs Placebo	Normal progressors M3.0 vs Placebo	Full study population normal + fast progressors M4.5 vs Placebo	Full study population normal + fast progressors M3.0 vs Placebo
	Number of subject	105:113	110:113	128:132	131:132
	Primary endpoint Absolute change from baseline to week 48 in ALSFRS-R	Diff. of mean 3.39 p-value 0.0157	Diff. of mean 2.73 p-value 0.0661	Diff. of mean 2.09 p-value 0.1202	Diff. of mean 1.80 p-value 0.1918
	Secondary endpoints				

Title: A prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 2 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS)					
Study identifier	AB10015 EudraCT number: 2010-024423-24 ClinicalTrials.gov number NCT02588677				
	Median PFS Gain in Median PFS Median [95%CI]	+4 months 20[14;30] vs 16[11;19] p-value 0.0386	0 months 16[14;17] vs 16[11;19] p-value 0.1003	+3 months 17 [14;22] vs 14[11;17] p-value 0.1389	0 months 14 [12;17] Vs 14 [11;17] p-value 0.3073
	ALSAQ-40 mLOCF Rule 1	Diff. of mean -7.76 p-value 0.0078	Diff. of mean -8.04 p-value 0.0057	Diff. of mean -6.59 p-value 0.0148	Diff. of mean -7.15 p-value 0.0077
	FVC	Diff. of mean 7.55 p-value 0.0296	Diff. of mean 4.99 p-value 0.1562	Diff. of mean 5.63 p-value 0.0914	Diff. of mean 3.35 p-value 0.3220
	CAFS	Relative benefit 14.8% p-value 0.0776	Relative benefit 15.1% p-value 0.0698	Relative benefit 11.9% p-value 0.1185	Relative benefit 9.7% p-value 0.1943
	Median OS Gain in Median OS	NE p-value 0.4858	NE p-value 0.7637	-1month p-value 0.5928	NE p-value#0.5924
Database lock	14 June 2020				
	Long-term overall survival analysis				
Analysis population and time point description	Primary analysis was performed on the ITT dataset and according to the full follow-up period cut off of 14 June 2020. - Step 1 of the primary analysis was OS analysis on patients having moderate (non-severe) ALS, defined as a baseline score of at least 2 on each individual component of the ALSFRS-R (i.e., prior to any complete loss or severe impairment of functionality) and a ΔFS of less than 1.1 points/month. - Step 2 was OS analysis on patients having moderate and severe ALS, defined as a baseline score of at least 1 on each individual component of the ALSFRS-R (i.e., prior to any complete loss of functionality) and a ΔFS of less than 1.1 points/month. - Step 3 was OS analysis on the cohort of patients having moderate, severe, and very severe ALS (i.e., any baseline ALSFRS-R score) and a ΔFS of less than 1.1 points/month.				
Descriptive statistics and estimate variability	Treatment group	STEP #1 Moderate ALS	STEP #2 Moderate/severe ALS	STEP #3 Moderate/severe/very severe ALS	
	Normal progressors M4.5 vs Placebo				
	Number of subject MAS:PBO	45:62	85:104	106 :114	
	Median OS [95%CI] MAS/PBO	69[45;NE]/ 44[33;62]	53[36;NE]/ 43[31;49]	46[33;69]/ 40[30;48]	
	ΔOS (months)	+25	+10	+6	
	P-value (Log rank)	0.0477	0.0395	0.1054	
	Hazard Ratio [95%CI]	0.555 [0.321-0.961]	0.699 [0.475-1.029]	0.773 [0.546-1.096]	
	Reduced risk of death	44%	30%	23%	
	p-value	0.0355	0.0695	0.1489	
	Full study population comprising normal + fast progressors M4.5 vs Placebo				

Title: A prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 2 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS)				
Study identifier	AB10015 EudraCT number: 2010-024423-24 ClinicalTrials.gov number NCT02588677			
	Number of subject MAS:PBO	50:63	97:115	130:133
	Median OS [95%CI] MAS/PBO	59[44;NE]/ 44[33;62]	46[30;69]/ 39[30;48]	36[28;48]/ 37[28;44]
	ΔOS (months)	+15	+7	-1
	P-value (Log rank)	0.0477	0.1152	0.1507
	Hazard Ratio [95%CI]	0.569 [0.332-0.976]	0.767 [0.538-1.094]	0.808 [0.592-1.102]
	Reduced risk of death	43%	23%	19%
	p-value	0.0407	0.1435	0.1778

2.6.5.3. Clinical studies in special populations

During the assessment, results in older patients were requested as ALS incidence is highest at older ages (60-75 years). The applicant provided aged-based analysis in normal progressor mITT subpopulation for primary endpoint and secondary CAFS endpoint. No data were submitted for ITT and full study population.

The primary endpoint showed a numerical benefit for Masitinib AB Science over placebo, both in patient ≤60 (ΔALSFRS-R of 2.49 (95% CI [-0.91–5.90]) and in patients >60 (ΔALSFRS-R of 4.65 (95% CI [-0.20–9.50]). This numerical benefit in both treatment arms was observed with other analyses using alternative rules for imputation of missing data (namely rule 6, multiple imputation, and multiple imputation with jump to reference).

There was a numerical benefit on CAFS in favour of Masitinib AB Science over placebo, both in patient ≤60 (relative benefit of 9.7%) and in patients >60 (relative benefit of 24.6%).

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.6. Supportive study(ies)

N/A

2.6.6. Discussion on clinical efficacy

In this Application for a CMA, the development programme of Masitinib AB Science in ALS comprises a completed phase 2/3 study (AB10015), including long-term survival follow-up analysis. The applicant also indicated an ongoing phase 3 study (AB19001); however, no data has been submitted for this study.

The applicant initially applied for an indication as for the treatment of adult patients with ALS in combination with riluzole. During the procedure, the applicant proposed a new indication as for the treatment of adult patients with ALS in combination with riluzole *prior to any loss of function.*

Design and conduct of clinical studies

The phase 2b/3 international, multicentre, phase 2/3, randomised, double-blind, placebo-controlled study AB10015 is proposed as a single pivotal study to assess efficacy and safety of Masitinib AB Science in ALS patients. The primary objective of study AB10015 was to evaluate the efficacy of Masitinib AB Science in combination with riluzole based on the change in the ALSFRS-R from baseline to week 48. Only after an amendment while the study was already ongoing (see below further details), the primary objective of the study was changed to primarily assess the efficacy of Masitinib AB Science in combination with riluzole in the normal progressor subpopulation. Initially, the trial was planned as a phase 2 dose-finding study comparing two treatment arms.

A triggered GCP inspection (GCP/2017/001) was requested by the CHMP on the conduct of the clinical study AB10015 in the context of a previous marketing authorisation application for ALS. The triggered GCP inspection reported critical and major inspection findings affecting different aspects of the study, which impact on the reliability of the study data. Major findings were observed at qualification and training, trial master file, clinical conduct of the trial, safety reporting, investigational medicinal product, source data verification and clinical study report. The GCP inspection concluded that the data obtained at the sites inspected are not trustworthy.

It is noted that at the time of the GCP inspection, the applicant presented a series of corrective and preventive actions which have been assessed by the inspectors and were not found sufficient to recommend the use of data. In accordance with the GCP inspection report conclusion, after the evaluation of the responses submitted by the applicant, the Inspection Team considered that due to the departures from GCP observed, it cannot be ensured that the data inspected are trustworthy and are likely to have an impact on the final results. Data integrity is high likely to be impaired as several protocol deviations at eligibility, conduct and in other aspects inspected.

Given the nature of the findings, the systematic deficiencies observed (i.e. massive number of protocol deviations) and the fact that some findings such as the deficiencies during inclusion/exclusion criteria verification and subjects' follow up (critical finding 1 in the inspection report) cannot be corrected retrospectively, the proposed corrective actions presented by the applicant were not considered adequate to address all the concerns raised.

As part of this current application, the applicant claimed that the GCP findings were addressed with implementation of preventive actions across study and functions within AB Science. The applicant also claimed that for study AB10015, corrective actions were implemented wherever feasible. The measures which the applicant claims to have implemented after the inspection, have been assessed as part of the current marketing authorisation procedure and were found insufficient to address the issues raised and re-assure CHMP on the trustworthiness of the data.

During the procedure, the applicant argued that GCP findings related to ALSFRS-R were not systematic and the ALSFRS-R scores data are reliable, it is feasible to perform re-monitoring and manage retrospective/impact analysis and refers to the EMA guidelines EMA/868942/2011. In addition, during the procedure the applicant performed an impact analysis of protocol deviations and concluded that GCP

inspection findings which are likely to influence the evaluation of the primary efficacy endpoint, whether correctable or not, had no significant impact on the study's outcomes. The applicant's conclusions that the primary endpoint is not affected are not agreed by the CHMP. In addition, it should be noted that even the execution of the different analysis excluding just one or two inspected sites are often not meaningful since these do not address the uncertainty regarding the non-inspected sites (EMA/8689942/2011).

The applicant has provided justifications for the GCP aspects during the procedure including expanded written discussions after the oral explanation. The applicant provided numerous arguments on the extensive corrective actions implemented after the inspection conducted in the context of the previous marketing authorisation application and other regulatory authorities, including an impact analysis of identified protocol deviations. The applicant upholds the position that the corrective actions implemented after the GCP inspection and the applicant interpretation of the guidelines on benefit/risk evaluation demonstrates an absence of impact on the results of the AB10015 study. Following the review of the information submitted in support of this application, including the implemented corrective measures, it is considered that the issues identified cannot be resolved by performing re-monitoring and retrospective analyses at the study sites. The numerous retrospectives analyses applied by the applicant do not compensate for the deficiencies in the conduct of the study and thus the data are not considered reliable. The applicant has reiterated the relevance of the impact analysis of identified deviations during GCP inspections, however the applicant's claim that the primary endpoint is not affected is not agreed by the CHMP. From this point of view, the primary and secondary endpoint results (i.e. ALSFRS-R) of the single pivotal study are based on dataset of compromised quality and reliability. The statement of the applicant that "the CHMP's decision to base its findings solely on the inspectors' position from 2017, fails to take into consideration the entire sum of evidence now available and is not therefore consistent with guidelines on benefit-risk assessment" is not agreed with.

Therefore, despite the fact, that the applicant has provided impact analysis and arguments, the existing evidence of data quality does not assure CHMP that the AB10015 trial data is trustworthy. The applicant's provided impact analysis and arguments are not sufficient to assure CHMP that the AB10015 trial data is trustworthy. considering the conclusions of GCP inspection and the presented implemented corrective actions. The data from clinical study AB10015 cannot be relied upon. The CHMP is of the opinion that this conclusion is in line with EMA/8689942/2011 document "Points to consider on GCP inspection findings and the benefit-risk balance".

Treatment

In the pivotal trial patients were randomly allocated to one of the three following groups: group 1: Masitinib AB Science at 4.5 mg/kg/day + riluzole; group 2: Masitinib AB Science at 3 mg/kg/day + riluzole; group 3: placebo of masitinib + riluzole.

Study duration

Patients received treatment for 48 weeks. It consisted of a 48-week double-blind treatment period with an open-label extension phase. The duration of the double-blind period of 48 weeks is considered acceptable and in line with EMA/531686/2015, Corr.1. Open label extension phase was used to evaluate OS.

Population

Participants were recruited from 34 sites in 9 countries (Spain, Argentina, Slovakia, Portugal, Mexico, Italy, Greece, Netherlands, and Canada). The key inclusion criteria were definite diagnosis of familial or sporadic ALS diagnosed according to El Escorial revised criteria, disease duration no more than 36 months from the onset of symptoms, BMI above 18, stable dose of riluzole and FVC equal or more than 60 % of predicted value. El Escorial criteria have been validated pathologically and are commonly used

for diagnosing ALS. Key exclusion criteria were patients with tracheotomy and /or gastrostomy and patients with various cardiac disorders. Defined inclusion criteria, such as FVC equal of more than 60% of predicted value, BMI above 18 and exclusion criteria for participants with tracheotomy or gastrostomy excludes patients with complex disease leads to selective population that is not fully representative of the overall ALS population.

The protocol of AB10015 study underwent multiple amendments. There were four protocol amendments while the study remained blinded. One of the key amendments was transforming phase 2 study into phase 2/3 study. The initially planned AB1015 study was a 3-group phase 2 dose finding study. After the decision to upgrade the study to phase 3 confirmatory trial the endpoints have not been modified, and the sample size calculation was based on a difference of the ALSFRS-R between baseline and week 48. Such upgrade presents limitations in chosen endpoints and study population because the primary endpoint ALSFRS-R without another co-primary or key secondary measurement to assess muscle strength or overall benefit on survival would be acceptable only under a phase 2 programme. Upon transformation into the phase 3 study there were the changes in the patients' population definition: from the ITT population to mITT population.

The second key amendment is *post hoc* division of enrolled participants in two subgroups: fast and normal progressors. The division into two subpopulations was made based on the mITT population. Normal progressors were defined as the primary analysis population while the study was already ongoing. During the assessment, the applicant was requested to justify this approach. The applicant claimed that such approach reduces heterogeneity in trial population. The reasoning for reducing heterogeneity is understood but the approach with *post hoc* dichotomization while the study is ongoing is not supported. The applicant appealed to the guideline EMA/CHMP/539146/2013 (section 5.4. Assessment scenario 3) to justify the validity of the division into groups. Indeed, the section 5.4. Assessment scenario 3 presents the situation in which the clinical data presented fail to establish statistically persuasive evidence in the primary analysis population but there is interest in identifying a subgroup where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed (guideline EMA/CHMP/539146/2013). It should be noted that no further confirmatory conclusions are possible in a clinical trial where the primary null hypothesis cannot be rejected in the total ITT population. To remind: "*a statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population*". The introduction of the subpopulations as an attempt to rescue the study is acceptable by the guideline only in certain situations. The guideline states that interpretation of subgroup findings should be done with caution. Credibility of the subgroup findings, in other words, the extent to which subgroup findings can be concluded as being well substantiated and hence, relied on for decision making depends on the degree of well-founded, a priori definition, the biological plausibility for a particular finding and replication. Indeed, the guideline EMA/CHMP/539146/2013 in section 6.1 states the assessors should have "*expected to find discussion in the trial protocol of the expected degree of heterogeneity of the patient population*". However, the "*restrictions of a trial population to a sub-population of the target population should be justified, detailing whether restrictions are made due to safety concerns, anticipated lack of efficacy, or other operational considerations*" at the planning stage of the study (EMA/CHMP/539146/2013). Indeed, if the study results indicate that the treatment effect may vary according to the levels of a particular factor, subsequent investigations might need to be based on a categorisation (for a continuous factor) or collapsing categories (for an ordered categorical variable with a higher number of levels). This is because these categories should relate to criteria that might ultimately be used in product labelling or clinical decision-making ((EMA/CHMP/539146/2013). However, this possibility should be carefully considered at the planning stage, pre-specifying categories that might ultimately serve this purpose. Analyses investigating the choice of cut-off on the robustness of conclusions should also be planned as well (EMA/CHMP/539146/2013). The applicant claims that the normal progressors' subpopulation is the pre-planned primary analysis population of study AB10015. However, the applicant recognised that the

dichotomisation of patients into 'fast' and 'normal' progressors was implemented after the study start, which is not agreed. This approach can generate the questionable results, as "*post-baseline covariates may be affected by treatment received and will not usually be appropriate to define subgroups for the investigation of a treatment effect*" (EMA/CHMP/539146/2013). Moreover, if a particular factor is considered prognostic for outcome or at least some biological plausibility or external evidence such that an inconsistent response might be observed, the CHMP expected to find a discussion of subgroup of investigations conducted and their consideration.

In the opinion of the CHMP, the aforementioned criteria for subgroup analyses (guideline EMA/CHMP/539146/2013) were not met nor for the normal progressor subpopulation selected by the applicant after amendments to the protocol while the study was ongoing.

During the assessment, the applicant argued that categorisation of patients as Normal and Fast progressors was endorsed by the CHMP scientific advice (SA). This is not agreed, as the SA addressed the use of ΔFS as a potential inclusion criterion for the Phase 3 AB10019 study. The applicant insisted on that this categorisation of the population is supported in terms of clinical relevance, statistical design, and pathophysiology of ALS. Although changes in the ALSFRS-R could be considered a useful measure of disease progression in some studies. However, its use as a single indicator for convincing prediction of the progression of ALS is not acceptable, because ΔFS alone has relatively low predictive value of progression (Thakore et al, 2017) and is not stable throughout the course of disease (Requardt, 2021). For this reason, a linear assumption for the ΔFS decline (average rate of change from onset to randomization) might lead to misclassification of patients. Additionally, despite the fact that delta FS from the first symptom to time of diagnosis or during the whole disease could be reliable predictor of survival, it possesses uncertainties related to the patient's knowledge of the exact time of the first symptoms as well as the investigator knowledge of the exact time of the first symptoms' set up. The justifications for the cut-off (ΔFS 1.1) provided by the applicant during the assessment were not convincing and the applicant was repeatedly informed during the application assessment that the delta FS cut-off 1.1 points/months for the categorization of patients into normal and fast progressors is not acceptable as a single indicator of the progression.

During the extended discussion after the OE, the applicant insisted on that the cut-off 1.1 of delta FS is based on the best evidence found in the literature at the moment of study development. According to the applicant, the calculation of the cut off level 1.1 of delta FS is based on the study of Kollewe et al J. (2008). Referring to Kollewe et al (2008) the applicant has explained the calculation of cut-off of delta FS: "*the median delta FS calculated between onset and first examination was 1.0 points/month and the median delta FS calculated over the whole course of disease was 1.185 points/month, a range therefore of approximately 1.0 – 1.2 points/month. The choice of 1.1 points/month is situated at the midpoint of this range*". However, the authors highlighted in the referred publication that if the investigators fail to note exact time there will be no correct calculation for ALSFRS-R score ratio between first symptom and first examination. Additionally, the authors noted that the change of ALSFRS-R score over the whole course of disease is not useful to establish, because only the endpoint defined as death or tracheotomy allows assuming it. They concluded that ALSFRS-R score ratio within a defined period (i.e. 100 days) could solve the problem. They proposed to compute this parameter as "*difference of ALSFRS-R score between two visits divided by days between two visits*". Notably, the conclusion of the authors was that the ratio of ALSFRS-R score within 100 days is a useful parameter for clinical trials and they proposed <0.25; 0.25-0.65 and >0.65 cut-off levels of delta FS. Based on all above, it could be concluded that the applied cut-off level by the applicant seems to be chosen arbitrarily and, therefore, the quantitative choice of delta FS cut-off at 1,1 is not supported for the distinction patients into Normal and Fast progressors. The CHMP stressed again that the distinction into normal and Fast progresses are unlikely to happen in the clinical practice by simply applying a cut-off level 1.1.

The applicant states that showed benefit in ALSFRS-R and PFS and a trend towards benefit on OS and CAFS is in alignment with EMA guidance (ref.: EMA/531686/215, Corr. 1.1.). According to the applicant, many ALS studies, including pivotal studies of registered products such as tofersen (EMA approval), have used delta FS as a patients' selection criterion without providing justification that defined cut-off is stable over time. Based on this, the applicant believes that there is no precedent to reject a study based on the categorization of its population via delta FS. In response to the applicant's argument about the delta FS use in other trials, it is acknowledged that the calculation of delta FS has been used in clinical studies, however the exact cut-off of delta FS to distinct fast or normal progressors is questionable. Indeed, the numerous clinical studies operate with a variety of slope of ALSFRS-R, which could be defined as early, late, pre-randomised or run-in slope, and they range from 0.25 to 1.7. However, no exact cut-off level can be defined for the categorization of disease progression, as the higher delta FS simply indicates the higher chance or probability of the survival event (death or tracheotomy) compared with lower one. The CHMP considers that the distinction into normal and fast progresses are unlikely to happen in the clinical practice taking into account the variety of ALS phenotypes or predominated type of onset of disease and severity of disease at the baseline. As per reference to Tofersen, the applicant categorised the population using two factors the delta ALSFRS-R and type of SOD1-ALS. Results from the Tofersen clinical data suggested that two factors did not adequately discriminate the probability progression of ALSFRS-R. The data suggested that the baseline level of neurofilaments was a better prognostic factor (Tofersen EPAR). It is believed that, yet no new convincing data or arguments were presented that would alter previous assessment and CHMP conclusions about efficacy demonstration in the full study population, thus issue is not resolved.

During the assessment, the applicant proposed a newly target population including adult patients with ALS prior to any function loss. This subpopulation was also not pre-specified in the protocol, and it was only identified after the result of the OS analyses (data driven). In the opinion of the CHMP, the aforementioned criteria for subgroup analyses (guideline EMA/CHMP/539146/2013) were also not met for adults with ALS prior to any loss of function. Further, the definition of newly target population may not reflect a target population existing in the clinical practice.

Outcomes

The primary endpoint was change from baseline to week 48 in ALSFRS-Revised. Functional decline averages about 1 point per month in untreated patients (Castrillo-Viguera 2010). The ALSFRS and the revised version that includes respiratory function (ALSFRS-R) is the most widely used instrument to measure function in ALS clinical studies, therefore it is recommended to be used in the ALS clinical studies. The change in ALSFRS-R, i.e. delta FS, was accepted as a primary endpoint, however, to demonstrate the effect of Masitinib AB Science on ALS progression using the delta FS alone is not enough. It should have been supported with the muscle strength measurements. According to the guideline EMA/531686/2015, Corr.1 1, the muscle strength and function are considered the most important endpoints and should show consistency in effect. Notably, it was recommended by the SA to support this primary endpoint delta FS with muscle strength measurements.

Secondary endpoints were PFS, OS, CAFS, TFS, change from baseline in ALSAQ- 40 and change in FVC. These endpoints are considered relevant measures for ALS and are in line with EMA/531686/2015, Corr.1.

The SAP included additional composite endpoint "*Survival defined as the time from randomization to the date of documented death or first tracheotomy*" which was not presented elsewhere. The applicant was asked to clarify this definition. The applicant provided an explanation on secondary endpoint TFS defined as the time from randomization to the date of documented death or first tracheostomy. There was no significant difference (p=0.7382) observed between Masitinib AB Science (4.5 mg/kg/day) and placebo for time to TFS in the normal progressor subpopulation. The applicant states that TFS has been impacted

by three imbalances that could affect the Masitinib AB Science arms, in particular the Masitinib AB Science 4.5 mg/kg/day treatment arm. These three imbalances are i) disease duration at baseline, ii) severity at baseline, and iii) speed of deterioration at baseline.

In accordance with "Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS)" (EMA/531686/2015, Corr.1) criteria for tracheostomy and continuous assisted ventilation dependence as a study endpoint event should be carefully pre-specified and standardised since patient management varies considerably between countries and regions. Where these endpoints are used, an additional analysis using only time to death as the endpoint should also be provided to allow evaluation of the consistency of the results.

In this study criteria for tracheostomy were not carefully pre-specified and standardised. Since tracheostomy analysis can be biased due to different confounding factors, the applicant preplanned a PFS analysis, which is combining decline in ALSFRS-R score (9 points) and death. Time to event analysis, defined as median PFS was added to the final statistical analysis plan to comply with EMA guidance (EMA/531686/2015, Corr.1).

Since lack of efficacy time to tracheostomy (primary defined secondary endpoint) have not shown benefits and secondary endpoint PFS analysis, which is combining decline in ALSFRS-R score (9 points) and death, was added to the final statistical analysis plan, uncertainty about the claimed efficacy of masitinib in connection with other findings remains.

Importantly, there was no endpoint for muscle strength measurement. This is considered an important issue as muscle strength is one of the key indicators of disease progression.

Randomisation

Randomisation was performed with a minimization algorithm on progression of ALSFRS-R score (point/month), site of onset (Bulbar vs Others), ALSFRS-R score at baseline, age at baseline and region. Proposed method is acceptable. According to EMA/CHMP/295050/2013 dynamic allocation (in this case minimisation method) can be used if stratification is needed for several prognostic factors. Concern with this method relates to the fact that conventional methods may not allow for Type I error control in data analysis. This can be mitigated by using re-randomisation method, which has been used by the applicant.

Blinding

Blinding procedure is acceptable. There were no attempts to assess success of masking.

Statistical methods

Sample size was calculated in a 1:1 randomisation ratio for the comparison of each Masitinib AB Science group to the placebo group making the same hypothesis for each masitinib group.

The total sample size estimation was expanded from 45 to 381394 following the different amendments of the protocol. It was estimated that for normal progressor subpopulation 300 patients and for the full study population comprising normal + fast progressors 381 patients are required to detect a 3.3(+/-7.5) and (+/-9) point difference between groups (each of the Masitinib AB Science groups vs placebo group) in order to achieve a power of 80% with a significance level for a two-sided test of 5%.

Approach for estimating sample size is supported. The applicant considered that 3.3-point difference in ALSFRS-R score is considered clinically relevant. The applicant has provided justification for the clinical relevance of 3.3-point difference. A 3.3 ALSFRS-R point difference over a 12-month period is equivalent to a difference in slope decline of 0.275 points/month (i.e., 3.3/12). It is well-established in the literature that ALS patients demonstrate approximately a 1.0-point decline on ALSFRS-R score per month. Furthermore, a survey of past ALS clinical studies reveals that there is precedence for basing statistical

hypothesis on a treatment-effect similar to that used in study AB10015. Study AB10015 is therefore consistent with historical study design in terms of treatment-effect hypothesis.

The applicant has presented sample size considerations for some of the secondary endpoints such as CAFS and FVC, but not for PFS and OS. The applicant confirmed that OS and PFS analysis were not powered for this study.

The mITT population was used for the primary analyses. The analysis with ITT population is preferred and was also conducted by the applicant but was not initially presented in the clinical study report. The applicant has presented ITT data for Normal progressors subpopulation; however, despite request from the CHMP no ITT data are presented for overall population. Considering that results were negative in the primary population and differences between ITT and mITT populations were small it is unlikely that ITT analysis would show different results.

Absolute change from baseline to week 48 in ALSFRS-R was estimated using a ANCOVA model adjusted on following factors: treatment (Masitinib AB Science / placebo), and stratification criteria- ALS patients population, progression of ALSFRS-R score (point/month) from date of first symptom to baseline, site of onset (bulbar versus others), ALSFRS-R score at baseline, age at baseline and region. In the study protocol, the applicant planned multiple sensitivity analysis including multivariate ANCOVA analysis which accounts for non-linear relationship between variables and covariates. Primary analysis and sensitivity analysis 1- and 2- will be repeated using observed cases method (i.e., no imputation of missing data) and using multiple imputation for missing data. Primary analysis and sensitivity analysis 1-, 2-, 3-, 4- and 5- will be repeated on the ITT and PP populations. For the primary endpoint missing data were imputed via mLOCF when patients discontinued before week-48 for documented reasons of toxicity or lack of efficacy. If patient died before week-54 (included) after randomization, ALSFRS-R score was replaced by zero (0). Patients discontinuing prematurely for the following documented reasons were not imputed (lost to follow-up, non-compliance, travel, procedure, protocol deviation, any other reason not mentioned above). There were number of sensitivity analysis provided using mLOCF method.

The study had approximately 30% of missing data in each Masitinib AB Science arm despite highly selective patient population. In the clinical trial, high rates of treatment discontinuation were showed, the regulatory interest is to handle this intercurrent event with a treatment policy strategy. In particular, mainly after treatment discontinuation, high proportions of missing data were observed in each Masitinib AB Science arm despite highly selective patient population. Therefore, an adequate choice of statistical methods for handling missing data which are appropriately conservative and not biased in favour of the investigational treatment under realistic data generating mechanisms is critical for the trustworthiness of the study results.
The methods for handling missing data applied by the applicant and requested by CHMP includeD:

- a mLOCF approach that assumes that the benefit experienced until the time of missing data is also retained thereafter.
- a Copy increments from reference (CIR) method was used that assumes that the outcome develops similarly from that point onward to the placebo group.
- a J2R method was used that assumes that the benefit experienced until the point of missing data is not retained and instead the outcome would correspond to the outcome in the reference group.

In the situation of ALS, only the J2R method is considered to not potentially overestimate the missing outcome and hence lead to a biased treatment effect estimate in favour of the investigational treatment. Therefore, only the J2R approach is considered to be appropriately conservative. In order to account for missing data after treatment discontinuation, the applicant used the mLOCF method for the first and secondary endpoints. More conservative approaches were also provided such as the J2R, but only to handle missing data after discontinuations that were attributed to lack of efficacy or toxicity, whereas missing data after discontinuations for other reasons were presumably handled with a mLOCF approach.

A detailed description of the statistical methods is not available, which further increases the uncertainty about the appropriateness of this analysis approach.
Additionally, as an underlying assumption, the applicant is assuming that it can ascertain which missing case are MAR (protocol deviation / non-compliance, etc.) and which cases are MNAR (efficacy/toxicity). The applicant does not provide convincing arguments that substantiate this categorisation, hence the handling of missing data following discontinuations for different reasons with different methods is not considered adequate.

Further, the applicant has presented a tipping point analysis based on the mLOCF approach, where the assumed retained effect as compared to baseline is reduced by increasingly larger percentages.

In the clarification after the OE the applicant maintains that CHMP is inconsistent with its recommendations on acceptability of tipping point analysis above 75% and CIP with p value below 5%. The methods for handling missing data applied by the applicant and requested by CHMP include mLOCF, CIR and J2R methods. The statistical analyses applied by the applicant were assessed respectively. Moreover, the applicant is acknowledged for the providing the multiple statistical analyses requested by CHMP. Indeed, the applicant has presented a tipping point analysis based on the mLOCF approach, where the assumed retained effect as compared to baseline is reduced by increasingly larger percentages.

The applicant shows that retaining 24% of the difference to baseline still leads to p-value smaller than 5% in the corresponding analysis and argues that this should be sufficient proof of efficacy since the same threshold had been accepted in a different regulatory procedure. However, this argument does not hold since the suitable statistical method for analysis (including an assumption about a realistic and acceptable loss in efficacy in the imputation model) depends on the specific clinical context. In this situation, the analysis assuming the retainment of some effect is still considered not as adequate as the J2R approach, which assumes that patients discontinuing treatment have outcomes similar to the control group.

Overall, the applicant’s position that the mLOCF and the cluster method are the most appropriate methods to address missing data in the AB10015 trial is not acceptable. Considering the progressive nature of ALS and that, the effect of treatment will not be maintained after discontinuation of medication, the J2R method is considered the most appropriately conservative method in this setting. This analysis does not show a convincing result in favour of Masitinib AB Science.

Multiplicity across primary and secondary endpoints was handled using fixed sequence method. This is considered acceptable approach to preserve the study-wise type I error rate. However, it should be considered that fixed sequence was amended while the study was ongoing to align with the change in the primary efficacy population (from the full study population comprising normal and fast progressors to normal progressors subpopulation). Further, secondary endpoints were considered part of the hierarchical testing procedure, however. since second test for the amended primary efficacy analysis did not result in statistically significant differences, multiplicity is no longer controlled for secondary endpoints. It is also noted that testing hierarchy for secondary endpoints is defined differently in SAP and clinical study protocol.

Efficacy data and additional analyses

Population characteristics

The cut-off date for the primary analysis is 05 December 2016, which is the date the last patient completed the last visit. A total of 394 patients were randomised from 34 sites in 9 countries.

The average follow-up of patients including double-blind extension period - from randomization of the first patient (April 2013) until date of study data readout (November 2017), was 34.1 ± 10.1 months.

In the normal progressor subpopulation, 330 participants were included in the ITT population, 328 in the mITT population, 323 in PP population set, and 329 in the safety population.

In the full study population comprising Normal + Fast progressors, 394 participants were included in the ITT, 391 in the mITT, 386 in PP and 393 in safety population.

31.1 % discontinued before week 48 in Masitinib AB Science 4.5 mg group, 30.9% in Masitinib AB Science 3mg group and 27.3% in placebo group. Most frequent reasons for discontinuation were AE related and lack of efficacy. 7 people died in placebo, 2 in Masitinib AB Science 4.5 mg and 7 in masitinib 3 mg group.

Baseline characteristics of treatment arms were comparable. For main predictive indicators for progression and survival, such as ALSFRS-R at baseline, age, site of onset and lung function treatment arms were similar. Baseline data shows that normal progressor subpopulation had mean of 0.41 (placebo and Masitinib AB Science 4.5.mg) and full study population comprising norma l+ fast progressors had mean of 0.71 (placebo) and 0.73 (Masitinib AB Science 4.5 mg) point per month decline before randomization. This might suggest that the trial included rather selective population. It is also noted that baseline characteristics, including main predictive indicators for normal progressor subpopulation and full study population comprising normal + fast progressors are similar further suggesting that distinguishing two subpopulations might not be clinically relevant. The applicant was asked to present delta-FS before randomization for normal and fast progressors as well as baseline characteristics and results for fast progressor subpopulation. For normal progressors, ΔFS was comparable between treatment arms, in terms of mean (0.49 and 0.50 points/month for placebo and Masitinib AB Science 4.5 mg/kg/day, respectively, median (0.48 and 0.49 points/month, respectively and range. However, there were some differences in terms of mean (1.98 and 1.76 points/month for placebo and Masitinib AB Science 4.5 mg/kg/day, respectively), and range in the Fast progressor subpopulation, participants appear to have worse ALSFRS-R scores compared to Masitinib AB Science group, however the sample size is small and meaningful conclusions cannot be made.

Primary analysis

The primary analyses were performed in a sequential manner so that the family-wise error rate was controlled at 5% level of significance. The predefined sequence of analyses was amended while the study was ongoing after the decision to dichotomise the study population into two subpopulations and the re-definition of the normal progressors subpopulation as the primary efficacy population. The amended sequence of analyses was I [Masitinib AB Science 4.5 mg/kg/day versus Placebo "normal progressor" subpopulation], II [Masitinib AB Science 3 mg/kg/day versus Placebo "normal progressor" subpopulation], III [Masitinib AB Science 4.5 mg/kg/day versus Placebo full study population comprising "normal + fast progressors"], IV [Masitinib AB Science 3 mg/kg/day versus Placebo full study population comprising "normal + fast progressors"].

Primary analysis for ALSFRS-R endpoint in normal progressor subpopulation:

- with Masitinib AB Science 4.5 mg/kg/day dose difference of means was 3.39 CI (0.65-6.13), p-value 0.0157. Various sensitivity analysis using LOCF imputation method showed consistent results.

- with Masitinib AB Science 3 mg/kg/day dose difference of means was 2.73 (-0.18-5.65), p=0.0661.

Primary analysis for ALSFRS-R endpoint in the full study population comprising Normal + Fast progressors:

- with Masitinib AB Science 4.5 mg/kg/day dose difference of means was 2.09 (-0.55-4.73) p=0.1202

- with Masitinib AB Science 3 mg/kg/day dose difference of means was 1.8 (-0.91;4.51) p=0.1918

First, the dichotomization of normal and fast progressors subpopulations and the selection of the normal progressor subpopulation as the primary efficacy population are not agreed as explained in the above section. The full study population comprising normal and fast progressors is considered the primary population of the pivotal study. Efficacy is not demonstrated in the full population.

Further, the mLOCF is not considered a conservative analysis in ALS, where patients usually progress quickly, even the nominated normal progressors subpopulation.

Secondary analysis

It needs to be considered that even using the amended hierarchical testing, all secondary endpoints can only be considered as descriptive (i.e. below p-values are $p_{nominal}$ values) because the null hypothesis was not rejected in the second analysis of Masitinib AB Science 3mg/kg/day.

PFS: In full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5mg/kg/day gain versus placebo group was 3 months (17 [14; 22] vs 14 [11; 17]), ($p_{nominal}$ =0.1389). In normal progressor subpopulation treated with Masitinib AB Science 4.5mg/kg/day gain versus placebo group was 4 months ((20 [14; 30] versus 16 [11; 19]), ($p_{nominal}$ =0.0159).

ALSAQ-40 (mLOCF Rule 1): In the full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5mg/kg/day difference of means versus placebo group was -6.59 ($p_{nominal}$ =0.0148). In normal progressor subpopulation treated with Masitinib AB Science 4.5mg/kg/day difference of means versus placebo group was -7.76 ($p_{nominal}$ =0.0078).

FVC: In full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5mg/kg/day dose difference of means versus placebo group was 5.63, ($p_{nominal}$ =0.0914). In normal progressor subpopulation treated with Masitinib AB Science 4.5mg/kg/day difference of means versus placebo group was 7.55 ($p_{nominal}$ =0.0296).

CAFS: In full study population comprising normal + fast progressors treated with Masitinib AB Science 4.5mg/kg/day relative benefit versus placebo group was 11.9%, ($p_{nominal}$ =0.1185). In normal progressor subpopulation treated with Masitinib AB Science 4.5mg/kg/day relative benefit versus placebo group was 14.8%, ($p_{nominal}$ =0.0776).

TFS: Result for the full study population comprising normal + fast progressors was not presented. In normal progressor subpopulation treated with Masitinib AB Science 4.5mg/kg/day there was no difference observed versus placebo group.

OS: Median OS could not be estimated during the double-blind period.

Long term overall survival

A *post hoc* long-term OS analysis was performed in an enriched patient population. The enriched population was defined as 'Moderate' ALS, based on baseline functional score severity (i.e., Baseline ALSFRS-R score≥2 on each item and rate of functional and ΔFS<1.1 point per month). Considering *post hoc* nature of these analysis, they are considered only as descriptive (i.e. below p-values are $p_{nominal}$ values).

Investigational sites were contacted with a request for an update on each patient's survival status. Overall survival was defined as the time elapsed between randomization and death from any cause. Hazard ratios were calculated via the Cox proportional-hazards model using the predefined covariates. The population of moderate ALS included in the long-term survival analysis had 107 patients (45 in Masitinib AB Science 4.5 mg/kg/day and 62 in placebo arm).

Following data readout for the main protocol period of study AB10015 (database lock on 05 December 2016), open-label follow-up period starts in November 2017. This allowed those patients still receiving Masitinib AB Science to continue treatment. 23% (30/131) of patients from the Masitinib AB Science 3.0 mg/kg/day treatment arm, and 22% (29/130) of patients from the Masitinib AB Science 4.5 mg/kg/day treatment arm continued the treatment. It was also allowed for patients from the AB10015 placebo arm to begin Masitinib AB Science treatment (19% (25/133) of patients from the placebo arm switched to receive Masitinib AB Science. Upon request, the applicant has provided the information on the patients which from the AB10015 placebo arm entered the NPP (n=25) and begun Masitinib AB Science treatment (n=5). As the applicant declares these patients have been included in the long-term OS analysis and were analysed based on their initial randomization scheme in AB10015 study, i.e., the placebo group. However, long-term OS of both Masitinib AB Science treatment-arms and NPP subpopulations are compared with Masitinib AB Science -naïve PBO: *cohort from AB10015 placebo arm that were alive on 01 November 2017 and did not enter NPP.* The Moderate ALS population had mean ΔFS of 0.41 in placebo arm vs 0.39 in Masitinib AB Science arm, mean ALSFRS-R score of 42, mean age of 55.0, mean FVC 92.9 in placebo arm vs 93.8 Masitinib AB Science arm. Site of onset was bulbar for 25.8% participants in placebo and 22.2% in Masitinib AB Science group. These baseline characteristics show that included patients had relatively better survival chance compared to overall ALS population.

In moderate ALS population, including ALS patients with ≥2 on each baseline ALSFRS-R item the between group difference in median OS was 25 if population was further restricted to pre-randomization ΔFS<1.10 (moderate ALS enriched cohort of restricted normal progressors subpopulation) or 15 months if regardless of baseline ΔFS (restricted full study population comprising normal and fast progressors) corresponding to a 43-44% reduced risk of death. However, these results are for selective cohorts including 45-50 patients treated with Masitinib AB Science 4.5mg/kg/day and 62-63 patients treated with placebo. Results from this cohort cannot be generalised to overall ALS population that is targeted by proposed indication.

When analysis was conducted in population that more closely corresponds to full study population of pivotal study and hence, the overall ALS population OS was not observed. The between mean difference for the moderate/severe/very severe ALS enriched cohort of restricted full study population comprising normal and fast progressors [i.e. regardless of (any) baseline ALSFRS-R item) regardless of ΔFS] was 1 month (median OS of 36 versus 37 months) for patients receiving Masitinib AB Science 4.5 mg/kg/day (n=130) versus placebo (n=133).

The CHMP considers that the compelling evidence of efficacy on all clinically relevant endpoints including PFS and OS was not demonstrated. The long-term assessment of the available data encompassed five distinct periods. Notably, the categorization of patients into normal and fast progressions were conducted with third amendment, while the open label post study follow-up period from November 2017 until June 2020 was added as the fifth the amendment. During the open label period patients were followed for overall survival, however, the PFS and OS results generated in the open label conditions inherit potential biased information on survival events, because of impact of various factors, which occurred under unrandomised conditions (i.e. used medicines in the post pivotal study period, tracheostomy events, needs for the non-/invasive ventilation etc.). Therefore, the long-term survival data presented by the applicant is derived from a highly selected patients' population defined *post hoc* therefore, can be considered only as descriptive not confirmatory of Masitinib AB Science efficacy in the proposed indication. Further, in order to address the concern of CHMP regarding an indication for ALS treatment that excludes fast progressors, the applicant has presented a modified indication, based on up-dated efficacy and safety analyses, to the "treatment of ALS patients prior to any loss of function" (wherein loss of function is defined as a score of zero on any item of the ALSFRS-R). However, the strategies to *post hoc* identify new target populations ("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version

of section 4.1 of the SmPC) are considered as data driven decisions and are, therefore, not acceptable. In the response, the applicant has reiterated previously assessed data and justifications. The *post hoc* subgroup analysis may be performed at the initiative of the applicant according to the guidelines EMA/CHMP/539146/2013. However, the guideline Scenario 2 criteria "*Replication of subgroup findings from other relevant trials or if not available the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally strong*" is considered not fulfilled, as the effect observed in the subgroup is not replicated across trials by the time of opinion.

Overall, the efficacy is not considered demonstrated for proposed indication in the full study population of patients. As discussed above, the full study population (normal + fast progressors) is regarded as primary population and statistically significant difference was not demonstrated for primary endpoint in this population. Furthermore, no benefit was shown with secondary endpoints, including highly relevant endpoints such as CAFS or TFS and since not all the endpoints are pointing in a favourable direction for Masitinib AB Science or are statistically significant, the study is considered failed. The data from the open label follow-up period do not show meaningful OS gain in ALS population corresponding to proposed indication.

Additional efficacy data needed in the context of a conditional MA

The applicant applied for conditional marketing authorisation.

As per the requested CMA, the applicant initially presented study AB19001 as proposed specific obligation that would provide comprehensive evidence on efficacy and safety of Masitinib AB Science post approval. Study AB19001 is a multicentre, randomised, double-blind, placebo-controlled, parallel groups, phase 3 study to evaluate the efficacy and safety of Masitinib AB Science as add-on therapy in ALS patients treated with Riluzole. Patients will be randomised (1:1:1) to receive Masitinib AB Science 6 mg/kg/day, Masitinib AB Science 4.5mg/kg/day or matching placebo. The primary endpoint is the absolute change in ALSFRS-R from baseline to week 48 week. In this study, the secondary endpoints include measures of muscle strength and survival. As per the study population, the applicant still proposes categorization of the full study population into three subpopulations of progressors based on the change in ALSFRS-R score from onset to screening and from screening to baseline. More importantly, the applicant also establishes that the primary efficacy population will be the one comprising patients with an ALSFRS-R total score progression between onset of the disease and screening of > 0.3 and <1.1 point/month and an ALSFRS-R total score decrease of ≥ 1 point between screening and baseline. All aforementioned considerations on the categorization of the study population and the selection of a restricted subpopulation of the full study population as the primary efficacy population are applicable here. It is considered that these study design features could lead to a study population that is not representative of the target indication.

During the procedure, the applicant stated that the enrolment in study AB19001 has been slow due to the restrictive design features of that study (i.e. long 3 months run-in period, with no control of FVC at baseline / Moderate ALS only / approved treatment in the USA - Edaravone, Relyvrio – not allowed / blinded extension at week 48). Consequently, the applicant proposed to conduct a new confirmatory study post approval - AB23005 study- and presented the AB19001 study as an exploratory study.

Study AB23005 is a multicentre, randomised, double-blind, placebo-controlled, parallel groups, phase 3 Trial to evaluate the efficacy and safety of masitinib as add-on therapy in ALS patients treated with standard of care. Patients will be randomised (1:1) to receive Masitinib AB Science 4.5 mg/kg/day or matching placebo and Masitinib AB Science 6 mg/kg/day will not be pursued further in the study AB23005. The primary endpoint is the absolute change in ALSFRS-R from baseline to week 48. In this study, the secondary endpoints include measurements of muscle strength, progression free survival and overall survival. According to the synopsis of the study provided during the procedure, the primary efficacy population will be the ITT (all randomised full study population). The applicant specifies two

measures of ALSFRS-R progression rate (point/month) will be evaluated at screening to categorise ALS patient as slow, moderate, or fast progressor. As per the inclusion criteria, only patients with a ALSFRS-R progression rate between > 0.3 and <1.1 point/month as measured between onset of the disease and screening AND as measured by any available ALSFRS-R assessment during the period ranging from 7 months to 2 months prior to screening and screening, reassessed and documented by certified rater performing ALSFRS-R assessment from screening visit onward will be enrolled (synopsis of AB23005 protocol). Further restriction is included as per the baseline ALSFRS-R scores as a total score of at least 15 points of ALSFRS-R at baseline and screening [at least 3 in item3; at least 2 in item12; at least 1 in each of the other items] is also requested as inclusion criterion. All aforementioned considerations on using delta FS to select study population are also applicable here. While no further categorization is proposed to be done after enrolment (i.e. primary efficacy population is full study population), it is considered that the mentioned inclusion criteria could lead to the inclusion of a restricted ALS population. Moreover, it is considered that a duration of the study AB23005 (48 weeks) might not be long enough to generate sufficient data on survival events, which are necessary to support the primary endpoint and considering that the positive data on survival or survival equivalent are expected.

- Besides to the above considerations on the study design features and the potential impact on the ability of Study AB23005 to provide comprehensive evidence, the CHMP was concerned about the feasibility to properly conduct that study if Masitinib AB Science is authorised in the EU. It needs to be bear in mind that ALS is a fatal condition for which the only therapeutic options in the EU are symptomatic treatment and riluzole for all ALS patients except those with SOD1-ALS. Hence, the CHMP is concerned that the authorisation of Masitinib AB Science will impact the recruitment and the conduction of the AB23005 study in the EU sites as ALS patients will likely start (i.e. impact on recruitment) or shift (i.e. impact on conduction) to the commercial Masitinib AB Science when available. The new confirmatory AB23005 study is expected to enrol 408 patients. The applicant presented a feasibility analysis and concluded that a total of 855 patients could be enrolled over a 12-month period including 583 patients in non-EU countries and US. The applicant claimed that Study AB23005 can be completed within 2.5 years with involvement of site from USA and other non-EU countries or within 3 years with involvement of site only from other non-EU countries. These figures assume the study starts in Q2 2024. Thus, the applicant position is that confirmatory study AB23005 is feasible outside of the EU and further facilitated since Relyvrio is withdrawn from market in USA and Canada. However, considering the numerous changes undertaken in the protocol of the pivotal study during its execution as well as the slow enrolment in the study AB19001, which became an exploratory study later on , the applicant capability of properly conduct this study is still unclear, despite the applicant’s declared commitment.

In view of the above, high uncertainties remain with regard to the possibility to provide comprehensive clinical data, should a CMA have been granted.

2.6.7. Conclusions on the clinical efficacy

The data from the pivotal clinical study AB10015 cannot be relied upon. Despite the applicant’s arguments, and the implementation of corrective measures, the deficiencies identified during previous GCP inspection cannot be resolved by performing re-monitoring and retrospective analyses at the study sites and cannot be corrected retrospectively. Beside the data not being reliable, the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS, because a statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population; the approach to categorise the population into normal and fast progressors is not supported; considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data including statistical assumptions on missingness and the definition

of intercurrent events in J2R strategy are not considered acceptable and the strategies to *post hoc* identify new target populations (M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1 for analyses of survival and ALS patients prior to any loss of function) as proposed in the latest version of 4.1 of the SmPC) are considered as data driven decisions and are, therefore, not acceptable. Therefore, the CHMP considers that the efficacy of Masitinib AB Science in the claimed indication has not been demonstrated.

2.6.8. Clinical safety

Safety data are derived from a phase 2/3 placebo-controlled study (AB10015) in patients with ALS. The total number of subjects for safety analysis in this study is 393 patients. Exposure duration for ALS patients were 48 weeks with possible extension; exposure duration for non-oncology studies ranged from 8 to 48 weeks. In ALS studies Masitinib AB Science was used as add-on therapy to riluzole compared to riluzole. ALS patients were exposed to either Masitinib AB Science 3 mg/kg/day or Masitinib AB Science 4.5 mg/kg/day doses. In previous non-ALS studies patients were exposed also to higher dose of Masitinib AB Science 6 mg/kg/day.

It seems that long-term data at from patients enrolled in the extended phase following to week 48 are available for 153 Masitinib AB Science exposed patients with 73 patients exposed to higher intended dose 4.5 mg/kg/day.

Safety data are also obtained from phase 2 and 3 clinical studies for non-oncological indications. Those are 19 completed or stopped studies in patients with mastocytosis (AB04010, AB06013), asthma (AB04026, AB07015, AB14001), rheumatoid arthritis (AB04012, AB06010, AB06012), Crohn's disease (AB04014, AB11003), active ankylosing spondylitis (AB04013), chronic psoriasis (AB04029), multiple sclerosis (AB04011, AB04018, AB07002), Alzheimer's disease (AB04024, AB09004), supranuclear palsy (AB13004), pulmonary arterial hypertension associated with scleroderma (AB05038).

Safety data are presented further in following groupings:

1 - ALS study population (study AB10015)

2 - Non-oncology Studies (19 studies for non-oncological indications mentioned above)

In the safety assessment the main focus has mainly been put on the safety profile of Masitinib AB Science administered in ALS patients and data from previous studies were presented as supportive.

Additionally, conclusions on safety in 114 healthy subjects were provided as well from 6 clinical pharmacology studies: AB03001, AB03003, AB04015, AB05031, AB14004, AB17001. Safety results of phase 1/2 study AB10009 were not included into safety analysis as all 5 treated subjects were patients with Alzheimer's disease.

2.6.8.1. Patient exposure

In Masitinib AB Science clinical development programme 2,184 patients have received at least one dose of Masitinib AB Science, and 1,137 patients have received at least one dose of placebo. The accrued "time-on-treatment" is 2663 patient-years of exposure for Masitinib AB Science and 1516 patient-years of exposure for placebo.

All 114 healthy subjects in phase 1 studies received at least one dose of Masitinib AB Science with dosing regimens ranging from 3.0 mg/kg/day to 11.5 mg/kg/day for up to 15 days.

In 2/3 phase study AB10015 ALS patients received doses as described further: 131 patients received Masitinib AB Science at 3.0 mg/kg/day+ riluzole, 129 patients received Masitinib AB Science at 4.5 mg/kg/day + riluzole, and 133 patients received active control (placebo+ riluzole). The duration of this

study (main protocol period) was 48 weeks. After completion of the 48-week treatment period, eligible patients were allowed to continue in the extension period.

Of 19 non-oncology studies (AB10015 study included), a total of 2184 patients received Masitinib AB Science at dose 3.0, 4.5 or 6.0 mg/kg/day (287 patients at a dose of 3.0 mg/kg/day and 590 patients at a dose of 4.5 mg/kg/day and 1307 patients received Masitinib AB Science 6.0 mg/kg/day [Flat + titration]) and a total of 1137 patients received placebo (+active comparator). The duration of these studies ranged from 8 to 48 weeks.

Table 51: Extent of exposure in non-oncology studies by indication and treatment groups

Statistics	M3	M4.5	M6.0T	M6.0F	All	Placebo*	Blinded	Total
Patients on Treatment	**287**	**590**	**728**	**579**	**2184**	**1137**	**119**	**3440**
Neurodegenerative Studies	191	513	421	69	1194	662	9	1865
Chronic Inflammatory Studies	96	77	307	510	990	475	24	1489
Infectious Studies	0	0	0	0	0	0	86	86
Time on Treatment (years)	**322**	**772**	**906**	**663**	**2663**	**1516**	**19**	**4198**
Neurodegenerative Studies	246	715	521	61	1543	966	3	2512
Chronic Inflammatory Studies	76	57	385	602	1120	550	13	1684
Infectious Studies	0	0	0	0	0	0	2	2

Source: Table 1.1.1 Number of Randomised Patients and Patient-Years of Exposure by Indication Category (Safety Population)" dated 15MAR2022; Patient time exposure figures have been rounded. Abbreviations: M 3= 3.0 mg/kg/day masitinib, M 4.5= 4.5 mg/kg/day masitinib, M 6.0T = 6.0 mg/kg/day masitinib with Dose titration, M 6.0F=6.0 mg/kg/day masitinib Flat Dose, M-All=Masitinib all doses Note: Placebo*= 75 Active control (i.e., Methotrexate) patients added to placebo from study AB06012.

Patient population at each respective Masitinib AB Science dose:

- At a Masitinib AB Science dose of 3.0 mg/kg/day: 131 patients from ALS study and 156 patients from controlled unblinded studies.
- At a Masitinib AB Science dose of 4.5 mg/kg/day: 129 patients from ALS study and 461 patients from controlled unblinded studies.
- At a Masitinib AB Science dose of 3.0 and/or 4.5 mg/kg/day: 260 ALS patients, 617 patients from other non-oncology studies

In total, 3340 patients (including placebo/active control/blinded) were included in this safety analysis.

Table 52: Treatment duration in ALS study – main protocol period

	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
Time on Treatment (weeks)			
n	133	131	129
Median	48.0	47.9	47.9
Range	1.0; 56.6	3.1; 55.7	1.3; 52.9

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.

Table 53: Treatment Duration in ALS study – extension period

Time on Treatment (weeks)	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)
n	80	80	73
Median	15.4	25.3	25.0
Range	0.1; 142.6	1.7; 139.0	0.1; 139.6

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.

Table 54: Dose and duration of exposure to Masitinib AB Science, planned dose – ALS study, main protocol period

Number of patients exposed (months)		All	>6 months	>12 months
ALS Study	M 3.0 + R	131	100	73
	M 4.5 + R	129	99	70

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. *Blinded estimates. Source: Statistical

Table 55: Dose and duration of exposure to masitinib, the last daily dose – ALS study, extension period

Number of patients exposed for ≥12 months	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
All	-	73	70
>12 months	-	73	70
≥24 months	-	14	17
≥36 months	-	2	3

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Source:

Table 56: Dose and duration of exposure to masitinib, planned dose – non-oncology studies

		All	>6M	>12M
Non-Controlled studies	Masitinib 3.0	9	4	2
Controlled studies	Masitinib 3.0	147	66	37
Controlled studies	Masitinib 4.5	461	261	207

Table 57: Demographics of Patients - ALS study (Safety population)

Number of patients	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=130)
Sex			
Female	53 (39.8%)	50 (38.2%)	47 (36.4%)
Male	80 (60.2%)	81 (61.8%)	82 (63.6%)
Age			
≤65	110 (82.7%)	105 (80.2%)	105 (81.4%)
>65	23 (17.3%)	26 (19.8%)	24 (18.6%)
Region			
Eastern Europe	8 (6.0%)	5 (3.8%)	7 (5.4%)
North America and West Europe	86 (64.7%)	83 (63.4%)	79 (61.2%)
Other	39 (29.3%)	43 (32.8%)	43 (33.3%)

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.

Table 58: Demographics of Patients - All Non-oncology Studies (Safety population)

Tim	Masitinib		
	3.0 N=156	4.5 N=461	All N=1924
Number of patients			
Sex			
Female	120(76.9%)	283(61.4%)	1237(64.3%)
Male	36(23.1%)	178(38.6%)	687(35.7%)
Age			
18-65	93(59.6%)	298(64.6%)	1398(72.7%)
> 65	63(40.4%)	163(35.4%)	526(27.3%)
Ethnic or Racial Origin			
Caucasian, White or North African	105(67.3%)	422(91.5%)	1430(74.3%)
American Indian or Alaska Native	1(0.6%)	0	23(1.2%)
Asian	21(13.5%)	21(4.6%)	146(7.6%)
Black or African American	0	1(0.2%)	12(0.6%)
Other	1(0.6%)	4(0.9%)	20(1.0%)
Unknown	28(17.9%)	13(2.8%)	293(15.2%)

2.6.8.2. Adverse events

The treatment emergent adverse events are referred to as AEs. The AEs reported during the administration of study treatment or up to 28 days after the last dose of study treatment are listed below.

Adverse events in study AB10015

During 48 weeks of treatment, at least 1 AE was reported by 83.7% of patients: 104 patients (78.2%) in the active control arm, 111 (84.7%) in the 3.0 mg/kg Masitinib AB Science arm, and 114 (88.4%) in the 4.5 mg/kg/day Masitinib AB Science arm.

Table 59: Summary of AEs over time - Study AB10015 (Main protocol period and protocol extension period)

Number (%) of patients with at least one	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)
	W0-W48			Extension		
AE	104 (78.2%)	111 (84.7%)	114 (88.4%)	39 (48.8%)	45 (56.3%)	46 (63.0%)
Fatal SAE	12 (9.0%)	11 (8.4%)	10 (7.8%)	7 (8.8%)	13 (16.3%)	14 (19.2%)
Non-fatal SAE	24 (18.0%)	30 (22.9%)	40 (31.0%)	8 (10.0%)	12 (15.0%)	14 (19.2%)
Severe AE	26 (19.5%)	28 (21.4%)	39 (30.2%)	11 (13.8%)	19 (23.8%)	22 (30.1%)
AE leading to study treatment permanent discontinuation (excluding deaths)	11 (8.3%)	20 (15.3%)	21 (16.3%)	2 (2.5%)	1 (1.3%)	5 (6.8%)
AE leading to study treatment dose reduction	3 (2.3%)	3 (2.3%)	4 (3.1%)	0 (0.0%)	0 (0.0%)	2 (2.7%)

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

More frequently reported AEs in one of the Masitinib AB Science arms vs placebo arm were maculo-papular rash, nausea, peripheral oedema, iron deficiency anaemia, respiratory failure, and dyspnoea. Majority of them were mild to moderate in intensity and their occurrence and severity appeared to be dose related.

The most common AEs leading to dose modification or discontinuation in Masitinib AB Science were dysphagia, weight decreased, maculopapular rash, and diarrhoea.

The most frequently reported Serious AEs (SAEs) in patients receiving masitinib mesilate categorised under the MedDRA SOC was gastrointestinal disorders, then Respiratory, Thoracic and Mediastinal Disorders, Infections and Infestations, Injury Poisoning and Procedural Complications, and Investigations. Other MedDRA SOCs involved less than 5% of the remaining reported events.

Table 60: Frequent AEs (PT≥5%) in Study AB10015 - ALL

	P + R (N=133)		M 3.0 + R (N=131)		M 4.5 + R (N=129)	
Causality	All					
Severity	All	Severe	All	Severe	All	Severe
All	**104 (78.2)**	**26 (19.5)**	**111 (84.7)**	**28 (21.4)**	**114 (88.4)**	**39 (30.2)**
Blood and Lymphatic System Disorders	**2 (1.5)**	**0 (0.0)**	**11 (8.4)**	**3 (2.3)**	**19 (14.7)**	**2 (1.6)**
Iron Deficiency Anaemia	1 (0.8)		3 (2.3)	1 (0.8)	9 (7.0)	
Gastrointestinal Disorders	**33 (24.8)**	**4 (3.0)**	**48 (36.6)**	**4 (3.1)**	**61 (47.3)**	**7 (5.4)**
Dysphagia	14 (10.5)	3 (2.3)	18 (13.7)	4 (3.1)	17 (13.2)	6 (4.7)
Nausea	6 (4.5)		9 (6.9)		16 (12.4)	
Diarrhoea	5 (3.8)		11 (8.4)		10 (7.8)	
Abdominal Pain Upper	3 (2.3)		4 (3.1)		9 (7.0)	
Dyspepsia	3 (2.3)		3 (2.3)		9 (7.0)	
General Disorders and Administration Site Conditions	**9 (6.8)**	**1 (0.8)**	**12 (9.2)**	**0 (0.0)**	**20 (15.5)**	**0 (0.0)**
Oedema Peripheral	1 (0.8)		7 (5.3)		9 (7.0)	
Infections and Infestations	**28 (21.1)**	**3 (2.3)**	**33 (25.2)**	**2 (1.5)**	**45 (34.9)**	**1 (0.8)**
Viral Upper Respiratory Tract Infection	6 (4.5)		9 (6.9)		7 (5.4)	
Injury, Poisoning and Procedural Complications	**15 (11.3)**	**0 (0.0)**	**13 (9.9)**	**2 (1.5)**	**21 (16.3)**	**4 (3.1)**
Fall	9 (6.8)		9 (6.9)	1 (0.8)	13 (10.1)	1 (0.8)
Investigations	**34 (25.6)**	**5 (3.8)**	**30 (22.9)**	**6 (4.6)**	**38 (29.5)**	**6 (4.7)**
Weight Decreased	12 (9.0)	2 (1.5)	14 (10.7)	1 (0.8)	12 (9.3)	
Nervous System Disorders	**13 (9.8)**	**1 (0.8)**	**18 (13.7)**	**4 (3.1)**	**24 (18.6)**	**4 (3.1)**
Headache	8 (6.0)		6 (4.6)		9 (7.0)	
Psychiatric Disorders	**18 (13.5)**	**0 (0.0)**	**22 (16.8)**	**1 (0.8)**	**22 (17.1)**	**0 (0.0)**
Depression	9 (6.8)		12 (9.2)		11 (8.5)	
Insomnia	6 (4.5)		9 (6.9)		5 (3.9)	
Anxiety	1 (0.8)		5 (3.8)	1 (0.8)	7 (5.4)	
Respiratory, Thoracic and Mediastinal Disorders	**16 (12.0)**	**8 (6.0)**	**19 (14.5)**	**12 (9.2)**	**35 (27.1)**	**13 (10.1)**
Respiratory Failure	6 (4.5)	5 (3.8)	8 (6.1)	7 (5.3)	13 (10.1)	9 (7.0)
Dyspnoea	1 (0.8)		3 (2.3)		8 (6.2)	2 (1.6)
Skin and Subcutaneous Tissue Disorders	**16 (12.0)**	**0 (0.0)**	**27 (20.6)**	**1 (0.8)**	**39 (30.2)**	**2 (1.6)**
Rash Maculo-Papular	1 (0.8)		6 (4.6)		11 (8.5)	1 (0.8)
Rash	4 (3.0)		2 (1.5)		10 (7.8)	

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.

Table 61: Frequent AEs (PT≥5%) in Study AB10015 - RELATED

	P + R (N=133)		M 3.0 + R (N=131)		M 4.5 + R (N=129)	
Causality	Related					
Severity	All	Severe	All	Severe	All	Severe
All	**36 (27.1)**	**1 (0.8)**	**58 (44.3)**	**1 (0.8)**	**78 (60.5)**	**7 (5.4)**
Blood and Lymphatic System Disorders	**2 (1.5)**	**0 (0.0)**	**4 (3.1)**	**0 (0.0)**	**13 (10.1)**	**2 (1.6)**
Iron Deficiency Anaemia	1 (0.8)		0 (0.0)		6 (4.7)	
Gastrointestinal Disorders	**10 (7.5)**	**0 (0.0)**	**25 (19.1)**	**0 (0.0)**	**33 (25.6)**	**0 (0.0)**
Dysphagia	0 (0.0)		1 (0.8)			
Nausea	3 (2.3)		7 (5.3)		11 (8.5)	
Diarrhoea	3 (2.3)		8 (6.1)		6 (4.7)	
Abdominal Pain Upper	1 (0.8)		3 (2.3)		4 (3.1)	
Dyspepsia	2 (1.5)		1 (0.8)		6 (4.7)	
General Disorders and Administration Site Conditions	**0 (0.0)**	**0 (0.0)**	**6 (4.6)**	**0 (0.0)**	**9 (7.0)**	**0 (0.0)**
Oedema Peripheral			4 (3.1)		6 (4.7)	
Infections and Infestations	**0 (0.0)**	**0 (0.0)**	**5 (3.8)**	**0 (0.0)**	**8 (6.2)**	**0 (0.0)**
Viral Upper Respiratory Tract Infection						
Injury, Poisoning and Procedural Complications	**1 (0.8)**	**0 (0.0)**	**2 (1.5)**	**0 (0.0)**	**2 (1.6)**	**0 (0.0)**
Fall			1 (0.8)		1 (0.8)	
Investigations	**5 (3.8)**	**1 (0.8)**	**4 (3.1)**	**0 (0.0)**	**8 (6.2)**	**2 (1.6)**
Weight Decreased						
Nervous System Disorders	**1 (0.8)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**	**3 (2.3)**	**0 (0.0)**
Headache	1 (0.8)				2 (1.6)	
Psychiatric Disorders	**2 (1.5)**	**0 (0.0)**	**3 (2.3)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**
Depression	1 (0.8)		1 (0.8)		1 (0.8)	
Insomnia						
Anxiety	1 (0.8)		2 (1.5)			
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.8)**	**0 (0.0)**	**1 (0.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Respiratory Failure						
Dyspnoea						
Skin and Subcutaneous Tissue Disorders	**12 (9.0)**	**0 (0.0)**	**23 (17.6)**	**1 (0.8)**	**33 (25.6)**	**2 (1.6)**
Rash Maculo-Papular	1 (0.8)		5 (3.8)		11 (8.5)	1 (0.8)
Rash	4 (3.0)		2 (1.5)		6 (4.7)	

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.

Adverse events in all non-oncology patients

Overall, 89% of patients reported at least one AE during neurodegenerative and chronic inflammatory studies. According to Applicant, the most frequently reported AEs were consistent with events related to the diseases under study and with the known safety profile of Masitinib AB Science.

The most common AEs included general gastrointestinal symptoms - decreased appetite, nausea, vomiting, abdominal pain and diarrhoea. They were experienced by up to 70% of patients in clinical studies. Up to 60% of patients experienced uncomplicated cutaneous reactions, such as maculopapular erythema with or without pruritus. Up to 30% of patients reported constitutional symptoms, i.e. mild myalgia, pain, fatigue, and dizziness. Up to 20% of patients experienced fluid retention and superficial oedema.

Most of mentioned AEs were mild to moderate in intensity, usually more frequent at the start of therapy and manageable with symptomatic treatments and dose reductions.

Table 62: Summary of TEAEs by dose – non-oncology excluding AB10015

	Masitinib			
	3.0 N=156	4.5 N=461	All N=1924	Placebo* N=1004
No. of Subjects with at least one				
All AEs	136 (87.2%)	421 (91.3%)	1702 (88.5%)	834 (83.1%)
SAE (non-fatal) (all)	32 (20.5%)	98 (21.3%)	423 (22.0%)	134 (13.3%)
Fatal (all)	0	5 (1.1%)	13 (0.7%)	11 (1.1%)
Leading to permanent discontinuation (excl Death)	49 (31.4%)	110 (23.9%)	467 (24.3%)	66 (6.6%)
Leading to dose reduction	1 (0.6%)	25 (5.4%)	143 (7.4%)	20 (2.0%)
Severe (Grade 3 and above)	37 (23.7%)	145 (31.5%)	732 (38.0%)	288 (28.7%)

A comparative analysis of the safety of Masitinib AB Science in the ALS and in the supporting non-oncology studies, when dose used was 4.5mg/kg/day or 3mg/kg/day

The percentage of patients with AE in the Masitinib AB Science arm was comparable in the ALS study and the controlled-unblinded studies (88.4%/84.7% vs. 91.3%/87.2%). Frequency of severe AEs was comparable in ALS vs. non-oncology (30.2%/21.4% vs. 31.5%/23.7%). More SAEs reported in the 4.5 mg/kg/day arm in ALS compared to the non-oncology studies (31.0% vs 21.3%). Overall, less patients discontinued in the ALS study vs. non-oncology studies (16.3%/15.3% versus 23.9%/31.4%).

Table 63: TEAEs with a difference of more than 5% compared to placebo - non-oncology excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
No. of Subjects with at least one	**n (%)**	**events**	**n (%)**	**events**	**n (%)**	**events**	**n (%)**	**events**
All AEs	**136 (87.2%)**	**1013**	**421 (91.3%)**	**3667**	**1702 (88.5%)**	**15064**	**834 (83.1%)**	**6930**
Eye Disorders	**10 (6.4%)**	**12**	**41 (8.9%)**	**56**	**222 (11.5%)**	**314**	**36 (3.6%)**	**60**
Eyelid Oedema	0	0	19 (4.1%)	21	122 (6.3%)	150	9 (0.9%)	11
Gastrointestinal Disorders	**51 (32.7%)**	**96**	**158 (34.3%)**	**302**	**719 (37.4%)**	**1756**	**214 (21.3%)**	**478**
Nausea	8 (5.1%)	10	37 (8.0%)	50	277 (14.4%)	365	54 (5.4%)	70
Diarrhoea	16 (10.3%)	19	62 (13.4%)	81	274 (14.2%)	400	78 (7.8%)	103
General Disorders and Administration Site Conditions	**26 (16.7%)**	**35**	**93 (20.2%)**	**129**	**438 (22.8%)**	**783**	**148 (14.7%)**	**240**
Skin and Subcutaneous Tissue Disorders	**48 (30.8%)**	**71**	**145 (31.5%)**	**250**	**615 (32.0%)**	**1185**	**143 (14.2%)**	**243**
Rash	9 (5.8%)	10	31 (6.7%)	36	125 (6.5%)	153	16 (1.6%)	19
Pruritus	6 (3.8%)	7	22 (4.8%)	27	114 (5.9%)	145	34 (3.4%)	45
Rash Maculo-Papular	5 (3.2%)	7	31 (6.7%)	37	98 (5.1%)	119	13 (1.3%)	16

Adverse events in healthy subjects

30% of healthy subjects (29/96) receiving masitinib mesilate reported regarding 154 AEs. The most common ones were nausea, vomiting, diarrhoea, abdominal pain, rash, dizziness, and episodes of headaches. Two cases of severe AE neutropenia were reported, one of which was then later considered a laboratory error. The majority of AEs were assessed as related to Masitinib AB Science.

Analysis of most common AEs

Table 64: Classification of analyses of most common AEs (W0 to W48)

AEs included	MedDRA terms included
Rash	Acute generalized exanthematous pustulosis, Chronic spontaneous urticaria, Dermatitis, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Ear pruritus, Eczema, Eczema asteatotic, Eczema eyelids, Eczema infected, Eczema nummular, Erythema, Erythema nodosum, Erythema of eyelid, Erythrosis, Eyelids pruritus, Generalised erythema, Hand dermatitis, Macule, Mechanical urticaria, Mucocutaneous rash, Nodular rash, Palmar erythema, Papule, Perianal erythema, Plantar erythema, Prurigo, Pruritus, Pruritus generalized, Rash, Rash erythematous, Rash generalized, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Scrotal erythema, Skin irritation, Skin lesion, Skin reaction, Urticaria, Urticaria contact, Vasculitic rash, Vulvovaginal erythema
Nausea	Nausea
Vomiting	Regurgitation of food, Vomiting
Diarrhoea	Abnormal faeces, Defaecation urgency, Diarrhoea, Diarrhoea haemorrhagic,
Oedema	Allergic oedema, Breast oedema, Circumoral oedema, Eye oedema, Eye swelling, Eyelid oedema, Face oedema, Fluid Overload, Fluid Retention, Generalised oedema, Gingival oedema, Gingival swelling, Lip oedema, Lip swelling, Local swelling, Localised oedema, Lymphoedema, Mouth swelling, oedema, oedema Genital, oedema Mouth, oedema Peripheral, Orbital oedema, Papilloedema, Penile oedema, Penile swelling, Periorbital oedema, Peripheral swelling, Scrotal oedema, Scrotal swelling, Swelling, Swelling face, Swollen fongue, Testicular oedema, Testicular swelling, Tongue oedema, Vaginal oedema, Vulval oedema
Anaemia	Anaemia, Anaemia folate deficiency, Anaemia macrocytic, Anaemia of chronic disease, Anaemia vitamin B12 deficiency, Aplasia pure red cell, Aplastic anaemia, Cold type haemolytic anaemia, Deficiency anaemia, Erythropenia, Haemorrhagic anaemia, Hypochromic anaemia, Haemolytic anaemia, Iron deficiency anaemia, microcytic anaemia, Normochromic normocytic anaemia, Pancytopenia, Haemoglobin decreased, Mean cell haemoglobin concentration decreased, Mean cell haemoglobin decreased, and Red blood cell count decreased

Rash

Table 65: Summary of Skin Rash – in Study AB10015 (W0-W48, N=393)

	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
	All			Related		
Rash	12 (9.0%)	27 (20.6%)	33 (25.6%)	11 (8.3%)	23 (17.6%)	29 (22.5%)
Severe Cases	0	1 (0.8%)	2 (1.6%)	0	1 (0.8%)	2 (1.6%)
Serious cases (non-fatal)	1 (0.8%)	2 (1.5%)	2 (1.6%)	1 (0.8%)	2 (1.5%)	2 (1.6%)
Death	0	0	0	0	0	0
Discontinuation	0	3 (2.3%)	5 (3.9%)			
Outcome (worst, including fatal cases if any)						
n (patients with Rash)	12	27	33			
Resolved without sequelae	11	25	33			
Resolved with sequelae	0	0	0			
Time of occurrence (days)						
n (AEs)	14	35	54	-	-	-
Median	48	31	31	-	-	-

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

Source:. Note: All frequencies are in number of patients, excepted for Time of occurrence that is in number of AEs.

Rash was a very common AE in ALS patients treated with Masitinib AB Science. It was dose-dependent and mostly mild, short lived and fully recoverable.

Table 66: Most frequent AEs in SOC skin and Subcutaneous Tissue Disorders - excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
No. of Subjects with at least one	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**
All AEs	**136 (87.2%)**	**1013**	**421 (91.3%)**	**3667**	**1702 (88.5%)**	**15064**	**834 (83.1%)**	**6930**
Skin and Subcutaneous Tissue Disorders	**48 (30.8%)**	**71**	**145 (31.5%)**	**250**	**615 (32.0%)**	**1185**	**143 (14.2%)**	**243**
Rash	9 (5.8%)	10	31 (6.7%)	36	125 (6.5%)	153	16 (1.6%)	19
Pruritus	6 (3.8%)	7	22 (4.8%)	27	114 (5.9%)	145	34 (3.4%)	45
Rash Maculo-Papular	5 (3.2%)	7	31 (6.7%)	37	98 (5.1%)	119	13 (1.3%)	16
Erythema	3 (1.9%)	3	14 (3.0%)	18	55 (2.9%)	63	14 (1.4%)	20
Dry Skin	1 (0.6%)	1	11 (2.4%)	12	43 (2.2%)	47	7 (0.7%)	7
Urticaria	1 (0.6%)	2	3 (0.7%)	3	39 (2.0%)	51	7 (0.7%)	10
Eczema	3 (1.9%)	4	2 (0.4%)	2	33 (1.7%)	49	14 (1.4%)	14
Rash Macular	4 (2.6%)	4	6 (1.3%)	7	33 (1.7%)	38	5 (0.5%)	5
Skin Exfoliation	1 (0.6%)	1	5 (1.1%)	6	33 (1.7%)	42	4 (0.4%)	4
Dermatitis Allergic	3 (1.9%)	3	9 (2.0%)	9	31 (1.6%)	32	4 (0.4%)	4
Rash Generalised	1 (0.6%)	1	8 (1.7%)	10	28 (1.5%)	31	1 (0.1%)	1
Pruritus Generalised	3 (1.9%)	3	4 (0.9%)	4	23 (1.2%)	25	1 (0.1%)	1
Swelling Face	3 (1.9%)	3	3 (0.7%)	4	21 (1.1%)	25	2 (0.2%)	2

Up to 32% of non-oncology patients treated with Masitinib AB Science (excluding ALS) experienced at least one occurrence of cutaneous reactions. They were more prevalent in the beginning of treatment, mostly mild to moderate, dose-related, and self-limited and were manageable through dose reductions and interruptions. Their frequency and severity usually decrease over time.

GI symptoms

GI symptoms - mild abdominal discomfort, nausea, vomiting and diarrhoea - are known adverse drug reactions to masitinib and other TKI products. GI symptoms were mostly dose-dependent, mild, short-lived, and fully recoverable. Usually, it was observed in the beginning of treatment.

Nausea

Table 67: Summary of Nausea – in Study AB10015 (W0-W48, N=393)

	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
	All			Related		
Nausea	6 (4.5%)	9 (6.9%)	16 (12.4%)	3 (2.3%)	7 (5.3%)	11 (8.5%)
Severe Cases	0	0	0	0	0	0
Serious cases (non-fatal)	0	0	0	0	0	0
Death	0	0	0	0	0	0

Discontinuation	0	1 (0.8%)	1 (0.8%)			
Outcome (worst, including fatal cases if any)						
n (patients with Nausea)	6	8	16			
Resolved without sequelae	6	8	16			
Resolved with sequelae	0	0	0			
Time of occurrence (days)						
n (AEs)	6	10	17	-	-	-
Median	44	17	38	-	-	-

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.
Note: All frequencies are in number of patients, excepted for Time of occurrence that is in number of AEs.

Table 68: Nausea - non-oncology excluding AB10015

	Masitinib							
	3.0 N=156		**4.5 N=461**		**All N=1924**		**Placebo* N=1004**	
No. of Subjects with at least one	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**Events**
Gastrointestinal Disorders	**51 (32.7%)**	**96**	**158 (34.3%)**	**302**	**719 (37.4%)**	**1756**	**214 (21.3%)**	**478**
Nausea	8 (5.1%)	10	37 (8.0%)	50	277 (14.4%)	365	54 (5.4%)	70

Vomiting

Table 69: Summary of vomiting – in Study AB10015 (W0-W48, N=393)

Number (%) of subject with at least one AE	**P + R (N=133)**	**M 3.0 + R (N=131)**	**M 4.5 + R (N=129)**
Vomiting- All AEs	0	0	3 (2.3%)
Severe Cases	0	0	0
Serious cases (non-fatal)	0	0	0
Death	0	0	0
Discontinuation	0	0	0
Time of occurrence (days)			
n (AEs)	-	-	4
Median	-	-	44

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Note: All frequencies are in number of patients, excepted for Time of occurrence that is in number of AEs.

Table 70: Vomiting - non-oncology excluding AB10015

	Masitinib							
	3.0 N=156		**4.5 N=461**		**All N=1924**		**Placebo* N=1004**	
No. of Subjects with at least one	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**Events**
Gastrointestinal Disorders	**51 (32.7%)**	**96**	**158 (34.3%)**	**302**	**719 (37.4%)**	**1756**	**214 (21.3%)**	**478**
Vomiting	9 (5.8%)	15	27 (5.9%)	34	144 (7.5%)	199	32 (3.2%)	42

7.5% of non-oncology patients treated with Masitinib AB Science (excluding ALS patients) experienced at least one episode of vomiting vs. 3.2% of the patients in placebo groups.

Diarrhoea

Table 71: Summary of Diarrhoea – in Study AB10015 (W0-W48, N=393)

Number (%) of subject with at least one AE	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
Diarrohea- All AEs	5 (3.8%)	11 (8.4%)	10 (7.8%)
Severe Cases	0	0	0
Serious cases (non-fatal)	0	1 (0.8%)	1 (0.8%)
Death	0	0	0
Discontinuation	0	0	0
Time of occurrence (days)			
n (AEs)	5	13	13
Median	51	56	123

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Note: All frequencies are in number of patients, except for Time of occurrence that is in number of AEs.

Most of the diarrhoea and related AEs were observed in the initial 6 months of the start of Masitinib AB Science treatment. All the cases were manageable with temporary interruption or dose reductions.

Table 72: Diarrhoea - non-oncology excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
No. of Subjects with at least one	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**Events**
Gastrointestinal Disorders	**51 (32.7%)**	**96**	**158 (34.3%)**	**302**	**719 (37.4%)**	**1756**	**214 (21.3%)**	**478**
Diarrhoea	16 (10.3%)	19	62 (13.4%)	81	274 (14.2%)	400	78 (7.8%)	103

Oedema

Superficial oedemas are common and well described ADRs of TKIs including Masitinib AB Science. It occurs due to peripheral fluid retention, which is explained by the pharmacological mechanism of action of Masitinib AB Science (or other TKIs) by blocking the PDGFR pathway. In most cases, superficial oedema-related events are dose-dependent, mild, short-lived, and fully recoverable.

Table 73: Summary of Oedema – in Study AB10015 (W0-W48, N=393)

Number (%) of subject with at least one AE	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
Oedema- All AEs	1 (0.8%)	8 (6.1%)	16 (12.4%)
Severe Cases	0	0	0
Serious cases (non-fatal)	0	0	0
Death	0	0	0
Discontinuation	0	0	2 (1.6%)
Time of occurrence (days)			
n (AEs)	1	10	21
Median	80	41	28

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Note: All frequencies are in number of patients, except for Time of occurrence that is in number of AEs.

The median time of occurrence of oedema in ALS patients exposed to Masitinib AB Science was between 28 to 41 days. No risk of oedema observed with long term usage of study drug.

Table 74: Selected terms 'Oedema' - in non-oncology studies excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
No. of Subjects with at least one	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**Events**
All AEs	**136 (87.2%)**	**1013**	**421 (91.3%)**	**3667**	**1702 (88.5%)**	**15064**	**834 (83.1%)**	**6930**
Eye Disorders								
Eyelid Oedema	0	0	19 (4.1%)	21	122 (6.3%)	150	9 (0.9%)	11
Periorbital Oedema	2 (1.3%)	4	1 (0.2%)	1	14 (0.7%)	17	3 (0.3%)	4
Eye Oedema	1 (0.6%)	1	1 (0.2%)	1	8 (0.4%)	8	1 (0.1%)	1
Gastrointestinal Disorders								
Lip Oedema	0	0	2 (0.4%)	2	9 (0.5%)	9	0	0
Oedema Mouth	0	0	1 (0.2%)	1	3 (0.2%)	3	0	0
Tongue Oedema	0	0	1 (0.2%)	1	3 (0.2%)	3	0	0
Gastrointestinal Oedema	0	0	0	0	0	0	1 (0.1%)	1
Gingival Oedema	0	0	0	0	1 (0.1%)	1	0	0
General Disorders and Administration Site Conditions								
Oedema Peripheral	8 (5.1%)	11	23 (5.0%)	24	114 (5.9%)	134	20 (2.0%)	22
Face Oedema	2 (1.3%)	2	6 (1.3%)	7	57 (3.0%)	69	6 (0.6%)	6
Oedema	1 (0.6%)	1	2 (0.4%)	2	15 (0.8%)	20	3 (0.3%)	3
Localised Oedema	0	0	1 (0.2%)	1	8 (0.4%)	8	3 (0.3%)	3
Generalised Oedema	0	0	1 (0.2%)	1	4 (0.2%)	4	1 (0.1%)	2
Reproductive System and Breast Disorders								
Oedema Genital	0	0	0	0	1 (0.1%)	1	0	0
Vulval Oedema	0	0	0	0	0	0	1 (0.1%)	1
Skin and Subcutaneous Tissue Disorders								
Circumoral Oedema	0	0	1 (0.2%)	1	1 (0.1%)	1	0	0

Anaemia

Increase in frequency of anaemia in ALS patients exposed to Masitinib AB Science was a dose dependent. Asymptomatic decrease in red blood count is common for Masitinib AB Science. The median time of occurrence of anaemia-related AEs in patients exposed to masitinib was between 27 to 47 days. Anaemia is an uncommon (<1%) AE for riluzole. There was no imbalance of severe anaemia observed with long term Masitinib AB Science usage.

Table 75: Summary of Anaemia – in Study AB10015 (W0-W48, N=393)

Number (%) of subject with at least one AE	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
Anaemia-All AEs	3 (2.3%)	9 (6.9%)	20 (15.5%)
Severe Cases	0	2 (1.5%)	2 (1.6%)
Serious cases (non-fatal)	0	1 (0.8%)	1 (0.8%)
Death	0	0	0
Discontinuation	0	0	2 (1.6%)
Time of occurrence (days)			
n (AEs)	6	26	10
Median	47	27	47

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day Note: All frequencies are in number of patients, except for Time of occurrence that is in number of AEs.

Table 76: Summary of Anaemia - in non-oncology studies excluding AB10015

			Masitinib		
MedDRA PT		3.0 N=156	4.5 N=461	All N=1924	Placebo* N=1004
PT NAME					
Aplastic Anaemia	No. of patients(all)	0	0	1 (0.1%)	0
	Mild	0	0	1 (0.1%)	0
Erythropenia	No. of patients(all)	1 (0.6%)	3 (0.7%)	6 (0.3%)	3 (0.3%)
	Mild	1 (0.6%)	3 (0.7%)	6 (0.3%)	3 (0.3%)
Microcytic Anaemia	No. of patients(all)	0	0	1 (0.1%)	1 (0.1%)
	Mild	0	0	1 (0.1%)	1 (0.1%)
Red Blood Cell Count Decreased	No. of patients(all)	15 (9.6%)	44 (9.5%)	114 (5.9%)	24 (2.4%)
	Mild	15 (9.6%)	44 (9.5%)	114 (5.9%)	24 (2.4%)
	Missing	0	0	1 (0.1%)	0
Reticulocyte Count Decreased	No. of patients(all)	0	0	1 (0.1%)	0
	Mild	0	0	1 (0.1%)	0

Anaemia related AEs were more common in patients exposed to Masitinib AB Science vs. placebo (6.3% vs. 2.8%). Some of Anaemia related AEs are further discussed in 4.5 Laboratory findings.

Table 77: Severe AEs (Risk ≥1% in any PT) – in Study AB10015 (W0-W48, N=393)

Number (%) of subject with at least one severe AE	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
	All			Related		
All AEs	26 (19.5%)	28 (21.4%)	39 (30.2%)	1 (0.8%)	1 (0.8%)	7 (5.4%)
Cardiac Disorders	2 (1.5%)	5 (3.8%)	2 (1.6%)	0	0	0
Cardio-Respiratory Arrest	1 (0.8%)	4 (3.1%)	1 (0.8%)	0	0	0
Gastrointestinal Disorders	4 (3.0%)	4 (3.1%)	7 (5.45)	0	0	0
Dysphagia	3 (2.3%)	4 (3.1%)	6 (4.7%)	0	0	0
Investigations	5 (3.8%)	6 (4.6%)	6 (4.7%)	1 (0.8%)	0	2 (1.6%)
Blood Phosphorus Decreased	0	0	3 (2.3%)	0	0	0
Nervous System Disorders	1 (0.8%)	4 (3.1%)	4 (3.1%)	0	0	0
Brain Oedema	0	2 (1.5%)	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	8 (6.0%)	12 (9.2%)	13 (10.1%)	0	0	0
Respiratory Failure	5 (3.8%)	7 (5.3%)	9 (7.0%)	0	0	0
Dyspnoea	0	0	2 (1.6%)	0	0	0

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

Table 78: Severe AEs - in non-oncology studies excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
No. of Subjects with at least one	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**
All AEs	**37 (23.7%)**	**49**	**145 (31.5%)**	**231**	**732 (38.0%)**	**1791**	**288 (28.7%)**	**568**
Blood and Lymphatic System Disorders	**5 (3.2%)**	**5**	**18 (3.9%)**	**20**	**94 (4.9%)**	**114**	**23 (2.3%)**	**29**
Neutropenia	5 (3.2%)	5	10 (2.2%)	10	59 (3.1%)	63	10 (1.0%)	12
Lymphopenia	0	0	5 (1.1%)	5	13 (0.7%)	15	1 (0.1%)	1
Cardiac Disorders	**0**	**0**	**5 (1.1%)**	**5**	**20 (1.0%)**	**22**	**8 (0.8%)**	**8**
Gastrointestinal Disorders	**3 (1.9%)**	**3**	**7 (1.5%)**	**10**	**83 (4.3%)**	**174**	**15 (1.5%)**	**25**
Diarrhoea	0	0	4 (0.9%)	4	36 (1.9%)	45	5 (0.5%)	6
Nausea	0	0	1 (0.2%)	1	22 (1.1%)	23	1 (0.1%)	1
General Disorders and Administration Site Conditions	**0**	**0**	**4 (0.9%)**	**5**	**75 (3.9%)**	**123**	**15 (1.5%)**	**19**
Asthenia	0	0	1 (0.2%)	1	32 (1.7%)	41	4 (0.4%)	5
Hepatobiliary Disorders	**0**	**0**	**4 (0.9%)**	**4**	**24 (1.2%)**	**25**	**3 (0.3%)**	**4**
Infections and Infestations	**2 (1.3%)**	**2**	**8 (1.7%)**	**9**	**73 (3.8%)**	**95**	**25 (2.5%)**	**30**
Injury - Poisoning and Procedural Complications	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Accidental Overdose	0	0	0	0	0	0	0	0
Injury, Poisoning and Procedural Complications	**1 (0.6%)**	**3**	**2 (0.4%)**	**2**	**20 (1.0%)**	**24**	**11 (1.1%)**	**13**
Investigations	**8 (5.1%)**	**9**	**68 (14.8%)**	**96**	**246 (12.8%)**	**344**	**103 (10.3%)**	**131**
Blood Phosphorus Decreased	2 (1.3%)	2	18 (3.9%)	23	48 (2.5%)	59	9 (0.9%)	11
Lymphocyte Count Decreased	1 (0.6%)	1	11 (2.4%)	12	39 (2.0%)	43	9 (0.9%)	10
Gamma-Glutamyltransferase Increased	0	0	9 (2.0%)	11	38 (2.0%)	43	15 (1.5%)	18
Neutrophil Count Decreased	1 (0.6%)	1	6 (1.3%)	6	23 (1.2%)	23	7 (0.7%)	7
Blood Potassium Increased	0	0	6 (1.3%)	6	18 (0.9%)	20	7 (0.7%)	8
Metabolism and Nutrition Disorders	**2 (1.3%)**	**2**	**8 (1.7%)**	**8**	**57 (3.0%)**	**65**	**28 (2.8%)**	**40**
Musculoskeletal and Connective Tissue Disorders	**1 (0.6%)**	**1**	**1 (0.2%)**	**1**	**44 (2.3%)**	**69**	**8 (0.8%)**	**14**
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**0**	**0**	**10 (2.2%)**	**10**	**23 (1.2%)**	**26**	**9 (0.9%)**	**11**
Nervous System Disorders	**1 (0.6%)**	**1**	**11 (2.4%)**	**11**	**53 (2.8%)**	**74**	**16 (1.6%)**	**19**
Psychiatric Disorders	**0**	**0**	**3 (0.7%)**	**3**	**24 (1.2%)**	**28**	**6 (0.6%)**	**7**
Renal and Urinary Disorders	**2 (1.3%)**	**2**	**5 (1.1%)**	**9**	**23 (1.2%)**	**28**	**4 (0.4%)**	**4**
Respiratory, Thoracic and Mediastinal Disorders	**4 (2.6%)**	**4**	**7 (1.5%)**	**7**	**176 (9.1%)**	**312**	**80 (8.0%)**	**161**
Asthma	2 (1.3%)	2	2 (0.4%)	2	145 (7.5%)	271	77 (7.7%)	156
Skin and Subcutaneous Tissue Disorders	**6 (3.8%)**	**7**	**10 (2.2%)**	**15**	**98 (5.1%)**	**154**	**10 (1.0%)**	**12**
Pruritus	0	0	1 (0.2%)	3	19 (1.0%)	23	3 (0.3%)	3
Rash Maculo-Papular	4 (2.6%)	5	3 (0.7%)	3	16 (0.8%)	19	0	0
Vascular Disorders	**8 (5.1%)**	**9**	**11 (2.4%)**	**11**	**47 (2.4%)**	**53**	**26 (2.6%)**	**30**
Hypertension	7 (4.5%)	8	10 (2.2%)	10	29 (1.5%)	33	17 (1.7%)	20

Long-term safety analysis

130 of the 233 patients (55.8%) reported at least one AE during the extension period: 39 patients (48.8%) in the active control arm, 45 (56.3%) in the Masitinib AB Science 3mg/kg/day arm, and 46 (63.0%) in the Masitinib AB Science 4.5 mg/kg/day arm.

More frequently reported AEs in one of the Masitinib AB Science arms vs. placebo arm were dysphagia, depression, lower respiratory tract infection, and weight decrease. Occurrence and severity of AEs are dose related. According to Applicant, most of AEs were related to underlying progression of the disease, therefore, the increased frequency of these AEs in the Masitinib AB Science arm could be caused, at least partially, by the longer median treatment exposure in these arms.

Table 79: Frequent AEs (Risk ≥5% in any PT) – study AB10015, extension period

Number (%) of subject with at least one AE	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)
	All			Related		
All AEs	**39 (48.8)**	**45 (56.3)**	**46 (63.0)**	**1 (1.3)**	**8 (10.0)**	**8 (11.0)**
Gastrointestinal Disorders	**7 (8.8)**	**11 (13.8)**	**19 (26.0)**	**0**	**0**	**2 (2.7)**
Dysphagia	7 (8.8)	8 (10.0)	12 (16.4)	0	0	0
Infections and Infestations	**16 (20.0)**	**16 (20.0)**	**15 (20.5)**	**1 (1.3)**	**1 (1.3)**	**1 (1.4)**
Lower Respiratory Tract Infection	1 (1.3)	5 (6.3)	1 (1.4)	0	0	0
Pneumonia	3 (3.8)	2 (2.5)	5 (6.8)	0	0	0
Investigations	**11 (13.8)**	**12 (15.0)**	**10 (13.7)**	**0**	**1 (1.3)**	**2 (2.7)**
Weight Decreased	3 (3.8)	6 (7.5)	4 (5.5)	0	1 (1.3)	0
Psychiatric Disorders	**2 (2.5)**	**10 (12.5)**	**7 (9.6)**	**0**	**1 (1.3)**	**1 (1.4)**
Affect Lability	0	4 (5.0)	0	0	0	0
Depression	0	4 (5.0)	4 (5.5)	0	1 (1.3)	1 (1.4)
Respiratory, Thoracic and Mediastinal Disorders	**10 (12.5)**	**13 (16.3)**	**10 (13.7)**	**0**	**0**	**0**
Respiratory Failure	5 (6.3)	7 (8.8)	4 (5.5)	0	0	0

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.

The safety profile of Masitinib AB Science was comparatively better in the extension period vs. main protocol period. There was lower frequency of the overall AEs and TEAEs.

Table 80: Summary of frequent risks (combined PTs) - study AB10015, extension period

Number (%) of subject with at least one AE	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)
	All			**Related**		
Nausea	0	1 (1.3%)	0	0	0	0
Vomiting	0	1 (1.4%)	0	0	0	0
Diarrohea	0	2 (2.5%)	2 (2.7%)	0	0	1 (1.4%)
Oedema	0	0	0	0	0	0
Anaemia	2 (2.5%)	2 (2.5%)	1 (1.4%)	0	0	0
Rash	0	1 (1.3%)	4 (5.5%)	0	1 (1.3%)	3 (4.1%)
Severe Cases	0	0	0	0	0	0
Serious cases (non-fatal)	0	0	1 (1.4%)	0	0	0

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

No discontinuations were recorded in the extension period.

The frequency of rash in Masitinib AB Science arms was lower vs. main protocol period and was still dose proportionally increased vs. placebo arm. During the extension period, 5 patients experienced rash, none in placebo arm, 1 patient (1.3%) in the Masitinib AB Science 3 mg/kg/day arm, and 4 patients (5.5%) in the Masitinib AB Science 4.5 mg/kg/day arm.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Deaths in Study AB10015

According to Applicant, there was no increase in the frequency of fatal SAEs in patients treated with Masitinib AB Science during the main protocol period.

33 patients had a fatal SAEs. Of them, 12 patients (9.0%) in placebo arm, 11 patients (8.4%) in the Masitinib AB Science 3.0 mg/kg/day arm, and 10 patients (7.8%) in the Masitinib AB Science 4.5 mg/kg/day arm. The most common causes of death were related to underlying conditions, i.e. respiratory failures, respiratory infections, obstructive disorders. None of the on-treatment deaths were assessed by the investigators as treatment-related. None of the on-treatment deaths was associated with known adverse reactions of Masitinib AB Science or other TKIs. According to the applicant, detailed assessment of each death confirmed that events leading to death were due to natural progression and complications observed in patients with advanced ALS. Although several events of cardiac and respiratory arrests were reported, these are not infrequently seen in patients with severe ALS, often resulting from massive aspiration followed by respiratory and cardiac arrest. There were no unanticipated causes of death reported in the study.

Table 81: Serious AEs Resulting in Death – in Study AB10015 (W0-W48, N=393)

SYSTEM ORGAN CLASS PREFERRED TERM	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
	All			Related		
All deaths	**12 (9.0)**	**11 (8.4)**	**10 (7.8)**	**0**	**0**	**0**
Cardiac Disorders	**2 (1.5)**	**4 (3.1)**	**1 (0.8)**	**0**	**0**	**0**
Cardio-Respiratory Arrest	1 (0.8)	3 (2.3)	1 (0.8)	0	0	0
Cardiopulmonary Failure	1 (0.8)	1 (0.8)	0	0	0	0
General Disorders and Administration Site Conditions	**1 (0.8)**	**0**	**0**	**0**	**0**	**0**
Euthanasia	1 (0.8)	0	0	0	0	0
Infections and Infestations	**2 (1.5)**	**0**	**0**	**0**	**0**	**0**
Pneumonia	2 (1.5)	0	0	0	0	0
Investigations	**0**	**0**	**1 (0.8)**	**0**	**0**	**0**
Aspiration Bronchial	0	0	1 (0.8)	0	0	0
Neoplasms Benign, Malignant and Unspecified	**1 (0.8)**	**0**	**0**	**0**	**0**	**0**
Pleural Mesothelioma	1 (0.8)	0	0	0	0	0
Nervous System Disorders	**1 (0.8)**	**1 (0.8)**	**0**	**0**	**0**	**0**
Brain Oedema	0	1 (0.8)	0	0	0	0
Hypercapnic Coma	1 (0.8)	0	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**6 (4.5)**	**8 (6.1)**	**8 (6.2)**	**0**	**0**	**0**
Respiratory Failure	4 (3.0)	4 (3.1)	5 (3.9)	0	0	0
Dyspnoea	0	0	2 (1.6)	0	0	0
Acute Respiratory Failure	1 (0.8)	0	1 (0.8)	0	0	0
Chronic Respiratory Failure	0	1 (0.8)	0	0	0	0
Obstructive Airways Disorder	0	1 (0.8)	0	0	0	0
Pulmonary Oedema	0	1 (0.8)	0	0	0	0
Respiratory Arrest	0	1 (0.8)	0	0	0	0
Pneumonia Aspiration	1 (0.8)	0	0	0	0	0

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

Deaths in non-oncology studies excluding AB10015

24 patients died in the unblinded studies. Of them, 10 patients died in a study of Alzheimer's disease (AB09004), 6 patients in studies of severe asthma (AB04026, AB07015, AB14001), 5 patients in a study

of progressive multiple sclerosis (AB07002), 2 patients in studies of rheumatoid arthritis (AB06010; AB06012) and 1 patient in a study of severe mastocytosis (AB06006).

Table 82: Patients with Fatal SAEs - in non-oncology studies excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
MedDRA System Organ Class(SOC)	**Event**	**n(%)**	**Event**	**n(%)**	**Event**	**n(%)**	**Event**	**n(%)**
All MedDRA SOC	**0**	**0**	**6**	**5(1.1%)**	**16**	**13(0.7%)**	**13**	**11(1.1%)**
Infections and Infestations	0	0	1	1(0.2%)	3	3(0.2%)	1	1(0.1%)
General Disorders and Administration Site Conditions	0	0	1	1(0.2%)	3	3(0.2%)	4	4(0.4%)
Cardiac Disorders	0	0	1	1(0.2%)	2	2(0.1%)	4	4(0.4%)
Respiratory - Thoracic and Mediastinal Disorders	0	0	0	0	0	0	0	0
Vascular Disorders	0	0	0	0	2	2(0.1%)	1	1(0.1%)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	1	1(0.2%)	1	1(0.1%)	2	2(0.2%)
Injury, Poisoning and Procedural Complications	0	0	0	0	1	1(0.1%)	1	1(0.1%)
Nervous System Disorders	0	0	1	1(0.2%)	2	2(0.1%)	0	0
Renal and Urinary Disorders	0	0	0	0	0	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	0	1	1(0.2%)	2	2(0.1%)	0	0
Gastrointestinal Disorders	0	0	0	0	0	0	0	0

Source: Table 1: Patients with Fatal SAEs excluding AB10015. Human Safety Report 20222. Dated on 15MAR22

Deaths in healthy subjects

No deaths in healthy subjects reported.

Other (Non-fatal) SAEs

SAEs in Study AB10015

Increase in the frequency of non-fatal SAEs in Masitinib AB Science arms was dose-dependent during the main protocol period. 94 patients experienced SAEs, of those, 24 patients (18.0%) in placebo arm, 30 patients (22.9%) in the Masitinib AB Science 3 mg/kg/day arm, and 40 patients (31.1%) in the Masitinib AB Science 4.5 mg/kg/day arm.

The most common SAEs in Masitinib AB Science arms vs. placebo were respiratory failure, dysphagia, transaminase increase, fall, and dyspnoea. Of those, Respiratory failure, dysphagia, and dyspnoea are associated with ALS disease progression and none of these SAEs were reported as treatment related.

Table 83: Non-Fatal Serious AEs (Risk ≥1% in any PT) – in Study AB10015 (W0-W48, N=393)

SYSTEM ORGAN CLASS PREFERRED TERM	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
	All			Related		
All	24 (18.0)	30 (22.9)	40 (31.0)	1 (0.8)	5 (3.8)	9 (7.0)
Gastrointestinal Disorders	**10 (7.5)**	**15 (11.5)**	**14 (10.9)**	**0 (0.0)**	**2 (1.5)**	**1 (0.8)**
Dysphagia	9 (6.8)	14 (10.7)	11 (8.5)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**4 (3.0)**	**7 (5.3)**	**13 (10.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Respiratory Failure	2 (1.5)	5 (3.8)	8 (6.2)	0	0	0
Dyspnoea	1 (0.8)	2 (1.5)	3 (2.3)	0	0	0
Infections and Infestations	**7 (5.3)**	**3 (2.3)**	**10 (7.8)**	**0 (0.0)**	**0 (0.0)**	**2 (1.6)**
Bronchitis	1 (0.8)	1 (0.8)	2 (1.6)	0 (0.0)	0 (0.0)	1 (0.8)
Lower Respiratory Tract Infection	2 (1.5)	2 (1.5)	2 (1.6)	0	0	0
Injury, Poisoning and Procedural Complications	**1 (0.8)**	**1 (0.8)**	**6 (4.7)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Fall	0	1 (0.8)	2 (1.6)	0	0	0
Investigations	**2 (1.5)**	**4 (3.1)**	**5 (3.9)**	**0 (0.0)**	**0 (0.0)**	**3 (2.3)**
Transaminases Increased	0	0	2 (1.6)	0	0	2 (1.6)
Blood and Lymphatic System Disorders	**0**	**2 (1.5)**	**1 (0.8)**	**0**	**1 (0.8)**	**1 (0.8)**
Neutropenia	0	2 (1.5)	0	0	1 (0.8)	0

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

SAEs in non-oncology studies excluding AB10015

Table 84: Patients with Non-Fatal SAEs (≥0.5% Total Population) - excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
MedDRA System Organ Class (SOC)	**Event**	**n(%)**	**Event**	**n(%)**	**Event**	**n(%)**	**Event**	**n(%)**
All MedDRA SOC	**36**	**32(20.5%)**	**156**	**98(21.3%)**	**736**	**423(22.0%)**	**213**	**134(13.3%)**
Skin and Subcutaneous Tissue Disorders	6	6(3.8%)	19	17(3.7%)	95	77(4.0%)	3	3(0.3%)
Respiratory, Thoracic and Mediastinal Disorders	4	4(2.6%)	8	8(1.7%)	92	67(3.5%)	37	26(2.6%)
Infections and Infestations	2	2(1.3%)	17	15(3.3%)	89	81(4.2%)	33	23(2.3%)
Gastrointestinal Disorders	1	1(0.6%)	17	11(2.4%)	62	47(2.4%)	9	7(0.7%)
Nervous System Disorders	1	1(0.6%)	19	16(3.5%)	52	44(2.3%)	29	23(2.3%)
Blood and Lymphatic System Disorders	5	5(3.2%)	12	12(2.6%)	51	47(2.4%)	6	5(0.5%)
Musculoskeletal and Connective Tissue Disorders	4	4(2.6%)	1	1(0.2%)	36	25(1.3%)	12	10(1.0%)
General Disorders and Administration Site Conditions	1	1(0.6%)	3	3(0.7%)	32	26(1.4%)	9	7(0.7%)
Renal and Urinary Disorders	0	0	13	6(1.3%)	29	21(1.1%)	6	6(0.6%)
Investigations	3	3(1.9%)	6	6(1.3%)	27	25(1.3%)	2	2(0.2%)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	0	0	10	10(2.2%)	27	25(1.3%)	13	11(1.1%)
Injury, Poisoning and Procedural Complications	3	1(0.6%)	8	5(1.1%)	25	16(0.8%)	22	16(1.6%)
Surgical and Medical Procedures	1	1(0.6%)	3	2(0.4%)	25	15(0.8%)	3	3(0.3%)
Hepatobiliary Disorders	0	0	4	4(0.9%)	18	18(0.9%)	6	5(0.5%)
Cardiac Disorders	1	1(0.6%)	5	5(1.1%)	17	16(0.8%)	5	4(0.4%)
Metabolism and Nutrition Disorders	2	2(1.3%)	0	0	12	12(0.6%)	2	2(0.2%)
Vascular Disorders	1	1(0.6%)	3	3(0.7%)	11	9(0.5%)	3	3(0.3%)

SAEs in healthy subjects

There was 1 severe treatment-related SAE of uncomplicated neutropenia in 1 subject after repeated doses of 400 mg Masitinib AB Science (corresponding to ~6.0 mg/kg/day) in Study AB03003. The event fully resolved.

Long-term safety analysis - Deaths

34 patients had fatal SAEs, i.e. 7 placebo patients (8.8%), 13 patients (16.3%) in the Masitinib AB Science 3 mg/kg/day arm, and 14 patients (19.2%) in the Masitinib AB Science 4.5 mg/kg/day arm.

According to the applicant, imbalance in the death rate between the treatment arms may be attributable to:

- Poorer performance status of patients in the active control arm, who decided not to participate in the extension phase of the study due to lack of positive benefit/risk. There was an excess of 5 patients dropping out of the study at the initiation of the extension period in placebo arm as compared with the combined Masitinib AB Science arms. Should these patients have entered the extension phase, they might had contributing to additional fatal SAEs recorded during the extension phase on the active control arm.
- Longer duration under treatment for Masitinib AB Science treated patients in the extension period. The median treatment time was 15.4 weeks with placebo, versus 25.3 weeks with Masitinib AB Science 3 mg/kg/day and 25.0 weeks with Masitinib AB Science 4.5 mg/kg/day.

Table 85: SAEs Resulting in Death - Study AB10015, extension period

SYSTEM ORGAN CLASS/ PREFERRED TERM	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)	P + R (N=80)	M 3.0 + R (N=80)	M 4.5 + R (N=73)
	All			Related		
All non-fatal SAEs	**7 (8.8)**	**13 (16.3)**	**14 (19.2)**	**0**	**0**	**0**
Cardiac Disorders	**0**	**2 (2.5)**	**1 (1.4)**	**0**	**0**	**0**
Cardio-Respiratory Arrest	0	2 (2.5)	1 (1.4)	0	0	0
Gastrointestinal Disorders	**0**	**0**	**1 (1.4)**	**0**	**0**	**0**
Dysphagia	0	0	1 (1.4)	0	0	0
Infections and Infestations	**2 (2.5)**	**1 (1.3)**	**5 (6.8)**	**0**	**0**	**0**
Pneumonia	1 (1.3)	1 (1.3)	3 (4.1)	0	0	0
Lower Respiratory Tract Infection	1 (1.3)	0	1 (1.4)	0	0	0
Respiratory Tract Infection	0	0	1 (1.4)	0	0	0
Investigations	**0**	**1 (1.3)**	**0**	**0**	**0**	**0**
Aspiration Bronchial	0	1 (1.3)	0	0	0	0
Nervous System Disorders	**1 (1.3)**	**0 (0.0)**	**2 (2.7)**	**0**	**0**	**0**
Amyotrophic Lateral Sclerosis	1 (1.3)	0	1 (1.4)	0	0	0
Hypercapnic Coma	0	0	1 (1.4)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**6 (7.5)**	**9 (11.3)**	**7 (9.6)**	**0**	**0**	**0**
Respiratory Failure	3 (3.8)	6 (7.5)	3 (4.1)	0	0	0
Respiratory Arrest	0	1 (1.3)	3 (4.1)	0	0	0
Acute Respiratory Failure	0	2 (2.5)	1 (1.4)	0	0	0
Dyspnoea	2 (2.5)	0	1 (1.4)	0	0	0
Pulmonary Embolism	1 (1.3)	0	0	0	0	0
Vascular Disorders	**1 (1.3)**	**0**	**0**	**0**	**0**	**0**
Deep Vein Thrombosis	1 (1.3)	0	0	0	0	0

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

Source: Statistical Table 14.3.1.3.2 (CSR-AB10015).

According to the applicant, during the main protocol period, the death rates were comparable amongst treatment groups, with a trend towards lower rates in the Masitinib AB Science groups vs. placebo.

During the extension period, the trend was reversed with higher rates observed in the Masitinib AB Science groups vs. placebo.

Table 86: Deaths in Study AB10015 – main protocol period vs. extension period

	Placebo (N=133)	Masitinib 4.5 mg/kg (N=129)	Masitinib 3.0 mg/kg (N=131)	All (N=393)
Treatment Period	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total Deaths from Fatal SAEs	**19 (14.3)**	**24 (18.6)**	**24 (18.3)**	**67 (17.0)**
Main period (48 Weeks)	12 (9.0)	10 (7.8)	11 (8.4)	33 (8.4)
Extension period (up to Dec 5, 2016)	7 (5.3)	14 (10.9)	13 (9.9)	34 (8.7)

Abbreviations: N = number of patients in population

A trend towards higher mortality in the Masitinib AB Science groups vs. placebo during the extension period was further investigated. Variables that could potentially impact mortality were reviewed for patients who extended treatment beyond week 48. Overall, no particular imbalance at baseline or differences during the study could be identified except for a difference in the median treatment duration after the week 48 protocol period.

Patients in the Masitinib AB Science groups remained on study treatment significantly longer than placebo patients. The median on-treatment duration after week 48 in the extension period was up to 66% longer in the Masitinib AB Science arms vs. placebo.

Table 87: Median Treatment Time in Study AB10015 – main protocol period vs. extension period

Treatment Period	Placebo (N=133)	Masitinib 4.5 mg/kg (N=129)	Masitinib 3.0 mg/kg (N=131)
Main period (up to visit week 48)	48	48	48
Extension period (up to Dec 5, 2016)	15	25	25

Abbreviations: N = number of patients in population

According to the applicant, the most frequent causes of deaths were related to underlying ALS conditions such as respiratory failure events, cardio-respiratory events, infection events, and aspirations. None of the fatal SAEs were assessed as related to study treatment by the investigators.

An analysis of the elapsed time after last study treatment intake before death was performed. It revealed that the difference in reported deaths amongst treatment groups stemmed mainly from deaths occurring within less than 1 day after last intake. The causes of deaths occurring within 24 hours of last intake displayed the same similarities both in nature and frequency as all other deaths reported in the study. The majority of deaths resulted from typical ALS complications, such as respiratory failures, aspirations, and respiratory infections. According to the available case information, most unexpected cardio-respiratory arrests occurred at home, often in bed and without health professional eyewitnesses. However, despite the challenges of reporting accurate death information, sudden and unexpected cardio-respiratory arrests are not uncommonly reported in patients with advanced ALS conditions [Rosenbohm, 2017].

The applicant emphasised that from a methodological point of view, the protocol and the case report forms were not designed to collect unexpected fatal events with sufficient level of detail required to conduct accurate analyses. For instance, the date and time of last treatment intake for patients who died were often solely based on declaration made by family member to the investigator sometimes weeks

later. These made the collection of accurate data such as last intake, and cause of death challenging for the investigators.

Table 88: Patients who died from fatal SAEs within 24 hours after last intake

System Organ Class	Placebo (N=133)	Masitinib 4.5 mg/kg (N=129)	Masitinib 3.0 mg/kg (N=131)
Preferred Term	n (%)	n (%)	n (%)
At Least One Fatal Serious Adverse Event (24 hours)	**5 (3.8%)**	**7 (5.4%)**	**14 (10.7%)**
Respiratory, Thoracic and Mediastinal Disorders	**3 (2.3%)**	**3 (2.3%)**	**8 (6.1%)**
Respiratory Failure	2 (1.5%)	2 (1.6%)	2 (1.5%)
Respiratory Arrest		1 (0.8%)	2 (1.5%)
Acute Respiratory Failure			1 (0.8%)
Chronic Respiratory Failure			1 (0.8%)
Dyspnoea	1 (0.8%)		
Aspiration		1 (0.8%)	1 (0.8%)
Pulmonary Oedema			1 (0.8%)
Cardiac Disorders	**1 (0.8%)**	**2 (1.6%)**	**6 (4.6%)**
Cardio-Respiratory Arrest		2 (1.6%)	5 (3.8%)
Cardiac Arrest	1 (0.8%)		
Cardiopulmonary Failure			1 (0.8%)
Nervous System Disorders		**1 (0.8%)**	**1 (0.8%)**
Amyotrophic Lateral Sclerosis		1 (0.8%)	
Brain Oedema			1 (0.8%)
Infections and Infestations	**1 (0.8%)**		**1 (0.8%)**
Pneumonia	1 (0.8%)		1 (0.8%)

Source: AB10015 Mortality Analysis Doc Tae_socpt_dth24hr; Abbreviations: N = number of patients in population. n = number of patients with a fatal SAE.

Other Significant Adverse Events

TKI products have been associated with acute adverse reactions, such as peripheral and superficial oedema, skin toxicity, gastrointestinal reactions such as nausea and diarrhoea, and laboratory related reactions such as leukopenia, anaemia, and liver toxicity.

The carcinogenicity of Masitinib AB Science was identified in 2 preclinical studies in mice (in male mice - urinary bladder cell carcinoma and malignant transitional cell carcinoma) and rats (in female rats at the highest dose - an increase in adenocarcinomas, and in incidence of benign tumours in the lung and in the thyroid).

In study AB10015, 2 patients (1.5%) in placebo and none in Masitinib AB Science arms were reported with malignancies. Although no risk of carcinogenicity was observed with study drug in ALS study, considering the limited duration of this study, no concluding statement can be made for this risk with Masitinib AB Science.

In regard to all non-oncology studies, 39 patients (1.3% of total safety population) were diagnosed with new or recurrent malignancies. Of those, there were 25 patients on Masitinib AB Science (1.3%) as compared to 14 patients on placebo (1.4%).

2.6.8.4. Laboratory findings

Haematology Parameters

Study AB10015, during W0-W48

Neutrophils Count

The number of patients with low neutrophil counts was higher in the Masitinib AB Science arms. Severe neutropenia was reported for one patient (0.8%) in the active control arm (G3), two patients (1.6%) in masitinib 3 mg/kg/day arm (G4) and one patient (0.8%) in Masitinib AB Science 4.5 mg/kg/day arm (G3). The risk of severe neutropenia with Masitinib AB Science was observed at 0.8%. (Table 89)

Haemoglobin

Both high and low abnormal haemoglobin values were noted in the study, and they both were higher in the Masitinib AB Science arms (Table 89). A severe increase (G3) of haemoglobin was reported for two patients (1.6%) in Masitinib AB Science 3 mg/kg/day arm and none in placebo and Masitinib AB Science 4.5 mg/kg/day arms. A severe decrease (G3) of haemoglobin was reported for two patients (1.8%) in Masitinib AB Science 3 mg/kg/day arm and none in placebo and Masitinib AB Science 4.5 mg/kg/day arms.

Leukocytes

Both high and low abnormal leukocytes counts were observed, and they both were higher in the Masitinib AB Science arms (Table 89). No case of severe increased or decreased leukocyte count with Masitinib AB Science was reported.

Lymphocytes

Both low and high abnormal lymphocytes counts were observed, and they both were higher in the Masitinib AB Science arms (Table 89). No case of severe increased or decreased lymphocytes count was recorded.

Platelets

Low platelet counts were noted in masitinib arms, all of them were of Grade 1. More details below.

Table 89: Frequency of Abnormal Blood Cell Counts (Shift from Normal/High to Low or from Normal/Low to High) – in Study AB10015 (W0-W48, N=393)

Parameter	Abnormality	Worst grade during study	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
Neutrophils	Low	n	130	126	129
		Abnormal	7 (5.4%)	15 (11.9%)	18 (14.0%)
		G1	4 (3.1%)	6 (4.8%)	13 (10.1%)
		G2	1 (0.8%)	7 (5.6%)	3 (2.3%)
		G3	1 (0.8%)	-	1 (0.8%)
		G4	-	2 (1.6%)	-
		Missing	1 (0.8%)	-	1 (0.8%)
Hemoglobin	Low	n	121	112	115
		Abnormal	39 (32.2%)	49 (43.8%)	66 (57.4%)
		G1	36 (29.8%)	45 (40.2%)	61 (53.0%)
		G2	2 (1.7%)	2 (1.8%)	4 (3.5%)
		G3	-	2 (1.8%)	-
		G4	-	-	-
		Missing	1 (0.8%)	-	1 (0.9%)
Leukocytes	Low	n	129	124	128
		Abnormal	16 (12.4%)	22 (17.7%)	30 (23.4%)
		G1	14 (10.9%)	18 (14.5%)	26 (20.3%)
		G2	1 (0.8%)	4 (3.2%)	3 (2.3%)
		G3	-	-	-
		G4	-	-	-
		Missing	1 (0.8%)	-	1 (0.8%)
Lymphocytes	Low	n	124	120	121
		Abnormal	20 (16.1%)	39 (32.5%)	51 (42.1%)
		G1	11 (8.9%)	27 (22.5%)	31 (25.6%)
		G2	8 (6.5%)	12 (10.0%)	20 (16.5%)
		G3	-	-	-
		G4	-	-	-
		Missing	1 (0.8%)	-	-
Platelets	Low	n	129	130	125
		Abnormal	6 (4.7%)	10 (7.7%)	9 (7.2%)
		G1	5 (3.9%)	10 (7.7%)	8 (6.4%)
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	1 (0.8%)	-	1 (0.8%)
Hemoglobin	High	N	129	126	125
		Abnormal	39 (30.2%)	49 (38.9%)	66 (52.8%)
		G1	36 (27.9%)	45 (35.7%)	61 (48.8%)
		G2	2 (1.6%)	2 (1.6%)	4 (3.2%)
		G3	-	2 (1.6%)	-
		G4	-	-	-
		Missing	1 (0.8%)	-	1 (0.8%)
Leukocytes	High	N	132	130	129
		Abnormal	16 (12.1%)	22 (16.9%)	30 (23.3%)
		G1	14 (10.6%)	18 (13.8%)	26 (20.2%)
		G2	1 (0.8%)	4 (3.1%)	3 (2.3%)
		G3	-	-	-
		G4	-	-	-
		Missing	1 (0.8%)	-	1 (0.8%)
Lymphocytes	High	N	130	129	128
		Abnormal	20 (15.4%)	40 (31.0%)	51 (39.8%)
		G1	11 (8.5%)	28 (21.7%)	31 (24.2%)
		G2	8 (6.2%)	12 (9.3%)	20 (15.6%)
		G3	-	-	-
		G4	-	-	-
		Missing	1 (0.8%)	-	-

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. N=Number of patients in the arm. n=Number of patients with a normal (i.e., not low if calculating low and not high if calculating high) baseline and at least one post-baseline measure.

Biochemistry Parameters

Study AB10015, during W0-W48

No specific safety signal was identified after review of the laboratory data. Most of the laboratory abnormalities were of Grade 1 or 2. The risk of severe high alanine aminotransferase with Masitinib AB Science was observed at 1.1%. The risk of severe low phosphate with Masitinib AB Science was observed at 2.5%.

Table 90: Abnormal Biochemistry Values (Shift from Normal/High to Low) – in Study AB10015 (W0-W48, N=393)

Parameter	Abnormality	Worst grade during study	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
Albumin	Low	n	131	125	128
		Abnormal	7 (5.3%)	2 (1.6%)	13 (10.2%)
		G1	4 (3.1%)	-	8 (6.3%)
		G2	-	-	1 (0.8%)
		G3	-	1 (0.8%)	1 (0.8%)
		G4	-	-	-
		Missing	3 (2.3%)	1 (0.8%)	3 (2.3%)
Glucose	Low	n	128	127	125
		Abnormal	12 (9.4%)	9 (7.1%)	8 (6.4%)
		G1	5 (3.9%)	5 (3.9%)	1 (0.8%)
		G2	-	-	1 (0.8%)
		G3	-	-	-
		G4	-	-	-
		Missing	7 (5.5%)	4 (3.1%)	6 (4.8%)
Calcium	Low	n	131	128	126
		Abnormal	23 (17.6%)	13 (10.2%)	17 (13.5%)
		G1	16 (12.2%)	8 (6.3%)	9 (7.1%)
		G2		1 (0.8%)	1 (0.8%)
		G3		1 (0.8%)	
		G4	-	-	-

Parameter	Abnormality	Worst grade during study	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
		Missing	7 (5.5%)	3 (2.5%)	7 (5.8%)
Phosphate	Low	n	127	125	120
		Abnormal	13 (10.2%)	20 (16.0%)	38 (31.7%)
		G1	2 (1.6%)	9 (7.2%)	8 (6.7%)
		G2	4 (3.1%)	6 (4.8%)	21 (17.5%)
		G3	-	-	3 (2.5%)
		G4	-	-	-
		Missing	7 (5.5%)	5 (4.0%)	6 (5.0%)
Potassium	Low	n	131	130	129
		Abnormal	12 (9.2%)	4 (3.1%)	8 (6.2%)
		G1	3 (2.3%)	1 (0.8%)	2 (1.6%)
		G2	1 (0.8%)		
		G3	1 (0.8%)	1 (0.8%)	1 (0.8%)
		G4			
		Missing	7 (5.3%)	2 (1.5%)	5 (3.9%)
Sodium	Low	n	130	130	126
		Abnormal	16 (12.3%)	12 (9.2%)	17 (13.5%)
		G1	9 (6.9%)	7 (5.4%)	12 (9.5%)
		G2			
		G3		1 (0.8%)	
		G4		1 (0.8%)	
		Missing	7 (5.4%)	3 (2.4%)	5 (4.0%)

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. N=Number of patients in the arm. n=Number of patients with a normal (i.e., not low if calculating low and not high if calculating high).

Table 91: Abnormal Biochemistry Values (Shift from Normal/Low to High) – in Study AB10015 (W0-W48, N=393)

Parameter	Abnormality	Worst grade during study	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
Alanine aminotransferase	High	n	92	101	86
		Abnormal	22 (23.9%)	37 (36.6%)	45 (52.3%)
		G1	21 (22.8%)	32 (31.7%)	41 (47.7%)
		G2	-	3 (3.0%)	-
		G3	-	1 (1.0%)	1 (1.2%)
		G4	-	-	-
		Missing	1 (1.1%)	1 (1.0%)	3 (3.5%)
Aspartate aminotransferase	High	n	104	104	103
		Abnormal	22 (21.2%)	34 (32.7%)	58 (56.3%)
		G1	18 (17.3%)	31 (29.8%)	55 (53.4%)
		G2	-	2 (1.9%)	-
		G3	2 (1.9%)	-	1 (1.0%)
		G4	-	-	-
		Missing	2 (1.9%)	1 (1.0%)	2 (1.9%)
Alkaline phosphatase	High	n	130	124	126
		Abnormal	6 (4.6%)	7 (5.6%)	15 (11.9%)
		G1	4 (3.1%)	6 (4.8%)	10 (7.9%)
		G2	-	-	1 (0.8%)
		G3	-	-	-
		G4	-	-	-
		Missing	2 (1.5%)	1 (0.8%)	4 (3.2%)
Gamma glutamyl transferase	High	n	109	98	106
		Abnormal	14 (12.8%)	10 (10.2%)	18 (17.0%)
		G1	10 (9.2%)	8 (8.2%)	13 (12.3%)
		G2	1 (0.9%)	-	2 (1.9%)
		G3	-	-	-
		G4	-	-	-
		Missing	3 (2.8%)	2 (2.0%)	3 (2.8%)
Bilirubin	High	n	114	119	115
		Abnormal	20 (17.5%)	29 (24.4%)	40 (34.8%)
		G1	13 (11.4%)	20 (16.8%)	32 (27.8%)
		G2	4 (3.5%)	8 (6.7%)	4 (3.5%)
		G3	-	-	1 (0.9%)
		G4	-	-	-
		Missing	3 (2.6%)	1 (0.8%)	3 (2.6%)
Creatinine	High	n	128	127	129
		Abnormal	2 (1.6%)	2 (1.6%)	9 (7.0%)
		G1	1 (0.8%)	1 (0.8%)	6 (4.7%)
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	1 (0.8%)	1 (0.8%)	3 (2.3%)
Cholesterol	High	n	45	65	46
		Abnormal	20 (44.4%)	14 (21.5%)	7 (15.2%)
		G1	18 (40.0%)	12 (18.5%)	6 (13.0%)
		G2	1 (2.2%)	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	1 (2.2%)	2 (3.1%)	1 (2.2%)
Triglycerides	High	n	90	87	88
		Abnormal	33 (36.7%)	17 (19.5%)	24 (27.3%)
		G1	24 (26.7%)	12 (13.8%)	18 (20.5%)
		G2	2 (2.2%)	1 (1.1%)	1 (1.1%)
		G3	-	-	-
		G4	-	-	-
		Missing	7 (7.8%)	4 (4.6%)	5 (5.7%)

		n	113	107	113
		Abnormal	40 (35.4%)	32 (29.9%)	48 (42.5%)
		G1	32 (28.3%)	27 (25.2%)	39 (34.5%)
Glucose	High	G2	1 (0.9%)	1 (1.0%)	3 (2.7%)
		G3	-	-	-
		G4	-	-	-
		Missing	7 (6.2%)	4 (3.7%)	6 (5.3%)
		n	120	115	117
		Abnormal	23 (19.2%)	13 (11.3%)	17 (14.5%)
		G1	16 (13.3%)	8 (7.0%)	9 (7.7%)
Calcium	High	G2	-	1 (0.9%)	1 (0.9%)
		G3	-	1 (0.9%)	-
		G4	-	-	-
		Missing	7 (5.8%)	3 (2.6%)	7 (6.0%)
		n	128	127	129
		Abnormal	11 (8.6%)	3 (2.4%)	8 (6.2%)
		G1	3 (2.3%)	1 (0.8%)	2 (1.6%)
Potassium	High	G2	1 (0.8%)	-	-
		G3	1 (0.8%)	-	1 (0.8%)
		G4	-	-	-
		Missing	6 (4.7%)	2 (1.6%)	5 (3.9%)
		n	133	126	129
		Abnormal	16 (12.0%)	12 (9.5%)	17 (13.2%)
Sodium	High	G1	9 (6.8%)	7 (5.6%)	12 (9.3%)
		G2			
		G3		1 (0.8%)	
		G4		1 (0.8%)	
		Missing	7 (5.3%)	3 (2.4%)	5 (3.9%)

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. N=Number of patients in the arm. n=Number of patients with a normal (i.e., not low if calculating low and not high if calculating high).

Study AB10015, during extension period

Neutrophils Count

A low neutrophil count was reported for one patient in placebo arm, two patients in Masitinib AB Science 3 mg/kg/day arm and none in Masitinib AB Science 4.5 mg/kg/day arm. All the cases were of Grade 1 or 2.

Haemoglobin

An increased haemoglobin (Grade 1) was observed for one patient in Masitinib AB Science 3 mg/kg/day arm, and none in placebo and Masitinib AB Science 4.5 mg/kg/day arm.

Number of patients with decreased haemoglobin was higher in the Masitinib AB Science arms during the protocol extension period: 19.0% of the patients in placebo arm, 35.8% in Masitinib AB Science 3 mg/kg/day arm and 28.1% in Masitinib AB Science 4.5 mg/kg/day arm. A severe decrease (G3) of haemoglobin was reported for one patient in Masitinib AB Science 3 mg/kg/day arm and none in other two arms. The risk of severe decrease of haemoglobin with Masitinib AB Science was observed at 0.9% during the protocol extension period of the study.

Leukocytes

Decreased leukocytes count was higher in placebo arm: 7.4% in placebo arm, 1.6% in Masitinib AB Science 3 mg/kg/day arm and 3.1% in Masitinib AB Science 4.5 mg/kg/day arm. No case of severe decreased leukocyte count was reported.

Lymphocytes

Decreased lymphocytes count was higher in the Masitinib AB Science arms: 7.9% in placebo arm, 21.4% in Masitinib AB Science 3 mg/kg/day arm and 36.1% in Masitinib AB Science 4.5 mg/kg/day arm. No case of severe decreased lymphocytes count was reported.

Platelets

Low platelet counts were reported in 2 patients (3.0%) in placebo arm, 2 patients (3.2%) in the Masitinib AB Science 3 mg/kg/day arm and one patient (1.6%) in the Masitinib AB Science 4.5 mg/kg/day arm during the protocol extension. All of them were of Grade 1.

Table 92: Frequency of Abnormal Biochemistry (Hepatobiliary Enzymes) Values (Shift from Normal/High to Low and from Normal/Low to High) - (Extended Period)

Parameter	Abnormality	Worst grade during study	P + R	M 3.0 + R	M 4.5 + R
Alanine aminotransferase	High	N	46	44	40
		Abnormal	8 (17.4%)	11 (25.0%)	8 (20.0%)
		G1	8 (17.4%)	11 (25.0%)	8 (20.0%)
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-
Aspartate aminotransferase	High	N	51	46	54
		Abnormal	5 (9.8%)	10 (21.7%)	16 (29.6%)
		G1	5 (9.8%)	10 (21.7%)	16 (29.6%)
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-
Alkaline phosphatase	High	N	61	59	62
		Abnormal	2 (3.3%)	1 (1.7%)	-
		G1	2 (3.3%)	1 (1.7%)	-
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-
Gamma glutamyl transferase	High	N	54	44	56
		Abnormal	6 (11.1%)	6 (13.6%)	2 (3.6%)
		G1	6 (11.1%)	6 (13.6%)	1 (1.8%)
		G2	-	-	1 (1.8%)
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-
Albumin	Low	N	66	58	62
		Abnormal	1 (1.5%)	0	0
		G1	1 (1.5%)	-	-
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-
Bilirubin		N	60	57	56
		Abnormal	4 (6.7%)	8 (14.0%)	12 (21.4%)
	High	G1	3 (5.0%)	7 (12.3%)	11 (19.6%)
		G2	1 (1.7%)	1 (1.8%)	1 (1.8%)
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.
N=Patients with available data at baseline
Source: Statistical Table 14.3.4.48

Table 93: Frequency of Abnormal Biochemistry (Renal Enzyme) Values (Shift from Normal/High to Low and from Normal/Low to High) - (Extended Period)

Parameter	Abnormality	Worst grade during study	P + R	M 3.0 + R	M 4.5 + R
Creatinine	High	N	66	62	64
		Abnormal	1 (1.5%)	0	1 (1.6%)
		G1	1 (1.5%)	-	1 (1.6%)
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.
N=Patients with available data at baseline
Source: Statistical Table 14.3.4.48

Table 94: Frequency of Abnormal Biochemistry (Lipoproteins) Values (Shift from Normal/High to Low and from Normal/Low to High) - (Extended Period)

Parameter	Abnormality	Worst grade during study	P + R	M 3.0 + R	M 4.5 + R
Cholesterol	High	N	21	30	26
		Abnormal	6 (28.6%)	4 (13.3%)	1 (3.8%)
		G1	6 (28.6%)	4 (13.3%)	1 (3.8%)
		G2	-	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-
Triglycerides	High	N	44	41	42
		Abnormal	13 (29.5%)	10 (24.4%)	10 (23.8%)
		G1	12 (27.3%)	10 (24.4%)	10 (23.8%)
		G2	1 (2.3%)	-	-
		G3	-	-	-
		G4	-	-	-
		Missing	-	-	-

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.
N=Patients with available data at baseline
Source: Statistical Table 14.3.4.48

The percentage of patients with high AST values during the protocol extension period was observed to be higher in the Masitinib AB Science arms; 9.8% in the active control arm, 22.2% in Masitinib AB Science 3 mg/kg/day arm and 29.6% in Masitinib AB Science 4.5 mg/kg/day arm. Only Grade 1 of high AST values were reported during the extension period. No risk of severe high AST with Masitinib AB Science was observed.

The percentage of patients with high bilirubin values during the extension period was higher in the Masitinib AB Science arms; 6.7% in the active control arm, 14.0% in Masitinib AB Science 3 mg/kg/day arm and 21.4% in Masitinib AB Science 4.5 mg/kg/day arm. The majority of patients (%) experienced Grade 1 or 2 of high bilirubin values. No risk of severe high bilirubin with Masitinib AB Science was observed.

Other abnormal biochemistry values were in general similar in placebo and masitinib groups.

No important safety information was observed. Much less abnormal blood cell counts/biochemistry were reported during the extension period comparing with the main period (26 vs. 168 AEs). During the extension period, no action was taken with the study drug for them. No case of positive dechallenge or dechallenge was reported. During both main and extension period, most of abnormal blood cell counts/biochemistry resolved without drug interruption/discontinuation and were in generally mild to moderate and transient.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Elderly population

There were 73 elderly patients (18.6%) aged >65 years and 320 non-elderly patients (81.4%) in the age group 18 to 65 years in ALS study. The safety profile of Masitinib AB Science seems to be better in the non-elderly patients as compared to the elderly patients at a dose of 3.0 mg/kg/day, and comparable at a dose of 4.5 mg/kg/day.

Table 95: Safety profile of masitinib in patients aged 18 to 65 year and >65 years – in Study AB10015 (W0-W48, N=393)

Number (%) of patients with at least one	18 to 65 years (N=320)			>65 years (N=73)		
	P + R	M 3.0 + R	M 4.5 + R	P + R	M 3.0 + R	M 4.5 + R
	(N=110)	(N=105)	(N=105)	(N=23)	(N=26)	(N=24)
AE	86 (78.2%)	89 (84.8%)	92 (87.6%)	18 (78.3%)	22 (84.6%)	22 (91.7%)
Death	8 (7.3%)	9 (8.6%)	8 (7.6%)	4 (17.4%)	2 (7.7%)	2 (8.3%)
Non-fatal SAE	21 (19.1%)	21 (20.0%)	33 (31.4%)	3 (13.0%)	9 (34.6%)	7 (29.2%)
Severe AE	20 (18.2%)	20 (19.0%)	30 (28.6%)	6 (26.1%)	8 (30.8%)	9 (37.5%)
Discontinuation (excluding deaths)	9 (8.2%)	13 (12.4%)	14 (13.3%)	2 (8.7%)	7 (26.9%)	7 (29.2%)

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day.

Table 96: Summary of TEAEs by dose and Patients aged 18-65 year and above 65 years - in non-oncology studies excluding AB10015

	18-65 years				➢ 65 years			
	M3.0	M4.5	M-All	Placebo*	M3.0	M4.5	M-All	Placebo*
No. of Subjects with at least one	(N= 93)	(N= 298)	(N= 1398)	(N= 707)	(N= 63)	(N= 163)	(N= 526)	(N= 297)
All AEs	80 (86.0%)	273 (91.6%)	1242 (88.8%)	584 (82.6%)	56 (88.9%)	148 (90.8%)	460 (87.5%)	250 (84.2%)
SAE (non-fatal) (all)	19 (20.4%)	68 (22.8%)	320 (22.9%)	101 (14.3%)	13 (20.6%)	30 (18.4%)	103 (19.6%)	33 (11.1%)
Death (all)	0	0	6 (0.4%)	5 (0.7%)	0	5 (3.1%)	7 (1.3%)	6 (2.0%)
Leading to permanent discontinuation (excl Death)	30 (32.3%)	72 (24.2%)	315 (22.5%)	43 (6.1%)	19 (30.2%)	38 (23.3%)	152 (28.9%)	23 (7.7%)
Leading to dose reduction	0	13 (4.4%)	105 (7.5%)	9 (1.3%)	1 (1.6%)	12 (7.4%)	38 (7.2%)	11 (3.7%)
Severe (Grade 3 and above)	20 (21.5%)	91 (30.5%)	562 (40.2%)	211 (29.8%)	17 (27.0%)	54 (33.1%)	170 (32.3%)	77 (25.9%)

There was no safety analysis performed in detailed elderly groups (refer to the table below)

Table 97: Occurrence of Treatment-Emergent Adverse Events - Number and Percent of Subjects by age group Classic frequency: Number (%) of patients (Main Period) Safety Population

MedDRA PTs	Age <65 (N=310)	Age 65-74 (N=80)	Age 75-84 (N=3)	Age 85+ (N=0)
Total AEs	258 (83.2)	68 (85.0)	3 (100.0)	0
Serious AEs - Total	90 (29.0)	27 (33.8)	1 (33.3)	0
- Fatal	24 (7.7)	9 (11.3)	0	0
- Hospitalization/prolong existing hospitalization	58 (18.7)	15 (18.8)	1 (33.3)	0
- Life-threatening	4 (1.3)	1 (1.3)	0	0
- Disability/incapacity	2 (0.6)	1 (1.3)	0	0
- Other (medically significant)	14 (4.5)	2 (2.5)	0	0
AE leading to drop-out(excl. death)	35 (11.3)	17 (21.3)	0	0
Psychiatric disorders	47 (15.2)	15 (18.8)	0	0
Nervous system disorders	43 (13.9)	11 (13.8)	1 (33.3)	0
Accidents and injuries	41 (13.2)	7 (8.8)	1 (33.3)	0
Cardiac disorders	11 (3.5)	7 (8.8)	0	0
Vascular disorders	19 (6.1)	4 (5.0)	0	0
Cerebrovascular disorders	3 (1.0)	2 (2.5)	0	0
Infections and infestations	83 (26.8)	23 (28.8)	0	0
Anticholinergic syndrome	49 (15.8)	13 (16.3)	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	30 (9.7)	6 (7.5)	0	0
<other AE appearing more frequently in older patients>				
Abdominal Discomfort	1 (0.3)	0	1 (33.3)	0
Abdominal Pain	1 (0.3)	2 (2.5)	0	0
Abdominal Pain Upper	13 (4.2)	3 (3.8)	0	0
Anaemia	4 (1.3)	2 (2.5)	0	0
Anxiety	12 (3.9)	1 (1.3)	0	0
Aspartate Aminotransferase Increased	5 (1.6)	2 (2.5)	0	0
Back Pain	6 (1.9)	2 (2.5)	0	0
Blood Phosphorus Decreased	2 (0.6)	3 (3.8)	0	0
Blood Urea Increased	1 (0.3)	1 (1.3)	1 (33.3)	0
Bronchitis	11 (3.5)	4 (5.0)	0	0
Cardio-Respiratory Arrest	2 (0.6)	4 (5.0)	0	0

MedDRA PTs	Age <65 (N=310)	Age 65-74 (N=80)	Age 75-84 (N=3)	Age 85+ (N=0)
Constipation	7 (2.3)	3 (3.8)	0	0
Cough	8 (2.6)	1 (1.3)	0	0
Cystitis Bacterial	7 (2.3)	6 (7.5)	0	0
Decreased Appetite	4 (1.3)	4 (5.0)	0	0
Depression	22 (7.1)	10 (12.5)	0	0
Diarrhoea	21 (6.8)	4 (5.0)	1 (33.3)	0
Dysarthria	2 (0.6)	2 (2.5)	0	0
Dyspepsia	12 (3.9)	3 (3.8)	0	0
Dysphagia	38 (12.3)	11 (13.8)	0	0
Dyspnoea	7 (2.3)	4 (5.0)	1 (33.3)	0
Dyspnoea Exertional	1 (0.3)	0	1 (33.3)	0
Eosinophil Count Decreased	0	0	1 (33.3)	0
Eosinophil Count Increased	6 (1.9)	1 (1.3)	1 (33.3)	0
Erythema	11 (3.5)	3 (3.8)	0	0
Fall	26 (8.4)	5 (6.3)	0	0
Fatigue	4 (1.3)	2 (2.5)	0	0
Foot Fracture	0	0	1 (33.3)	0
Gastrooesophageal Reflux Disease	5 (1.6)	2 (2.5)	0	0
Haematocrit Decreased	2 (0.6)	3 (3.8)	0	0
Haematuria	0	2 (2.5)	0	0
Haemoglobin Decreased	5 (1.6)	2 (2.5)	0	0
Headache	18 (5.8)	5 (6.3)	0	0
Hypertension	13 (4.2)	4 (5.0)	0	0
Hypokalaemia	0	2 (2.5)	0	0
Influenza	8 (2.6)	2 (2.5)	0	0
Insomnia	14 (4.5)	6 (7.5)	0	0
Iron Deficiency Anaemia	10 (3.2)	1 (1.3)	2 (66.7)	0
Lymphocyte Count Decreased	4 (1.3)	1 (1.3)	1 (33.3)	0
Lymphopenia	1 (0.3)	2 (2.5)	0	0
Muscle Spasms	5 (1.6)	2 (2.5)	0	0

MedDRA PTs	Age <65 (N=310)	Age 65-74 (N=80)	Age 75-84 (N=3)	Age 85+ (N=0)
Muscular Weakness	7 (2.3)	1 (1.3)	0	0
Nausea	27 (8.7)	4 (5.0)	0	0
Neutropenia	2 (0.6)	2 (2.5)	0	0
Oedema Peripheral	12 (3.9)	5 (6.3)	0	0
Oral Fungal Infection	0	2 (2.5)	0	0
Pneumonia	2 (0.6)	3 (3.8)	0	0
Pruritus	5 (1.6)	3 (3.8)	0	0
Pruritus Generalised	7 (2.3)	0	0	0
Rash	11 (3.5)	5 (6.3)	0	0
Rash Maculo-Papular	17 (5.5)	1 (1.3)	0	0
Red Blood Cell Count Decreased	5 (1.6)	3 (3.8)	0	0
Respiratory Failure	22 (7.1)	5 (6.3)	0	0
Salivary Hypersecretion	2 (0.6)	2 (2.5)	0	0
Sciatica	2 (0.6)	0	1 (33.3)	0
Upper Respiratory Tract Infection	7 (2.3)	0	0	0
Urinary Tract Infection	9 (2.9)	3 (3.8)	0	0
Vertigo	1 (0.3)	2 (2.5)	0	0
Viral Upper Respiratory Tract Infection	17 (5.5)	5 (6.3)	0	0
Weight Decreased	31 (10.0)	7 (8.8)	0	0
White Blood Cell Count Increased	0	2 (2.5)	0	0
White Blood Cells Urine Positive	2 (0.6)	1 (1.3)	1 (33.3)	0

Abbreviations: N = number of patients in age group (Safety population).

Limited information is available on elderly patients due to very small number of patients from 75 years old (3 subjects in age group 75-84 and 0 subjects in age group 85 and more). In general, number of AEs in total and serious AEs was similar in both subjects up to 64 years old and for subjects from 65 to 74 years old, with slight increase in older group. Fatal AEs were more frequent in patients of 65 years old and more versus patients younger than 65 (7.7 vs. 11.3%) as well as AE leading to drop-out (excl. death) (11.3 vs. 21.3%). No new safety issues were identified in elderly population.

Pregnant and breast-feeding women

All pregnant or breast-feeding women were excluded from participation in any of the Masitinib AB Science clinical trials. Additionally, pregnancy and breast-feeding were contraindicated being under Masitinib AB Science treatment, or within 1 month of their last intake.

One female patient in study AB04010 (Mastocytosis,) became pregnant in, 2006 despite hormonal contraception. The patient underwent an abortion and study drug was maintained.

Two cases of pregnancies were reported in study AB14001, 117 and 174 days respectively after the first intake of Masitinib AB Science. Treatment with study drug was permanently discontinued for those two patients soon after the confirmation of pregnancies. In both cases patients gave birth to healthy babies and had a normal post-partum.

There were no reported cases of women breast-feeding in any of the Masitinib AB Science clinical trials.

Patients with renal impairment

Patients with pre-existing severe renal impairment or with abnormal laboratory results at screening and baseline (CrCl < 60 mL/min or proteinuria > 30 mg/dL (1+) on dipstick; in case of the proteinuria ≥ 1+ on the dipstick, 24 hours proteinuria must be > 1.5g/24 hours) were excluded in all Masitinib AB Science clinical trials.

Patients with hepatic impairment

Patients with history of hepatic disorders, with a known liver disease, recent alcohol abuse or with abnormal laboratory results at screening and/or baseline (hepatic transaminase levels > 2 ULN, or total

bilirubin level > 1.5 ULN, or both hepatic transaminase levels and total bilirubin level outside of the normal ranges, or albuminaemia < 1 x LLN) were excluded in all Masitinib AB Science clinical trials.

Children

No patients aged less than 18 years old were included in any Masitinib AB Science study.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No case of DDI was reported in the ALS study or the non-oncology studies.

The PK interactions with itraconazole were characterised in healthy volunteers in Study AB14004. This was a repeat dose study with administration of itraconazole 200 mg QD for 5 days, (from day 9 to 13) in 12 healthy volunteers. On the morning of Day 12, a single dose of Masitinib AB Science 3.0 mg/kg was administered 1 hour after the administration of 200 mg itraconazole. The results indicated a trend of increase in C_{max} and $AUC_{0-\infty}$ of Masitinib AB Science when using concomitantly with itraconazole. The increase was of 27% for C_{max} and 43% for $AUC_{0-\infty}$, however the coefficients of variations were of 45% and 36% for C_{max} and of 42% and 30% for $AUC_{0-\infty}$, for Masitinib AB Science alone and Masitinib AB Science with itraconazole respectively. It may suggest a DDI risk between Masitinib AB Science and concomitant treatments interacting with CYP3A4.

Depending on the interactions between Masitinib AB Science and a concomitant treatment, the plasma concentration of Masitinib AB Science or the concomitant treatment can either be increased or decreased. Thus, may result in either increase in related ADRs or decrease in the efficacy of masitinib or the concomitant treatment.

Possible interactions between masitinib and concomitant treatments interacting with cytochromes P450:

- Masitinib **may increase** plasma concentration of certain medicinal products

There is a risk of DDI with medicinal products which are substrates for CYP3A4, P-gp and BCRP. The extent has not been elucidated *in vivo*. Concomitant administration of these substrates should be avoided for narrow therapeutic index drugs and carefully monitored for medicinal products with large therapeutic window. If monitoring is not possible in practice, then co-administration should be avoided especially in case of long-term prescribed medications. No data are available for the inhibitory potential of Masitinib AB Science on CYP2B6, so caution recommended when taken concomitantly.

- Masitinib **may decrease** plasma concentration of certain medicinal products

There is a risk of DDI with medicinal products for which the uptake depends on BCRP. Concomitant oral administration of substrates of BCRP (e.g. anthracyclines, topotecan) is not recommended unless the healthcare practitioner considers that the potential benefit justifies the risk.

Concomitant administration of Masitinib AB Science with medicinal products which are substrates of P-gp transporters or OCT2 transporters could decrease the plasma concentration to these substances. Caution should be taken when administering Masitinib AB Science with substrates of P-gp transporters with a narrow therapeutic window (e.g. digoxin, loperamide, berberine). It is recommended to take the concomitant treatment in between the two daily doses of Masitinib AB Science.

- Plasma concentration of masitinib **may be decreased** by certain medicinal products

Concomitant administration of Masitinib AB Science with inducers of CYP3A4 could decrease Masitinib AB Science plasma concentrations. Administration of Masitinib AB Science with inducers of CYP3A4 is contraindicated. The selection of an alternative medication that has no, or minimal enzyme induction potential is recommended.

- Plasma concentration of masitinib **may be increased** by certain medicinal products

Concomitant administration of Masitinib AB Science with CYP3A4 inhibitors or P-gp inhibitors could increase masitinib plasma concentrations. There was an increase in exposure to Masitinib AB Science in healthy subjects when it was co-administered with itraconazole (a CYP3A4 inhibitor and P-gp inhibitor). The mean C_{max} and AUC_{0-t} of masitinib rose by 26% and 41.6%, respectively. Patients taking Masitinib AB Science with inhibitors of CYP3A4 (e.g. itraconazole, erythromycin, grapefruit juice) or inhibitors of P-gp (e.g. itraconazole, cyclosporine) should be monitored for adverse effects of masitinib. CYP2C8 is partially responsible for Masitinib AB Science *in vitro* biotransformation. Because of the lack of *in vivo* DDI investigations, the coadministration of Masitinib AB Science with CYP2C8 inhibitors should be avoided.

Medicinal product that moderate pH in the gut

Because of the lack of interaction studies with pH modifier drugs, H2 antagonist and PPI should be taken 2 hours after Masitinib AB Science, while antacid medicinal products should be administered 2 hours before or 2 hours after masitinib. If this particular restriction is not possible to respect, the co-administration with medicinal products that moderate pH should be avoided.

Interactions with riluzole and masitinib

Riluzole is metabolised by CYP1A2. This P450 isoenzyme is not inhibited by Masitinib AB Science and Masitinib AB Science is not an inducer or substrate of CYP1A2. DDI with Masitinib AB Science due to the major metabolizing enzyme of riluzole are therefore unlikely. In addition, Masitinib AB Science is mainly metabolised by CYP3A4 to its demethylated metabolite AB3280. Riluzole is not a substrate/inhibitor or inducer of CYP3A4 and therefore, DDI due to the major metabolizing enzyme of Masitinib AB Science is not expected.

2.6.8.8. Discontinuation due to adverse events

Table 98: AEs Leading Permanently to Discontinuation (Risk ≥1% in any PT) - Study AB10015

SYSTEM ORGAN CLASS PREFERRED TERM	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)	P + R (N=133)	M 3.0 + R (N=131)	M 4.5 + R (N=129)
	All			Related		
All	**11 (8.3)**	**20 (15.3)**	**21 (16.3)**	**3 (2.3)**	**8 (6.1)**	**15 (11.6)**
Gastrointestinal Disorders	**6 (4.5)**	**7 (5.3)**	**5 (3.9)**	**0 (0.0)**	**3 (2.3)**	**1 (0.8)**
Dysphagia	6 (4.5)	3 (2.3)	4 (3.1)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	**2 (1.5)**	**4 (3.1)**	**1 (0.8)**	**0**	**0**	**0**
Respiratory Failure	1 (0.8)	3 (2.3)	1 (0.8)	0	0	0
Investigations	**1 (0.8)**	**4 (3.1)**	**3 (2.3)**	**1 (0.8)**	**0 (0.0)**	**3 (2.3)**
Weight Decreased	0	4 (3.1)	0	0	0	0
Transaminases Increased	0	0	2 (1.6)	0	0	2 (1.6)
Nervous System Disorders	**0**	**3 (2.3)**	**1 (0.8)**	**0**	**0**	**0**
Amyotrophic Lateral Sclerosis	0	2 (1.5)	1 (0.8)	0	0	0
Skin and Subcutaneous Tissue Disorders	**0**	**3 (2.3)**	**6 (4.7)**	**0**	**3 (2.3)**	**6 (4.7)**
Rash Maculo-Papular	0	2 (1.5)	1 (0.8)	0	2 (1.5)	1 (0.8)

P = placebo; R = riluzole; M3.0 = masitinib 3.0 mg/kg/day; M4.5 = masitinib 4.5 mg/kg/day. Related = suspected or not assessable.

Number of AEs leading to study treatment permanent discontinuation during extension period is provided above.

Table 99: AEs Leading Permanently to Discontinuation (Risk ≥1% in any PT) – in non-oncology studies excluding AB10015

	Masitinib							
	3.0 N=156		4.5 N=461		All N=1924		Placebo* N=1004	
No. of Subjects with at least one	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**	**n(%)**	**events**
All AEs	**49 (31.4%)**	**68**	**110 (23.9%)**	**161**	**467 (24.3%)**	**773**	**66 (6.6%)**	**103**
Blood and Lymphatic System Disorders	**8 (5.1%)**	**8**	**13 (2.8%)**	**14**	**57 (3.0%)**	**64**	**4 (0.4%)**	**4**
Neutropenia	8 (5.1%)	8	6 (1.3%)	6	37 (1.9%)	37	1 (0.1%)	1
Gastrointestinal Disorders	**10 (6.4%)**	**11**	**23 (5.0%)**	**32**	**104 (5.4%)**	**150**	**7 (0.7%)**	**12**
Diarrhoea	5 (3.2%)	5	7 (1.5%)	8	36 (1.9%)	37	4 (0.4%)	4
Nausea	1 (0.6%)	1	6 (1.3%)	6	34 (1.8%)	34	0	0
Vomiting	1 (0.6%)	1	4 (0.9%)	4	19 (1.0%)	19	2 (0.2%)	2
General Disorders and Administration Site Conditions	**3 (1.9%)**	**4**	**6 (1.3%)**	**6**	**42 (2.2%)**	**55**	**3 (0.3%)**	**3**
Oedema Peripheral	2 (1.3%)	2	1 (0.2%)	1	8 (0.4%)	8	0	0
Infections and Infestations	**2 (1.3%)**	**2**	**4 (0.9%)**	**5**	**27 (1.4%)**	**31**	**2 (0.2%)**	**5**
Investigations	**4 (2.6%)**	**4**	**6 (1.3%)**	**6**	**33 (1.7%)**	**60**	**8 (0.8%)**	**14**
Weight Decreased	2 (1.3%)	2	1 (0.2%)	1	5 (0.3%)	5	1 (0.1%)	1
Metabolism and Nutrition Disorders	**1 (0.6%)**	**1**	**5 (1.1%)**	**5**	**27 (1.4%)**	**27**	**10 (1.0%)**	**10**
Musculoskeletal and Connective Tissue Disorders	**6 (3.8%)**	**6**	**4 (0.9%)**	**4**	**22 (1.1%)**	**23**	**2 (0.2%)**	**2**
Rheumatoid Arthritis	4 (2.6%)	4	0	0	6 (0.3%)	6	1 (0.1%)	1
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**0**	**0**	**6 (1.3%)**	**6**	**11 (0.6%)**	**13**	**8 (0.8%)**	**10**
Nervous System Disorders	**4 (2.6%)**	**5**	**10 (2.2%)**	**12**	**37 (1.9%)**	**49**	**12 (1.2%)**	**15**
Amnesia	2 (1.3%)	2	0	0	2 (0.1%)	2	0	0
Respiratory, Thoracic and Mediastinal Disorders	**4 (2.6%)**	**4**	**8 (1.7%)**	**9**	**31 (1.6%)**	**35**	**5 (0.5%)**	**5**
Asthma	3 (1.9%)	3	4 (0.9%)	4	11 (0.6%)	11	5 (0.5%)	5
Skin and Subcutaneous Tissue Disorders	**18 (11.5%)**	**19**	**37 (8.0%)**	**45**	**156 (8.1%)**	**182**	**1 (0.1%)**	**1**
Rash Maculo-Papular	3 (1.9%)	3	9 (2.0%)	9	34 (1.8%)	34	0	0
Rash	4 (2.6%)	4	8 (1.7%)	8	28 (1.5%)	28	0	0
Pruritus Generalised	2 (1.3%)	2	1 (0.2%)	1	5 (0.3%)	5	0	0

Discontinuation in healthy subjects

Seven subjects discontinued for safety reasons. Of those, 4 subjects withdrew because of moderate abdominal pain, diarrhoea, nausea and vomiting, and 3 subjects who withdrew due to moderate skin-related adverse events, including macular papular rashes and urticaria.

2.6.8.9. Post marketing experience

Masitinib AB Science is not yet approved or marketed in any country.

2.6.9. Discussion on clinical safety

Primary clinical safety data on Masitinib AB Science received from the Phase 2/3 study in patients with ALS. Safety analysis from nineteen (19) 2 and 3 phase studies for non-oncological indications and supportive safety information from 6 phase 1 studies in healthy subjects is available as well.

In study AB10015 during the main study protocol period (48 weeks), at least 1 AE was reported by 83.7% of patients. Of them, 78.2% in placebo, 84.7% in the 3.0 mg/kg, 88.4% in the 4.5 mg/kg Masitinib AB Science arm. More frequently reported AEs in one of the Masitinib AB Science versus placebo arm were maculo-papular rash, nausea, peripheral oedema, iron deficiency anaemia, respiratory failure, and dyspnoea. Majority of them were mild to moderate in intensity and their occurrence and severity appeared to be dose related. Severe AEs were more expressed in Masitinib AB Science 3.0 mg/kg/day and Masitinib AB Science 4.5 mg/kg/day groups comparing with placebo: 21.4%, and 30.2% respectively vs. 19.5%.

In regard to abnormal blood cell counts, percentage of such cases (both low and high) was higher in masitinib arms. Three cases of severe neutropenia were recorded on masitinib. Patients recovered after study treatment was temporally interrupted. Two cases of decreased haemoglobin grade 3 and one case of increased haemoglobin grade 3 were recorded on masitinib. Most of cases of abnormal blood cell counts were grade 1 or 2. In regard to increased biochemistry values, there were seven grade 3 values (ALT, AST, bilirubin, calcium, potassium, sodium) and one grade 4 value (sodium) recorded in masitinib arms vs. three grade 3 values (AST, potassium) in placebo arm. Increase in AST, ALT, Alkaline phosphatase values was highly dependent on Masitinib AB Science dose. In regard to decreased biochemistry values, there were ten grade 3 values (albumin, calcium, phosphate, potassium, sodium) and one grade 4 value (sodium) recorded in Masitinib AB Science arms vs. one grade 3 value (potassium) in placebo arm.

In regard to abnormal Biochemistry values during extension period, the percentage of patients with high AST values during the protocol extension period was observed to be higher in the Masitinib AB Science arms; 9.8% in the active control arm, 22.2% in Masitinib AB Science 3 mg/kg/day arm and 29.6% in Masitinib AB Science 4.5 mg/kg/day arm. Only Grade 1 of high AST values were reported during the extension period. No risk of severe high AST with Masitinib AB Science was observed.

The percentage of patients with high bilirubin values during the extension period was higher in the Masitinib AB Science arms; 6.7% in the active control arm, 14.0% in Masitinib AB Science 3 mg/kg/day arm and 21.4% in Masitinib AB Science 4.5 mg/kg/day arm. The majority of patients (%) experienced Grade 1 or 2 of high bilirubin values. No risk of severe high bilirubin with Masitinib AB Science was observed.

Other abnormal biochemistry values were in general similar in placebo and Masitinib AB Science groups.

Much less abnormal blood cell counts/biochemistry were reported during the extension period comparing with the main period (26 vs. 168 AEs). During the extension period, no action was taken with the study drug for them. No case of positive dechallenge or dechallenge was reported. During both main and extension period, most of abnormal blood cell counts/biochemistry resolved without drug interruption/discontinuation and were in generally mild to moderate and transient.

Increase in the frequency of non-fatal SAEs in Masitinib AB Science arms was dose dependent. 94 patients experienced SAEs: 24 placebo patients (18.0%), 30 patients (22.9%) in the Masitinib AB Science 3 mg/kg/day, and 40 patients (31.1%) in the Masitinib AB Science 4.5 mg/kg/day arm. The most frequently reported non-fatal SAEs in Masitinib AB Science patients under MedDRA SOC were Gastrointestinal Disorders, then Respiratory, Thoracic and Mediastinal Disorders, Infection and Infestations, Injury Poisoning and Procedural Complications, and Investigations. The most frequent PTs

were Dysphagia, Respiratory Failure, Dyspnoea, Lower Respiratory Tract Infection, Bronchitis, Fall, Transaminases Increased, Weight Decreased, and Neutropenia. According to the applicant, Respiratory failure, Dysphagia, and Dyspnoea were associated with ALS disease progression and were not reported as drug related. Above mentioned AEs, except for Lower Respiratory Tract Infection, Bronchitis and Weight Decreased were agreed to be added to SmPC section 4.8. by the applicant.

33 patients had a fatal SAEs. Of them, 12 patients (9.0%) in placebo arm, 11 patients (8.4%) in the 3.0 mg/kg/day Masitinib AB Science arm, and 10 patients (7.8%) in the 4.5 mg/kg/day Masitinib AB Science arm.

In study AB10015 during extension period, at least 1 AE was reported in 48.8% placebo, 56.3% of the Masitinib AB Science 3 mg/kg/day, 63.0% of the Masitinib AB Science 4.5 mg/kg/day arm. Most of mentioned AEs were mild to moderate in intensity, usually more frequent at the start of therapy and manageable with symptomatic treatments and dose reductions. In regard to abnormal blood cell counts, a severe decrease (G3) of haemoglobin was reported for one patient in Masitinib AB Science 3 mg/kg/day arm. None of severe abnormal blood cell counts were reported during extension period.

Overall, in non-oncological studies 89% of patients reported at least 1 AE. The most frequently reported SOC were Eye Disorders, GI Disorders, Skin and Subcutaneous Tissue Disorders and General Disorders and Administration Site Disorders. The most frequently reported PTs in Masitinib AB Science patients were Nausea, Diarrhoea, Rash, Eyelid Oedema, Pruritus and Rash Maculo-Papular. Of most frequently reported AEs, such as Cutaneous adverse reaction, Gastrointestinal disorders, Superficial oedema are known AEs of the THIs. Gastrointestinal disorders were experienced by up to 70% of patients, uncomplicated cutaneous reactions – up to 60%, constitutional symptoms (myalgia, pain, fatigue, dizziness) - up to 30%, oedema related events - up to 20% of patients.

In non-oncology studies the most frequently reported non-fatal SAEs under SOC in Masitinib AB Science versus placebo patients were Skin and Subcutaneous Tissue Disorders (4.0% versus 0.3%), Infections and Infestations (4.2% versus 2.3%), Blood and Lymphatic Disorders (2.4% versus 0.5%), Gastrointestinal Disorders (2.4% versus 0.7%) and Investigations (1.3% vs 0.2%).

In study with healthy subjects, 30% of population reported 154 AEs. The most common ones were nausea, vomiting, diarrhoea, abdominal pain, rash, dizziness, and episodes of headaches. The majority of AEs were assessed as related to Masitinib AB Science.

Number of deaths increased during ALS study extension period. During extension, 34 deaths were recorded: 7 placebo patients (8.8%), 13 patients (16.3%) in the Masitinib AB Science 3 mg/kg/day and 14 patients (19.2%) in the Masitinib AB Science 4.5 mg/kg/day arm.

The applicant stated that this imbalance may be explained by:

- the longer duration of treatment in Masitinib AB Science groups as compared to placebo group.
- the imbalance in terms of duration of disease from onset to randomization: patients from Masitinib AB Science groups had a longer duration of disease progression prior to randomization.
- the imbalance in terms of severity of clinical status at baseline: more very severe patients were enrolled in masitinib groups, which is likely to bias the interpretation of mortality rates.
- an increased rate of tracheostomy due to disadvantage at baseline/at start of extension period in masitinib patients (higher severity and longer duration of progression of the disease).
- a longer delay between disease onset and tracheostomy in Masitinib AB Science patients, despite disadvantage at baseline.
- an imbalance in severity of bulbar onset forms.

All deaths in Masitinib AB Science patients were assessed as not related to study drug, but it has to be noted as well, that assessment was performed by investigators and not by independent committee. It is agreed by CHMP, that factors mentioned above could be a reasonable explanation for imbalance between two study arms. However, long-term safety should be further characterised using additional pharmacovigilance activities. Also, increased number of deaths on Masitinib AB Science raised concern regarding efficacy of the drug, it will not be discussed further during safety evaluation.

Limited information is available on elderly patients due to very small number of patients from 75 years old (3 subjects in age group 75-84 and 0 subjects in age group 85 and more). In general, number of AEs in total and serious AEs was similar in both subjects up to 64 years old and for subjects from 65 to 74 years old, with slight increase in older group. Fatal AEs were more frequent in patients of 65 years old and more versus patients younger than 65 (7.7 vs. 11.3%) as well as AE leading to drop-out (excl. death) (11.3 vs. 21.3%). No new safety issues were identified in elderly population.

By increasing the dose of Masitinib AB Science all kinds of AEs, except for fatal SAEs during main protocol period – AEs in total, fatal/non-fatal SAE, severe AE, AE leading to treatment discontinuation or dose reduction - have been increased. Especially it was noticeable during extension period. It can be stated, that from safety point of view 3.0 mg/kg dose is preferable to with 4.5 mg/kg.

Most of patients in the ALS study reported at least one AE. Higher dose dependent incidence of AEs was reported in the Masitinib AB Science + riluzole groups (84.7% in Masitinib AB Science 3 mg/kg/day and 88.4% in 4.5 mg/kg/day Masitinib AB Science + riluzole groups vs 78% in placebo + riluzole groups).

In ALS patients the most common AEs in all study groups by System Organ Class (SOC) were Gastrointestinal Disorders, Infection and Infestations and Investigations. The most frequently reported adverse in patients receiving masitinib categorised under the MedDRA System Organ Class were Gastrointestinal Disorders, Skin and Subcutaneous Tissue Disorders and Respiratory, Thoracic and Mediastinal Disorders.

The most common AEs with reported more than > 5% higher incidence in the blood and lymphatic system disorders (more specifically discussed further in Section 4.5) (8.4% in Masitinib AB Science 3mg/kg/day group and 14.7% in Masitinib AB Science 4.5 mg/kg/day group vs 1.5% in placebo group); nausea (6.9% in Masitinib AB Science 3mg/kg/day group and 12.45 in Masitinib AB Science 4.5 mg/kg/day group vs 4.5% in placebo group); diarrhoea (8.4% in Masitinib AB Science 3mg/kg/day group and 7.8% in Masitinib AB Science 4.5 mg/kg/day group vs 3.8% in placebo group); dyspepsia (7% in Masitinib AB Science 4.5 mg/kg/day group versus 2.3% in placebo group); peripheral oedema (5.3% in Masitinib AB Science 3mg/kg/day group and 7% in Masitinib AB Science 4.5 mg/kg/day group versus 0.8% in placebo group); nervous system disorders (18.6% in Masitinib AB Science 4.5 mg/kg/day group versus 9.8% in placebo group); respiratory and thoracic disorders (27.1% in Masitinib AB Science 4.5 mg/kg/day group versus 12% in placebo group including reported respiratory failure in 10.1% patients in Masitinib AB Science 4.5 mg/kg/day group vs 4.5 % in placebo group and dyspnoea 6.2% in Masitinib AB Science 4.5 mg/kg/day group versus 0.8% in placebo group); skin and subcutaneous tissue disorders (20.6% in Masitinib AB Science 3 mg/kg/day group and 30.2% in Masitinib AB Science 4.5 mg/kg/day group versus 12% in placebo group); infections and infestations (34.9% in Masitinib AB Science 4.5 mg/kg/day group versus 21.15 in placebo group). Skin and subcutaneous tissue disorders and gastrointestinal disorders were the most frequently reported AEs also for other non-oncology patients exposed to masitinib. These events are all representing well known safety profile of tyrosine kinase inhibitors. However, it seems that nausea, vomiting, rash, and peripheral oedema are more commonly associated with masitinib exposure across various indications. Reported higher proportion of Respiratory and thoracic disorders in Masitinib AB Science exposed ALS patients is of particular concern in the context of ALS as a fatal neurodegenerative disease with respiratory failure as one of primary reasons of death.

Dose dependent respiratory and thoracic disorders were reported in Masitinib AB Science 4.5 mg/kg/day group with more than twice higher incidence compared to placebo group, including 10,1% severe AEs in Masitinib AB Science group compared to 6% in placebo group. The applicant discussed possible reasons leading to the reported dose dependent increase in incidence of AEs in the SOC of respiratory and thoracic disorders in masitinib exposed ALS patients. Indeed, number of very severe patients enrolled in Masitinib AB Science group was significantly higher (18 patients in placebo group vs 31 patient in Masitinib AB Science 3 mg/kg/day group and 33 patients in Masitinib AB Science 4.5 mg/kg/day group) most likely leading to the reported higher incidence of the AES typical for ALS progression.

Gastrointestinal disorders were most frequently reported disorders in ALS and non-ALS Masitinib AB Science exposed patients. Some aspects again were not specifically discussed in the context of ALS patients. Most frequently related AEs in the SOC of GI disorders were dysphagia, nausea, and diarrhoea. While nausea and diarrhoea were among frequently reported AEs also in non-ALS patients, in ALS patients dysphagia was reported with the higher incidence in Masitinib AB Science exposed patients (13.7% in Masitinib AB Science 3 mg/kg/day group and 13.2% in Masitinib AB Science 4.5 mg/kg/day group versus 10.5% in placebo group, including two-fold higher incidence of severe dysphagia reported in Masitinib AB Science 4.5 mg/kg group vs 2.3% in placebo group). The applicant explains the reason for dysphagia by justifying it with a higher number of very severe patients represented in masitinib groups compared to placebo group. It is agreed that the apparent increased incidence of severe dysphagia can be explained by higher number of very severe ALS patients enrolled in masitinib groups. Additionally, it seems that masitinib is intended for use as add-on therapy to riluzole. Gastrointestinal AEs including nausea, vomiting and diarrhoea are very common and common AEs reported for riluzole and the most common reason for discontinuation of riluzole treatment. The applicant has agreed that there is some cumulative effect of riluzole and Masitinib AB Science in terms of gastrointestinal adverse events. The applicant pointed that information to be included in the SmPC sufficiently reflects reported gastrointestinal disorders in Masitinib AB Science exposed patients. The cumulative effect of riluzole and Masitinib was agreed to be adequately addressed in the SmPC Section 4.4.

Markedly higher incidence of infections and infestations were reported in the higher Masitinib AB Science 4.5 mg/kg/day group (34.9%) compared to in placebo group (21.1%). It is generally agreed that the higher incidence of infections reported in Masitinib AB Science groups might be due to the higher number of very severe ALS patients enrolled in the masitinib groups.

Additional safety data needed in the context of a conditional

The CHMP noted that data from clinical study AB10015 cannot be relied upon, increasing the uncertainties and limitations also regarding safety data. However, data from other trials evaluating safety of Masitinib AB Science in non-oncological indications were assessed to further understand the safety profile of Masitinib AB Science. Overall, the CHMP considers that the safety profile for Masitinib AB Science has been reasonably characterised for a CMA. However, the safety profile is characterised based on non-comprehensive evidence.

Both Study AB19001 – initially presented as confirmatory study- and the newly presented confirmatory AB23005 study were proposed by the applicant as specific obligations. While these studies are primarily focused on efficacy, they include safety secondary objectives that could have helped to further characteriseise the important identified risks as well as to the missing information about the long-term safety.

2.6.10. Conclusions on the clinical safety

The safety profile of mentioned medicinal product is considered acceptable for a CMA. The uncertainties and limitations regarding reliability of safety data of the pivotal clinical trial are alleviated by the safety

data from the trials in non-oncological conditions. It is considered that the safety concerns could have been manageable with risk minimisation measures as highlighted in the RMP.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Severe cutaneous adverse reactions Hepatotoxicity Infection due to Severe neutropenia Cardiotoxicity Acute Kidney Injury Carcinogenicity Risk of fractures Reproductive toxicity
Missing information	Long-term safety

2.7.2. Pharmacovigilance plan

Table Part III.3: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
none				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
AB19001	Study AB19001 is a multicenter, randomised, double-blind, placebo-controlled, phase 3 study to compare the efficacy and safety of two ascending dose titrations of masitinib (dose titration to 4.5 mg/kg/day; dose titration to 6.0 mg/kg/day) in combination with riluzole (50 mg b.i.d) versus matching placebo in combination with riluzole (50 mg b.i.d) in the treatment of patients diagnosed with ALS.	-Serious Cutaneous Adverse Reactions -Hepatotoxicity -Infections due to severe neutropenia -Cardiotoxicity -Risk of acute kidney injury -Carcinogenicity -Risk of fractures -Reproductive toxicity -Long-term safety	Protocol submission Study initiation Study completion Clinical study report	22 May 2020 26 Jan 2021 31 Dec 2024 31 Dec 2025
AB23005 planned	A prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 3 Trial to compare the efficacy and safety of masitinib in combination with standard of care versus placebo in combination with standard of care in the treatment of patients suffering from Amyotrophic Lateral Sclerosis	-Serious Cutaneous Adverse Reactions -Hepatotoxicity -Infections due to severe neutropenia -Cardiotoxicity -Risk of acute kidney injury -Carcinogenicity -Risk of fractures -Reproductive toxicity -Long-term safety	Protocol submission Study initiation Study completion Clinical study report	31 May 2024 31 Dec 2024 31 Dec 2027 30 Jun 2028

Category 3 - Required additional pharmacovigilance activities				
none				

2.7.3. Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimization activities by safety concern.

Safety concern	Risk minimization measures	Pharmacovigilance activities
IMPORTANT POTENTIAL RISKS		
Severe cutaneous reactions	Routine Risk Communication: • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.8 Undesirable effects • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 Special warnings and precautions of use: recommendations for monitoring	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.
Hepatotoxicity	Routine Risk Communication: • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.8 Undesirable effects • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 Special warnings and precautions of use: recommendations for monitoring and dose modifications	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.
Infections due to severe neutropenia	Routine Risk Communication: • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 Special warnings and precautions of use: recommendations for monitoring	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.
Cardiotoxicity	Routine Risk Communication • SmPC Section 4.2 Posology and method of administration • PL section 4	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.

	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 Special warnings and precautions of use: recommendations for monitoring	
Acute Kidney Injury	Routine Risk Communication: • SmPC Section 4.2 Posology and method of administration Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4 Special warnings and precautions of use: recommendations for monitoring	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.
Carcinogenicity	Routine Risk Communication: • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Section 4.4 Special warnings and precautions of use: recommendations for monitoring	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.
Risk of fractures	Routine Risk Communication: • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.8 Undesirable effects • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Section 4.4 Special warnings and precautions of use: recommendations for monitoring	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.
Reproductive toxicity including embryotoxicity and teratogenicity	Routine Risk Communication: • Section 4.6 Fertility, pregnancy and lactation Routine risk minimisation activities recommending specific clinical measures to address the risk: • Section 4.4 Special warnings and precautions of use: recommendations for monitoring	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.
MISSING INFORMATION		
Long term safety	Routine risk minimisation activities: Not applicable	AB19001 Clinical study (category 2 study) as additional pharmacovigilance activity. AB23005 Clinical study (category 2 study) as additional pharmacovigilance activity.

2.7.4. Conclusion

The CHMP, having considered the data submitted in the application was of the opinion that due to the

concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

Not applicable.

2.9. Product information

In light of the negative recommendation, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

ALS is a neurodegenerative disorder affecting primarily the motor system, but in which extra-motor manifestations are increasingly recognised. The loss of UMN and LMN in the motor cortex, the brain stem nuclei and the anterior horn of the spinal cord gives rise to progressive muscle weakness and wasting. ALS often has a focal onset but subsequently spreads to different body regions, where failure of respiratory muscles typically limits survival to 2–5 years after disease onset.

3.1.2. Available therapies and unmet medical need

Riluzole is currently the only medical product specifically authorised in the EU for ALS. Tofersen has recently been authorised for the treatment of SOD1-ALS, representing 2% of ALS. The cornerstone of disease management for ALS patients remains multidisciplinary care which has a positive effect on patient satisfaction and outcome. Several discomforting symptoms of ALS can be managed by symptomatic treatment options, including pharmacological and non-pharmacological interventions. Non-invasive ventilation is the preferred life-prolonging treatment for respiratory insufficiency. Currently, there is no cure for ALS, and it is agreed that the unmet medical need remains substantial for the majority of the ALS patients.

3.1.3. Main clinical studies

The main efficacy study was a phase 2/3, randomised, double-blind, placebo-controlled study (AB10015). The study was initially planned as a phase 2 dose-finding study and only after an amendment it was upgraded to a phase 3 pivotal study for this application. The primary objective of study AB10015 was to evaluate the efficacy of Masitinib AB Science in combination with riluzole based on the change in the ALSFRS-R (ΔALSFRS-R) from baseline to week 48 in the full study population. Only while the study was ongoing, the applicant amended the protocol to redefine the primary efficacy population as the "normal progressors" subpopulation. A total of 394 patients from 34 sites in 9 countries were available for the main study efficacy analysis (132, 131, and 128 patients in the placebo, Masitinib AB Science 3 mg/kg/day, and Masitinib AB Science 4.5 mg/kg/day treatment-arms, respectively). A total of 267 patients completed the week 48 main protocol period at week 48. A long-term survival follow-up analysis of this study has been provided.

A phase 3 study (AB19001) is ongoing, but no data were provided.

3.2. Favourable effects

The analysis of the primary endpoint in the full study population comprising normal + fast progressors in the Masitinib AB Science 4.5 mg/kg/day group showed a difference of 2.09 95%CI (-0.55-4.73) $p_{nominal}$=0.1202. In the amended primary analysis, a statistically significant difference in the 48-week change from baseline in the ALSFRS-R score was claimed between Masitinib AB Science 4.5 mg/kg/day and placebo (difference of least-square means=3.39; p=0.0158) in the "normal progressor" subpopulation.

The difference in PFS in the full study population comprising normal + fast progressors was 3 months gain in favour of Masitinib AB Science 4.5 mg/kg/day group ($p_{nominal}$ 0.1389). In the "Normal progressor" subpopulation, median PFS was increased by 4 months with Masitinib AB Science 4.5 mg/kg/day as compared with placebo arm ($p_{nominal}$ = 0.0159).

Analysis of ALSAQ-40 (mLOCF Rule 1) showed difference of means -6.59, $p_{nominal}$ 0.0148 in the full study population including normal + fast progressors and difference of -7.76, $p_{nominal}$ 0.0078 in favour of Masitinib AB Science 4.5 mg/kg/day group in normal progressor subpopulation.

In analysis of FVC in the full study population comprising normal + fast progressors difference of means was 5.63, $p_{nominal}$ 0.0914 and in normal progressor subpopulation difference of means was 7.55, $p_{nominal}$ 0.0296 in favour of Masitinib AB Science 4.5 mg/kg/day group.

A summary of long-term median OS results (cut off June 2020) for various patient cohorts of the AB10015 study population has been submitted. In moderate ALS population, including ALS patients with ≥2 on each baseline ALSFRS-R item the between group difference in median OS was 25 if population was further restricted to pre-randomization ΔFS<1.10 (moderate ALS enriched cohort of restricted normal progressors subpopulation) or 15 months if regardless of baseline ΔFS (restricted full study population comprising normal and fast progressors) corresponding to a 43-44% reduced risk of death.

3.3. Uncertainties and limitations about favourable effects

A triggered GCP inspection was requested by the CHMP on the conduct of the clinical study AB10015 in the previous MAA for the same medicinal product as a treatment for ALS. Major and critical findings were identified, and GCP inspection concluded that the data obtained at the sites inspected are not trustworthy. In accordance with the GCP inspection report conclusion, after the evaluation of the responses submitted by the applicant, the Inspection Team considered that in view of the observed departures from GCP, it cannot be ensured that the data inspected are trustworthy and the aforementioned deficiencies are likely to have an impact on the final results. Data integrity is high likely to be impaired as several protocol deviations at eligibility, conduct and in other aspects inspected. The applicant claims that the GCP findings were addressed with implementation of preventive actions across study and functions within AB Science. The applicant also claims that for study AB10015, corrective actions were implemented wherever feasible. It is noted that the measures specified by the applicant have been assessed in the current marketing authorisation procedure and were not found sufficient to recommend the use of data.

Given the nature of the findings, the systematic deficiencies observed (i.e. massive number of protocol deviations) and the fact that some findings such as the deficiencies during inclusion/exclusion criteria verification and subjects' follow up (Critical finding 1 in the inspection report) cannot be corrected retrospectively, the corrective actions presented are not considered adequate to address all the concerns raised. Data from clinical study AB10015 cannot be relied upon.

The total population (normal + fast progressors) is regarded as primary population and statistically significant difference was not demonstrated for the primary endpoint in this population.

In a study amendment while the study was already ongoing, the applicant introduced division of enrolled participants in two subgroups: fast and normal progressors. Normal progressors were re-defined as the population for the primary analysis with aim to reduce heterogeneity in study population. This approach is not supported. First, the dichotomisation was implemented during the ongoing study as recognised by the applicant and it is not supported by the CHMP. Second, it leads to selective subgroup that is not representative of general ALS population. Additionally, the chosen cut-off point (ΔFS 1.1) is of no clinical relevance and is not based on pathophysiology of ALS or mechanism of action of masitinib. Furthermore, ΔFS alone has relatively low predictive value of progression (Thakore et al, 2017) and is not stable throughout the course of disease (Requardt, 2021) thus, a linear assumption for the ΔFS decline (average rate of change from onset to randomization) might lead to misclassification of patients.

There was a substantial number of early dropouts across study arms. To account for missing data, the applicant used mLOCF method and provided various sensitivity analysis. The approach is not supported, because in the context of progressive ALS it overestimates effect. Considering the progressive nature of ALS and that the effect of treatment will not be maintained after discontinuation of medication, the J2R method is considered the most appropriate method. For this method, the applicant maintained that the defined intercurrent events are lack of efficacy or related toxicity. However, this definition is considered too narrow and is not supported.

As per the data on survival or survival equivalents that is requested as per the EMA guideline, the applicant provided data on long-term overall survival. A limitation of this analysis is that no information on the post-study use of invasive ventilation was collected, nor was information regarding which drugs were taken following withdrawal from study AB10015 or its associated NPP. Also, more than 20% of participants have discontinued the treatment before the open-label extension phase due to the lack of efficacy. Therefore, due to this discontinuation, analysis of long-term overall survival could cause bias in favour to Masitinib AB Science treatment arms.

The effect in the long-term survival claimed by the applicant is derived from a highly selected patients' population defined *post hoc* therefore can be considered only as descriptive not confirmatory of Masitinib AB Science efficacy in the proposed indication. When analysis was conducted in population that more closely corresponds to full study population of pivotal study and hence, the overall ALS population OS was not observed. The between mean difference for the moderate/severe/very severe ALS enriched cohort of restricted full study population comprising normal and fast progressors [i.e. regardless of (any) baseline ALSFRS-R item) regardless of ΔFS] was 1 month (median OS of 36 versus 37 months) for patients receiving Masitinib AB Science 4.5 mg/kg/day (n=130) versus placebo (n=133). Based on up-dated efficacy and safety analyses, the applicant presented a proposal for a modified indication to the "*treatment of ALS patients prior to any loss of function" (wherein loss of function is defined as a score of zero on any item of the ALSFRS-R)*. However, the strategies to *post hoc* identify new target populations (M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version of 4.1) are considered as data driven decisions and are, therefore, not acceptable.

3.4. Unfavourable effects

In study AB10015 during main study protocol period (48 weeks), at least 1 AE was reported by 83.7% of patients. Of them, 78.2% in placebo, 84.7% in the 3.0 mg/kg, 88.4% in the 4.5 mg/kg Masitinib AB Science arm.

More frequently reported AEs in one of the Masitinib AB Science versus placebo arm were maculo-papular rash, nausea, peripheral oedema, iron deficiency anaemia, respiratory failure, and dyspnoea.

The most frequently reported non-fatal SAEs in Masitinib AB Science patients under MedDRA SOC were Gastrointestinal Disorders, then Respiratory, Thoracic and Mediastinal Disorders, Infection and Infestations, Injury Poisoning and Procedural Complications, and Investigations. The most frequent PTs were Dysphagia, Respiratory Failure, Dyspnoea, Lower Respiratory Tract Infection, Bronchitis, Fall, Transaminases Increased, Weight Decreased, and Neutropenia.

According to the applicant, Respiratory failure, Dysphagia, and Dyspnoea were associated with ALS disease progression and were not reported as drug related.

The most common AEs with reported more than > 5% higher incidence in ALS patients were in the blood and lymphatic system disorders (8.4% in Masitinib AB Science 3mg/kg/day group and 14.7% in Masitinib AB Science 4.5 mg/kg/day group versus 1.5% in placebo group); nausea (6.9% in 3 mg/kg/day group and 12.45 in Masitinib AB Science 4.5 mg/kg/day group versus 4.5% in placebo group); diarrhoea (8.4% in Masitinib AB Science 3 mg/kg/day group and 7.8% in Masitinib AB Science 4.5 mg/kg/day group versus 3.8% in placebo group); dyspepsia (7% in Masitinib AB Science 4.5 mg/kg/day group versus 2.3% in placebo group); peripheral oedema (5.3% in Masitinib AB Science 3 mg/kg/day group and 7% in Masitinib AB Science 4.5 mg/kg/day group versus 0.8% in placebo group); nervous system disorders (18.6% in Masitinib AB Science 4.5 mg/kg/day group versus 9.8% in placebo group); respiratory and thoracic disorders (27.1% in Masitinib AB Science 4.5 mg/kg/day group versus 12% in placebo group including reported respiratory failure in 10.1% patients in Masitinib AB Science 4.5 mg/kg/day group vs 4.5 % in placebo group and dyspnoea 6.2% in Masitinib AB Science 4.5 mg/kg/day group versus 0.8% in placebo group); skin and subcutaneous tissue disorders (20.6% in Masitinib AB Science 3 mg/kg/day group and 30.2% in Masitinib AB Science 4.5 mg/kg/day group versus 12% in placebo group); infections and infestations (34.9% in Masitinib AB Science 4.5 mg/kg/day group versus 21.15 in placebo group).

Cardiovascular disorders were identified as an important potential risk and patients with current or history of severe cardiovascular disease were excluded from the study. Nonetheless, 3 severe cardiac events were reported in masitinib exposed patients including 2 death events. Although none of them

was reported as study drug related, potential cardiotoxicity remains as a significant and not properly addressed safety risk.

ALS is a disease, which leads to death mainly from respiratory complications; however, also has underestimated cardiovascular effects, like increased heart rate variability, malignant arrhythmias, and sudden death (Orsini et al, 2021). Furthermore, cardiac symptoms in ALS patients may develop at any stage of the disease and initial cardiac symptoms if not closely monitored may go unnoticed in ALS patients.

3.5. Uncertainties and limitations about unfavourable effects

Important uncertainty of unfavourable effects is also related to the reliability of data. Many deviations from the protocol have been found during the inspections of the study centres. As part of this marketing authorization Applicant presented implemented preventive actions across study and functions within AB Science. Given the nature of the findings, the systematic deficiencies observed (i.e. massive number of protocol deviations) and the fact that some findings such as the deficiencies during inclusion/exclusion criteria verification and subjects' follow up (Critical finding 1 in the inspection report) cannot be corrected retrospectively, the corrective actions presented are not considered adequate to address all the concerns raised. Data from clinical study AB10015 cannot be relied upon, increasing the uncertainties and limitations also regarding unfavourable effects.

The uncertainties and limitations regarding reliability of safety data of the pivotal clinical trial are alleviated by the safety data from the trials in non-oncological conditions. It is considered that the safety concerns could have been manageable with risk minimization measures as outlighted in the RMP.

3.6. Effects Table

Table 100: Effects Table for Masitinib AB Science

Effect	Short Description	Unit	Masitinib 4.5 mg	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Difference in ALSFRS-R	Normal progressors Between groups, LS	score			Difference 3.39 CI (0.65-6.13), p-value 0.0157 Uncertainties for all estimates: multiple imputation suboptimal, reliability of data, high levels of treatment discontinuation.	(1)
	Normal + Fast progressors	score	-10.89	-12.97	Difference 2.09 (-0.55-4.73) p=0.1202	
Median PFS	Normal progressors, Between groups, LS	months	20	16	4 months, p-value 0.0159.	(1)
	Normal + Fast progressors		17	14	3 months, p-value 0.1389	

Effect	Short Description	Unit	Masitinib 4.5 mg	Placebo	Uncertainties/ Strength of evidence	References
Quality of life	Normal progressors Between groups, LS ALSAQ-40	score	mLOCF Rule 1 19.42 mLOCF Rule 5 18.79	mLOCF Rule 1 27.18 mLOCF Rule 5 25.51	difference of means 7.76, p-value 0.0078 (mLOCF Rule 1). -6.72, p-value 0.0143 (mLOCF Rule 5)	(1)
	Normal + Fast progressors		21.58	28.17	difference of means -6.59, p-value 0.0148	
FVC	Normal progressors Between groups, LS	change from baseline	mLOCF Rule 1 -26.45 mLOCF Rule 5-25.62	mLOCF Rule 1 -33.99 mLOCF Rule 5 -32.01	difference of means 7.55, p-value 0.0296 (mLOCF Rule 1). 6.40, p-value 0.0511 (mLOCF Rule 5)	(1)
	Normal + Fast progressors		-30.81	-36.45	difference of means 5.63, p-value 0.0914	
TFS	Normal progressors	months	30	32	p-value 0.7382	
	Normal + Fast progressors		Not presented	Not presented		
CAFS	Normal progressors	score	115.72	100.77	difference 14.95, p-value 0.0776.	
	Normal + Fast progressors		135.83	121.40	Difference of means 14.43, p-value 0.1185	
Survival OS	Normal progressors Between groups, LS	months	Median OS not reached	Median OS not reached	p-value 0.3727	(1)
	Normal + Fast progressors		Median OS not reached	Median OS not reached	p-value 0.4862	
Unfavourable Effects						
Deaths	Number (and Percent of Patients)	Number	10 (7.8)	12 (9.0)	Up to week 48 SoE: longer duration of treatment and more severe patients in masitinib arm	(2)
Gastrointestinal Disorders	Number (and Percent of Patients)	Number	14 (10.9)	10 (7.5)	Up to week 48 Unc: cumulative effect of riluzole and masitinib in terms of GI events.	(2)
Respiratory, Thoracic and Mediastinal Disorders	Number (and Percent of Patients)	Number	13 (10.1)	4 (3.0)	Up to week 48 SoE: larger # of very severe patients in masitinib arm	(2)

Effect	Short Description	Unit	Masitinib 4.5 mg	Placebo	Uncertainties/ Strength of evidence	References
Infections and Infestations	Number (and Percent of Patients)	Number	10 (7.8)	7 (5.3)	Up to week 48 SoE: larger # of very severe patients in masitinib arm	(2)
Transaminases Increased	Number (and Percent of Patients)	Number	2 (1.6)	0	Up to week 48	(2)

Abbreviations: ALSFRS-R - Amyotrophic lateral sclerosis functional rating scale-revised, ALSAQ-40 - Amyotrophic Lateral Sclerosis Assessment Questionnaire, long form, 40 questions, FP - Fast Progressors, FVC - Forced vital capacity, LS-Difference of least-square means, median PFS – median progression-free survival, TD - Treatment Difference M vs P, M = ALSITEK + Riluzole ; P = Placebo + Riluzole.
Notes: (1) Clinical Study Report Protocol No. AB10015, (2) 2.7.4 Summary of Clinical Safety

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

ALS is a neurodegenerative disease with limited treatment options with overall survival of 2–5 years after disease onset.

The current application is based on one pivotal study (AB10015); A prospective, multicentre, randomised, double-blind, placebo controlled, parallel groups, phase 2/3 study to compare the efficacy and safety of two doses of Masitinib AB Science versus placebo in the treatment of patients suffering from ALS. The primary endpoint was originally the change from baseline to week 48 in the ALSFRS-R in the full study population.

A triggered GCP inspection was requested by the CHMP on the conduct of the clinical study AB10015 in the previous MAA for masitinib use in ALS. Major and critical findings were identified, and the GCP report concluded that the data obtained at the sites inspected are not trustworthy. As part of this submission the applicant claims that the GCP findings were addressed with implementation of preventive actions across study and functions within AB Science. The applicant also claims that for study AB10015, corrective actions were implemented wherever feasible. It is noted that the measures specified by the applicant in this application have been assessed and were not found sufficient to reassure the CHMP to recommend the use of data. Therefore, data from clinical study AB10015 cannot be relied upon.

In 2014, an amendment to the study protocol introduced a distinction between "normal progressor" patients and "fast progressor" subpopulations while the study was ongoing, and the primary efficacy analysis was to be done in the normal progressor subpopulation randomised to an initial Masitinib AB Science dose of 4.5mg/kg/day versus placebo patients at a 5% alpha-level. This categorization is not considered acceptable for the following reasons: the categorization was implemented while the study was ongoing, the use of ALSFRS-R score as the only variable to inform the progression of ALS, the linear assumption of ALSFRS-R decline being unreliable for long time periods, the use of arbitrary cut-offs for the categorization that are not based on clinical relevant thresholds, ALS pathology or mechanism of action of Masitinib AB Science. The full study population comprising normal + fast progressors is regarded as primary population.

Considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. In order to account for missing data after treatment discontinuation, the applicant used the mLOCF method for the first and secondary endpoints. A mLOCF approach assumes that the benefit experienced until the time of missing data is also retained thereafter. This is a strong assumption for imputing data after treatment discontinuation. This approach of handle missing data is prone to overestimate the effects of Masitinib AB Science. The applicant provided more conservative approaches such as J2R that assumes that the benefit experienced

until the point of missing data is not retained and instead the outcome would correspond to the outcome in the reference group. However, J2R was only used by the applicant to handle missing data after discontinuations that were attributed to lack of efficacy or toxicity, whereas missing data after discontinuations for other reasons were presumably handled with a mLOCF approach. A detailed description of the statistical methods is not available, which further increases the uncertainty about the appropriateness of this analysis approach. Additionally, as an underlying assumption, the applicant is assuming that it can ascertain which missing case are MAR (protocol deviation / non-compliance, etc.) and which cases are MNAR (efficacy/toxicity). The applicant does not provide convincing arguments that substantiate this categorisation, hence the handling of missing data following discontinuations for different reasons with different methods is not considered adequate. The CHMP is of the opinion that as conservative methods such J2R are considered the preferred option in the view of the progressive nature of ALS.
The primary statistical analysis in the phase 2/3 main efficacy study revealed a statistically significant difference in the ALSFRS-R score between Masitinib AB Science 4.5 mg/kg/day and placebo (difference of least-square means=3.39; p=0.0158) in "normal progressor" subpopulation. However significant difference was not observed in the full study population comprising normal and fast progressors subpopulations, which is considered the primary population of this trial. With respect to secondary endpoints, in the "normal progressor" subpopulation, median PFS was increased by 4 months in the Masitinib AB Science 4.5 mg/kg/day group compared with placebo, ($p_{nominal}$=0.016). However, these effects were not seen in the full study population comprising normal and fast progressors.

A summary of long-term median OS results for various patient cohorts of the AB10015 study population has been provided (cut-off date 14 June 2020). No long-term survival advantage was observed for the overall Masitinib AB Science 4.5 mg/kg/day cohort. The results indicating prolonged survival in a *post hoc* selected, enriched population (cohortLT-M4.5 with ≥2 on each baseline ALSFRS-R item, and ΔFS<1.1) is not considered robust and is not representative for the population intended to be treated. The new proposed indication (*ALS patients prior to any loss of function*) based on *post hoc* analyses is not acceptable as it is considered data driven.

Dose dependent respiratory and thoracic disorders were reported in 4.5 mg/kg/day Masitinib AB Science group with more than twice higher incidence compared to placebo group, including 10,1% severe AEs in Masitinib AB Science group compared to 6% in placebo group. Furthermore, it is a concern that data reliability issues identified in the triggered GCP inspection also affects proper reporting of safety data. Nevertheless, the safety profile was further characterised based on safety data of trials conducted in non-oncological conditions. It is considered that the safety profile is reasonably characterised for a CMA (i.e. based on non-comprehensive data) and that the proposed specific obligations could have provided comprehensive data during the post-authorisation phase.

3.7.2. Balance of benefits and risks

The provided analyses of the single pivotal study are not considered to establish efficacy in the target population of patients with ALS. In addition, a triggered GCP inspection has concluded that the data from clinical study AB10015. Data cannot be relied upon and the corrective measures presented by the applicant have not resolved this issue.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation (CMA) was requested by the applicant in the initial submission. The CHMP agrees that the data is not

comprehensive. The application is based on a single pivotal trial, study AB10015, which was designed as a phase 2 dose-finding trial. Only upon a protocol amendment, it was upgraded to a phase 3 pivotal trial. The study population of AB10015 study is not considered fully representative of the overall ALS population and the efficacy endpoints did not include any measures of muscle strength. These features could have been acceptable for a phase 2 dose-finding trial but are considered serious limitations for a phase 3 pivotal study intended to provide comprehensive evidence of efficacy and safety. Moreover, a triggered GCP inspection has concluded that the data from clinical study AB10015 are not trustworthy Data cannot be relied upon, and the corrective measures presented by the applicant have not resolved this issue.

The CHMP considers that the product cannot be recommended for a CMA as the benefit-risk balance is negative (as discussed), the applicant is unlikely to be able to provide comprehensive data after authorisation, it has not been demonstrated that the product will address an unmet medical need, and the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required.

1. Positive benefit/risk balance:

The applicant argued that results from Study AB10015 are valid and demonstrate efficacy of Masitinib AB Science for patients with ALS with an adequate safety profile. The CHMP position is that a positive benefit/risk balance of Masitinib AB Science for the treatment of patients with ALS cannot be established because the data from the pivotal clinical study AB10015 cannot be relied upon. Despite the applicant's arguments and corrective measures, the current assessment concluded that the deficiencies identified during previous GCP inspection cannot be resolved by performing re-monitoring and retrospective analyses at the study sites and cannot be corrected retrospectively. Beside the data not being reliable, the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS, because a statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population; the approach to categorise the population into normal and fast progressors is not supported (the categorization was implemented while the study was ongoing, the use of ALSFRS-R score as the only variable to inform the progression of ALS, the linear assumption of ALSFRS-R decline being unreliable for long time periods, the use of arbitrary cut-offs for the categorization that are not based on clinical relevant thresholds, ALS pathology or mechanism of action of Masitinib AB Science); considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data including statistical assumptions on missingness and the definition of intercurrent events in J2R strategy are not considered acceptable and the strategies to *post hoc* identify new target populations (M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and ALS patients prior to any loss of function as proposed in the latest version of 4.1 of the SmPC) are considered as data driven decisions and are, therefore, not acceptable.

2. It is likely that the applicant will be able to provide comprehensive data

As per the requested CMA, the applicant initially presented Study AB19001 as the one that would lead to comprehensive evidence on efficacy and safety of Masitinib AB Science. Study AB19001 is a multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 3 study to evaluate the efficacy and safety of masitinib as add-on therapy in Amyotrophic Lateral Sclerosis (ALS) patients treated with Riluzole. Patients will be randomised (1:1:1) to receive Masitinib AB Science 6 mg/kg/day, Masitinib AB Science 4.5mg/kg/day or matching placebo. The primary endpoint is the absolute change in ALSFRS-R from baseline to week 48 week. In this study, the secondary endpoints include measures of muscle strength and survival. Within this study, the applicant presented categorization of the full study population into three subpopulations of progressors based on the change in ALSFRS-R score from onset to screening and also from screening to baseline. More importantly, the applicant establishes the

primary efficacy population as the one including moderate progressors, i.e. patients with an ALSFRS-R total score progression between onset of the disease and screening of > 0.3 and <1.1 point/month and an ALSFRS-R total score decrease of ≥ 1 point between screening and baseline. All regulatory considerations aforementioned detailed are applicable here. It is considered that these study design features could lead to a study population that is not fully representative of the broad ALS population.

During the procedure, the applicant stated that the enrolment in study AB19001 has been slow due to the restrictive design features of that study (i.e. long 3 months run-in period, with no control of FVC at baseline / Moderate ALS only / Approved treatment in the USA - Edaravone, Relyvrio – not allowed / blinded extension at week 48). Consequently, the applicant proposed a new confirmatory study - AB23005 study- and presented the previously proposed confirmatory AB19001 study as an exploratory one.

Study AB23005 is a multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 3 Trial to evaluate the efficacy and safety of masitinib as add-on therapy in ALS patients treated with standard of care. Patients will be randomised (1:1) to receive Masitinib AB Science 4.5 mg/kg/day or matching placebo and Masitinib AB Science 6 mg/kg/day will not be pursued further in the study AB23005. The primary endpoint is the absolute change in ALSFRS-R from baseline to week 48. In this study, the secondary endpoints include measurements of muscle strength, progression free survival and overall survival. According to the synopsis of the study provided during the procedure, the primary efficacy population will be the ITT (all randomised full study population). The applicant specifies two measures of ALSFRS-R progression rate (point/month) will be evaluated at screening to categorise ALS patient as slow, moderate, or fast progressor. As per the inclusion criteria, only patients with a ALSFRS-R progression rate between > 0.3 and <1.1 point/month as measured between onset of the disease and screening AND as measured by any available ALSFRS-R assessment during the period ranging from 7 months to 2 months prior to screening and screening, reassessed and documented by certified rater performing ALSFRS-R assessment from screening visit onward will be enrolled (synopsis of AB23005 protocol). Further restriction is included as per the baseline ALSFRS-R scores as a total score of at least 15 points of ALSFRS-R at baseline and screening [at least 3 in item3; at least 2 in item12; at least 1 in each of the other items] is also requested as inclusion criterion. All aforementioned considerations on using delta FS to select study population are also applicable here. While no further categorization is proposed to be done after enrolment (i.e. primary efficacy population is full study population), it is considered that the mentioned inclusion criteria could lead to the inclusion of a restricted ALS population. Moreover, it is considered that a duration of the study AB23005 (48 weeks) might not be long enough to generate sufficient data on survival events, which are necessary to support the primary endpoint and taking into account that the positive data on survival or survival equivalent are expected.

Besides to the above considerations on the study design features and the potential impact on the ability of Study AB23005 to provide comprehensive evidence, the CHMP was concerned about the feasibility to properly conduct that study if Masitinib AB Science is authorised in the EU. It needs to be bear in mind that ALS is a fatal condition for which the only therapeutic options in the EU are symptomatic treatment and riluzole for all ALS patients expect those with SOD1-ALS. Hence, the CHMP is concerned that the authorisation of Masitinib AB Science will impact the recruitment and the conduction of the AB23005 study in the EU sites as ALS patients will likely start (i.e., impact on recruitment) or shift (i.e. impact on conduction) to the commercial Masitinib AB Science when available. The new confirmatory AB23005 study is expected to enrol 408 patients. The applicant presented a feasibility analysis and concluded that a total of 855 patients could be enrolled over a 12-month period including 583 patients in non-EU countries and US. The applicant claimed that Study AB23005 can be completed within 2.5 years with involvement of site from USA and other non-EU countries or within 3 years with involvement of site only from other non-EU countries. These figures assume the study starts in Q2 2024. Thus, the applicant position is that confirmatory study AB23005 is feasible outside of the EU and further facilitated since

Relyvrio is withdrawn from market in USA and Canada. However, considering the numerous changes undertaken in the protocol of the pivotal study during its execution as well as the slow enrolment in the study AB19001, which became an exploratory study later on the applicant capability of properly conduct this study is still unclear, despite the applicant's declared commitment.

In view of the above, high uncertainties remain with regard to the possibility to provide comprehensive clinical data, should a CMA have been granted.

3. Fulfilment of unmet medical need

The third criterion requires that unmet medical needs will be fulfilled. As other medicinal products for the treatment of ALS are authorised in EU, the applicant should justify that Masitinib AB Science provides a major therapeutic advantage (MTA) over each existing authorised medicinal products in an overlapping indication, in case a CMA would be granted. The currently authorised medicinal products for ALS are riluzole and tofersen (the latter, only for SOD1-ALS).

The pivotal study AB10015 of this CMA is a prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase II/III study to compare the efficacy and safety of Masitinib AB Science versus placebo in ALS patients. The study objective was to evaluate efficacy and safety of Masitinib AB Science as add-on therapy to riluzole. Indeed, all patients included in this pivotal study received riluzole. Hence, this pivotal trial is designed to measure causal effects (efficacy) of Masitinib AB Science on top of Riluzole. If efficacy was demonstrated for Masitinib AB Science on top of riluzole in this pivotal trial, the differences in ALSFRS-R score and survival equivalent (PFS) estimates observed in the pivotal trial in favour of Masitinib AB Science arms in principle could have been considered as meaningful improvements of morbidity or mortality of the disease and thus supporting that Masitinib AB Science provides MTA versus riluzole. However, as efficacy was not demonstrated, it cannot be concluded whether Masitinib AB Science provides a MTA versus riluzole.

On the other hand, the applicant provided a succinct justification of an MTA over tofersen during the oral explanation. The applicant claimed that Masitinib AB Science and tofersen have different mechanisms of action. This is agreed; however, a different mechanism of action does not automatically justify for MTA, it needs to be justified that the new mechanism of action provides a significant clinical advantage versus the existing therapies. In accordance with the Guideline on the scientific application and the practical arrangements necessary to implement Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 MTA would normally be based on meaningful improvement of efficacy or clinical safety or, in exceptional cases, on major improvements to patient care. Furthermore, the applicant claimed that SOD1-ALS represents approximately 2% of people living with ALS. This is also correct, but the MTA needs to be justified in the overlapping indication. Hence, in view of the claimed indication for Masitinib AB Science, it is still the case that the applicant has to demonstrate that Masitinib AB Science provides MTA versus tofersen in the SOD1-ALS subpopulation. Finally, the applicant claimed during the oral explanation that Masitinib AB Science makes a major contribution to patient care with a benefit on ALSFRS, QOL, and PFS, OS (+ 12 months).

Based on the above, it is understood the applicant is claiming MTA based on improved efficacy and major contribution to patient care. With regard to the first claim (i.e. improved efficacy), it needs to be considered that the pivotal trial did not enrol any patient treated with Qalsody. It is unclear whether SOD1-ALS patients were enrolled at all in the pivotal trial. The applicant has not sufficiently justified that the claimed benefits– if finally accepted by the CHMP- could be extrapolable to the SOD1-ALS subpopulation who could benefit from a more targeted therapy (Tofersen addressed overexpression of SOD1 as a key pathological mechanism of damage in SOD1-ALS) and thus, provides meaningful improvement of efficacy versus tofersen in this ALS sub-population. With regard to the third claim (i.e.

major contribution to patient care), the applicant has not sufficiently justified which is exactly the contribution to the patient care.

4. The benefit of immediate availability outweighs the risks

The applicant position is that benefit associated with the immediate availability of Masitinib AB Science based on number of deaths avoided and total gain in life-years as estimated based on study AB10015 (pivotal study for this CMA) outweighs the risk of adverse events.

However, taking all above into account, especially since the benefit risk balance has not been determined as positive, the benefits to public health of the immediate availability of Masitinib AB Science do not outweigh the risks inherent in the fact that additional data are still required.

Third Party Interventions

The CHMP received correspondences from two patient organisations (hereinafter referred to as "third parties") which expressed their position on the unmet medical need for ALS and on their understanding of the efficacy and safety profile of Masitinib AB Science.

The CHMP considered the intervention and concluded that the arguments put forward by the third-party did not impact the CHMP conclusions.

3.8. Conclusions

The overall benefit/risk balance of Masitinib AB Science is negative.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Masitinib AB Science in the treatment of adult patients with amyotrophic lateral sclerosis (ALS) prior to any loss of function in combination with riluzole, the CHMP considers by consensus that the quality and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- The suitability of the proposed dissolution method to ensure proper control of the medicinal products during the lifecycle of the medicinal product, especially for the 200 mg strength, and therefore to ensure batch to batch consistency has not been sufficiently demonstrated. Several deficiencies and the lack of an acceptable explanation for the significant differences of dissolution data between the 100 mg strength and the 200 mg strength, as well as differences in dissolution profiles between different batches of the 200 mg strength remain at the time of opinion. The applicant has not convincingly demonstrated that tablet hardness and film-coating are the main issues for differences in dissolution results between 100 mg and 200 mg tablets as dissolution results do not correlate with these parameters. Moreover, the potential reasons of different dissolution results between 200 mg batches (intra-batch and inter-batches) were not discussed in order to ensure that, e.g., the manufacturing process is adequate to obtain a product with the intended high quality.
- A positive benefit/risk balance of Masitinib AB Science for the treatment of patients with ALS cannot be established based on the following:

    1. The data from the pivotal clinical study AB10015 cannot be relied upon. Despite the applicant's arguments and the implementation of corrective measures, the deficiencies identified during

previous GCP inspection cannot be resolved by performing re-monitoring and retrospective analyses at the study sites and cannot be corrected retrospectively.

2. Beside the data not being reliable, the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS, because:
    - A statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population.
    - The approach to categorise the population into normal and fast progressors is not supported.
    - Considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data including statistical assumptions on missingness and the definition of intercurrent events in J2R strategy are not considered acceptable.
    - The strategies to *post hoc* identify new target populations ("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version of 4.1) are considered as data driven decisions and are, therefore, not acceptable.

- A CMA requires that all requirements as described in Article 4 of Commission Regulation (EC) No. 507/2006 are met. In addition to not fulfilling the first criterion, which relates to the positive benefit / risk balance, also other CMA criteria are not considered fulfilled: it is considered unlikely that the applicant will be in a position to provide comprehensive clinical data post-authorisation, the applicant has not sufficiently justified that Masitinib AB Science would provide a major therapeutic advantage versus tofersen and, taking all the above into account, it is considered that the benefits to public health of the immediate availability of Masitinib AB Science do not outweigh the risks inherent in the fact that additional data are still required.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in Appendix 5.2.

5. Re-examination of the CHMP opinion of 27 June 2024

Following the CHMP conclusion that Masitinib AB Science was not approvable, the Applicant submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the Applicant

5.1.1. Ground #1

The suitability of the proposed dissolution method to ensure proper control of the medicinal products during the lifecycle of the medicinal product, especially for the 200 mg strength, and therefore to ensure batch to batch consistency has not been sufficiently demonstrated. Several deficiencies and the lack of an acceptable explanation for the significant differences of dissolution data between the 100 mg strength and the 200 mg strength, as well as differences in dissolution profiles between different batches of the

200 mg strength remain at the time of opinion. The applicant has not convincingly demonstrated that tablet hardness and film-coating are the main issues for differences in dissolution results between 100 mg and 200 mg tablets as dissolution results do not correlate with these parameters. Moreover, the potential reasons of different dissolution results between 200 mg batches (intra-batch and inter-batches) were not discussed in order to ensure that, e.g., the manufacturing process is adequate to obtain a product with the intended high quality.

Applicant´s position on the Ground for re-examination

The Applicant presented first their interpretation of the CHMP position

The Applicant confirmed that batches No 2006325, 2211821 (100 mg) and 2103375, 2211820 (200 mg) were manufactured in a site between April 2020-September 2022 with the proposed formulation and manufacturing process. Therefore, they could be considered as representative.

The Applicant repeated the conclusion that both 100 rpm and 75 rpm gave similar *in vitro* dissolution profiles supporting the selection of 75 rpm for the conditions of the dissolution method which is aimed to be discriminatory.

Slight differences in disintegration time between 100 mg and 200 mg, as well as differences in tablet mass and tablet hardness and tablet coating where provided as possible root causes for the variability observed regarding the dissolution data of 100 mg and 200 mg at 100 rpm and 75 rpm. However, these explanations deserve further reflection and altogether do not adequately justify the variability of the dissolution data provided for the additional 200 mg batches submitted with the responses of the previous round.

The Applicant has not performed comparative dissolution testing between two 100 mg tablets and one 200 mg tablet, as suggested, in order to obtain data that could potentially reveal the causes of the different and variable dissolution results. The Applicant indicated that it is not relevant as sink conditions are achieved. Although it is stated in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) that above mentioned test could be necessary when not all strengths can reach sink condition, it should be noted that in connection with this application, the aim of this experiment is to reveal the causes of the significant differences in the dissolution profile between both strengths, e.g., due to hydrodynamic processes.

During the development, the tablet hardness acceptance criteria were adjusted several times and the following process parameters are set for the industrial batches (Module 3.2.P.3.3):

For three 100 mg strength batches and seven 200 mg strength batches, comparative hardness and sequential dissolution data can be found in Module 3.2.P.2, however, not all batches were tested for dissolution at 5- and 15-minutes time points. See industrial batch data extracted by assessor below:

The Applicant has concluded (section 3.2.P.2, p.91-92/102) that the hardness of the tablet at the highest limit affects dissolution in the first 5 minutes, but at the specification time point (20 minutes) the results are acceptable.

However, at the same time the Applicant has performed tableting tooling study (section 3.2.P.2, p.90-92/102) in order to investigate the influence of the tablet hardness on drug product characteristics. The influence of tablets hardness to dissolution rate also was investigated.

According to dissolution data obtained during tableting tooling study, only extreme tablets' hardness has influence on dissolution results in first 5 minutes. The established in-process specification for hardness for 100 mg tablets is 70-110N and for 200 mg tablets – 130-170N.

Taking into account the above mentioned, no obvious conclusion can be made that tablet hardness is the main issue for differences in dissolution results between 100 mg and 200 mg tablets.

Moreover, dissolution data of batch No 1409991 have been used in the development of the dissolution method (RSD % exceeds the fluctuations determined in the Reflection paper at 15 min at both rotation speeds). For other batches used to justify the suitability of the dissolution method (e.g., 200 mg batches No 1600847, 2103375, 2211820), no hardness versus dissolution data is available. The argument about the effect of the tablet coating is not clear because, as the Applicant already pointed out, the coating has no functional purpose, which is also demonstrated by the dissolution data of the 200 mg strength batch No 0911434. Additionally, the Applicant stated that Opadry® from Colorcon was selected as film agent as it is used as a suspension in water, it disintegrates quickly and it does not change significantly dissolution (section 3.2.P.2, p.7/102).

For finished product batches of 200 mg strength where results of dissolution do not exceed 85% in 15 minutes and high RSD% values have been observed, it was requested to confirm the similarity with 100 mg strength by statistical methods other than F2 calculation (e.g., bootstrap method etc). No such statistical data has been submitted by the Applicant. The quality control method to be used during the life cycle of the drug product should be suitable for all strengths, regardless of, e.g., tablet mass, hardness etc. properties. In the case of larger fluctuations in dissolution results (see EMA/CHMP/CVMP/QWP/336031/2017), it should be demonstrated by statistical methods that the results obtained with the specific test method are comparable. If this cannot be demonstrated, then the question of the suitability of the method remains open, because there are doubts about the suitability of the method for proper routine quality control of the drug product (an issue not related with bioavailability).

The Applicant stated that the variability of the in vitro dissolution results between batches are at 5 min and 10 minutes time points and it correlates with the disintegration times. However, also at 15 min there is still differences between dissolution data gathered at 75 rpm and 100 rpm and between batches for the 200 mg strength. Potential reasons of different dissolution results between 200 mg batches (intra-batch and inter-batches) are not discussed at all which may raise also the concern on whether not only on the suitability of the selected dissolution method as quality control method for both strengths but whether the manufacturing process is adequate to obtain the 200 mg strength with consistent quality. For this reason, this part of the major objection is not considered resolved.

AB Science Response

Note: During the two previous registration procedures (EMEA/H/C/004398: resolved at D150 (appendix 1a and appendix 1b); EMEA/H/C/004159/0000: resolved at D195 (appendix 2a and appendix 2b)),

i) the selected parameters of the *in vitro* dissolution method, ii) the discriminance of the dissolution method at 100 rpm and iii) the specification limits were considered acceptable. Indeed, during the two procedures, the assessment of the Applicants responses were considered as "Solved" at the end of these procedures.

1- About the *in vitro* dissolution testing method

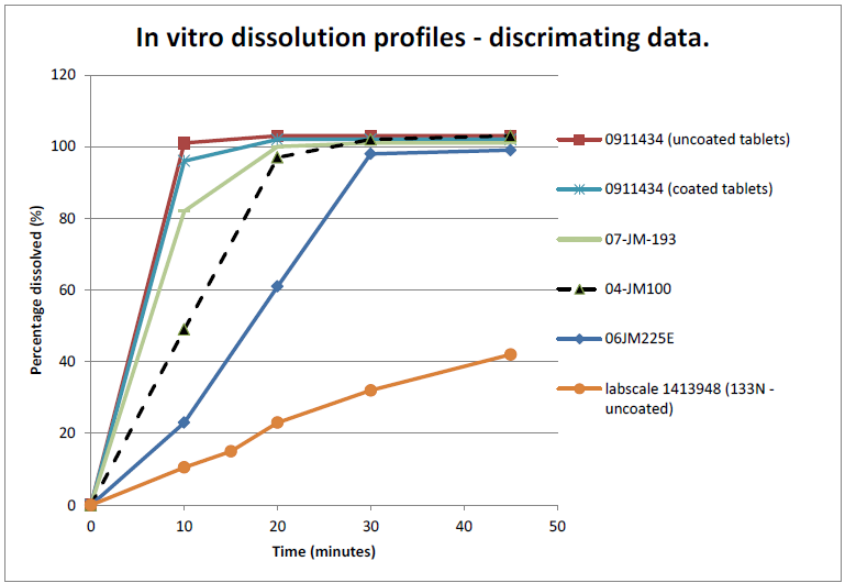
During the current procedure, the Applicant provided additional information (refers section 3.2.P.2 and response to D180 1st and 2nd LoI answers) to demonstrate the accuracy of the dissolution method.

Based on the results collected on the proposed formulation with the proposed manufacturing process, we demonstrated that the proposed dissolution method at 100 rpm provided the closest results to the EMA guidelines recommendations. In addition, this 100 rpm method was able to exclude batches which would not be compliant with the proposed specifications (Figure 8).

However, following the clarification meeting held on 7 February 2024 and submitted data for 2nd D180 LoI, AB Science subsequently proposed a dissolution method at 75 rpm since this speed is more in line with *in vitro* dissolution testing rules and generate comparable dissolution results with 100 rpm.

Considering that during the previous two procedures, the 100 rpm dissolution method was considered acceptable by the CHMP, the Applicant proposes to keep this dissolution method at 100 rpm instead of the 75 rpm.

Figure 8: In vitro dissolution tests profiles – granulation parameters investigations



2- About intra/inter batch variability investigations

The issue of intra-batch and inter-batches variability occurs at the 5 and 10 minutes time points, not at the proposed specification time point at 20 minutes.

A comparative dissolution testing between two 100 mg tablets and one 200 mg tablet has been initiated. Results are expected by end of September 2024 and will be communicated to the Rapporteurs. However, as the sink conditions are largely fulfilled, difference between two 100mg tablets and 200mg tablet are not expected.

Still, potential reasons of different dissolution results between 200 mg batches (intra-batch and inter-batches) have been investigated (32P2 section) and the following causes could be ruled out

a. API particle size distribution: Not the root cause

b. Excipients functional characteristics: Their key physico-chemical properties are tested and no potential impact are expected

The following causes were also investigated and had a slight impact, but only at the 5 and 10 min time points, without impacting the 20 min time point (the proposed specification time point)

c. Tablet harness (uncoated tablet): The selected hardness range would only have a slight impact at the highest hardness values (ref the tooling study -3.2.P.2.3.2.3 B).i) and therefore is not the main reason for the variability.

d. Coating agent: Very slight impact on the profile.

The intra difference (or inter-difference) on a granulated batch might be a potential explanation. Indeed, it was demonstrated during the product development that the granulation might have an impact on the *in vitro* dissolution profiles (see fig 1). However, testing this hypothesis would require to manufacture industrial/semi industrial batches using the same equipment and formulation, which is not feasible within the timeline of the procedure.

To complete these arguments and referring back to the point 1- , the over-discriminance of the method, especially at 75 rpm, could not be excluded.

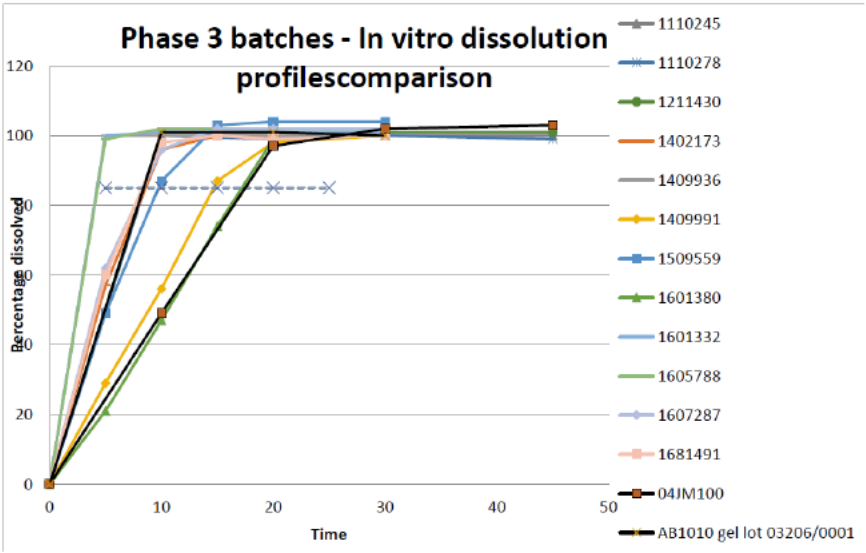
3- Potential impact and risks

The issue of intra-batch and inter-batches variability does not impact the patient safety and treatment efficacy because it has not impact on the bioavailability of the treatment.

This is supported by a bioequivalence study which demonstrate equivalence between a fast dissolving form (capsule – batch 03206/0001) and the proposed formulation (coated tablet with the proposed formulation and manufacturing process – batch 04JM100).

By examining the *in vitro* dissolution profiles of the clinical phase III batches used for the purpose of the clinical study AB10015, it is clearly proved that any batch is in the range of the bioequivalence (see here after).

Figure 9: Phase 3 batches – in vitro dissolution profiles comparison



Please note that batches 1110245, 1110278 and 1211430 were not analyzed at 5 min time point. The values at 10 min time point are respectively 100%, 100% and 101%. The argument remains valid.

In summary, both the 75 rpm and the 100 rpm dissolution methods comply with EMA guidance at the proposed specification 20 minutes time point. Potential reasons for intra difference or inter-difference at 5 min and 10 minutes time points were investigated whenever feasible. No root cause is well identified at that time but the bioequivalence of the batches is not affected by the intra difference or inter-difference at 5 min and 10 minutes. This method is discriminant, could exclude non-compliant batches with the proposed specification and could then be used as a quality control tool.

CHMP position on the Ground for re-examination

The Applicant's conclusions are unconvincing, as no sound justifications to the specific ground of refusal (GfR) raised by the CHMP has been provided, but rather hypothesis that needs to be confirmed.

1- About the in vitro dissolution testing method

The studies conducted are insufficient to draw robust conclusions on the appropriateness of the dissolution method and, consequently, its reliability to detect product quality attributes, that, if altered,

could affect *in vivo* performance.

It is worth noting that in addressing the grounds for refusal, the Applicant referred to the dissolution behaviour of the medicinal product by presenting dissolution profiles (graphs), without providing clear information regarding the nature of the batches reported or the conditions under which the dissolution methods were conducted.

The Applicant's response on the adequacy of the speed selected for the dissolution method is not discussed in light of findings obtained by a study of the discriminatory power but only mentioning previous masitinib applications, where the same speed of the dissolution method was accepted by the CHMP. This approach is not endorsed, as each marketing authorisation procedure and dossier is unique, and assessed on its own merit based on the data presented in the application. Furthermore, additional data compared to the previous applications was presented by the Applicant, and this additional data was also taken into account during assessment and in reaching the conclusions.

According to the relevant EMA guidelines, the discussion on the dissolution method development should be performed in a sequential manner. For example, when discussing the stirring speed for paddle the starting point should be 50 rpm. If deemed inappropriate, the subsequent stirring speed should be discussed. In this case, the 50 rpm was not evaluated, and the exclusion of the 75 rpm stirring speed was not substantiated by a sound justification. In fact, in the Applicant’s response to GfR it is stated that, although the speed at 75 rpm is more in line with in vitro dissolution testing rules and produces comparable dissolution results with 100 rpm, the Applicant preferred to keep the dissolution method at 100 rpm, considering the previous experience with the two earlier procedures where the 100 rpm was accepted.

However, the higher stirring speed of 100 rpm is expected to lead to a reduced discriminatory power, by decreasing variability of the results and obtaining a more rapid complete dissolution. This approach should be avoided, since the stirring speed should not be selected at the expense of the discriminatory power.

2- About intra/inter batch variability investigations

The deficiencies and the lack of a satisfactory explanation for the significant differences of dissolution data between the 100 mg and the 200 mg strengths, as well as differences in dissolution profiles between different batches of the 200 mg strength, remain unsolved since the Applicant has not clarified the reasons of intra-batch (or inter-batches) difference. Indeed, in the re-examination dossier the Applicant declared that tablet hardness and film-coating were no more identified as the main causes of dissolution variability, as they were found to have only a minor impact at the 5 and 10 min time points, without impacting the 20 min time point. Thus, excluding these causes, the Applicant suggested that granulation might be a potential explanation of the intra-batch (or inter-batches) difference. However, this aspect has not been substantiated, as according to the Applicant, generating new data on industrial/semi-industrial batches using the same equipment and formulation intended for the market is not feasible within the re-examination procedure.

The identification of the granulation step as a possible cause of variability in dissolution results raises concerns on the adequacy of the drug product development and, consequently on the know-how of the production process.

The Applicant stated that a comparative dissolution testing between two 100 mg tablets and one 200 mg tablet has been initiated and results are expected by end of September 2024. While this is acknowledged, it is reminded that the re-examination procedure can be based only on the scientific data available at the time of initial opinion and cannot take into account new data, and above all the issue on the intra-batch differences would remain unsolved, since only results on the comparison of the two strengths would be available.

3- Potential impact and risks

The Applicant reiterated that the issue of intra-batch and inter-batches variability does not impact patient safety and treatment efficacy, as it does not affect the bioavailability of the treatment. This claim is supported by the bioequivalence study, which demonstrates equivalence between a fast dissolving form (2x50 mg capsule – batch 03206/0001) and the proposed formulation (1x100 mg coated tablet with the proposed manufacturing process – batch 04JM100).

However, the in vivo results cannot overcome the need to establish the suitability of the dissolution method for proper routine quality control of the drug product. Thus, concerns regarding batch to batch consistency remain, since the discriminatory power of the dissolution method was not demonstrated. Moreover, according to the Applicant's hypothesis on the impact of the granulation step on the variability observed in the dissolution profiles, the manufacturing process has not been demonstrated adequate to obtain a product with the intended quality.

Unless it is not unequivocally demonstrated that the manufacturing process is robust and adequate to produce uniform and consistent batches, doubts persist about the reliability of the bioavailability results.

Overall Conclusion

The GfR related to the quality of masitinib remain unsolved. The Applicant has not presented compelling arguments to resolve the quality issues.

Point not resolved

5.1.2. Ground #2.1

The data from the pivotal clinical study AB10015 cannot be relied upon. Despite the Applicant's arguments and the implementation of corrective measures, the deficiencies identified during previous GCP inspection cannot be resolved by performing re-monitoring and retrospective analyses at the study sites and cannot be corrected retrospectively.

Applicant´s position on the Ground for re-examination

The Applicant presented first some statements already detailed in section 2.6.6 – Discussion on clinical efficacy of this CHMP AR:

A triggered GCP inspection (GCP/2017/001) was requested by the CHMP on the conduct of the clinical study AB10015 in the context of a previous marketing authorisation application for ALS. The triggered GCP inspection reported critical and major inspection findings affecting different aspects of the study, which impact on the reliability of the study data. Major findings were observed at qualification and training, trial master file, clinical conduct of the trial, safety reporting, investigational medicinal product, source data verification and clinical study report. The GCP inspection concluded that the data obtained at the sites inspected are not trustworthy.

It is noted that at the time of the GCP inspection, the Applicant presented a series of corrective and preventive actions which have been assessed by the inspectors and were not found sufficient to recommend the use of data. In accordance with the GCP inspection report conclusion, after the evaluation of the responses submitted by the Applicant, the Inspection Team considered that due to the departures from GCP observed, it cannot be ensured that the data inspected are trustworthy and are likely to have an impact on the final results. Data integrity is high likely to be impaired as several protocol deviations at eligibility, conduct and in other aspects inspected.

Given the nature of the findings, the systematic deficiencies observed (i.e. massive number of protocol deviations) and the fact that some findings such as the deficiencies during inclusion/exclusion criteria

verification and subjects' follow up (critical finding 1 in the inspection report) cannot be corrected retrospectively, the proposed corrective actions presented by the Applicant were not considered adequate to address all the concerns raised.

As part of this current application, the Applicant claimed that the GCP findings were addressed with implementation of preventive actions across study and functions within AB Science. The Applicant also claimed that for study AB10015, corrective actions were implemented wherever feasible. The measures which the Applicant claims to have implemented after the inspection, have been assessed as part of the current marketing authorisation procedure and were found insufficient to address the issues raised and re-assure CHMP on the trustworthiness of the data.

During the procedure, the Applicant argued that GCP findings related to ALSFRS-R were not systematic and the ALSFRS-R scores data are reliable, it is feasible to perform re-monitoring and manage retrospective/impact analysis and refers to the EMA guidelines EMA/868942/2011. In addition, during the procedure the Applicant performed an impact analysis of protocol deviations and concluded that GCP inspection findings which are likely to influence the evaluation of the primary efficacy endpoint, whether correctable or not, had no significant impact on the study's outcomes. The Applicant's conclusions that the primary endpoint is not affected are not agreed by the CHMP. In addition, it should be noted that even the execution of the different analysis excluding just one or two inspected sites are often not meaningful since these do not address the uncertainty regarding the non-inspected sites (EMA/8689942/2011).

The Applicant has provided justifications for the GCP aspects during the procedure including expanded written discussions after the oral explanation. The Applicant provided numerous arguments on the extensive corrective actions implemented after the inspection conducted in the context of the previous marketing authorisation application and other regulatory authorities, including an impact analysis of identified protocol deviations. The Applicant upholds the position that the corrective actions implemented after the GCP inspection and the Applicant interpretation of the guidelines on benefit/risk evaluation demonstrates an absence of impact on the results of the AB10015 study. Following the review of the information submitted in support of this application, including the implemented corrective measures, it is considered that the issues identified cannot be resolved by performing re-monitoring and retrospective analyses at the study sites. The numerous retrospectives analyses applied by the Applicant do not compensate for the deficiencies in the conduct of the study and thus the data are not considered reliable. The Applicant has reiterated the relevance of the impact analysis of identified deviations during GCP inspections, however the Applicant's claim that the primary endpoint is not affected is not agreed by the CHMP. From this point of view, the primary and secondary endpoint results (i.e. ALSFRS-R) of the single pivotal study are based on dataset of compromised quality and reliability. The statement of the Applicant that "the CHMP's decision to base its findings solely on the inspectors' position from 2017, fails to take into consideration the entire sum of evidence now available and is not therefore consistent with guidelines on benefit- risk assessment" is not agreed with.

Therefore, despite the fact, that the Applicant has provided impact analysis and arguments, the existing evidence of data quality does not assure CHMP that the AB10015 trial data is trustworthy.. The Applicant's provided impact analysis and arguments are not sufficient to assure CHMP that the AB10015 trial data is trustworthy considering the conclusions of GCP inspection and the presented implemented corrective actions. The data from clinical study AB10015 cannot be relied upon. The CHMP is of the opinion that this conclusion is in line with EMA/8689942/2011 document "Points to consider on GCP inspection findings and the benefit-risk balance".

AB Science Response

Argument 1.1: AB Science has a legitimate doubt regarding the potential bias of the ALS inspection and urge the Rapporteurs to take into account all available information, in particular actions implemented by AB Science after the inspection

CHMP currently adheres strictly to the conclusions of the inspection report, without evaluating the additional analyses provided by AB Science.

We faced two negative concomitant trial inspections, one in mastocytosis and one in ALS. The inspection in mastocytosis was led by an inspector who later wrote to the *Autorité des Marchés Financiers*, that triggered an investigation for insider trading. This investigation, which is now closed, concluded that there was no insider trading and demonstrated the profound bias of the said inspector.

AB Science has a legitimate doubt regarding the potential bias of the ALS inspection by the Mastocytosis inspection.

For these reasons, we urge the Rapporteurs to:

- assess all correspondence between the Mastocytosis and the ALS inspectorates and share them in transparency with AB Science,
- take the conclusion of the inspection with extreme caution
- take into consideration the actions implemented by AB Science and the impact analysis on the benefit -risk assessment, which shows there is no impact. There were several measures taken by AB science post- inspection to overcome the drawbacks of the clinical study conduct. One of them being an impact analysis, which was performed in a GCP-compliant system, was not reviewed or assessed by the EMA inspectors.

Argument 1.2: According to guidance EMA/8689942/2011 evaluators must go beyond inspection report

Guidance EMA/8689942/2011 clearly states that "*GCP inspectors and clinical assessors have different roles in the overall regulatory process of evaluating new medicines. Hence, it should be acknowledged that the focus of the GCP inspectors and clinical assessors is different and as a consequence the evaluation of the significance of the findings may also differ. For the assessors, the focus is on the particular medicine under assessment to ensure that the benefit-risk balance is favourable before licensing and that the overall ethical conduct is acceptable*".

There have been instances where similar conclusions from the Inspectors have not led the CHMP to inevitably dismiss that data, including for example EPAR EMA/174182/2014, wherein the inspection report concluded that "*Inspectors cannot recommend that the presented data and CSR is accepted by the CHMP or used for further assessment"* and where no major objection was raised as the CHMP noted that "*The Applicant, in response to the inspector's findings, provided a follow-up of the post inspection corrective action plan. The Applicant has responded to the numerous GCP inspection findings with corrective measures whenever possible*".

Four examples of negative GCP findings and positive Benefit- Risk assessments are provided in Appendix 1.

Argument 1.3: The other inspections reports available, as well as audit reports; are consistent and they do not conclude that data are not trustworthy or should be disregarded. Therefore, they have to be considered as well

The conclusions of the EMA Inspection were divergent from: i) inspections conducted by other health regulatory authorities and ii) the audits conducted at the request of AB Science, although findings were comparable.

A total of four GCP inspections of study AB10015 were conducted: EMA, Health Canada, ANMAT (Argentina), and Infarmed (Portugal) andthe second largest recruiting site, was inspected by both EMA and Argentina

While EMA found the data unreliable, other authorities such as Health Canada and Infarmed did not find critical issues affecting data integrity.

- Conclusion from site inspection in Argentina by ANMAT

The Argentina health agency inspected the second largest recruiting site, before inspection of the same site by EMA.

ANMAT did not conclude to the rejection of the data at the site. The translation of the conclusion, from the inspection report is provided below.

"In conformity with the verified findings, the result of the inspection is the following:

- *Official Action Indicated point 12.2, Section D, ANMAT Disposition 6677/10 for the PI to carry out the following actions: Sign a commitment letter with the Administration for the future clinical trials to be conducted.*
- *Official Action Indicated for the Sponsor LAT Research to carry out the following actions: Sign a commitment letter with the Administration for the future clinical trials to be conducted".*

- Conclusion from site inspection in Canada by Health Canada

The outcome of inspection by Canadian Health Regulatory Authority showed no critical findings to AB Science and the authority rated the study as "Compliant".

The translation of the conclusion, from the inspection report is provided below.

"As a result of this inspection, the above noted clinical trial has been assigned a Compliant (C) rating, meaning that at the time of the inspection, the regulated party has demonstrated that the activities it conducts are in compliance with the Food and Drugs Act and its associated Regulations. A Compliant rating does not mean that there are no observations or corrective actions required".

- Conclusion from site inspection in Portugal by Infarmed

The inspection carried out by Infarmed did not conclude that the study data were not trustworthy. Five Major and Four minor findings were identified. No critical noncompliance was identified.

The translation of the conclusion, from the inspection report is provided below.

"During this inspection it has been confirmed that the monitoring by the Sponsor of centre has not been sufficiently robust and this has caused the occurrence of several non-compliances described above. The selection of participants was made by fulfilling the inclusion criteria (although with certain shortcomings in the documentation process). There were no indications of a possible relationship between the publication of results of the interim analysis that might have put into question the concealment of the trial in this centre.

Critical non-compliances were not identified.

Five (5) major non-compliances were identified related to: conformity of the eCRF to the protocol in force; monitoring process; deviations from the protocol, recording of data, verification of compliance of EM.

Four (4) minor non-compliances were detected relating to: training in the field of GCP; calibration of measuring instruments, management of secure data and temperature monitoring records during transportation of the EM."

- Conclusion

Among the four inspections carried-out, only EMA inspectors conclude that data are not trustworthy.

The EMA has a framework that allows it to rely on inspection reports from other competent authorities under mutual recognition agreements (MRAs). These agreements are in place with several countries, including the United States, Canada, Japan, and others, to facilitate regulatory processes and reduce duplication of inspections. The mutual recognition agreements ensure that inspections carried out by regulatory authorities in these countries are recognized as meeting the necessary standards for compliance with good manufacturing practices (GMP).

Additionally, the EMA collaborates with the World Health Organization (WHO) through the WHO collaborative registration procedure, which involves sharing detailed assessment reports, including inspection reports, to facilitate faster regulatory approvals in participating countries. This procedure emphasizes reliance on inspections and assessments carried out by recognized regulatory authorities like the EMA, thus streamlining the approval process and reducing the administrative burden.

Therefore, the CHMP should take into account conclusion from other inspections regarding trustworthiness of the data for benefit-risk assessment.

In addition, the Applicant conducted extensive audits by external, independent professionals to ensure full compliance and integrity of the study data. A total of 16 audits were performed at the request of AB Science between 18 May 2017 and 28 December 2017, across six countries. The audited patients in those sites accounted for than 30% of the total randomized patients at those sites. The findings and conclusions of these 16 audits were in line with the inspections conducted by ANMAT, Health Canada and Infarmed, and similarly to these inspections, did not conclude that the data were not trustworthy. One critical finding was identified related to the fact that *"changes to a protocol, particularly those related to safety reporting/monitoring or to interpretation of the protocol should be setup through an amendment and submitted as substantial amendment"*. Several major findings were reported, including inconsistencies in AE/SAE reporting, delayed reporting, documentation errors, and administrative oversights. For instance, incorrect start/end dates for SAEs, missing documentation, and the use of correction fluid on SAE documentation were noted. Additionally, there were instances of unreported concomitant medications and unsigned SUSAR reports. These audits were not reviewed during the EMA GCP inspection as the EMA inspection was only a site inspection, not a Sponsor inspection.

Despite these audits being conducted in accordance with industry standards and providing comprehensive insights into the study's conduct, it appears that the rapporteurs did not fully account for these independent audits in their assessment.

Argument 1.4: The conclusion of the EMA GCP inspection diverges from the conclusions of all audits and other inspections

Before the EMA GCP inspection of two sites in late 2017 and early 2018, we conducted 16 audits. Additionally, as mentioned in previous section, three sites were inspected before the EMA GCP inspection. These audits and inspections did not identify the critical non-compliances level, later highlighted by EMA inspectors, suggesting that the EMA findings may not reflect a systematic issue across all sites.

To demonstrate this, we can categorize the site quality as follows:

Excellent Quality Sites:	0 Critical Findings / 0 Major Findings
Good Quality Sites:	0 Critical Findings / 1-2 Major Findings
Moderate Quality Sites:	0 Critical Findings / 3-5 Major Findings
At Risk Sites:	1 critical finding and/or 6-10 Major findings
Critical Risk Quality Sites	More than 1 Critical Finding an/or more than 10 major findings

The results of this categorization are detailed in the table below and can be summarized as follows:

- **Excellent and Good Quality Sites**: **48%**
    - 6 sites had 0 critical and 0 major findings, and 4 sites had 0 critical and 1 or 2 major finding.
    - This indicates that a considerable percentage of sites - approximately **48%** - were managed with excellent or good quality.
- **Moderate Quality Sites: 19% (4 sites)**
    - 5 sites showed more findings, categorized as moderate risk,
- **At risk and High-Risk Sites: 33%**
    - 5 sites showed more serious findings, categorized as *"at risk".*
    - But these sites present still a less critical level of quality than those identified at sites inspected by the EMA and categorized as high-risk in the table below:

START AUDIT DATE	CRITICAL FINDINGS	MAJOR FINDINGS	Site category	Patients Randomized
10-juil-17	0	0	Excellent	9
05-juil-17	0	0	Excellent	30
18-oct-17	0	0	Excellent	7
24/Aug/2017	0	0	Excellent	16
06-juil-17	0	0	Excellent	18
04-juil-17	0	0	Excellent	16
10-juil-17	0	1	Good	25
06-juil-17	0	1	Good	5
28/Dec/2017	0	2	Good	4
04-juil-17	0	2	Good	4
18/Dec/2017	0	3	Moderate	6
04-juil-17	0	4	Moderate	106 (2)
05-juil-17	0	4	Moderate	10
24-oct-16	0	5	Moderate	3
27-sept-17	0	6	at-risk	9
01/Apr/2016	0	6	at-risk	2
27/Dec/2017	0	8	at-risk	22
29/May/2017	0	9 observations (1)	at-risk	53 (2)
18/May/2017	1 (2)	7	at-risk	14

Note: Total Number of patients randomized in the trial = 391

(1) Not the same system of findings evaluation

(2) The patients of these sites were categorized as "a critical risk" by EMA inspection

The last audit was conducted on 28 December 2017, just before the EMA inspections in late 2017 and early 2018. These audits did not highlight the level of critical non-compliances later highlighted by EMA inspectors, suggesting that the EMA findings may not reflect a systematic issue across all sites. Moreover,

inspections by ANMAT, Canada, INFARMED and the audits, while identifying similar problems, do not conclude that these issues are systemic or that the data are not trustworthy. We can highlight that it concerns sites which enrolled **92 %** of all the randomized patients. For accuracy, please find enclosed the wording of the unique critical finding identified during an audit:

(3) The CRITICAL finding identified in one Italian site is: "Changes to a protocol, particularly those related to safety reporting/monitoring or to interpretation of the protocol should be setup through an amendment and submitted as substantial amendment"

The auditor concludes that "Because the critical finding is from 2013, …, the global recommendations are:

- The guidelines/documentation/training aimed at improving performance and monitoring of a study are to be improved (refer to CAPAs).
- AB Science can go on with this site, in performing a monitoring closer to GCP and stricter.

This finding does not impact the efficacy nor the safety data.

At the end of the trial, a total of 134 patients randomized were followed by sites with excellent and good level of quality (6 sites with 0 critical and 0 major finding and 4 sites with 0 critical and 1/2 major finding) which represents 34% of all patients randomized.

- 40% of all patients randomized were followed during the trial by sites inspected by EMA
  1. 30% - 122 – at randomized at the time of the inspection
  2. 10 % - followed up after the inspection with better level of follow-up as impact of the inspection
- 34% (134) of all patients randomized were followed by sites with excellent and good quality level
- 5% of all patients randomized were followed by sites with moderate quality level
- 12% of all patients randomized were followed by sites at risk
- **Only 32 patients were followed by a site non audited and non-inspected: 9%**

Is it justified to claim that all the study data are misleading, given the lack of uniformity in site management quality and considering that only 8% of patients were followed by sites that were neither inspected nor audited, which means we have a fairly good understanding of the site typologies in the study?

The results of the audits and other inspections, clearly differ from the highly negative outcomes of the EMA inspections. A significant proportion of the sites (29%) exhibited excellent or good quality, which is substantial. Less than 6 % of sites are at critical-risk and this distribution supports the assertion that the critical issues identified at the two EMA-inspected sites are not systematic across all study sites.

Consequently, there is a real divergence in conclusions between EMA inspection and all other audits and inspections:

- The heterogeneity in site management quality further suggests that the data integrity concerns raised by the EMA are not representative of the entire study. It cannot be concluded that the issues identified by the EMA are systemic.

No audit or inspection, other than the EMA inspection, has concluded that the data from the entire study are not trustworthy. Given that only 32 patients, representing 9%, were followed by a site that was neither audited nor inspected, this is an important consideration.

Argument 1.5: Inspectors and the Rapporteurs did not account for analyses done after inspection

Rapporteurs stated that "*It is noted that at the time of the GCP inspection, the Applicant presented a series of corrective and preventive actions which have been assessed by the inspectors and were not found sufficient to recommend the use of data. In accordance with the GCP inspection report conclusion, after the evaluation of the responses submitted by the Applicant, the Inspection Team considered that due to the departures from GCP observed, it cannot be ensured that the data inspected are trustworthy and are likely to have an impact on the final results*".

However, numerous actions were taken after the EMA GCP inspection report, rendering, to a certain extent, the inspection report obsolete.

As a reminder, the following actions were implemented for the quality system and the reliability of the data.

- **Post-Inspection Corrective Actions:** We have undertaken significant corrective actions (and preventive actions) to address the quality system deficiencies when possible and it included re-monitoring of adverse events, vital signs, and lab values at 31 out of 34 study sites. This extensive re- monitoring ensured that all source data were accurately reflected in the updated clinical study report (CSR v3.0), which has not been reviewed by the inspectors.
- **Reinforced Data Integrity and historical Data Validation:** Critical data from the trial, particularly the primary endpoint (ALSFRS-R) and safety data, were re-evaluated and validated through multiple layers of independent audits and verifications, ensuring their reliability. These validations demonstrated that, despite the quality system issues, the data integrity for the primary endpoint was maintained
- **Safety data and continuous improvement after inspection but before CSR v3.0:** The corrective actions implemented after the EMA GCP inspection confirmed that the safety data, derived from the same continuously improved quality framework, are reliable for risk assessment. Detailed impact analyses of protocol deviations (on all sites, all patients, eligibility protocol deviations, all other kind of protocol deviations), demonstrating that these deviations did not significantly affect the primary efficacy or safety outcomes**.**

The inspectors did not have the opportunity to review our post-inspection corrective measures, including the updated CSR and additional impact analyses.

- EMA GCP inspection report was completed in February 2018, based on the CSR V1.0.
- The re-monitoring occurred during the period between the data extraction of the CSRV1.0 date and the data extraction of the CSR v3.0 and included an additional 97 monitoring in 31 sites (91% of the 34 sites).
- The detailed impact analysis was communicated for the first time at D180.

As a reminder also, two CGP inspections report were provided, ANSM inspection report (GCP-181801-FR) and MHRA inspection report (INSP GCP 21687/22860-0003), indicating that the CSR v3.0 was released within a GCP compliant environment, as demonstrated by.

i. *ANSM Inspection*

The ANSM inspection primarily concerned the vigilance system and the integrity of masitinib safety data. Review of CAPA required for deficiencies related to PV, which were identified during previous inspections. Post Inspection Report Follow-up until resolution of last Major Corrective Actions. Reassessment of the

safety profile of masitinib with impact analysis of the corrective actions and release of a new investigator brochure [Edition 2018-1] was performed by AB Science.

The conclusion of the final inspection report, dated 27 March 2019, considered "*that the evolution of AB Science's vigilance system and the recovery of all the vigilance data carried out to date provide a sufficient response to points a, b and of the last recital of the decision of 11 May 2017 suspending the clinical trials promoted by the company AB Science*".

ii. *MHRA Inspection*

The MHRA inspection covered various activities (Quality management, pharmacovigilance, project management, monitoring, data-management, and biometry). Review of CAPA required for deficiencies which were identified during previous inspections. Post Inspection Report Follow-up occurred until resolution of findings according to MHRA.

The conclusion of the final inspection report, dated 11 November 2021, considered that "*The organisation has provided corrective and preventative actions in response to the inspection report. These have been reviewed by the GCP Inspectorate and are considered acceptable. This inspection can be considered closed*".

A summary of the main improvements and a summary of the impact analysis is available (please refer to the hyperlink in the table below).

A summary and analysis ANSM and MHRA inspection reports is available. ANSM and MHRA inspection reports are available (please refer to the hyperlink in the table below).

Finally, to reiterate our position, provided below is the timeline of events which demonstrate that the inspectors did not have access to the new documents/findings and therefore, the conclusions of the EMA inspection were

Chronology of the actions taken with respect to the GCP inspection of study AB10015

Period	Date	Action	Document
Pre EMA Inspection	11 AUG 2017	Clinical study report provided for initial MA application and inspected	AB10015_CSR v1.0_11aug2017_Final
Inspection	18 DEC 2017 until 12 JAN 2018	**Investigator site GCP inspection** Conducted at two sites (one in Spain and one in Argentina). on 07 FEB 2018.	
Post-EMA Inspection	07 FEB 2018	Integrated inspection report GCP/2017/001	EMA Masitinib_FINAL Integrated Inspection Report (IIR)

Actions ~~Initiated Before, But~~ finalized AFTER or impacting AFTER, the GCP Inspection

Date	Action	Document
MAY 2017- DEC 2017	**Audit plan** A campaign of 16 audits was performed by external auditors	List of audits
JULY 2017-SEPT 2018	**Re-monitoring** Conducted between the data extraction dates of CSR V1.0 and CSR V3.0, involving an additional 97 monitoring visits at 31 sites (91% of the 34 sites). Only 3 sites were not re-monitored (two in Canada, and one in Argentina).	List of monitoring visits performed between CSR v1.0 and V3.0 (provided in Response D180 1st LoI_Seq0008_Appendix 1)

19 FEB 2010	**Addendum to CSR** This addendum addresses one of the issues highlighted in the inspection report regarding certain discrepancies between the eCRF data and the CSR v1.0 At the time of DB lock for the efficacy analysis, many patients were still in the extension phase, and data in safety-related CRF pages of both the main protocol period and the extension protocol period continued to be added, cleaned and modified. In order to respond to the EMA's questions at D121 of initial MAA procedure (h0004398), a second DB extraction on 12 July 2017 was done to analyse the safety of the main protocol period. At the time of this second extraction, a total of 75 patients were still followed up in the extension phase and safety data continued to be recorded on the safety CRF pages. AB Science electronic data capture system is not setup to allow page lock at page or visit level. CRF lock is done at patient level. CRF pages dedicated to the main protocol period remained unlocked until completion of the extension period of each patient. Consequently, the DB continued to be updated, including data changes to the main protocol period. Our electronic data capture system has an audit trial and any changes made to the DB were recorded. Although data cleaning of the extension period had not been completed, safety data of the main protocol period had been completed. The DB was locked on 03 February 2018. A third extraction of the safety data was performed in order to repeat all safety analyses pertaining to the main protocol period (i.e. Week 48). The updated safety tables integrating the changes between the 12 July 2017 and 03 February 2018 are displayed in the present addendum to the CSR v1.0.	AB10015_CSR v1.0_Addendum_19feb2018
27 MAR 2019	The ANSM inspection primarily concerned the vigilance system and the integrity of masitinib safety data. Review of CAPA required for deficiencies related to PV, which were identified during previous inspections. Post Inspection Report Follow-up until resolution of last Major Corrective Actions. Reassessment of the safety profile of masitinib with impact analysis of the corrective actions and release of a new investigator brochure [Edition 2018-1] was performed by AB Science.	ANSM Inspection report (provided in Response D180 1st LoI_Seq0008_Appendix 6)
19 to 21 SEPT 2018	**ANSM GCP Inspection of the Sponsor** The ANSM inspection primarily concerned the vigilance system and the integrity of masitinib safety data. Review of CAPA required for deficiencies related to PV, which were identified during previous inspections. Post Inspection Report Follow-up until resolution of last Major Corrective Actions. Reassessment of the safety profile of masitinib with impact analysis of the corrective actions and release of a new investigator brochure [Edition 2018-1] was performed by AB Science. The final report was released the 27 Mar 2019 (after ANSM's review of the two impact analyses presented in the 2 lines below of the same table).	GCP-181801-FR - ANSM Final report_ CONCUSION _VEnglish
26 NOV 2018	**Analysis of the masitinib safety profile following legacy PV case reevaluation and integration into the new validated PV database.** Since October 2018, AB Science has implemented a new validated pharmacovigilance (PV) database system. All legacy safety reports received prior to the launch of this new system have been fully reassessed and re-entered into the new system. A comparison between this new PV database and the safety data recorded in the clinical trial database was conducted to ensure the adequacy and accuracy of the safety profile of masitinib, as described in the approved Investigator's Brochure (Edition 2018-1). Differences were analyzed in terms of their potential impact on the product's safety profile, and no impact was identified. During the previous ANSM inspection, it was acknowledged that this impact report would be submitted to ANSM for review by their internal evaluators. This report played a major role in the decision to lift the hold.	ABS Impact Analysis Safety Profile masitinib_Nov 2018(provided in Response D180 1st LoI_Seq0008_Appendix 4b)
15 JAN 2019	**MEDDRA coding reconciliation and analysis of impact** As part of the Data Quality Control Plan supporting the implementation of the new AB Science Pharmacovigilance System, a comparison between MedDRA coded AEs stored in PV247 and those available in the clinical database was performed to ensure the adequacy and accuracy of the safety data. During the previous ANSM inspection, it was acknowledged that this impact report would be submitted to ANSM for review by their internal evaluators. This report played a major role in the decision to lift the hold.	ABS Impact Analysis MedDRA Coding masitinib_Jan2019 (provided in Response D180 1st LoI_Seq0008_Appendix 4c)

16 SEP 2021	**2021 CSR for AB10015** Clinical study report, based on safety dataset extraction December 2018 provided for current CMA application	CSR_AB10015_v3.0 September 2021
11 NOV 2021	**MHRA GCP inspection** The MHRA inspection covered various activities (Quality management, pharmacovigilance, project management, monitoring, data-management, and biometry). Review of CAPA required for deficiencies which were identified during previous inspection (2017). Post Inspection Report Follow-up occurred until resolution of findings according to MHRA	MHRA GCP Inspection Statement Science 11 November 2021 (provided in Response D180 1st LoI_Seq0008_Appendix 6)
30 APR 2024	**Impact analysis of eligibility protocol deviations on efficacy and safety data, for all sites and all patients:** A thorough, broad detection, systematic review of the final locked database (Cut-off date: 03 December 2018) was performed to identify eligibility criteria queries. These were then assessed to establish deviation status, deviation impact on safety, and separately deviation impact on efficacy. In this manner, all eligibility criteria queries were assessed on a case- by-case basis and subsequently categorized according to seriousness (i.e., negligible query, minor deviation, and major deviation) and potential impact (i.e., no impact, possible impact). The methodology was reviewed and validated by an independent expert a , coordinator of the French rare diseases network on ALS and motor neurone disease (FILSLAN). A matrix of deviations analysis is shown in table below	Responses to D180 2nd list of outstanding issues - Clinical Efficacy_V1.0_April- 2024: Page 10 + Appendix 1, 2 and 3 (Seq0010)
30 APR 2024	**Impact analysis of all protocol deviations (except eligibility criteria managed previously) on efficacy and safety data, for all sites and all patients:** As some deviation could not be resolved by corrective actions, we have performed an impact analysis.	Responses to D180 2nd list of outstanding issues - Clinical Efficacy_V1.0_April- 2024: Page 12 (Seq0010)
30 APR 2024	**Potential underdosing of riluzole was investigated and an impact analysis was performed** A total of 7 patients (1.8%) received sub-dosing of riluzole, including 6 patients in either M4.5 arm (n=3) or placebo arm (n=3). Sensitivity analysis excluding these 6 patients does not modify the study results.	Responses to D180 2nd list of outstanding issues - Clinical Efficacy_V1.0_April- 2024: Page 12 (Seq0010)
30 APR 2024	**Masitinib dosing deviations impact analysis** Identified deviations that were related to masitinib underdosing could only minimize masitinib efficacy and have no impact.	Responses to D180 2nd list of outstanding issues - Clinical Efficacy_V1.0_April- 2024 Page 13 _(Seq0010)
30 APR 2024	**Visit Windows deviation impact analysis** DSMB decided (25 Feb 2016) that no impact on efficacy data is expected if non-respect of visit windows is not higher than 28 days and not repeated at 2 consecutive visits. No visit window deviations to this rule occurred in the Masitinib 4.5 mg/kg/day treatment arm or placebo arm, thereby having no impact on the primary analysis.	Responses to D180 2nd list of outstanding issues - Clinical Efficacy_V1.0_April- 2024 Page 13 (Seq0010)

Argument 1.6: The Rapporteurs provided no review of AB Science corrective actions and impact analyses justifying why the data remain not trustworthy

From the very beginning of the procedure, the Rapporteurs adhered to the conclusions from the Inspectors and made not no attempt to evaluate the consequences of inspection findings in relation to the benefit-risk balance. This is not in line with the guidance recommendation.

In particular, the rapporteurs stated that "*the Applicant's provided impact analysis and arguments are not sufficient to assure CHMP that the AB10015 trial data is trustworthy considering the conclusions of GCP inspection and the presented implemented corrective actions*", however, these impacted analyses were communicated for the first time at D180, yet the Rapporteurs

- Maintained without altering them their conclusion that the data were not trustworthy before and after communication of these analyses at D180
- Did not share any information suggesting these analyses were assessed and how they were assessed

Argument 1.7: A complete reassessment of safety has been done and a new CSR has been released that the inspectors could not assess

The safety data are reliable for risk assessment, following the corrective actions that were implemented after EMA GCP inspection

EMA GCP inspection report was completed in February 2018, based on CSR v1.0. The following dates apply to the data reported in CSR v1.0.

- Cut-off date: 5 December 2016
- Efficacy dataset extraction date: 16 March 2017
- Safety dataset extraction date: 25 July 2017

The following dates apply to the data reported in CSR v3.0 submitted as part of the current application.

- Cut-off date: 5 December 2016
- Efficacy dataset extraction date: 16 March 2017
- Safety dataset extraction date: 03 December 2018

a) Re-monitoring was performed between the CSR V1.0 and the CSR V3.0 to support the integrity of the safety data

The re-monitoring occurred during the period between the data extraction of the CSRV1.0 date and the data extraction of the CSRV3.0 and included an additional 97 monitoring in 31 sites (91% of the 34 sites). Only 3 sites were not re-monitored, one site in Canada (2 patients randomized, Inspected by Health Canada), another site in Canada (1 patient randomized), and one site in Argentina (9 patients randomized).

The list of these re-monitoring visits are available as an appendix (provided in Response D180 1st LoI_Seq0008_Appendix 1)

b) Updated safety data between CSRV1.0 and CSRV3.0

An overview of the updates in safety data as a result of the re-monitoring activities is provided

below. The updates in the number of patients with at least one event was the following:

Adverse event: 1 patient previously identified was deleted in the control group. As compared with placebo, very slightly increase.

AE leading to death: No change

Non-fatal serious AE: No change

Severe AE Update for 6 patients

- 5 patients identified with serious adverse events, 1 in the masitinib 4.5 group and 4 with control group
- 1 patient previously identified was deleted with masitinib 3.0 group

Table 101 provides the summary of safety between v1.0 and v3.0 are a result of this re-monitoring activity.

Table 101: Summary of safety profile between CSR v1.0 and CSR v3.0

	W0 TO W48 - DATA IN CSR V1.0				
Number (%) of patients with at least one:	P[1] (N=133)	M4.5 [2] (N=129)	(M4.5 - P)	M3 [3] (N=131)	(M3 - P)
AE	105 (78.9%)	114 (88.4%)	9.4	111 (84.7%)	5.8
Leading to Death [4]	12 (9.0%)	10 (7.8%)	-1.2	11 (8.4%)	-0.6
Non-fatal SAE	24 (18.0%)	40 (31.0%)	13.0	30 (22.9%)	4.9
Severe AE	22 (16.5%)	38 (29.5%)	12.9	29 (22.1%)	5.6

	W0 TO W48 - DATA IN CSR V3.0				
Number (%) of patients with at least one:	P[1] (N=133)	M4.5 [2] (N=129)	(M4.5 - P)	M3 [3] (N=131)	(M3 - P)
AE	104 (78.2%)	114 (88.4%)	10.2	111 (84.7%)	6.5
Leading to Death [4]	12 (9.0%)	10 (7.8%)	-1.2	11 (8.4%)	-0.6
Non-fatal SAE	24 (18.0%)	40 (31.0%)	13.0	30 (22.9%)	4.9
Severe AE	26 (19.5%)	39 (30.2%)	10.7	28 (21.4%)	1.9

P [1]: Placebo + Riluzole - M4.5 [2]: 4.5 mg/kg/day Masitinib + Riluzole - M3 [3]: 3 mg/kg/day Masitinib + Riluzole.

Leading to Death [4]: Adverse events were recorded until 28 days after treatment interruption, and adverse events not resolved at the death of the patients were recorded as adverse events leading to death. Given the severity of the condition, several AEs in each treatment-arm were therefore recorded as adverse events leading to death. However, none of these adverse events were considered to be related to either masitinib or Riluzole.

Regarding the detail of severe AEs, the updates in the number of events were the following:

3 cases previously reported were deleted (1 case of blood triglycerides increased with masitinib 3 mg/kg/day, 1 case of Muscular Weakness and 1 case of Muscle atrophy with masitinib 4.5 mg/kg/day).

6 cases were added:

- Control group: + 2 events (1 case of cardiac arrest and 1 of blood pressure systolic increase).
- Masitinib 3 mg/kg/day group: + 2 events (1 chronic respiratory failure, 1 hypercapnia and 1 hypoxia).
- Masitinib 4.5 mg/kg/day group: + 1 event (1 peritoneal haemorrhage) All frequency of severe AE by SOC/PT changes available.

Argument 1.8: Safety profile being acceptable, what matters is ALSFRS-R data

The CHMP considered that "*the safety profile of mentioned medicinal product is considered acceptable for a CMA*". The guidance EMA EMA/868942/2011 states that:

- "*in superiority studies, once the study has been completed, and superiority has been established, inspection findings merely indicating increased variability and not introducing bias favouring one treatment over the other are relatively unproblematic in the interpretation of the study results*".

And

- "Further, it is important to assess whether the findings affect the interpretation of the primary efficacy endpoint or important safety endpoints. Needless to state, the findings have less significance for the benefit-risk assessment if they only have consequences for secondary or exploratory endpoints*"*.

Therefore, as per guideline, the main consideration for benefit -risk assessment is the ALSFRS-R data.

Argument 1.9: ALSFRS-R had no systemic errors according to the inspection

- Raters were experienced in ALSFRS-R scale according to inspectors.

Although inspection pointed out that the sites, particularly at one Spanish site, had experience with the scale used, there was a lack of documented formal training at the beginning of the trial. On September 2014, AB Science released ALSFRS-R guidelines/instruction which were drafted and validated by the PI of this site who became the international coordinating investigator of the study. 263 patients (66.8%) were randomized after September 08, 2014. A statement letter from each rater was collected by AB Science to document that the raters were experienced and trained before the study began. AB10015 raters certified that they strictly followed AB Science guidelines for the administration of ALSFRS-R when conducting ALSFRS-R assessment in AB10015 trials. The list of raters is available.

- Findings regarding the primary endpoint ALSFRS-R were not systematic.

In one of the two inspected sites (Argentina, n=53 randomized patients), for 3 subjects (4, 26, 55) the score recorded on the eCRF was different from the source data.

No discrepancy between source data and eCRF was found for ALSFRS-R data at other site (n=109 randomized patients).

Likewise, Infarmed inspection for one site (n=3 patients) and Health Canada inspection for other site (n=2 patients) did not identify such discrepancy between source data and eCRF for the ALSFR.

Argument 1.10: A complete reassessment of ALSFRS-R data by certified raters has been done that showed no impact

A retrospective analysis of ALSFRS-R source data was performed based on validated published methodology by Lechtzin showing that accurate ALSFRS-R scores can be generated from retrospective review of clinic notes.

Only 13 ALSFRS-R discrepancies (0.5% total) were observed in 9 patients (2.3%). In protocol period we have observed only 8 ALSFRS-R discrepancies (0.3% total) were observed in 7 patients (1.8%)

Patient number	Arm	Visit	Previous score	Updated score	Treatment arm		
					M4.5	M3	P
Change on ALSFRS-R Score – Protocol period					-8	-7	-12
	Masitinib 4.5	W24	19	18	-1		
	Masitinib 4.5	W36	30	29	-1		
	Placebo	W24	26	20			-6
	Placebo	W36	32	26			
	Placebo	W48	27	22			-2
	Placebo	W36	13	9			-4
	Masitinib 3	W24	37	30		-7	
	Masitinib 4.5	W48	31	25	-6		
No change on ALSFRS-R Score							
	Masitinib 4.5	W24	21	21			

There was no impact on the primary endpoint analysis as a result of this reassessment, using J2R analysis.

J2R (Jump to Reference)		With ALSFRS-R score **based on investigator assessment**			With ALSFRS-R score based on **retrospective reassessment**		
Treatment group	N	LS Mean	Diff. of means [95% CI]	p-value	LS Mean	Diff. of means [95% CI]	p-value
Control	113	-13.23	2.80 [0.14;5.46]	0.0387	-13.23	2.74 [0.09;5.40]	0.0428
Masitinib 4.5 mg	105	-10.43			-10.49		

Model based on post baseline data as per SAP

In conclusion, the deviations on ALSFRS-R score are limited and not systemic in nature.

- Out of 4 sites inspected, only one showed a discrepancy in the ALSFRS-R score between the source file and the eCRF for only 3 patients (1.8%) of the 168 patients inspected (43% of the study).
- All ALSFRS-R scores have been reevaluated by an independent certified rater and the 13/2758 data points (0.5%) inconsistencies identified in 9/394 patients do not impact the outcome.

In conclusion, ALSFRS was not affected in a systemic manner and the discrepancies were identified and have no impact.

Argument 1.11: The Applicant did not limit its effort on sites inspected but did an impact analysis of all sites

The following statement from the Rapporteurs, "*The Applicant's conclusions that the primary endpoint is not affected are not agreed by the CHMP. In addition, it should be noted that even the execution of the different analysis excluding just one or two inspected sites are often not meaningful since these do not address the uncertainty regarding the non-inspected sites (EMA/8689942/2011).*", does not reflect the actions carried out by the Applicant.

The Applicant conducted a holistic assessment that included sensitivity analyses, involving not just the inspected sites but all sites to ensure the robustness of the findings. When corrective actions could not be implemented, impact analyses were performed. These impact analyses concerned all study data, not just the data from the inspected sites.

- The re-monitoring implemented during the period between the data extraction of the CSRV1.0 date and the data extraction of the CSRV3.0 included an additional 97 monitoring in 31 sites (91% of the 34 sites). Only 3 sites were not re-monitored, one in Canada (2 patients randomized, Inspected by Health Canada), other site in Canada (1 patient randomized), and one site in Argentina (9 patients randomized).
- The reassessment of ALSFRS-R scores based on Lechtzin methodology, which is a validated methodology
- Exhaustive review of all eligibility criteria deviations was performed for all patients, using SAS programs and cut-off values for inclusion criteria, and using SMQs and medical history for exclusion criteria.
- Potential underdosing of riluzole, of masitinib, as well as visit windows, were investigated for all patients

These analyses consistently demonstrated that the primary endpoint results were stable and reliable.

Argument 1.12: Inspectors concluded that the protocol deviations were likely to negatively impact data reliability, but sponsor conducted an impact analysis and with certainty demonstrated that there was no impact

An impact analysis was performed. A detailed report is available.

- Analysis of deviations that could not be corrected and that could impact safety showed no impact on the safety profile of masitinib

On safety data, deviations of eligibility criteria that could not be corrected retrospectively have been analysed for their impact using a robust methodology, and there is no impact.

Impact of eligibility criteria deviations on safety was performed as recommended in EMA guideline (EMA/868942/2011)

- Exhaustive review of all eligibility criteria deviation
- For inclusion criteria, using SAS programs and cut-off values
- For exclusion criteria, using SMQs and medical history
- Categorization was done based on the nature and potential impact of deviations

Nature of deviation	**Negligible query**	**Minor Deviation**		**Major Deviation**	
	A technical infringement, that can be ignored	A case-by-case assessment for causality and seriousness based on the deviation's nature, magnitude, and medical history of the patient			
Potential Impact	No Impact	No Impact	Possible impact	No Impact	Possible impact

- The methodology was reviewed and validated by an independent expert coordinator of the French rare diseases network on ALS and motor neurone disease (FILSLAN).

389 eligibility criteria queries were generated, among which only 9 deviations in 5 patients (1.3%) having possible impact on safety.

Negligible Eligibility Query	**Minor Deviation (non-important)**			**Major Deviation (Important)**			**Total**
	No Impact	Possible Impact	Total	No Impact	Possible Impact	Total	
98	258	6	264	24	3	27	389

These eligibility criteria queries/deviations were well balanced across treatment arms

	PBO	**M3.0**	**M4.5**	**Total**
Total number (%) of deviations	135 (35%)	129 (33%)	125 (32%)	389

The 5 patients had the following deviations and subsequent AEs:

- 2 patients randomized in the placebo arm, with infectious screening tests missing (HIV and hepatitis testing) and infections TEAE: one presented diarrhoea related to Clostridium difficile infection at D67, of mild severity and non-serious, at D95, of moderate severity and serious;

Both episodes resolved without sequalae and were assessed as not related to study drug by investigators.

- 1 patient randomized in a Masitinib AB Science arm, with creatinine clearance low and medical history of lung fibrosis and creatinine increase TEAE. This moderate patient was randomized in the 4.5 mg/kg/day Masitinib AB Science arm with a creatinin clearance at 58.6 mL/min at screening. The clearance continued to decrease during study varying between 40 and 57 mL/min dropping to 40 mL/min at the end of study. The medical history included hypercholesterolemia, hypertension, treated with hydrochlothiazide, enalapril, atorvastatin. Creatinin increase at W36 was reported as TEAE. Considering creatinin clearance value closed to 60, this deviation is considered as minor but could have had an impact on safety. This patient had also a medical history of pulmonary fibrosis (fibrosis scar on right lung). This is considered as a minor deviation since FVC was in the range accepted by the protocol. No respiratory TEAEs were reported. This deviation had no impact on safety but could have had an impact on efficacy.
- 1 patient randomized in the placebo arm, with morbid obesity (screening & baseline): radiculalgia TEAE. This moderately severe patient with bulbar presentation was randomized in the placebo arm with a BMI above 40 kg/m². The morbid obesity might explain radicular pain L5 reported as TEAE. Possibly, an osteoporosis even not reported in medical history of this post-menopausal female patient might also have contributed to this TEAE. This is a major deviation with a possible impact on safety.
- 1 patient randomized in a masitinib arm, with medical history of toxic oil syndrome with no related TEAE. This severe, bulbar, middle aged patient was randomized in the 4.5 mg/kg/day Masitinib AB Science arm. A toxic oil syndrome is reported in his medical history. Toxic oil syndrome may have induced a chronic disease with neuromuscular symptoms, pulmonary infiltrates and liver impairment. ALT was high at screening 1.3xULN and raised at 1.7xULN with bilirubin at 1.9xULN at W4. ALT raised up to 2.5xULN at W48. This deviation could have had an impact on eligibility, therefore on efficacy and on safety because a participation of the toxic oil syndrome in his ALS symptomatology cannot be ruled out.

The impact of these 5 patients do not change the safety profile of Masitinib AB Science 4.5 mg/kg/day in ALS.

- Exclusion of patients with possible impact on efficacy from deviations to eligibility criteria does not modify efficacy outcome, even with J2R approach

  - First, all patients had ALS diagnosis confirmed (no deviation)
  - Data Review Committee before unblinding previously identified 5 patients with possible impact

Arm	W48	Deviation Description	Deviation Status	Deviation Impact
Data Review Committee				
PBO	No	Hb<10g/dL	Major	Possible impact
PBO	No	Bilirubin > 1.5 ULN	Major	Possible impact
M3.0	No	Suspicion of HBV infection	Major	Possible impact
M3.0	No	Creatinine Clearance < 60 mL/min	Minor	Possible impact
M4.5	No	Treatment with phenytoin (high risk of SJS)	Minor	Possible impact

  - Exhaustive new eligibility criteria deviation analysis identified 7 additional patients with possible impact

Exhaustive Impact Analysis				
M4.5	Yes	Forbidden medical history (toxic oil syndrome)	Major	Possible impact
PBO	Yes	BMI > 35 kg/m² (morbid obesity)	Major	Possible impact
M4.5	No	Forbidden medical history (pulmonary fibrosis)	Major	Possible impact
M3.0	Yes	BMI > 35 kg/m² (exceeded threshold by 5%)	Minor	Possible impact
M4.5	Yes	BMI > 35 kg/m² (exceeded threshold by 2%)	Minor	Possible impact
M4.5	No	Age > 75 years (exceeded threshold by 5%)	Minor	Possible impact
M4.5	Yes	Age > 75 years (exceeded threshold by 4%)	Minor	Possible impact

- Therefore, there were a total of 9 patients (3.4%) in the masitinib 4.5 mg/kg/day or placebo arms with deviation on eligibility criteria having a possible impact on efficacy

	PBO (n=133)	**M4.5 (n=130)**	**M3.0 (n=131)**	**TOTAL (n=394)**
DRC – Major deviation	2 (1.5%)	1 (0.8%)	2 (1.5%)	5 (1.3%)
Impact Analysis	1 (0.8%)	5 (3.8%)	1 (0.8%)	7 (1.8%)
Total	9 (3.4%)		3 (2.3%)	12 (3.0%)

- The impact analysis excluding these 9 patients did not modify the study outcome, using J2R analysis.

Primary efficacy population - Rule MI J2R with all patients					
	Arm	N	LS Mean	Diff. of means [95% CI]	p-value
Normal Progressor	PBO	113	-13.23	2.80 [0.14;5.46]	**0.0387**
	M4.5	105	-10.43		
Normal + Fast Progressor	PBO	132	-13.51	1.81 [-0.75;4.37]	0.1664
	M4.5	128	-11.70		

model based on post baseline data as per SAP

Sensitivity analysis - Rule MI J2R with 9 patients with eligibility deviation having a possible impact excluded					
	Arm	N	LS Mean	Diff. of means [95% CI]	p-value
Normal Progressor	PBO	111	-13.3414	2.87 [0.15;5.59]	**0.0390**
	M4.5	99	-10.4738		
Normal + Fast Progressor	PBO	130	-13.7293	1.83 [-0.79;4.45]	0.1720
	M4.5	122	-11.9034		

model based on post baseline data as per SAP

- Potential underdosing of riluzole was investigated and sensitivity analysis showed no impact

A total of 7 patients (1.8%) received sub-dosing of riluzole, including 6 patients in either M4.5 arm (n=3) or placebo arm (n=3).

Subject Number	Treatment	Compliance (%)	Planned Exposed Days	Cumulative Planned dose	Actual Exposed Day	Cumulative Actual dose
	M3	64.6	99	9900	99	6400
	M4.5	53	166	16600	88	8800
	M4.5	50	50	5000	50	2500
	M4.5	30.3	66	6600	83	2000
	PBO	8.8	329	32900	58	2900
	PBO	50	337	33700	337	16850

	PBO	52.9	87	8700	58	4600

Sensitivity analysis excluding these 6 patients does not modify the study results.

Primary efficacy population - Rule MI J2R with all patients					
	Arm	N	LS Mean	Diff. of means [95% CI]	p-value
Normal Progressor	PBO	113	-13.23	2.80 [0.14;5.46]	**0.0387**
	M4.5	105	-10.43		
Normal + Fast Progressor	PBO	132	-13.51	1.81 [-0.75;4.37]	0.1664
	M4.5	128	-11.70		

model based on post baseline data as per SAP

Sensitivity analysis - Rule MI J2R with 6 patients with riluzole sub-dosing					
	Arm	N	LS Mean	Diff. of means [95% CI]	p-value
Normal Progressor	PBO	110	-13.34	2.91 [0.23;5.59]	**0.0331**
	M4.5	105	-10.43		
Normal + Fast Progressor	PBO	129	-13.53	1.77 [-0.80;4.35]	0.1774
	M4.5	125	-11.75		

model based on post baseline data as per SAP

- Masitinib dosing deviations were evaluated and showed no impact

Identified deviations that were related to masitinib underdosing could only minimize masitinib efficacy and have no impact

Subject Number	**Arm**	**Category**	**Description**
	M 3	IMP Compliance	Patient was 22 days without take medication because he/she could not attend to visit week 72 due to hospitalization. Remote visit week 72 was performed and medication was sent and first intake two days after kits reception.
	M 3	Efficacy or Safety	visit 36 was delayed, study drug was not taken during four months
	M 3	IMP Allocation	Patient was randomized at 4.5 mg/kg/day 300mg. At week 12 visit sub investigator performed IMP assignation but by mistake she indicated that a dose reduction was needed, so the system assigned to patient only 100 mg kits, total daily dose 200 mg. So patient is taking the reduced dose of 200 mg instead of 300 mg.
	M 4.5	IMP Compliance	Patient experienced persistent diarrhea (severe) in 2016. According to the protocol in case of severe diarrhea the study treatment should be interrupted until return to baseline or mild intensity, then resume with a close exclusion 6 days after (SAE stop date), the patient was instructed to resume the medication with a dose reduction, however patient interrupted the medication until her next visit around 2 months later
	M 4.5	IMP Compliance	In masitinib dispensation for week 8 to week 12: subject was not dispensed with masitinib-placebo for 13 days .. IP compliance was 50 %
	PBO	IMP Compliance	Patient during the week 24 visit, returned all the previous IMP bottles that he had received at week 12 visit, except of this with number of Masitinib/placebo 100mg. The patient had discarded the respective bottle. IP compliance could not be calculated regarding the 100mg.
	PBO	Efficacy or Safety	Patient CME to w48 3 weeks later than scheduled. Patient was 21 days without medication
	PBO	IMP Allocation	Patient was dispensed with not enough IMP till next planned visit
	PBO	IMP Allocation	IWRS dispensation was done before the patient arrives at hospital, the same day the visit took place. The weight used for eCRF was an estimated weight given by caregiver by phone to investigators. This

			patient during a 12 weeks period, the dose administrated was less than should be given.

- Visit window deviations were evaluated and showed no impact

DSMB decided (25 Feb 2016) that no impact on efficacy data is expected if non-respect of visit windows is not higher than 28 days and not repeated at 2 consecutive visits.

According to this rule, no visit window deviations occurred in the Masitinib 4.5 mg/kg/day treatment arm or placebo arm, thereby having no impact on the primary analysis.

Subject Identifier for the Study	Treatment	Visit Week	ALSFRS-R score	Planned Date	Actual Visit date	Window Deviation From Plan Visit (in days)	More than 28 days twice in a row from Planned Visit(Y/N)	Window Deviation From Previous Visit (in days)	More than 28 days twice in a row from Previous Visit(Y/N)
	Masitinib 3	36	28	03/02/2015	13/03/2015	38	Y	36	Y
	Masitinib 3	48	29	28/04/2015	11/06/2015	44	Y	-30	Y
	Masitinib 3	36	36	09/07/2015	18/08/2015	40	Y	4	N
	Masitinib 3	48	35	01/10/2015	23/11/2015	53	Y	-9	N
	Placebo	36	31	08/08/2016	08/09/2016	31	Y	-11	N
	Placebo	48	35	31/10/2016	02/12/2016	32	Y	-5	N

Argument 1.13: An impact analysis on all items that could have impacted benefit risk assessment beyond primary efficacy and safety, as per guideline, and it showed no impact. This analysis has been rejected without any query from the Rapporteurs to the Applicant

The extensive impact analysis conducted by the Applicant covered all critical aspects that could influence the benefit-risk assessment. This includes detailed evaluations of protocol deviations, missing data, and their potential impact on primary efficacy and safety endpoints. This included sensitivity analyses, re-monitoring data, and reassessment of safety and efficacy endpoints. The results of these extended analyses support the conclusion that the overall data integrity and the primary endpoint are not compromised. By aligning the impact analysis with EMA guidelines, the Applicant demonstrated adherence to regulatory standards and best practices. This alignment should be a significant factor in the regulatory decision-making process, reinforcing the credibility of the presented data.

On the other hand, the CHMP based its decision on the EMA inspection of 2 sites and finally does not address the uncertainty regarding the non-inspected sites.

It is crucial to assess whether the quality system deficiencies significantly affected critical data, such as primary efficacy and safety endpoints. Since impact analyses show that the essential data remain robust and reliable. The inspectors did not review the presented impact analysis supporting that the critical data are still adequate for the benefit-risk assessment as per guideline EMA/8689942/2011.

Argument 1.14: Guideline states that if safety is acceptable and the primary variable is robust, then benefit risks is valid. Guideline should apply

Guidances (EMA/868942/2011; Good Clinical Practice Inspectors Working Group (GCP IWG). Chapter 2. General Notes on Findings) recommendations are fulfilled.

- In superiority studies, […], inspection findings merely indicating increased variability and not introducing bias favouring one treatment over the other are relatively unproblematic in the interpretation of the study results

- It is important to assess whether the findings affect the interpretation of the primary efficacy

endpoint or important safety endpoints

The Applicant's actions and analyses are in strict adherence to the EMA/8689942/2011 guidelines.

The comprehensive impact analysis, corrective actions, and validation efforts align with the "Points to consider on GCP inspection findings and the benefit-risk balance" guidelines, ensuring that the data are reliable.

The Applicant addressed the Rapporteurs concerns through:

i. Performing comprehensive data reviews to ensure the reliability of the primary endpoint and safety data.

ii. Conducting a thorough impact analysis of protocol deviations, demonstrating that there is no impact on efficacy and safety data.

iii. Including data from non-inspected sites in broader analyses.

iv. Ensuring all actions align with regulatory guidelines and standards.

These comprehensive measures and analyses demonstrated that the primary endpoint remained unaffected, and the data from clinical study AB10015 are reliable.

Argument 1.15: There is a contradiction with the initial position of the reviewers at the start of the procedure since the inspection reports conclusion was known. If nothing could be done, then why the Rapporteur asked to explain how the GCP issues were resolved

Stating that the numerous retrospectives analyses applied by the Applicant do not compensate for the deficiencies in the conduct of the study is contradictory with the position from the Rapporteurs during the during the pre-submission meeting held on 24 May 2022.

During the pre-submission meeting held on 24 May 2022, the Applicant stated very clearly that "*AB Science is willing to submit an application for CMA in ALS only if this is supported by the Rapporteur and the Co-rapporteur. AB Science would not file if there were no support Rapporteur and the Co-Rapporteur*". The Applicant further indicated that "*A new version of the CSR has been released after full reassessment of the safety data in a validated pharmacovigilance system*".

In response, the Rapporteur stated that "*The Rapporteur indicated AB Science should go back to the major points for refusal of the previous EPAR and explain how these issues were addressed, in particular GCP issues*".

If the conclusion expressed by the Rapporteurs was valid, it would/should have been notified to the Applicant at the time of the pre-submission meeting. Otherwise, it means that corrective actions and impact analyses perfomred can compensate for the deficiencies in the conduct of the study.

Argument 1.16: The argument of poor global quality is debatable since the same guideline indicates that if deviations show no impact on the primary efficacy variable nor safety then the benefit risk balance remains evaluable

The guidance EMA EMA/868942/2011 states that "it is important to assess whether the findings affect the interpretation of the primary efficacy endpoint or important safety endpoints. Needless to state, the findings have less significance for the benefit-risk assessment if they only have consequences for secondary or exploratory endpoints".

The corrective actions and the impact analyses performed are methodologically adequate to provide assurance that the study data reliable

- Re-Monitoring in regulatory guidance and industry experience versus in AB15001 trial

Re-monitoring is recognized as a viable approach under certain circumstances, as highlighted during the COVID-19 pandemic, where traditional on-site monitoring was often not feasible. The MHRA has shared insights from their experience during the pandemic, emphasizing that many trials had to adapt processes, leading to a significant increase in protocol:

- The MHRA advised a risk-based approach to documenting these deviations, emphasizing that deviations impacting participant safety and the reliability of results should be clearly identified and considered during data analysis. AB Science performed a risk-based analysis approach presented in the CAPA report proposed in answer to the EMA GCP inspection report and in this document.

- The MHRA also suggested that re-monitoring might be necessary in cases where there are concerns about data quality or when data are critical to the reliability of the trial results : *"Following questions arising on the quality of the data after carrying out remote monitoring, we have advised sponsors who have suggested to do re-monitoring once it is safe to be back on site that it needs to be done on a risk-based approach.* ***Therefore, if there are concerns about data quality, or there are data that are critical to the reliability of the results of the trial, such that you would only have confidence in the data if on-site monitoring took place, sponsors may want to consider re-monitoring."***

These regulatory perspectives reinforce that re-monitoring can be a valuable tool for ensuring data integrity, if applied with clear understanding of its scope and limitations: it depends on the nature of the data, the clarity of the source documentation, and the ability to unambiguously verify the accuracy and completeness of the data entries.

The re-monitoring in the AB10015 trial is particularly defendable and effective because:

- Source Data are available and clearly documented: AB10015 inspection outcomes did not identify questionable quality nor availability of source data.

- The Type of Data Concerned are adapted for an efficient re-monitoring:

  - **Documented Events as Adverse Events:** The occurrence, severity, and timing of adverse events can be re-verified through medical records, subject diaries, or investigator notes.

  - **Clear & Unambiguous data as some Eligibility Criteria:** Re-monitoring is efficient for criteria that are based on objective measures (e.g. lab values, age, specific medical history elements …)

  - **Efficacy Endpoint:** for quantifiable endpoints re-verification can be done against medical records. It is the case for the ALS Functional Rating Scale-Revised (ALSFRS-R) because:

    - *Objective & quantifiable:*

    1. The ALSFRS-R provides a quantifiable measure of a patient's functional status, with scores assigned to specific functional tasks. This quantification allows for objective re-assessment and comparison of data over time.

    - *Standardized Assessment:*

    2. The ALSFRS-R is a standardized tool used globally in ALS clinical trials and care settings. Its widespread use and standardization mean that re-monitoring can be reliably performed, provided the assessors are trained and the assessment conditions are consistent as in the AB15001 trial.

    - *Source Data Verification:*

3. If ALSFRS-R assessments are documented thoroughly, including notes on patient responses and any relevant observations during the assessment, these source documents can serve as a basis for re-monitoring. The EMA GCP did identify very limited discrepancies between source data and eCRF especially for the ALSFRS-R scale.

- Retrospective/Impact Analysis in AB10015 trial

  - **Why ALSFRS-R retrospective analysis is reliable?**

As patient medical files are maintained by neurologists experienced in treating ALS, the potential for accurately regenerating ALSFRS-R data is high. Neurologists' records are likely to contain detailed observations on motor functions and other relevant clinical aspects pertinent to ALSFRS-R domains. These details can provide indirect insights into the patient's functional status over time.

The article by Lechtzin et al. demonstrates that accurate ALSFRS-R scores can be generated from a retrospective review of clinic notes [Lechtzin 2009]. The study's findings are significant because they suggest that even in the absence of prospectively collected ALSFRS-R scores, valuable disease progression data can still be obtained from patients' medical records.

Attempting to rectify deficiencies retrospectively could introduce bias into the trial, so AB Science approached the matter cautiously. The process employed by AB Science to validate the integrity of ALSFRS-S data does not involve retrospective corrections of the scores. Trained raters conducted a second assessment based on accurate source data (re-monitoring). Subsequently, the results obtained were analyzed using a sensitivity analysis approach, yet the clinical database remained unaltered by the new scores obtained.

  - **Why protocol deviations impact analysis is reliable?**

In the AB10015 trial, some GCP issues cannot be resolved nor corrected after they occur, like protocol deviations but **their impact** on efficacy and safety data can be evaluated retrospectively (EMA/868942/2011 guidance) as inspections/audits and corrective actions have made it possible to ensure that:

- Source data are available and clearly documented (no issue identified during the EMA GCP inspection).

- Discrepancies between source data and clinical database are limited after re-monitoring for those critical data we are focusing on.

Argument 1.17: The position adopted by the CHMP for Qalsody and Albrioza in ALS shows that numerous protocol deviations are not an obstacle to registration if these deviations have no impact

EPAR (EMA/CHMP/487533/2023) of Albrioza indicates that the study supporting CMA application had 417 deviations for 137 patients (i.e., an average of 3 deviations per patient), with 91% of patients affected, therefore, clearly a systemic finding. This was not considered as a major objection, and the CHMP concluded with no inspection that it had no impact on benefit/risk, precising, in line with EMA/868942/2011 guidance that "*The percentage of subjects with protocol deviations was similar between treatment group*".

Similarly, in the pivotal study supporting the approval of Qalsody, 89% of patients have major protocol deviation and 63% of deviations affected efficacy. The deviations appeared to be systemic (EMA/276404/2024). Yet this drug was approved by the EMA.

The Applicant does not understand why the application of EMA guidelines appear to have been interpreted differently for similar past examples of studies with deviations.

The inconsistency in the application of EMA guidelines for different drug approvals raises questions about the uniformity of the regulatory process. If Albrioza and Qalsody, with significantly higher protocol deviations, were approved, it sets a precedent that similar studies, such as the one for Masitinib, should be evaluated with the same standard.

Argument 1.18: There is a perception that masitinib dossier is treated more severely than the other sponsors dossier

With all due respect, there is a perception that study AB10015 has been evaluated with excessive severity. We have noted EMA's position that deviations from eligibility criteria and subject follow-up procedures are likely to impact data integrity

- Balanced Impact: The Applicant's detailed analysis showed that eligibility deviations were balanced across treatment arms and did not impact safety or efficacy outcomes. The impact of these deviations has been assessed thoroughly, and it has been demonstrated that there is no significant impact on the overall study outcomes.

- *Post Hoc* Analysis: The inspectors did not have the benefit of reviewing our post-inspection corrective measures, including the updated CSR and additional impact analyses. These documents provide substantial evidence that the data from AB10015 are reliable.

- Protocol deviations need to be assessed based on their significance and impact on critical endpoints: The Applicant conducted a comprehensive impact analysis, showing that the identified deviations did not significantly affect the primary efficacy or safety outcomes. A risk-based approach focuses on deviations that have a material impact on study results rather than treating all deviations as equally critical.

- No Systematic Errors: Inspectors did not find systemic errors in ALSFRS-R but a minor number of errors, and a reassessment by certified raters proved there is no impact.

- In addition, ethical conduct is paramount in clinical trials and the Applicant has demonstrated that the rights, safety, and well-being of trial subjects were protected throughout the study. The corrective measures taken post-inspection, further ensure that all ethical standards were met.

Conclusion: The Applicant respectfully asserts that CHMP's decision to base its findings solely on the inspectors' position from 2017, fails to take into consideration the entire sum of evidence now available and is not therefore consistent with the guideline on benefit-risk assessment. The Applicant has demonstrated an absence of impact from any findings. The argument of overall poor quality overlooks the corrective actions implemented post-inspection and our interpretation of the guidelines on benefit/risk evaluation. Safety is deemed acceptable by EMA, and the primary variable (ALSFRS-R) does not suffer from systemic issues.

CHMP position on the Ground for re-examination

A triggered GCP inspection (GCP/2017/001) was requested by the CHMP on the conduct of the clinical study AB10015 in the context of a previous MAA of masitinib for the treatment of ALS (Alsitek, EMEA/H/C/004398/0000). In total, 8 critical and 12 major findings were identified during this inspection at the two inspected sites affecting different aspects of the study. Critical findings were related to the clinical conduct of the trial, management of the trial by the sponsor/CRO, safety reporting, source data review/verification and clinical trial monitoring. Major findings were observed at qualifications and training, trial master file, clinical conduct of the trial, safety reporting, investigational medicinal product, clinical data management, source data review/verification and clinical study report. Inspectors concluded that given the nature and relevance of the findings and also the systemic deficiencies observed i.e. massive number of protocol deviations meaning a general lack of adherence to the protocol, in addition to the suboptimal quality applied by the sponsor and CROs involved, are likely to have a negative impact on data reliability. The data obtained at the sites inspected were judged to be not trustworthy.

The current application (Masitinib AB Science, EMEA/H/C/005897/0000) is based on the same study AB10015 as submitted for the previous procedure, with the only difference being the addition of the OLE part of the study.

As part of the current application, the Applicant claimed that the GCP findings were addressed with implementation of preventive actions across study and functions within AB Science. The Applicant also claimed that for study AB10015, corrective actions were implemented wherever feasible. Moreover, the Applicant performed an impact analysis of protocol deviations and concluded that GCP inspection findings which are likely to influence the evaluation of the primary efficacy endpoint, whether correctable or not, had no significant impact on the study's outcomes.

However, despite the fact, that the Applicant has provided impact analysis and arguments, the existing evidence of data quality did not assure CHMP that the AB10015 trial data is trustworthy

In terms of GCP, the Applicants grounds for re-examination are based on the following main aspects:

[Argument 1.2-1.4] Highlighting that the other available inspection reports (Health Canada, ANMAT-Argentina, Infarmed - Portugal) and audit reports do not conclude that data are not trustworthy and that those reports should be considered in the assessment.

[Argument 1.1, 1.5-1.6] Claiming that Inspectors and the CHMP did not account for analyses done after inspection (specifically focussing on the detailed impact analysis that was communicated for the first time at D180). It is the Applicant’s position that from the very beginning of the procedure, the CHMP adhered to the conclusions from the Inspectors and made no attempt to evaluate the consequences of inspection findings in relation to the benefit-risk balance.

[Argument 1.7-1.8] Focusing on re-assessment of safety, highlighting the updated CSR V3.0.

[Argument 1.9-1.10] Focussing on re-assessment of the primary endpoint ALSFRS-R score, highlighting the retrospective analysis of ALSFRS-R source data.

[Argument 1.11 – 1.13] Highlighting and discussing results of the performed deviation impact analysis (Detailed Report Deviation Impact Analysis).

[Argument 1.14, 1.16] Referring to certain parts of the guideline on Points to consider on GCP inspection findings and the benefit-risk balance (EMA/868942/2011), underlining their claim that the B/R is evaluable and that the corrective actions e.g. re-monitoring and retrospective/impact analyses are valid.

[Argument 1.15] Claiming that a contradiction between feedback on the pre-submission meeting held on 24 May 2022 and the assessment of the current application.

[Argument 1.17-1.18] Referring to other products in ALS with similar amount of protocol deviations and claiming that the masitinib dossier is treated more strictly than other sponsor’s dossiers.

The main aspects are discussed in more detail below:

[Argument 1.2 – 1.4]

The Applicant is referring to marketing authorisation procedures where CHMP reached a positive benefit-risk conclusion despite negative GCP findings (Appendix 1 of the clinical grounds for re-examination). The precedents of marketing authorisations (MA) discussed by the Applicant are acknowledged, however it should be noted that every MA application is assessed on its own merit, based on the totality of the data presented in the application, in support of the claimed indication. There are multiple factors affecting the benefit-risk evaluation for each application. It is the totality of data which is taken into account in every individual dossier. Overarching comparisons are not possible.

Moreover, the Applicant argues that besides the EMA inspection three additional GCP inspections (Health

Canada, ANMAT Argentina, Infarmed Portugal) were performed, that did not conclude that data are not trustworthy. While it is agreed with the Applicant that other GCP inspections did not reject the data, several major findings were reported. The only overlapping site to be inspected was the second largest recruiting site in Argentina. The Applicant claims Argentinian regulatory authority inspected the site before EMA and did not conclude the data is untrustworthy. However, the ANMAT inspection outcome for the inspected site was Indication of Official Action (IAO), subpoint (i) - *Administrative and/or legal penalty against the investigator, Sponsor or CRO, after development of the pertaining disciplinary proceedings.* In other words, the inspection identified significant deficiencies and GCP non-compliances that required formal penalties against the investigator/CRO/Sponsor preceded by formal disciplinary proceedings. This process includes further review, evaluation and the opportunity of the involved parties to respond to the issues. The formal penalties are defined after the disciplinary procedures have been completed. It is further stated that the result of the inspection was that the principal investigator and the Sponsor had to sign a commitment letter with ANMAT for the future trials to be conducted. The contents of this commitment letter are not known. Overall, stating that the ANMAT inspection did not conclude the data is untrustworthy is factually correct, but fails to convey the information that deficiencies identified during the inspection warranted administrative and/or legal penalties against the PI and the Sponsor. Further, one site was inspected by Infarmed Portugal and five major non-compliances were identified related to conformity of the eCRF to the protocol in force, monitoring process, deviations from the protocol, recording of data, and verification of compliance of EM, which are largely in line with findings identified during the triggered GCP inspection requested by CHMP and coordinated by EMA. Importantly, sites inspected during the GCP inspection coordinated by EMA were the two largest recruiting sites, with 53 and 106 patients enrolled, accounting for >40% of the full study population, while sites inspected by Canada and Portugal only enrolled 2 and 3 patients respectively.

Besides the 4 GCP inspections, 16 audits were performed by an external professional on request of the Applicant. Audits are quality assurance activities performed by third parties on behalf of the Applicant, while inspections are quality assurance activities performed by the regulatory authority. Audits occur during the course of the trial and can point to activities to be improved during study conduct, while a triggered inspection is performed after the study has finished with the aim of determining if the data are trustworthy and can be used for regulatory purposes. Therefore, audits and inspections do not carry the same weight in the context of regulatory activities. Within the 16 audits, 19 sites were audited, including both sites inspected later on during the GCP inspection coordinated by EMA. In total, one critical finding and 58 major findings were reported, identifying similar problems as identified during the inspections. Even though the conducted audits did not conclude on unreliability of the data, it needs to be clarified that such conclusions are not in the scope of audits. Against the Applicant´s argumentation that audit outcomes did not conclude that data are not trustworthy, similar findings as during the GCP inspections were identified and hence the audit results are in line with the inspection findings.

The categorization of sites by quality level performed by the Applicant based on the audit outcomes is not standardized, therefore, considered informative but less relevant for the assessment. Indeed, as outlined by the Applicant, of all patients randomized, 40% were inspected during the GCP inspection coordinated by EMA, 51% were audited and 9% were neither inspected, nor audited, however, given the weighting of inspections and audits (see above), this information has to be looked at critically. Further, the scope of inspections by different regulatory authorities were not the same. Additionally, the scope of inspections might differ between routine and triggered inspections. The triggered GCP inspection, GCP/2017/001 is regarded as crucial one, and during the assessment the provisions of the EMA guideline EMA/868942/2011 were taken into account.

[Argument 1.1, 1.5-1.6]

The Applicant claims that there were several measures taken by AB Science post the GCP inspection coordinated by EMA to overcome the drawbacks of the clinical study conduct, that were not reviewed or

assessed by the inspectors or taken into account by CHMP. These measures include corrective and preventive actions e.g. re-monitoring of adverse events, vital signs, and lab values at 31 out of 34 study sites to ensure that all source data were accurately reflected in the updated clinical study report (CSR V3.0), re-evaluation of critical data from the trial, particularly the primary endpoint (ALSFRS-R) and safety data, detailed impact analyses of protocol deviations (on all sites, all patients, eligibility protocol deviations, potential underdosing of riluzole, masitinib dosing deviations and visit window deviations).

The Applicant's statement is not supported. First, it is noted that at the time of the GCP inspection, the Applicant presented a series of corrective and preventive actions in response to the GCP inspection findings (see EMA Inspection report, Addendum 1: Response form the sponsor or inspectee for both sites; dated 30 Jan 2018 site 1, and 01 Feb 2018 site 2) which have been assessed by the inspectors and were not found sufficient to recommend the use of data. Moreover, as outlined by the Applicant in the chronological listing of actions taken after the GCP inspection coordinated by EMA, it is indeed agreed that the majority of corrective measures were performed after the said GCP inspection. However, all information and documents (i.e. Addendum to CSR V1.0. CSR V3.0, ANSM GCP Inspection report GCP-181801-FR, MHRA GCP inspection report INSP GCP 21687/22860-0003 and the Impact analysis of protocol deviations on efficacy and safety data) that resulted from the Applicant's corrective actions were provided during the initial assessment procedure (although some of them late during the procedure e.g. with D180 responses) and were assessed by the CHMP, as stated in the CHMP report.

Moreover, as correctly cited by the Applicant, Guidance EMA/8689942/2011 clearly states that GCP inspectors and clinical assessors have different roles in the overall regulatory process of evaluating new medicines. Hence, it should be acknowledged that the focus of the GCP inspectors and clinical assessors is different and as a consequence the evaluation of the significance of the findings may also differ. For the assessors, the focus is on the particular medicine under assessment to ensure that the benefit-risk balance is favourable before licensing and that the overall ethical conduct is acceptable. It is reiterated, that the GCP inspectors' role is different from the clinical assessors' role in the evaluation process of the new medicine. The GCP inspection is aimed to verify whether the Applicant has a robust quality system in place to guarantee the quality of the data of the trial(s) inspected. While it is the assessors' task to evaluate whether corrective measures and re-assessments can outweigh findings identified during the GCP inspection and whether the B/R balance is favourable or not.

A more detailed assessment of corrective measures and impact analysis is given in the following sections.

[Argument 1.7-1.8]

The Applicant refers to re-monitoring actions (97 monitorings in 31 out of 34 sites) that occurred during the period between the data extraction of the CSR V1.0 (available at the time of inspection) and the data extraction of the CSR V3.0. After the inspections, adverse events, vital signs, and lab values were re-monitored to ensure that all source data were accurately reflected in the updated clinical study report CSR V3.0 (September 2021). The updated safety data between CSR V1.0 and CSRV 3.0 refer to the number of patients with at least one AE (1 patient deleted in control group) and severe AE data that was updated for 6 patients (5 patients additionally identified with severe AEs: 1 in the M4.5 group and 4 in the control group; 1 patient previously identified with a severe AE was deleted in the M3.0 group).

The CSR V3.0 was already provided during the initial assessment procedure, and it was concluded that the safety profile of mentioned medicinal product is considered acceptable for a CMA. As indicated in the initial opinion, *the uncertainties and limitations regarding reliability of safety data of the pivotal clinical trial are alleviated by the safety data from the trials in non-oncological conditions.*

Hence, it is agreed that the main considerations for the assessment on the impact of the inspection findings on the B/R are related to efficacy data. However, it still needs to be taken into account that the safety profile was characterized based on non-comprehensive evidence as corresponds to the requested

CMA.

[Argument 1.9-1.10]

During the GCP inspection coordinated by EMA, major issues were identified regarding proper training of the principal investigators on the ALSFRS-R. For both sites, lack of documented formal training on the ALSFRS-R at the beginning of the trial was identified. The main impact of not performing these meetings is related with several revisions of the ALSFRS-R scale (primary efficacy endpoint) due to mistakes and inconsistencies. Although it can be agreed with the Applicant that raters were likely familiar with ALSFRS-R evaluation based on their experience in treating ALS patients and based on the statement letters provided by each PI confirming that they were trained before the study began, and strictly followed AB Science ALSFRS-R guidelines/instruction, it is noted that the study was initiated in April 2013 and guidelines were available from September 2014, when appr. 33.2% of the study population were already randomized. Most critically, several discrepancies were identified in the ALSFRS-R score between source data and eCRF. In the Argentinian site, the inspection team reviewed all ALSFRS-R scales for the 53 randomized subjects. Corrections of the ALSFRS-R scales were identified and several of them were due to mistakes summing the single item points. For three subjects the score recorded on the eCRF was different from the source data. Furthermore, the Applicant did not mention that there were changes identified on the score of some scale points not contemporaneous and made months or one year later, that the score of W24 was not recorded on eCRF for subject 04, and that for subject 55 (W24, W36, W48) the score after reassessment was not recorded on eCRF. The list of differences and changes were identified during scale verification on the site, and are available in the IR. At the other inspected site , indeed, no discrepancies between source and eCRF were identified, however, the inspection report states that minor retrospective changes were done and the scale eCRF page was revised four times due to typos, mistakes and misinformation. Of note, one site randomised 69 out of 88 screened instead of 109 participants as erroneously stated in argument 1.9. Considering that the ALSFRS-R score is the primary outcome of the study, reliability of the ALSFRS-R score data is vital.

As a corrective measure, all ALSFRS-R scores have been re-evaluated by an independent certified rater based on clinical notes. Of the total 2758 data points, 13 discrepancies (in 9 patients) were identified between the initial PI assessment of the ALSFRS-R score and the retrospective re-assessment of the ALSFRS-R score by the independent rater. When excluding these 9 patients from the primary endpoint analysis, no relevant change in the outcome was observed. With this analysis, the Applicant intends to demonstrate that composing ALSFRS-R scores retrospectively from review of clinical notes is possible, and ALSFRS-R was not affected in a systemic manner. This is not fully agreed. The article referenced by the Applicant (Lechtzin et al.) indeed states that ALSFRS-R scores can be obtained from review of clinical notes and can be a useful research tool. However, it is further stated that ALSFRS-R scores should be completed in person or via telephone interview for clinical prognostication in individual patients. From the CSR V3.0, and Protocol Version 5.0, it is not evident how exactly ALSFRS-R was recorded for each patient – was a narrative of patient's functional abilities provided alongside the number per item on the ALSFRS-R questionnaire or not. If a narrative was provided, was it available for each of the 12 subscores and for 100% of patients. In the absence of a narrative/clinical notes, it is unclear how a retrospective calculation can be done and how it could differ from the initial score (apart from simple mathematical miscalculations). During the oral explanation on 16 October 2024 the Applicant explained that the re-evaluation of the ALSFRS-R scores was based on clinical notes, not solely based on re-calculating the scores. Data collected by the phone call visits not envisaged in the clinical study protocol are possible source of erroneous ALSFRS-R score data, some of which were not even documented. Moreover, results from the retrospective analysis provided within the table in Argument 1.10 are not fully understood. It is assumed that the discrepancy score for the placebo group should be -21, and not -12 as stated in the table (both discrepancy scores for that patient appear to be faulty). In any case, a retrospective analysis relies on the quality and accuracy of the initial data. As already stated, the deficiencies identified during

the inspection render data (inclusive of primary efficacy data) untrustworthy. This is not changed with a reanalysis.

Noticeably, 6 of the 9 identified patients with discrepancies in the ALSFRS-R score (PI assessment vs. retrospective assessment by external rater) came from one site (25 patients randomized, site was not inspected) pointing at possible issues in ALSFRS-R score assessment also at this site.

[Argument 1.11 – 1.13]

Inspectors concluded that data consistency is compromised, and its integrity is highly likely to be impaired as several protocol deviations at eligibility, conduct and in other aspects inspected were confirmed. Given the massive number of protocol deviations observed at the sites inspected and the relevant number of GCP departures, the inspection team could not confirm that the management of the trial has been adhering to all principles as laid down in ICH GCP.

Based on this critical finding, the Applicant performed an impact analysis where all eligibility criteria deviations were reviewed for all patients from all sites. Moreover, potential underdosing of riluzole, Masitinib AB Science dosing deviations and visit window deviations were investigated. A report of the impact analysis was provided. It is the Applicant's position, that the impact analysis demonstrated that those deviations had no impact on the assessment of the B/R. To begin with, the largest drawback of this analysis is that it was performed after the data base lock when data was already unblinded.

A systemic review of the final locked database (cut-off date: 03 December 2018) was performed to identify all deviations from in-exclusion criteria. Eligibility criteria queries were generated by considering 8 inclusion criteria and 8 exclusion criteria that are of relevance to safety and/or efficacy. Selection of these 8 in- and exclusion criteria was performed as recommended in EMA guideline EMA/868942/2011 (point 3. Categorization of findings). For the inclusion criteria, a SAS program was developed by the company's Biostatistics Department to perform queries based on deviation definitions using cut-off values defined in the study protocol. For exclusion criteria, different SMQs (Standardised MedDRA Queries) or specific Preferred Terms were used and evaluated by the Medical Review Department to identify eligibility criteria deviations from the medical history of patients. A total of 389 eligibility criteria deviations were identified (35% in the control group, 33% in the M3.0 group and 32% in the M4.5 group). The qualitative analysis, including categorization of deviations and whether those deviations have an impact on efficacy and/or safety was performed by the European qualified person for pharmacovigilance (EUQPPV), i.e., the Global Patient Safety Director & Head of Pharmacovigilance at AB Science. The 389 identified eligibility criteria deviations were categorized based on the nature (negligible, minor, major) and potential impact (no impact, possible impact) of the deviations. Regarding safety, 9 deviations in 5 patients were identified having possible impact on safety. When assessing case-by-case, it was concluded that the impact of these 9 deviations in 5 patients do not change the safety profile of masitinib 4.5 mg/kg/day in ALS.

Regarding efficacy, 7 deviations in 7 patients were identified, having possible impact on efficacy. In addition, the Data Review Committee previously (before the final database lock), identified 5 patients with possible impact on efficacy before unblinding. Hence, in total 12 patients with possible impact on efficacy were identified. Three out of these 12 patients participated in the M3.0 arm and were therefore not considered in the subsequent sensitivity analyses. The 9 identified patients (M4.5 arm n=6; control arm n=3) were excluded from the primary endpoint analysis, using MI J2R imputation method. The sensitivity analysis showed that there is minimal impact on efficacy due to the exclusion of these 9 protocol deviators (slightly larger confidence intervals and higher p-values).

In addition to eligibility criteria deviations, potential underdosing of riluzole, Masitinib AB Science dosing deviations and visit window deviations were investigated. A total of 7 patients received sub dosing of riluzole, including 3 patients in the M4.5 arm and 3 patients in the placebo arm. A sensitivity analysis

excluding these 6 patients did not modify the primary efficacy analysis. 9 deviations related to masitinib underdosing were identified. Since those were considered to only minimize Masitinib AB Science efficacy they were concluded to have no impact on the study result. While it is agreed that these dosing deviations do not positively impact Masitinib AB Science efficacy, underdosing might indeed have an impact on safety in favour of Masitinib AB Science. Six visit window deviations were identified. However, those were assessed to have no impact on the primary efficacy analysis since none of those deviations fulfilled a rule established by the DSMB (25 Feb 2016) i.e. no impact on efficacy data is expected if non respect of visit windows is not higher than 28 days and not repeated at 2 consecutive visits.

In principle, the impact analysis performed by the Applicant is acknowledged and considered informative. However, as stated above, the largest drawback of this analysis is that it was performed after the data base lock when data was already unblinded. Hence, although the approach can be followed, the autonomy of this analysis is not given. Moreover, the identification of eligibility deviations was performed by the company's own departments, and the identification and categorization of eligibility deviations was performed by the company's Global Patient Safety Director & Head of Pharmacovigilance. Hence, although the methodology was validated by an independent expert, objectivity of this analysis is questionable. No information regarding the identification of potential underdosing of riluzole events, Masitinib AB Science dosing deviations and visit window deviations were given.

Importantly, the Applicant performed an impact analysis for protocol deviations. However, during the inspection, data was deemed untrustworthy not solely due to protocol deviations. The problem was much deeper and much broader – it encompasses the lack of training, lack of monitoring, lack of proper record keeping, suboptimal trial management, data entry changes and other deviations.

Hence, it is agreed with the previous CHMP conclusion that the *post hoc* performed impact analysis cannot compensate for deficiencies identified during the conduct of the study and that the integrity of the primary endpoint is not given.

[Argument 1.14, 1.16]

The Applicant refers to guideline EMA/868942/2011 which states that if safety is acceptable and the primary variable is robust, then benefit risks is valid. It is the Applicant's opinion, that this criterion is fulfilled. While it is agreed, that in superiority trials indeed, poor quality of data may merely introduce variability and not introduce bias favouring one treatment over the other, the guideline also clearly states that this assumption can only be made once the study has been completed, and superiority has been established, which is not the case for Masitinib AB Science (please refer to GfR#2.2).

Moreover, the Applicant repeatedly refers to the paragraph in the EMA/868942/2011 guideline that states that it is important to assess whether the findings affect the interpretation of the primary efficacy endpoint or important safety endpoints. Needless to state, the findings have less significance for the benefit-risk assessment if they only have consequences for secondary or exploratory endpoints. This is acknowledged; however, it is not agreed that findings have no impact on the primary efficacy endpoint (see above). This aspect is particularly relevant since the clinical development programme is based on a single pivotal trial. The same guideline states that it should be born in mind that secondary endpoints may serve important purposes of ensuring internal consistency, in particular in applications with a single pivotal trial. Since the impact of inspection findings on secondary efficacy data was not considered/addressed, internal consistency is unclear.

Moreover, and most important, the guideline also states that even if individual findings in the intermediate and low-impact category may not affect the benefit-risk assessment looked upon in isolation, the combination of several of these findings is an indicator of overall poor data quality and therefore likely to become significant. This is considered to apply here.

It is agreed with the Applicant, that re-monitoring is recognized as a viable approach under certain

circumstances, as highlighted during the COVID-19 pandemic, where traditional on-site monitoring was often not feasible. However, in the case of the COVID-19 pandemic, re-monitoring was performed (on-site) if there were concerns about data quality/reliability following remote monitoring. This is different from the situation of Masitinib AB Science, where re-monitoring was intended to be used as corrective action following a negative GCP inspection.

The Applicant's justification that re-monitoring in the AB10015 trial is particularly defendable and effective because source data are available and clearly documented and the type of data concerned (AEs, ALSFRS-R) are adapted for an efficient re-monitoring is not supported. Although no critical findings were reported as regards the integrity of the source data, several issues regarding this aspect were seen and described throughout the inspection report. As an example, a common deficiency was detected at the site in Spain and Argentina regarding the report of PDs not documented on medical records/eCRF. Regarding the retrospective re-assessment of the ALSFRS-R score please refer to section above.

[Argument 1.15]

The Applicant claimed that as response to whether the Applicant should file a CMA for Masitinib AB Science, the CHMP Rapporteur of the initial application stated during the pre-submission meeting (24 May 2022) that "*The Rapporteur indicated AB Science should go back to the major points for refusal of the previous EPAR and explain how these issues were addressed, in particular GCP issues*". In the final minutes, it is reflected that the question on whether the CHMP Rapporteur of the initial application could support and encourage the filing of an application for CMA based on currently available data, and what would be the major considerations to be addressed was discussed. However, the minutes reflected that the CHMP Rapporteur of the initial application stated that no pre-assessment can be made until the application has been filed and that the CHMP Rapporteur will liaise with the initial CHMP Co-Rapporteur to provide further feedback to AB Science. It has been confirmed that no further feedback was provided. In the minutes, it is indeed reflected that the CHMP Rapporteur stated that "*The Rapporteur indicated AB Science should go back to the major points for refusal of the previous EPAR and explain how these issues were addressed, in particular GCP issues*" but this was a comment in relation to the discussion about issues raised in the previous EPAR. Whether to apply for a marketing authorisation or not is solely the decision and the responsibility of the Applicant.

[Argument 1.17-1.18]

The Applicant refers to other marketing authorisation procedures (Albrioza and Qalsody) where a similar/higher number of protocol deviations did not lead to major objections or refusal of MA. While it is noted that the marketing authorization for Albrioza was not granted, it is reiterated that every MA application is assessed on its own merit, based on the totality of the data presented. There are multiple factors affecting the benefit-risk evaluation for each application besides the number of protocol deviation. It is the totality of data which is taken into account in every individual dossier.

The Applicant's position that the Masitinib AB Science dossier is treated more strictly than dossiers by other sponsors is strongly disagreed on. As for every other dossier, B/R evaluation is based on the totality of provided evidence.

Overall conclusion

Although the Applicant's corrective measures and actions including re-monitoring and a detailed deviation impact analysis are acknowledged, they can only be considered as supportive but cannot compensate for the identified deficiencies during the conduct of the study. The previous CHMP opinion is upheld.

The note including clarifications on the GCP aspects provided by the Applicant during the evaluation time of the re-examination phase was assessed but the clarifications did not change the CHMP conclusions on

this ground.

Point not resolved

5.1.3. Ground #2.2

Beside the data not being reliable, the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS, because:

1. A statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population.
2. The approach to categorize the population into normal and fast progressors is not supported.
3. Considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data including statistical assumptions on missingness and the definition of intercurrent events in J2R strategy are not considered acceptable.
4. The strategies to *post hoc* identify new target populations ("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version of 4.1) are considered as data driven decisions and are, therefore, not acceptable.

Applicant´s position on the Ground for re-examination

The Applicant presented first some statements already detailed in sections 3.3 – Uncertainties and limitations about favourable effects and 2.6.6 – Discussion on clinical efficacy of this CHMP AR.

1. A statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population.

The total population (normal + fast progressors) is regarded as primary population and statistically significant difference was not demonstrated for the primary endpoint in this population. The second key amendment is *post hoc* division of enrolled participants in two subgroups: fast and normal progressors. The division into two subpopulations was made based on the mITT population. Normal progressors were defined as the primary analysis population while the study was already ongoing. During the assessment, the Applicant was requested to justify this approach. The Applicant claimed that such approach reduces heterogeneity in trial population. The reasoning for reducing heterogeneity is understood but the approach with *post hoc* dichotomization while the study is ongoing is not supported. The Applicant appealed to the guideline EMA/CHMP/539146/2013 (section 5.4. Assessment scenario 3) to justify the validity of the division into groups. Indeed, the section 5.4. Assessment scenario 3 presents the situation in which the clinical data presented fail to establish statistically persuasive evidence in the primary analysis population but there is interest in identifying a subgroup where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed (guideline EMA/CHMP/539146/2013). It should be noted that no further confirmatory conclusions are possible in a clinical trial where the primary null hypothesis cannot be rejected in the total ITT population. To remind: "*a statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population*". The introduction of the subpopulations as an attempt to rescue the study is acceptable by the guideline only in certain situations. The guideline states that interpretation of subgroup findings should be done with caution. Credibility of the subgroup findings, in other words, the extent to which subgroup findings can be concluded as being well substantiated and hence, relied on for decision making depends on the degree of well-founded, a priori definition, the biological plausibility for a particular finding and replication. Indeed, the guideline EMA/CHMP/539146/2013 in section 6.1 states the assessors should have "*expected to find discussion in the trial protocol of the expected degree of*

heterogeneity of the patient population". However, the "*restrictions of a trial population to a sub-population of the target population should be justified, detailing whether restrictions are made due to safety concerns, anticipated lack of efficacy, or other operational considerations*" at the planning stage of the study (EMA/CHMP/539146/2013). Indeed, if the study results indicate that the treatment effect may vary according to the levels of a particular factor, subsequent investigations might need to be based on a categorisation (for a continuous factor) or collapsing categories (for an ordered categorical variable with a higher number of levels). This is because these categories should relate to criteria that might ultimately be used in product labelling or clinical decision-making ((EMA/CHMP/539146/2013). However, this possibility should be carefully considered at the planning stage, pre-specifying categories that might ultimately serve this purpose. Analyses investigating the choice of cut-off on the robustness of conclusions should also be planned as well (EMA/CHMP/539146/2013). The Applicant claims that the normal progressors' subpopulation is the pre-planned primary analysis population of study AB10015. However, the Applicant recognized that the dichotomisation of patients into 'fast' and 'normal' progressors was implemented after the study start, which is not agreed. This approach can generate the questionable results, as "*post-baseline covariates may be affected by treatment received and will not usually be appropriate to define subgroups for the investigation of a treatment effect*" (EMA/CHMP/539146/2013). Moreover, if a particular factor is considered prognostic for outcome or at least some biological plausibility or external evidence such that an inconsistent response might be observed, the CHMP expected to find a discussion of subgroup of investigations conducted and their consideration.

In the opinion of the CHMP, the aforementioned criteria for subgroup analyses (guideline EMA/CHMP/539146/2013) were not met nor for the normal progressor was subpopulation selected by the Applicant after an amendment of the protocol while the study ongoing.

AB Science Response

Argument 2.1: The Rapporteurs' position that the Applicant justified the analysis in Normal progressors based on scenario 3 of guidance EMA/CHMP/539146/2013 is inaccurate. Such justification was never formulated by the Applicant as the analysis in the Normal progressors was prespecified in an amendment submitted prior to the availability of any study data and the study is positive on its planned amended protocol transitioning from phase 2 to phase 3, as validated by competent authorities

The main amendment introducing the distinction between "Normal" progressors and "Fast" progressors, was the amendment #3. This amendment was implemented in October 2014, approximately 2.5 years prior to trial completion (March 2017 for unblinding).

From this protocol version onward, a fixed sequence methodology was used to control the global family-wise error rate at the 0.05 significance level.

- Sequence 1 'Normal Progressor' population - Masitinib 4.5 mg/kg/day
- Sequence 2 'Normal Progressor' population - Masitinib 3 mg/kg/day
- Sequence 3 'Normal +Fast Progressor' population - Masitinib 4.5 mg/kg/day
- Sequence 4 'Normal +Fast Progressor' population - Masitinib 3 mg/kg/day

The amendment was submitted based on the justification provided below, which had nothing to do with the reasoning set in guidance EMA/CHMP/539146/2013.

Argument .2.2: The main amendment excluding Fast progressors from the primary analysis was recommended by principal investigator

Because of transition from phase 2 to phase 3, it was necessary to minimize expected high missing data due to discontinuations from Fast progressors in a study with a long time-point of 48-weeks and with a tablet formulation.

The distinction between normal and fast progressors with motivated by the need to have a more homogeneous population.

The distinction between normal and fast progressors with a cut-off of 1.1 points was recommended by the new coordinating investigator, who was appointed in July 2014.

Argument 2.3: The distinction between Normal and Fast progressors was widely endorsed by all Investigators and by ALS experts

This proposal was then validated by the steering members of the trial, as well as all investigators and other independent experts in ALS from the below countries

Table 102: List of investigators and external experts in ALS agreeing with the distinction between Normal and Fast progressors (redacted)

Status	Country
Investigator	Spain
Investigator	Spain
Investigator	Netherlands
Investigator	Portugal
Investigator	Italy
Investigator	Italy
Investigator	Italy
Investigator	Italy
Investigator	Italy
Investigator	Hungary
Investigator	Hungary
Investigator	Mexico
Investigator	Serbia
ALS Experts	Ireland
ALS Experts	Germany
ALS Experts	Germany
ALS Experts	USA
ALS Experts	Belgium
ALS Experts	Switzerland

Argument 2.4: The amendment was fully justified in the context of a phase 3 study in ALS with 48 week time point, as around 55% of fast progressors discontinued before week 48

AB Science provided new data showing discontinuation rate above 50% in Fast progressors at week 48, validating the necessity to exclude Fast progressors from the primary analysis.

Table 103: Rate of discontinuation at week 48

Patient Status	Placebo	M4.5
Normal	26.5%	30.5%
Fast	**52.6%**	**56.5%**

Argument 2.5: Retaining fast progressors in the primary analysis and accounting for the expected standard deviation would have required 800 patients for a phase 2b/3 which is contrary to the objective in an orphan drug development

Exclusion of fast progressors from the primary analysis was necessary, in particular for a week 48 study in ALS

At the time of transitioning from a phase 2 to a 48-week duration phase 3 clinical trial, patient selection criteria for study AB10015 were amended in order to better minimize data variability. This included mitigation of premature patient withdrawal by pre-empting and excluding those cohorts that represented a higher risk. Exclusion of fast progressors is therefore a strategy aimed at limiting the amount of missing data and data variance.

This design consideration is directly related to the EMA guidance EMA/CPMP/EWP/1776/99 Rev. 1 (2 July 2010) on Missing Data in Confirmatory Clinical Trials, which states that "… *by careful planning it is possible to reduce the amount of data that are missing. This is important because missing data are a potential source of bias when analysing data from clinical trials. Interpretation of the results of a trial is always problematic when the proportion of missing values is substantial." The guideline further insists that the study should be designed to minimize missing data "it is extremely important to avoid the presence of unobserved measurements as much as possible, by favouring designs that minimise this problem, …*".

If Normal and Fast progressors were to be kept for the primary analysis population, the sample size should have been around 1000 patients across three arms, as calculated below.

Because efficacy of masitinib was not yet established, it was considered more ethical to limit the sample size by performing the sequential analysis in Normal then in Normal + Fast progressors, rather that inflating the sample size.

To estimate the necessary sample size a study designed for normal + fast progressors, hypotheses would have been to detect a difference of 3.3 points in the mean change of ALSFRS-R score between the two masitinib arms (3.0 mg/kg/day and 4.5 mg/kg/day) and the corresponding placebo arm after 48 weeks of treatment.

But the major difference would have been to integrate in the sample size a Standard deviation of the change from baseline to week 48 in ALSFRS-R score estimated at 15 points

Alpha set to 2.5% for one -sided test

Global Power set to 80%

Randomization ratio 1:1:1 between masitinib 3mg/kg and masitinib 4.5mg/kg and placebo

With these assumptions, approximately 331 patients would have been necessary in each arm to detect a 3.3 point difference in ALSFRS-R score between the masitinib group and the corresponding placebo group, in order to achieve a global power above 80% with a significance level for a one-sided t-test of 0.025%.

In total the sample size would have been around 1,000 patients just because of the increase in standard deviation.

The sample-size calculations were performed by AB-Science using PASS.

Please note that the difference of 3.3 points in change in alsfrs for Normal+fast is what was observed when the bias of the subset of patients with at least one complete loss of function is removed.

Argument 2.6: The main amendment excluding Fast progressors from primary analysis was validated by all competent authorities

The amended protocol proposing the split into Fast and Normal Progressor subgroups was subsequently approved by the following national competent authorities, at a time when the study was already amended into a phase 3:

Table 104: Approval of amendment #3 by all countries

National Competent Authority	Protocol version	Approval date
Argentina	v3 ROW	30-Nov-14
Canada	v4 CAN	05-Aug-15
Greece	v3 ROW	06-Mar-15
Italy	v3 ROW	05-May-15
Mexico	v4 ROW	09-Mar-17
Netherlands	v4 EU	21-Sep-15
Portugal	v4 EU	19-Apr-17
Slovakia	v3 ROW	03-Feb-15
Spain	v4 Spain	01-Dec-14

Argument 2.7: Substantial protocol amendments during the enrolment period are not uncommon, especially for rare diseases

There are numerous examples of clinical studies transitioning phase status while the trial is on-going. Examples include studies NCT03149003, NCT02631876, NCT03941444 and NCT01224106).

Furthermore, a survey by Tufts Center for the Study of Drug Development revealed that occurrence of multiple substantial protocol changes during phase 3 studies is not uncommon, especially for rare diseases [Getz 2022; Getz 2024]. Analysis from the 2022 follow-up study, based on data provided by 19 major and mid-sized pharmaceutical companies and CROs, showed that overall, more than three quarters of protocols required at least one amendment, with a mean average of 3.3 amendments implemented per protocol when required. Considering breakdown by protocol phase, 88.2% of phase 2 protocols and 82.2% of phase 3 protocols had at least one substantial protocol amendment with an average of 3.3 and 3.5 amendments per protocol, respectively. More complex protocol designs were associated with a higher average number of substantial amendments, with an average of 3.7 being associated with rare disease protocols. Changes in clinical trial strategy and regulatory agency requests were consistently among the most common primary causes of amendments. Considering timing of amendment implementation, approximately 60% of phase 3 studies had amendments occurring during the enrolment period.

In study AB10015, three amendments were done, which is in line with Tufts publication.

Argument 2.8: Precedents exist for such substantial amendments to the pivotal studies of drugs granted marketing authorisation

In May 2023, the EMA granted Columvi (glofitamab) a conditional marketing authorzation for the treatment of relapsed or refractory diffuse large B-cell lymphoma. This was despite the study being initiated as a Phase 1 study that was upgraded to a Phase 1/2 study following a late protocol amendment (the ninth of ten), and that definition of the primary analysis cohort was made only after all data had been accrued.

While EMA decision is pending, the FDA approved, in July 2024, Kisunla (donanemab) injection for the treatment of Alzheimer's disease. Eli Lilly's TRAILBLAZER-ALZ 2 pivotal trial of donanemab in early symptomatic Alzheimer's disease, closely mirrors the two-tiered design of study AB10015. That is to say,

the main primary analysis population is a subgroup of the overall population, the latter of which was tested as a subordinate part of a hierarchical test procedure (see table below for comparison of the TRAILBLAZER-ALZ 2 design and amendments). Furthermore, both of these studies showed no treatment effect (post hoc analyses) in the smaller complement subgroup (i.e., the cohort added to the primary analysis subgroup to make the overall population), which had the result of diluting (lessening) the between group difference of the overall population analysis in both cases. Based on the striking similarities between the substantial amendments of studies AB10015 and TRAILBLAZER-ALZ 2 (in terms of nature and timing) and their amended statistical designs, it would seem logical that both studies will be held to the same regulatory standards regarding impact of said amendments and whether or not these allow for interpretation of the benefit-risk balance.

Table 105: Comparison of amendments for studies AB10015 and TRAILBLAZER-ALZ 2

	TRAILBLAZER-ALZ 2	**AB10015**
Substantial protocol amendments	The trial was originally designed as a phase 2 trial with a plan to enrol 500 participants but was subsequently amended to a phase 3 trial (n=1736) assessing a different primary outcome in a subgroup of the overall study population. *Amendment (17-Feb-2021) included:* - Transition from phase 2 to phase 3. - Increase in the sample size. - Changed the primary analysis **from** "CDR-SB in the low-medium (intermediate) tau pathology population" **to** "iADRS in the low-medium (intermediate) tau pathology population and the overall population (low-medium and high tau pathology)." *Amendment (Sep 2021) included:* - Increased sample size by 300 participants.	The trial was originally designed as a phase 2 trial with a plan to enrol 45 participants but was subsequently amended to a phase 2/3 trial (n=394) assessing a subgroup of the overall study population. *Amendment (July 2013)* included: - Transition from phase 2 to phase 2/3. - Increase in the sample size. *Amendment (Oct-2014)* included: - Changed the primary analysis population to "Normal Progressor" (ΔFS < 1.1 points/mo) while concurrently permitting assessment of the overall "Normal and Fast Progressor" population. - Increase in the sample size.
Timing of amendments	Enrolment began June 2020, and ended November 2021, indicating that these amendments occurred after a substantial number of patients had been recruited.	Amendments occurred early during the study, at a time when 9% (July 2013) and 36% (October 2014) of patients had been enrolled, corresponding to 0% and 12% patients having reached the primary outcome week-48 timepoint.
Trial blinding at amendments	No unblinded data analysis of TRAILBLAZER-ALZ 2 was performed or used to inform design or analyses.	No unblinded data analysis of AB10015 was performed or used to inform design or analyses.
Amended primary objective	To assess the effect of donanemab versus placebo on clinical progression in participants with early symptomatic AD, according to iADRS change from baseline through Week 76 in at least one of: - the low-medium (intermediate) tau pathology population or - the overall population (low-medium and high tau pathology)	To assess the effect of masitinib versus placebo on clinical progression in participants with ALS according to decline in ALSFRS-R from baseline to week 48 in: - the 'Normal Progressor' population - the overall population ('Normal and Fast Progressor')
Hypothesis testing scheme	Gating scheme. Statistical testing allocated α of .04 to testing low/medium tau population outcomes, with the remainder (.01) for combined population (low/medium and high tau) outcomes.	Stepwise manner (fixed sequence method), with the hierarchy of: 1. 'Normal Progressor' masitinib 4.5 mg/kg/day cohort 2. 'Normal and Fast Progressor' masitinib 4.5 mg/kg/day cohort

	TRAILBLAZER-ALZ 2	AB10015
Post Hoc Outcomes	Analysis of the smaller (n=552) high tau population alone (i.e., not combined with the low/medium tau population) was completed *post hoc* and showed that high tau participants demonstrated no differences on the primary outcome or on most secondary clinical outcomes in donanemab-treated compared with placebo-treated participants. Absence of treatment-effect reduced magnitude of difference in the overall population, but not to such an extent that it lost statistical significance (because of large treatment-effect driven by the low/medium tau population).	Analysis of the smaller (n=42) Fast Progressor population alone (i.e., not combined with the Normal Progressor population) was completed *post hoc* and showed that Fast Progressor participants demonstrated no differences on the primary outcome or on secondary clinical outcomes in masitinib-treated compared with placebo. Absence of treatment-effect reduced magnitude of difference in the overall population to such an extent that statistical significance was lost.

Argument 2.9: The integrity of the study was preserved, the amendment was done blinded

The amendments were implemented while the study remained blinded, thereby, preserving data integrity.

The GCP inspection did not report any finding related to potential unblinding of the study.

Argument 2.10: The amendment was implemented 2.5 years prior to study completion with only 12% of data acquired and excluding these data does not modify the study outcome

The amendment was implemented early (October 2014), approximately 2.5 years prior to trial completion (March 2017 for unblinding), with only 8 Fast Progressor patients across 3 arms who could have reach week 48.

Table 106: Number of patients by treatment group and ΔFS subgroup at time of amendment introducing the distinction between Normal and Fast Progressor (Protocol version v3.0, submitted 08 October 2014)

Number of patients n (%)	**Placebo** **N = 133**	**Masitinib 3.0** **N = 131**	**Masitinib 4.5** **N = 130**	**Total** **394**
Normal Progressor	15 (11.3)	13 (9.9)	10 (7.7)	38 (9.6)
Fast Progressor	3 (2.3)	2 (1.5)	3 (2.3)	8 (2.0)
All	18 (13.5)	15 (11.5)	13 (10.0)	46 (11.7)

Argument 2.11: Removing those 12% data would not have changed the outcome of the primary analysis

The sensitivity analysis excluding 40 Normal Progressors who could have reached the 48-week time point shows no impact (diff of 3.20, p=0.0384)

Table 107: Post hoc analysis of the AB10015 primary endpoint, excluding those patients who had reached week 48 by the time of submission of protocol introducing this distinction between Normal and Fast Progressor (Analysis Rule 1 – mLOCF, Normal Progressor)

Treatment group	N	LS Mean ALSFRS-R	Difference of means [95% confidence interval]	p-value (no re-randomization test)
Placebo	87	-12.31	3.20 [0.17;6.23]	0.0384
Masitinib 4.5	89	-9.11		

Argument 2.12: The interim analysis was positive in the overall study population and there was no amendment after the interim analysis

The preplanned interim analysis (March 2016) with Normal + Fast Progressor patients was positive (p=0.0213).

Table 108: Interim Analysis - Normal + Fast Progressor

Treatment group	N	LS Mean ALSFRS-R	Difference of means [95% confidence interval]	p-value (no re-randomization test)
Placebo	57	-14.50	4.29 [0.14;8.43]	0.0213
Masitinib 4.5	62	-10.21		

The CHMP recommended to continue the study and there was no amendment after the interim analysis.

2. The approach to categorize the population into normal and fast progressors is not supported.

The Applicant presented first some statements included in section 2.6.6 of this CHMP AR

During the assessment, the Applicant was arguing that categorization of patients in Normal and Fast progressors was endorsed by the CHMP scientific advice (SA). This is not agreed as the SA addressed the use of ΔFS as a potential inclusion criterion for the Phase 3 AB10019 study. The Applicant insisted on that this categorization of the population is supported in terms of clinical relevance, statistical design, and pathophysiology of ALS. Although changes in the ALSFRS-R could be considered a useful measure of disease progression in some studies. However, its use as a single indicator for convincing prediction of the progression of ALS is not acceptable, because ΔFS alone has relatively low predictive value of progression (Thakore et al, 2017) and is not stable throughout the course of disease (Requardt, 2021). For this reason, a linear assumption for the ΔFS decline (average rate of change from onset to randomization) might lead to misclassification of patients. Additionally, despite the fact that delta FS from the first symptom to time of diagnosis or during the whole disease could be reliable predictor of survival, it possesses uncertainties related to the patient's knowledge of the exact time of the first symptoms as well as the investigator knowledge of the exact time of the first symptoms' set up. The justifications for the cut-off (ΔFS 1.1) provided by the Applicant during the assessment were not convincing and the Applicant was repeatedly informed during the application assessment that the delta FS cut-off 1.1 points/months for the categorization of patients into normal and fast progressors is not acceptable as a single indicator of the progression.

During the extended discussion after the OE, the Applicant insisted on that the cut-off 1.1 of delta FS is based on the best evidence found in the literature at the moment of study development. According to the Applicant, the calculation of the cut off level 1.1 of delta FS is based on the study of Kollewe et al J. (2008). Referring to Kollewe et al (2008) the Applicant has explained the calculation of cut-off of delta FS: "*the median delta FS calculated between onset and first examination was 1.0 points/month and the median delta FS calculated over the whole course of disease was 1.185 points/month, a range therefore of approximately 1.0 – 1.2 points/month. The choice of 1.1 points/month is situated at the midpoint of this range*". However, the authors highlighted in the referred publication that if the investigators fail to note exact time there will be no correct calculation for ALSFRS-R score ratio between first symptom and first examination. Additionally, the authors noted that the change of ALSFRS-R score over the whole course of disease is not useful to establish, because only the endpoint defined as death or tracheotomy allows assuming it. They concluded that ALSFRS-R score ratio within a defined period (i.e. 100 days) could solve the problem. They proposed to compute this parameter as "*difference of ALSFRS-R score between two visits divided by days between two visits*". Notably, the conclusion of the authors was that the ratio of ALSFRS-R score within 100 days is a useful parameter for clinical trials and they proposed

<0.25; 0.25-0.65 and >0.65 cut-off levels of delta FS. Based on all above, it could be concluded that the applied cut-off level by the Applicant seems to be chosen arbitrarily and, therefore, the quantitative choice of delta FS cut-off at 1,1 is not supported for the distinction patients into Normal and Fast progressors. The CHMP stressed again that the distinction into normal and Fast progresses are unlikely to happen in the clinical practice by simply applying a cut-off level 1.1.

The Applicant states that showed benefit in ALSFRS-R and PFS and a trend towards benefit on OS and CAFS is in alignment with EMA guidance (ref.: EMA/531686/215, Corr. 1.1.). According to the Applicant, many ALS studies, including pivotal studies of registered products such and Tofersen (EMA approval), have used delta FS as a patients' selection criterion without providing justification that defined cut-off is stable over time. Based on this, the Applicant believes that there is no precedent to reject a study based on the categorization of its population via delta FS. In response to the Applicant's argument about the delta FS use in other trials, it is acknowledged that the calculation of delta FS has been used in clinical studies, however the exact cut-off of delta FS to distinct fast or normal progressors is questionable. Indeed, the numerous clinical studies operate with a variety of slope of ALSFRS-R, which could be defined as early, late, pre-randomized or run-in slope, and they range from 0.25 to 1.7. However, no exact cut-off level can be defined for the categorization of disease progression, as the higher delta FS simply indicates the higher chance or probability of the survival event (death or tracheotomy) compared with lower one. The CHMP considers that the distinction into normal and fast progresses are unlikely to happen in the clinical practice taking into account the variety of ALS phenotypes or predominated type of onset of disease and severity of disease at the baseline. As per reference to Tofersen, the Applicant categorized the population using two factors the delta ALSFRS-R and type of SOD1-ALS. Results from the Tofersen clinical data suggested that two factors did not adequately discriminate the probability progression of ALSFRS-R. The data suggested that the baseline level of neurofilaments was a better prognostic factor (Tofersen EPAR). It is believed that, yet no new convincing data or arguments were presented that would alter previous assessment and CHMP conclusions about efficacy demonstration in the full study population, thus issue is not resolved.

AB Science Response

Argument 3.1: The definition of fast progressors measured from onset of symptoms is the most classic way to define fast progressor and is widely used by sponsor

ΔFS can provide patient enrichment by selecting a more homogeneous population, and it has now become common practice for ALS clinical studies to use ΔFS related inclusion criterion for selecting a more homogenous population.

Examples include trials of edaravone, FNP122 (oral edaravone), tofersen, Nurown, rasagiline, ravulizumab, lenzumestrocel, bosutinib, nitrazine, beta hydroxybutyrate ester and high-caloric fatty diet (see table below).

Table 109: ALS clinical studies with patient selection based on ΔFS

Drug	Study	ΔFS patient selection criterion	Ref
Masitinib	AB10015, NCT02588677	Predefined primary analysis population: 'Normal Progressor' ΔFS <1.1 per month)	Mora 2020 Mora 2021
Beta Hydroxybutyrate Ester	KETO-ALS, NCT04820478	Inclusion criterion: ΔFS ≥0.33 per month since onset (first paresis), in the period between first symptoms and screening	clinicaltrials.gov

Drug	Study	ΔFS patient selection criterion	Ref
Bosutinib	NCT04744532	Inclusion criterion: Decrease of 1-3 points during 12-week observation period (equivalent to ΔFS 0.36–1.09 per month)	Imamura 2019
Edaravone	MCI186-19, NCT01492686	Inclusion criterion: Decrease of 1-4 points during 12-week observation period (equivalent to ΔFS 0.36–1.45 per month)	The Writing Group 2017
FNP122 (oral edaravone)	ADORE, NCT05178810	Inclusion criterion: ΔFS between 0.35 and 1.5 per month in the period between first symptoms and the screening visit	van Eijk 2022
High-caloric fatty diet	NCT02306590	Fast progression rate: ΔFS >0.65 per month (defined *post hoc*)	Ludolph 2020
Lenzumestrocel	NCT04745299	Inclusion criterion: intermediate rate of disease progression; ΔFS of 1.03±0.5 per month during a 17-week period	Nam 2022
Methylcobalamin	NCT03548311	Inclusion criterion: Decrease of 1-2 points during 12-week observation period (equivalent to ΔFS 0.36–0.72 per month)	Oki 2022
Nitrazine	NCT04950647	Inclusion criterion: Decrease of 1-4 points during 12-week observation period (equivalent to ΔFS 0.36–1.45 per month)	clinicaltrials.gov
NurOwn	NCT03280056	Inclusion criteria: ≥3 ALSFRS-R points decline during 12-weeks (equivalent to ΔFS ≥ 1.09 per month; i.e., 'Rapid Progressor')	Cudkowicz 2022
Rasagiline	NCT01879241	Normal to fast progression rate: ΔFS >0.5 per month (defined *post hoc*)	Ludolph 2018
Ravulizumab	NCT04248465	Inclusion criterion: ΔFS > 0.3 per month	Genge 2023
Tofersen	NCT02623699	Primary population: Faster Progressor subgroup defined as ΔFS ≥0.9 per month	Miller 2022
* For conversion between weeks and months, it is assumed that 1 month equals 4.348125 weeks (with mean month length of the Gregorian calendar being 30.436875 days).			

Argument 3.2: The definition of fast progressors measured from onset of symptoms is a highly robust, independent prognostic predictor of survival. ALSFRS-R is a surrogate of survival

ΔFS from onset of symptoms has been identified as being a highly robust independent prognostic predictor of survival. Research by Requardt and colleagues has shown that the clinical determinant of greatest prognostic importance for survival is the early ALSFRS-R slope (i.e., ΔFS from onset of symptoms), with a statistically significant hazard ratio (HR) of 1.50, $p < 0.0001$, according to univariable Cox regression for continuous measures, and an HR of 1.33 (95% confidence interval, 1.19–1.5, $p < 0.0001$), according to multivariable Cox regression model [Requardt 2021]. On the contrary, late ALSFRS-R slope (e.g., ΔFS calculated over a relatively short observation or lead-in period) showed no prognostic value under this clinical setting. Hence, ΔFS from onset of symptoms is an entirely independent clinical determinant of survival prognosis from that of run-in ΔFS, and therefore robust irrespective of any ΔFS instability over the duration of disease.

The importance of this latter point cannot be overstated; ΔFS is a timeframe dependent parameter meaning that different methods of calculating the ratio's denominator may have significant impact on the resulting value. Consequently, there are in fact different 'noncomparable' ΔFS measurements. It is

well-established that ALSFRS-R progression of ALS is curvilinear over the course of the disease, therefore, it is important to distinguish which part of the overall ALSFRS-R trajectory is being considered when defining or comparing ΔFS values. Hence, ΔFS is typically defined using one of the following, noncomparable, calculations:

- Post-onset (early slope) ΔFS = [(48 minus total ALSFRS-R score at diagnosis or initial assessment) divided by (symptom duration from onset in months)].

- Interval (late slope) ΔFS = [(total ALSFRS-R score at first assessment minus total ALSFRS-R score at follow-up assessment) divided by (follow-up time in months)].

Indeed, this timeframe dependence is well-illustrated by Kollewe and colleagues who defined ΔFS over three different timeframes; namely, ΔFS calculated from first symptom to time of diagnosis, ΔFS calculated over the whole course of disease (i.e., from first assessment until last assessment prior to death or tracheotomy), and ΔFS calculated within a defined period of 100 days [Kollewe 2008]. According to their study population, the median ΔFS calculated for each of these timeframes was 1.0, 1.185 and 0.65 points/month, respectively.

Another finding of the Requardt research was that patients frequently switched between ΔFS categories over time, i.e., there were significant differences between early and late ΔFS group distributions [Requardt 2021]. However, as explained above, this is entirely to be expected because the comparison being made is confounded by differences in the ΔFS methodology applied. To assess instability in ΔFS categorization it would be necessary to fix the timeframe's starting point, i.e., from first symptom, first assessment or a given baseline assessment. Hence, the ΔFS categorical instability observed by Requardt does not preclude stability in post-onset (early slope) ΔFS over time.

Moreover, in the context of excluding fast progressors as a strategy to limit the amount of missing data, a certain amount of misclassification around the chosen ΔFS cut-off is of little consequence because this approach will still achieve its aim of reducing data variance by excluding those patients with persistently fast progression. Indeed, it has been shown that study AB10015 was successful across a range of possible ΔFS cut offs, from 0.8 to 1.4 points/month.

Argument 3.3: The ΔFS eligibility criterion cut-off of 1.1 points/month was not arbitrary but based on available literature

The Rapporteurs has repeatedly concluded that the ΔFS eligibility criterion cut-off of 1.1 points/month applied in study AB10015, has been arbitrarily chosen and does not therefore support the categorization of patients into 'normal' and 'fast' progressors. The Applicant respectfully challenges this opinion and contends that the ΔFS eligibility criterion cut-off of 1.1 points/month was not chosen in an arbitrary manner but was based on the most credible evidence found in the literature at that time.

As a reminder, Kollewe and colleagues showed that ΔFS, whether calculated from first symptom to time of diagnosis, during the whole disease, or within an interval of 100 days, correlates with survival time and is a reliable, independent predictor of survival [Kollewe 2008]. The authors even concluded that *"Predictors of survival are not only an instrument for better management in individual ALS-patients but could also be helpful for the design of new trials, randomization of patients and studying different types of disease progression correctly."* This is exactly what the design of study AB10015 has endeavored to achieve, and now it would seem is being penalized for.

As mentioned above, Kollewe and colleagues defined ΔFS over three different timeframes; namely, ΔFS calculated from first symptom to time of diagnosis, ΔFS calculated over the whole course of disease (i.e., from first assessment until last assessment prior to death or tracheotomy), and ΔFS calculated within a defined period of 100 days. According to their study population, the median ΔFS calculated for each of these timeframes was 1.0, 1.185 and 0.65 points/month, respectively. The difference between these values highlights an important aspect of this measurement, in so far as ΔFS is a timeframe dependent parameter, meaning that different methods of calculating the ratio's denominator may have significant impact on the resulting value. Consequently, these are in fact different 'noncomparable' ΔFS

measurements. It was therefore necessary for the Applicant to choose one of these techniques (i.e., timeframes) as a basis for the study's ΔFS eligibility criterion. Each has its advantages and disadvantages, as discussed further below.

- The gold standard ΔFS for survival predication is logically that which is calculated over the whole course of disease; however, as pointed out by the authors, "*this is not useful to establish, because only the endpoint defined as death or tracheotomy allows to assume it*". Nevertheless, the findings from Kollewe established its strong correlation with survival time and the benchmark of 1.185 points/month as a rational criterion for categorization of patients into rapid (i.e., faster) and non-rapid (i.e., normal) progressors.

- ΔFS calculated from first symptom to time of diagnosis (i.e., post-onset ΔFS) has the advantage of being calculated over a relatively long timeframe, given that time to diagnosis is typically between 12 to 18 months, meaning that it better approximates the 'averaged' measurement of ΔFS during the whole disease and is less sensitive to short-term fluctuations (signal noise). This assumption is supported by the similar median ΔFS values of 1.0 and 1.185 points/month for these two calculations, indicating that a range of approximately 1.0 – 1.2 points/month is a rational criterion for categorization of patients into rapid (or faster) and non-rapid (i.e., normal) progressors. However, it was also stated by the authors that patient recall error regarding the date of first symptom onset could hinder this approach. Although recall error may introduce some uncertainty (for example, the month of onset can be recalled but not the exact day), this position is countered in a recent article by Ludolph and colleagues. In that article, it was concluded that because the clinical relevance of ΔFS is now so well-established and post-onset ΔFS is derived from information routinely collected as part of standard patient care and monitoring, it provides a suitable patient selection tool for treating physicians, with no obvious barriers regarding its application in clinical practice [Ludolph 2024].

- Finally, Kollewe and colleagues calculated ΔFS within a defined period of 100 days as a way to avoid the abovementioned problems. The Applicant rejected this approach, however, in part because the median ΔFS value of 0.65 points/month was very dissimilar to that of ΔFS during the whole disease (cf. 1.185 points/month), and more importantly because use of an untreated lead-in period was considered unethical in terms of the delay in starting the intervention and a probable hinderance in timely achievement of recruitment targets. In contrast, ΔFS calculated from first symptom to time of diagnosis shortens the interval from disease onset to therapy, potentially being favorable to detect a drug's efficacy because of less advanced motoneuron degeneration (which is a very important consideration for a neuroprotective drug such as masitinib).

For these reasons, the cut-off of 1.1 points/month, situated at the midpoint of the 1.0–1.2 points/month range and calculated from first symptom to time of diagnosis, provides a rational criterion for categorization of patients into fast and normal progressors.

Argument 3.4: The risk of misclassification is minimized by the fact that fast progressors is defined from onset of symptoms

Because progression in ALS is non-linear, it is important to distinguish which part of the overall ALSFRS-R trajectory is being considered when defining or comparing ΔFS values. Hence, ΔFS (points per unit time) is typically defined using one of the following, noncomparable, calculations:

- Post-onset (early) ΔFS = [(48 minus total ALSFRS-R score at diagnosis or initial assessment) divided by (symptom duration from onset in months)]
- Interval (late) ΔFS = [(total ALSFRS-R score at first assessment minus total ALSFRS-R score at follow-up assessment) divided by (follow-up time in months)]

Another distinguishing feature between these measures of ΔFS is the timeframe over which they are calculated. Meta-analysis (n=3367) from Thakore and colleagues estimated the median time from onset to first ALSFRS-R measurement was 16.9 months (IQR [11.3–23.7]) [Thakore 2018], while smaller cohorts have estimated mean diagnostic latency to be between 13.4 to 16.6 months [Kjældgaard 2021;

Requardt 2021]. Hence, post-onset ΔFS will typically be measured during the initial 12 to 24 months of the symptomatic disease phase. In contrast, interval ΔFS is more often measured over a shorter timeframe; for example, a 3-month lead-in (pretreatment) period. Post-onset ΔFS therefore has an advantage of being relatively insensitive to short-term intraindividual variations, whereas the 'snap-shot' interval ΔFS may be misrepresentative of the general disease progression trend.

Importantly, it has been shown that the clinical determinant of greatest prognostic importance for survival is post-onset ΔFS (i.e., the early ALSFRS-R slope), with a statistically significant hazard ratio (HR) of 1.50, $p < 0.0001$, according to univariable Cox regression for continuous measures, and an HR of 1.33 (95%CI [1.19–1.5]), $p<0.0001$, according to multivariable Cox regression model [Requardt 2021]. This finding is in marked contrast to other calculations of ΔFS (e.g., interval ΔFS), which showed no prognostic value.

Hence, according to Requardt and colleagues, the early ALSFRS-R slope (i.e., post-onset ΔFS) and late ALSFRS-R slope (i.e., interval ΔFS exemplified by lead-in period ΔFS or post-randomization ΔFS) are distinct clinical features in terms of prognostic value. By consequence, post-onset ΔFS is the most relevant and robust measure of ΔFS for patient selection. Moreover, there is no contradiction or negative impact to the validity of post-onset ΔFS categorization should an individual switch ΔFS categories between early and later stages of the disease course.

Argument 3.5: The study outcome is positive with a cut from 0.8 to 1.5 points decline

Verification that ΔFS represents an appropriate and robust tool for selection of the primary efficacy population in study AB10015, is provided by sensitivity analyses to determine the margin of error associated with the ΔFS cut-off and potential impact of misclassification from the requisite estimation of time to first symptom. As described in further detail below, results showed that the ΔFS cut-off value was well-judged and associated with a sizeable margin of error, while the possibility and impact of misclassification is small. This indicates that the ΔFS cut-off of 1.1 is not an absolute requirement because the primary analysis remains positive based on ΔFS cut-offs ranging from 0.8 to 1.5, as presented in the table below.

To test the robustness of this cut-off threshold, sensitivity analyses were performed based on the primary endpoint (rule 1 for handling of missing data) and using a ΔFS cut-off ranging from 0.8 (corresponding to a predefined sensitivity analysis cut-off from the Statistical Analysis Plan of study AB10015) until the cut-off at which treatment-effect became non-significant.

It is seen that treatment-effect remains in favour of masitinib until a ΔFS threshold of 1.4 (inclusive), accounting for 90% of patients. From this we can conclude that the positive treatment-effect seen for masitinib in study AB10015 cannot be dismissed as being a statistical anomaly of the dataset and its interaction with the ΔFS=1.1 cut-off, nor that this threshold makes for a highly volatile, changeable outcome. On the contrary, this analysis shows the categorization of patients based on our estimate of ΔFS=1.1 to be robust with a demonstrable 'buffer zone' (i.e., ΔFS cut-offs from 0.8 to 1.3 or 1.4 points/month, ΔFS = 1.1 ± 0.3) for maintained positive treatment-effect.

Table 110: Difference (masitinib 4.5 mg/kg/d versus placebo) in ALSFRS-R score among Normal Progressor with ΔFS ranging from 0.8 to 1.5 for selection of the Normal Progressor population

ΔFS cut-off	ΔLSM (ALSFRS-R)	95%[CI]	P-value	Proportion of randomized patients n, (%)
0.8	3.4951	[0.62;6.37]	0.0174	191 (73.5%)
0.9	3.3355	[0.56;6.11]	0.0188	204 (78.5%)
1.0	3.1453	[0.40;5.89]	0.0251	210 (80.8%)
1.1*	3.3878	[0.65;6.13]	0.0157	218 (83.9%)
1.2	3.2707	[0.55;5.99]	0.0186	223 (85.8%)
1.3	3.2972	[0.60;5.99]	0.0168	226 (86.6%)
1.4	2.6897	[0.01;5.37]	0.0495	233 (89.9%)
1.5	2.5620	[-0.08;5.21]	0.0576	241 (92.7%)

Primary efficacy population prospectively defined as 'Normal Progressor' patients receiving masitinib at 4.5 mg/kg/day versus placebo. 'Normal Progressor' dataset defined as patients with a post-onset ΔFS of less than 1.1 points/month. ΔFS = ALSFRS-R progression rate from disease-onset to baseline. ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. LSM = Least-squares means difference from baseline. ΔLSM = Between treatment-arm difference of LSM. 95% two-sided confidence intervals [95%CI].

Argument 3.6: The risk of inaccuracy due to the dependence of the recollection of date of onset is mitigated by the fact that patients would not change class if they remind month of symptoms

The range of days in time to first symptom (TTFS) whereby a patient with ΔFS of 1.1 would remain within the 'buffer zone' of ΔFS from 0.8 to 1.3, ranges from [-113; +277] days for a patient with a baseline score of 21, and from [-4; +11] days for a patient with a baseline score of 47.

Therefore, patients with baseline ALSFRS-R score ranging from 41 to 47 presents a greater of risk of misclassification due to error in TTFS, because a deviation by less than 30 days affects the classification Normal versus Fast progressor.

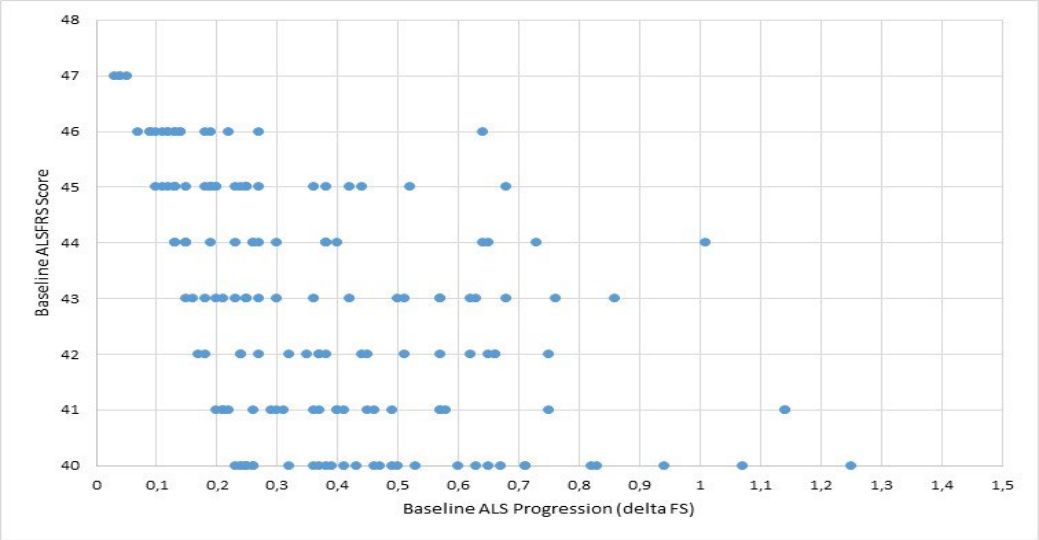
Table 111: Margin of Error on Time to First Symptoms (TTFS)

Days between onset date and baseline for (ΔFS) of	**Baseline score**																				
	21	**23**	**25**	**27**	**29**	**31**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**41**	**42**	**43**	**44**	**45**	**46**	**47**
1.1	736	682	627	573	518	464	409	382	355	327	300	273	245	218	191	164	136	109	82	55	27
1.3	623	577	531	485	438	392	346	323	300	277	254	231	208	185	162	138	115	92	69	46	23
0.8	1013	938	863	788	713	638	563	525	488	450	413	375	338	300	263	225	188	150	113	75	38
Range 1.1 to 1.3	**113**	**105**	**96**	**88**	**80**	**72**	**63**	**59**	**55**	**50**	**46**	**42**	**37**	**33**	**29**	**26**	**21**	**17**	**13**	**9**	**4**
Range 0.8 to 1.1	**277**	**256**	**236**	**215**	**195**	**174**	**154**	**143**	**133**	**123**	**113**	**102**	**93**	**82**	**72**	**61**	**52**	**41**	**31**	**20**	**11**
Overall range (buffer zone)	**390**	**361**	**332**	**303**	**275**	**246**	**217**	**202**	**188**	**173**	**159**	**144**	**130**	**115**	**101**	**87**	**73**	**58**	**44**	**29**	**15**

However, based on AB10015data, patients with baseline ALSFRS-R [41-47] have a low rate of disease progression with mean ΔFS (±SD) of 0.34 (±0.22) and median ΔFS of 0.27.

There are only 5 patients (1.25% of the ITT population) in the vicinity of the 1.1 cut-off (e.g. 1.1±0.2); specifically, 2 patients with baseline ΔFS >1.1 (none exceeded a ΔFS of 1.3) and 3 patients with baseline ΔFS between 0.9 to 1.1.

Figure 10: Distribution of ΔFS for patients with baseline ALSFRS [41-47]



The percentage of patient in AB10015 that could shift from category due to the amplitude in the time to first symptoms is provided below. We considered the following scenarios:

- Normal Progressors (ΔFS<1.1) that shift to Fast Progressors (ΔFS>1.4 (upper limit of efficacy)) due to inaccuracy and would therefore be excluded from treatment whereas they should actually receive treatment (i.e. false negative). In this scenario (i.e. classification shifts from Normal to Fast Progressor) only a shortening of the time to first symptom should generate misclassification.

- The complement scenario is when inaccuracy leads patients with baseline ΔFS of 1.4 to shift to ΔFS<1.1, therefore receiving treatment whereas they should be excluded (i.e. false positive). In this scenario (i.e. classification shifts from Fast to Normal Progressor) only a lengthening of the time to first symptom should generate misclassification.

Table 112: Shift in classification depending on error in time to first symptoms

Shift		**-30 days**	**+30 days**	**-45 days**	**+45 days**	**-60 days**	**+60 days**	**-75 days**	**+75 days**	**-90 days**	**+90 days**
Upper cut-off for ΔFS>1.4 (i.e. recall error in ΔFS of 0.3)											
From Normal (<1.1) to Fast (>1.4)	n	0	-	1	-	3	-	6	-	9	-
	%	0.0%	-	0.3%	-	0.8%	-	1.5%	-	2.3%	-
From Fast (>1.4) to Normal (<1.1)	n	-	0	-	0	-	1	-	2	-	8
	%	-	0.0%	-	0.0%	-	0.3%	-	0.5%	-	2.0%

Taken together, these analyses on margin of error associated with accuracy on the date of first symptoms show that the possibility of misclassification are marginal.

Argument 3.7: Post-onset ΔFS is derived from information routinely collected as part of standard patient care and monitoring, with no obvious barriers regarding its application in clinical practice

The CHMP has previously stated that it is questionable to assume that ALSFRS-R is documented in routine care of ALS patients as this is a scale used only in clinical trials.

This position is however countered by a recent article published in the journal *Muscle & Nerve* by

Professor Albert Ludolph and colleagues (including Professors Philippe Couratier, Philippe Corcia, Claude Desnuelle, Terry Heiman-Patterson, and Jesus Mora) [Ludolph 2024]. This article discusses the merits of using ΔFS as a relevant tool for innovative ALS study design. It concludes that post-onset ΔFS serves not only as a critical stratification factor and basis for patient enrichment, but also as a tool to explore differences in treatment response across the overall population for identification of preferential responder subgroups, and as such is recommended for inclusion in the design of clinical trials.

Importantly, the authors concluded that because post-onset ΔFS is derived from information routinely collected as part of standard patient care and monitoring, it provides a suitable patient selection tool for treating physicians, with no obvious barriers regarding its application in clinical practice [Ludolph 2024].

Argument 3.8: Qalsody defined fast progressors from onset of symptoms and a cut of 0.9 based on literature and EMA did not conclude this cut was arbitrary. Later sponsor amended Qalsody protocol to include fast progressors in the primary analysis population which improved P value

The EMA registered Qalsody based on a pivotal study with the primary population defined as fast progressors, with fast progressors also defined from onset of symptoms, and with a chosen 0.9 point cut-off for decline of the ALSFRS-R score also based on literature. The sponsor then amended the protocol to change the primary population to include non-fast progressors. The CHMP concluded this was acceptable.

In the Scientific advice procedure regarding the design of AB23005 phase 3 masitinib confirmatory study (EMADOC-360526170-1973369), the scientific advice working party (SAWP) confirmed that: "*Qalsody (tofersen) has been authorized for treating adults with a type of amyotrophic lateral sclerosis (ALS) caused by a mutation (defect) in the gene responsible for producing an enzyme called superoxide dismutase 1 (SOD1) (EMA/93332/2024) and, therefore, constitutes a regulatory precedence for ALS prespecified subgroups defined as Faster-Progressing Subgroup and Slower-Progressing Subgroup by Mutation type, pre-randomisation ALS Functional Rating Scale-Revised (ALSFRS-R slope), and Slow vital capacity (SVC) cutoff (EMA/276404/2024)*".

3. *Considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data including statistical assumptions on missingness and the definition of intercurrent events in J2R strategy are not considered acceptable.*

The Applicant presented first some statements included in section 2.6.2 of this CHMP AR.

The study had approximately 30% of missing data in each Masitinib AB Science arm despite highly selective patient population. In the clinical trial, high rates of treatment discontinuation were showed, the regulatory interest is to handle this intercurrent event with a treatment policy strategy. In particular, mainly after treatment discontinuation, high proportions of missing data were observed in each Masitinib AB Science arm despite highly selective patient population. Therefore, an adequate choice of statistical methods for handling missing data which are appropriately conservative and not biased in favour of the investigational treatment under realistic data generating mechanisms is critical for the trustworthiness of the study results.

The methods for handling missing data applied by the Applicant and requested by CHMP included:

- a mLOCF approach that assumes that the benefit experienced until the time of missing data is also retained thereafter.

- a Copy increments from reference (CIR) method was used that assumes that the outcome develops similarly from that point onward to the placebo group.

- a J2R method was used that assumes that the benefit experienced until the point of missing data is not retained and instead the outcome would correspond to the outcome in the reference group.

In the situation of ALS, only the J2R method is considered to not potentially overestimate the missing outcome and hence lead to a biased treatment effect estimate in favour of the investigational treatment. Therefore, only the J2R approach is considered to be appropriately conservative. In order to account for missing data after treatment discontinuation, the Applicant used the mLOCF method for the first and secondary endpoints. More conservative approaches were also provided such as the J2R, but only to handle missing data after discontinuations that were attributed to lack of efficacy or toxicity, whereas missing data after discontinuations for other reasons were presumably handled with a mLOCF approach. A detailed description of the statistical methods is not available, which further increases the uncertainty about the appropriateness of this analysis approach.

Additionally, as an underlying assumption, the Applicant is assuming that it can ascertain which missing case are MAR (protocol deviation / non-compliance, etc.) and which cases are MNAR (efficacy/toxicity). The Applicant does not provide convincing arguments that substantiate this categorisation, hence the handling of missing data following discontinuations for different reasons with different methods is not considered adequate.

Further, the Applicant has presented a tipping point analysis based on the mLOCF approach, where the assumed retained effect as compared to baseline is reduced by increasingly larger percentages

In the clarification after the OE the Applicant maintains that CHMP is inconsistent with its recommendations on acceptability of tipping point analysis above 75% and CIR with p value below 5%. The methods for handling missing data applied by the Applicant and requested by CHMP include mLOCF, CIR and J2R methods. The statistical analyses applied by the Applicant were assessed respectively. Moreover, the Applicant is acknowledged for the providing the multiple statistical analyses requested by CHMP. Indeed, the Applicant has presented a tipping point analysis based on the mLOCF approach, where the assumed retained effect as compared to baseline is reduced by increasingly larger percentages

The Applicant shows that retaining 24% of the difference to baseline still leads to p-value smaller than 5% in the corresponding analysis and argues that this should be sufficient proof of efficacy since the same threshold had been accepted in a different regulatory procedures. However, this argument does not hold since the suitable statistical method for analysis (including an assumption about a realistic and acceptable loss in efficacy in the imputation model) depends on the specific clinical context. In this situation, the analysis assuming the retainment of some effect is still considered not as adequate as the J2R approach, which assumes that patients discontinuing treatment have outcomes similar to the control group.

Overall, the Applicant’s position that the mLOCF and the cluster method are the most appropriate methods to address missing data in the AB10015 trial is not acceptable Considering the progressive nature of ALS and that, the effect of treatment will not be maintained after discontinuation of medication, the J2R method is considered the most appropriately conservative method in this setting. This analysis does not show a convincing result in favour of Masitinib AB Science.

AB Science Response

Argument 4.1: The quantity of missing data at 30% at week 48 is in line with other studies

Missingness in clinical trials of ALS is inherent to the disease and mostly results from premature discontinuations.

As displayedbelow , the amount of discontinuation is in line or even lower than what is observed in other clinical studies on ALS patients, with a rate of around 30% at week 48, similar to what was observed in studies of AMX0035, Edaravone, Levosimendam, Tirasemtiv and Ozanesumab.

Table 113: Comparison of discontinuation rates at week 48 timepoint

Study discontinuation rate	**Investigation Arm**	**Control Arm**
Masitinib AB10015 (DB 48-week) [a]	31.1% (33/106)	27.7% (31/114)
AMX0035 NCT05021536 (DB 48-week)	42% (167/397)	43% (115/267)
Edaravone NCT01492686 (Overall, 48-week) [b]	20.9% (14/67)	39.4% (26/66)
Levosimendan NCT03505021 (DB 48-week)	34.0% (112/329)	32.9% (55/167)
Tirasemtiv NCT02496767 (DB 48-week)		
Tirasemtiv 250 mg	36.5% (46/126)	29.8% (56/188)
Tirasemtiv 375 mg	48.4% (61/126)	
Tirasemtiv 500 mg	52.8% (66/125)	
Tirasemtiv (All)	45.9% (173/377)	
Ozanezumab NCT01753076 (DB 48-week)	30.3% (46/152)	27.1% (41/151)

DB = Double blind protocol period. OLE = Open label extension. (a) Normal Progressors (primary efficacy population). (b) Of patients completing the DB period, 2 patients in the edaravone group and 2 patients in the placebo group did not participate in the OLE.

Argument 4.2: mLOCF treatment of missing data for change of ALSFRS was the primary analysis but Applicant always recognized that this is the sensitivity analysis non LOCF that are supportive for registration

The Applicant did not argue that the mLOCF method was the most appropriate method to address missing data.

mLOCF method was the preplanned method for primary analysis and it the study was positive based on this method.

Various sensitivity analyses were implemented using methodologies recommended by the Rapporteurs.

What makes the results robust is that these analyses were convergent, both in term of statistical significance and treatment effect.

Argument 4.3: Among sensitivity analysis, cluster imputation, pre planned, and JTR based on discontinuation due to lack of efficacy and toxicity are demonstrative

- Preplanned cluster-based imputation analysis was positive

Cluster based imputation method imputed score at Week 48 based on last non-missing ALSFRS-R, plus average increments from Week 4 to Week 48 for all patients in that cluster with non-missing data from Week 4 to Week 48.

- Preplanned clusters

Two clusters were formed based on Site of Onset at baseline: Bulbar and Spinal.

Region was split between Western European and Canada (Italy, Netherlands, Portugal, Spain, Canada) and Rest of the World (Greece, Slovakia, Argentina, Mexico). Treatments groups also formed another level of clustering. The flow-chart given below details the formation of clusters.

Progression at baseline was taken into account in the protocol by splitting the normal progressors from Faster Progressors and therefore not further used for clustering.

- Justification for clustering

Patients with site of onset Bulbar at baseline are known to progress faster than spinal [Moura 2015]. Therefore, these patients belong to same cluster of faster progressing patients. All Spinal patients belonged to the cluster of slower progressors. Progression at baseline was considered in the protocol by splitting the normal progressors from Faster Progressors.

Rule 6 cluster imputation method was based on EMA guidance (EMA/CPMP/EWP/1776/99 Rev. 1): *Other simple approaches for single imputation of missing data are to replace the unobserved measurements by values derived from other sources. Possible sources include information from the same subject collected before withdrawal, from other subjects with similar baseline characteristics, a predicted value from an empirically developed model or historical data.*

- Results of analysis

The results for sensitivity analysis by Cluster based imputation is mean LS= 3.01; p-value = 0.0176, consistent with the primary analysis.

Table 114: Primary analysis population (M4.5 mg/kg/day vs placebo) – Rule 6 cluster-based imputation

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	113	-13.9611	3.01 [0.5306;5.4942]	0.0176
Masitinib 4.5	105	-10.9487		

model based on post baseline data as per sap

- JTR analysis requested by EMA was positive

We used Multiple Imputation with Jump to Reference for MNAR data. Expert working group of statisticians from London School of Hygiene and Tropical Medicine developed set of macros for this approach.

Referenced-Based Multiple imputation (RBMI) using JTR for reasons of discontinuation due to lack of efficacy or any adverse event (related or not) showed a significant (p=0.0387) advantage of Masitinib 4.5 of 2.80 ALSFRS-R points.

Table 115: AB10015 - NP - Masitinib 4.5 mg/kg/day - Primary endpoint Multiple Imputation Jump to Reference

JTR analysis	**JTR MI (Normal)**		
	Estimate	**95% confidence interval**	**p-value**
Lack of efficacy and Toxicity	2.80	[0.14; 5.46]	0.0387

Argument 4.4: In the JTR analysis, imputation of missing data after discontinuations for other reasons than lack of efficacy or toxicity did not rely on mLOCF approach

In the JTR analysis, imputation of missing data after discontinuations for other reasons than lack of efficacy or toxicity relied on copying increment from "similar" patients, also named cluster based imputation.

A detailed description of the statistical methods used for this cluster based imputation is described in SAP version 1.0 dated 16 March 2017, pages 11 to13.

The Imputed score at week 48 missing data after discontinuations for other reasons than lack of efficacy or toxicity is equal to: Last non-missing ALSFRS score + average increment, from week 4 to week 48, of all the patients in the cluster with non-missing compliant data from week 4 to week 48.

Argument 4.5: Reasons of discontinuation has been recorded in the eCRF by investigators. In case of multiple reasons recorded a central algorithm defined in the sap was used to define main reason

Reasons for discontinuation were documented in the eCRF and classification MNAR versus MAR was prespecified in the SAP before unblinding.

All reasons of discontinuation were assessed by investigator in the eCRF prior to unblinding.

Additionally, investigators made comments in the eCRF that were used to precise the main reason of discontinuation.

An algorithm encompassing data available in the eCRF was programmed to derive a single main reason for discontinuation.

This was done before database lock. This algorithm is available.

The reasons of discontinuations were classified between MNAR and MAR in the SAP prior to unblinding.

This classification was conventional with reasons MNAR being discontinuation for lack of efficacy or toxicity related or not and others being considered at random.

As stated by Kenward (Controlled multiple imputation methods for sensitivity analyses in longitudinal clinical trials with dropout and protocol deviation, Clinical Trial Methodology), considering all missing data as MNAR is extreme and may be seen as a worst-case scenario that in practice may be more relevant for treatments with only short-term effect.

Table 116: AB10015 - NP - Reasons of premature discontinuation

Type	Cause of discontinuation	Placebo N=113 n (%)	Masitinib 4.5 N=105 n (%)
MNAR	**ALL**	**10 (8.8)**	**24 (22.9)**
	AE Related	1 (0.9)	11 (10.5)
	Lack of Efficacy	9 (8.0)	13 (12.4)
Travel	**ALL**	**6 (5.3)**	**3 (2.9)**
MAR	**ALL**	**14 (12.4)**	**5 (4.8)**
	Cancer not related	2 (1.8)	1 (1.0)
	Death	7 (6.2)	2 (1.9)
	Non compliance (1)	0	2 (1.9)
	Procedure (2)	2 (1.8)	0
	Prohibited Concomitant treatment (3	1 (0.9)	0
	Protocol Deviation (4)	2 (1.8)	0

(1) Non-compliance means not compliant to the treatment
(2) Procedure means fed up with procedures of the protocol.
(3) Prohibited concomitant treatment means use of prohibited concomitant treatment not related to ALS
(4) Protocol Deviations means deviations to the eligibility criteria

As described in the table above, there was 22.9% of patients with discontinuations classified as MNAR in the masitinib group and 7.6% of patients with discontinuation classified as MAR (including 2.9% for travel), meaning that the majority of discontinuations were considered MNAR.

For placebo, this was the opposite, the discontinuation not missing at random represents 8.8% of the patients in the placebo group while the discontinuations considered missing at random represents 17.7% of the patients in the placebo group.

The difference in percentage of discontinuation at random comes from death because there were more deaths in the placebo group, which was classified as not related to treatment by the investigator.

Reviewers challenged one reason, which is travel.

Discontinuation due to travel encompassed patients who moved to another city but also patients who cannot travel to the hospital anymore, which could be confounded with lack of efficacy.

The sensitivity analysis presented in the next section shows that classifying travels as MNAR has no impact on the analysis of the primary endpoint.

Argument 4.6: EMA argument that only JTR with penalty on all discontinuation is demonstrative is "extreme" and not realistic

'Full penalty of all discontinuation' analysis used Jump to Reference (JTR) for the imputation of all missing data whatever the reason for discontinuation. This approach represents the worst-case scenario. Indeed, the seminal paper in which Carpenter and colleagues introduced referenced-based imputation approaches, described the JTR approach as follows: *"Such a change may be seen as extreme, and choosing the reference group to be the control group might be used as a* ***worst-case scenario*** *in terms of reducing any treatment effect since withdrawn patients on active will lose the effect of their period on treatment"* [Carpenter 2013].

Besides, the Jump to Reference imputation method assumes that as soon as a patient from the active arm discontinues the treatment, the mean distribution of his responses becomes identical to that of the reference arm. This assumption is adequately suited in the case of a purely symptomatic treatment, which effect disappears shortly following discontinuation.

Argument 4.7: The Applicant showed that best fit model validates the covariates lack of efficacy and toxicity among all reasons of discontinuations

CHMP says that no covariate analysis has been shown supporting the choice of discontinuation. An ex-post analysis shows that the best fit is obtained with MNAR being lack of efficacy or toxicity.

The selection of MNAR and MAR is based on clinical judgment and has been validated by predictive and covariate modeling. Additionally, classification was performed before unblinding and documented in the SAP. Our clinical approach is based on the nature of the dropout reasons and the observed data patterns.

Our model data used logistic regression analysis comparing different reasons for discontinuation in a stepwise manner with covariates. The inclusion of covariates significantly improved model fit, particularly in cases where dropout reasons are linked to treatment efficacy or toxicity (All adverse events). the Below tables compare the AIC, SC, and -2 Log L values for the various combinations of reasons for discontinuation.

Table 117 : Model with intercept and covariates

Reason for discontinuation	AIC	SC	-2 Log L
Lack of Efficacy/Toxicity	361.573	385.385	349.573
Lack of Efficacy/Toxicity/Lost to Follow-up	364.578	388.39	352.578
Lack of Efficacy/Toxicity/Lost to Follow-up/Non compliance	376.694	400.506	364.694
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel	401.053	424.865	389.053
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure	406.06	429.873	394.06
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death	443.974	467.786	431.974

Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death/Protocol Deviation	448.052	471.865	436.052
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death/Protocol Deviation/Cancer not related	455.723	479.536	443.723
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death/Protocol Deviation/Cancer not related/Prohibited Concomitant treatment	458.597	482.409	446.597

Table 118: Model with intercept only

Reason for discontinuation	AIC	SC	-2 Log L
Lack of Efficacy/Toxicity	375.497	379.466	373.497
Lack of Efficacy/Toxicity/Lost to Follow-up	378.458	382.426	376.458
Lack of Efficacy/Toxicity/Lost to Follow-up/Non compliance	392.76	396.728	390.76
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel	423.883	427.852	421.883
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure	430.998	434.967	428.998
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death	479.186	483.155	477.186
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death/Protocol Deviation	485.8	489.769	483.8
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death/Protocol Deviation/Cancer not related	490.509	494.477	488.509
Lack of Efficacy/Toxicity/Lost to Follow-up/Non-compliance/Travel/Procedure/Death/Protocol Deviation/Cancer not related/Prohibited Concomitant treatment	495.005	498.973	493.005

Argument 4.8: Full JTR has P value of 0.07 which exhibits a trend towards benefit

Still under this extreme scenario, this analysis shows a 2.31 benefit favouring Masitinib 4.5 over active control, that shortly fails to reach the conventional statistical significance threshold of 0.05 (p=0.0678). Note that the study was not powered for such a "worst-case" analysis, yielding still a clinically relevant treatment effect of 2.31, but smaller than the 3.3 effect the study was powered to detect.

The observed p=0.0678 in such a penalised analysis should be considered as indicative of an effect.

Table 119: AB10015 - NP - Masitinib 4.5 mg/kg/day - Primary endpoint Multiple Imputation Jump to Reference

JTR analysis	**JTR MI (Normal)**		
	Estimate	**95% confidence interval**	**p-value**
Full placebo imputation	2.31	[-0.17;4.80]	0.0678

Argument 4.9: CHMP noted that travel as not at random is debatable. Integrating travel in the reasons not at random does not change outcome that remains significant

Travel could be challenged as lack of efficacy.

As requested by the Rapporteurs, AB Science added travel as MNAR (i.e. interpreted as lack of efficacy).

This analysis showed a significant (p=0.0372) advantage of Masitinib 4.5 of 2.84 ALSFRS-R points.

Table 120: AB10015 - NP - Masitinib 4.5 mg/kg/day - Primary endpoint Multiple Imputation Jump to Reference

JTR analysis	JTR MI (Normal)		
	Estimate	95% confidence interval	p-value
Lack of efficacy and Toxicity and Travel	2.84	[0.17;5.51]	0.0372

Argument 4.10: Other MAR data not at random reasons are cancer not related to treatment, violation of eligibility criteria and non-compliance to treatment other than for lack of efficacy reason or toxicity

MAR data are Cancer not related (n=3), Non-compliance (meaning not compliant to the treatment, n=2), Procedure (meaning fed up with procedures of the protocol, n=2), Prohibited Concomitant treatment (meaning use of prohibited concomitant treatment not related to ALS, n=1), and Protocol Deviations (meaning deviations to the eligibility criteria, n=2).

These reasons for discontinuation were documented in the eCRF and MAR classification was prespecified in the SAP before unblinding.

These reasons for discontinuation can reasonably be considered at random events.

Argument 4.11: CHMP recommended in previous application of masitinib for conditional approval two methods, Tipping on full JTR which if above 75% was assessed as demonstrative and CIR which assumes progressive return to reference. Both analysis show benefit in favor of masitinib

- Tipping point analysis

As per recommendation of EMA Scientific Advice Working Party (SAWP) on 4 September 2018, as part of the protocol assistance procedure for the design of the new phase 3 study, the SAWP indicated "*a tipping point analysis is a valid approach to handle missing data*".

The tipping point analysis applies a penalty on all reasons of discontinuation.

Its results show the robustness of the findings with the tipping point corresponding to a 76% penalty on Masitinib effect.

Table 121: Tipping point 76% penalty all reasons

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
Placebo	113	- 14.0597	2.48 [0.0024;4.959]	0.0498
Masitinib 4.5	105	- 11.5790		

Model based on post baseline data as per sap

This 76% penalty corresponds to the assumption that patients discontinuing from masitinib would have experienced on average only 24% of the mean masitinib treatment-effect, while patients discontinued from the reference arm would have experienced the same deterioration as those completing the study in the reference arm.

This level of penalty was considered adequate by the CHMP in the former assessment of masitinib application (EMEA/H/C/4398, D180 JAR). Indeed, the following question was stated "*Rule #7 covers the lack of efficacy variability but not toxicity. Setting 76% penalty for lack of efficacy is within what would be empirically expected, but is a fair approach to the primary endpoint. It should also be applied to all*

key endpoints."

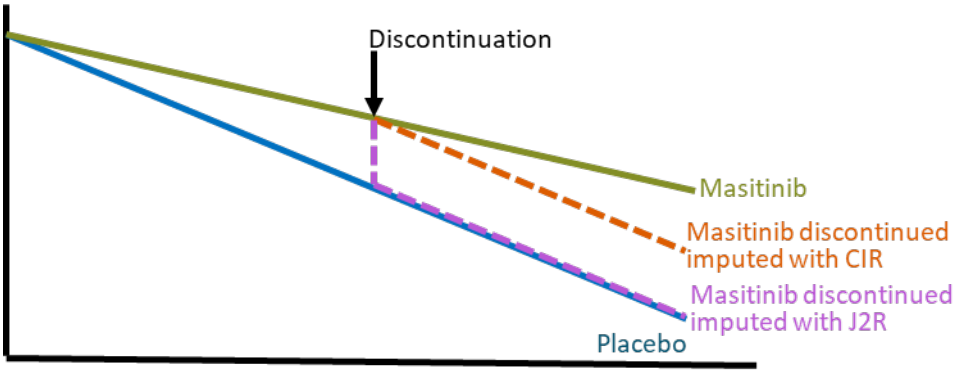
As a matter of fact, AB Science presented tipping point analysis for ALSAQ40 and FVC endpoints. On ALSAQ40, even with a penalty of 100%, Masitinib treatment effect was significantly better than placebo (Diff of means = -5.26 [-10.36; -0.15], p=0.0437). On FVC, with a penalty of 93%, Masitinib treatment effect was significantly better than placebo (Diff of means = 6.10 [0.01; 12.20], p=0.0497).

- Copy Increment in Reference

In the case of ALS, a progressively deteriorating disease, and taking into account the expected mechanism of action of Masitinib that is to slow down the deteriorative process, it is unlikely that a patient discontinuing Masitinib will abruptly "jump" back to the mean effect of the reference arm.

It is much more likely that the deterioration speed after discontinuation would become similar to that of the reference arm, while the patient would still benefit from the initial slower deterioration. The "Copy Increments in Reference" (CIR) imputation method from Carpenter would be more suitable in such a case [Carpenter 2013].

Figure 11: Schematic representation of J2R and CIR



CHMP recommended CIR in previous assessment (EMEA/H/C/4398, D150 JAR)

Therefore, we performed a new *post hoc* analysis using CIR imputation for all missing data whatever the reason for dropout. The results are presented in the table below:

Table 122: Normal Progressor Masitinib 4.5 mg/kg/day – CIR imputation, 100% penalty for all reasons

Treatment group	N	Estimate	[95% confidence interval]	p-value
Placebo	113	2.67	[0.03;5.32]	0.0477
Masitinib 4.5	105			

Model based on post baseline data as per sap

This "Full penalty on all discontinuations" using "Copy Increments in Reference" (CIR) imputation shows a statistically significant (p=0.0477) 2.67 benefit favouring Masitinib 4.5 over active control.

Argument 4.12: CHMP rejected the two previous recommendations justifying this was not done in the same context, whereas it is exactly in the same context

The recommendations expressed by the CHMP, regarding tipping (SAWP dated 4 September 2018 and EMEA/H/C/4398, D150 JAR) and CIR(EMEA/H/C/4398, D150 JAR) concerned the analysis of AB10015 study and the protocol for the phase 3 confirmatory study.

AB Science respectfully disagree with the position that these recommendations applied to a different

context.

As a matter of fact, in a different context, namely the assessment of Albrioza CMA (EMA/CHMP/487533/2023), the CHMP reiterated the same recommendations, stating that "*several approaches would be possible (i.e. jump to reference, copy reference, copy increments in reference…)*".

Argument 4.13: CAFS show a trend toward benefit of p=0.07

Study AB10015 was not designed to show any significant effect on CAFS, which was pre-planned as a secondary endpoint.

Still, there was a near significant effect (p = 0.0776; difference = 14.95) observed between masitinib (4.5 mg/kg/day) and active control for CAFS score in the Normal Progressor population, supporting the primary analysis. This endpoint is also consistent with the PFS data and supports the benefit when factoring survival.

Table 123: AB10015 – Normal Progressor - CAFS score – Masitinib 4.5 mg/kg/day

Treatment group	N	Mean Score	Difference of means	p-value
Active control	111	100.77	14.95	0.0776
Masitinib 4.5 + R	104	115.72		

A p-value of 0.078, approaching the conventionally statistically significant outcome of 5%, could represent an acceptable level, considering comments made by an ALS advocacy group.

The benefit/risk trade-offs in light of the severity and rapid progression of ALS coupled with the lack of effective treatments has been addressed in draft Guidance for Industry Drug Development for Amyotrophic Lateral Sclerosis [FDA/ALSA Guidance 2016] [FDA Guidance 2017]. This guidance highlights that there is a demonstrated appetite for risk of the patient population and the fact that roughly half of all patients will die within 2 years of diagnosis without the discovery of a new treatment justifies an appropriate choice of statistical standard [FDA/ALSA Guidance 2016]. ALS patients are reported to be more willing to take risks than some other populations with serious illnesses. Of the oncology patients surveyed, 83% would participate in a clinical study compared with 96% of patients with ALS. ALS patients are also reported to be less concerned regarding the possibility of adverse effects than surveyed oncology patients (22% versus 45%) [FDA Guidance 2017].

Of note, this guidance indicates that given their prognosis in the absence of treatment, some people with ALS may be willing to accept somewhat more uncertainty than 5% regarding whether the observations from a trial of a particular intervention are likely entirely due to chance, especially if there are no serious safety concerns associated with the intervention under study [FDA/ALSA Guidance 2016].

Argument 4.14: Secondary variables calculated with non LOCF methods show benefit on ALSAQ or trend towards benefit on FVC

- Significant ALSAQ40 benefit based on conservative imputation methods

The improvement in decline in ALSFRS-R did not come at the expense of quality of life.

Indeed, there was a statistically significant benefit on quality of life (measured by ALSAQ40), calculated based on non LOCF method.

Table 124: Normal Progressor Masitinib 4.5 mg/kg/day –ALSAQ-40 analysis

Analysis Method	Difference, [95% CI]	p-Value
Primary analysis - mLOCF	-7.76 [-13.45;-2.06]	0.0078

MI	-7.27 [-13.18; -1.37]	0.0161
MI+JTR	-5.99 [-11.55;-0.44]	0.0343
CIR	-6.04 [-11.51;-0.57]	0.0305

- Trend towards benefit for FVC based on conservative imputation methods

The clinical functional benefit was supported by a trend towards benefit on respiratory function (measure by FVC), calculated based on non LOCF method recommended for primary endpoint.

Table 125: Normal Progressor Masitinib 4.5 mg/kg/day –FVC analysis

Analysis Method	**Difference, [95% CI]**	**p-Value**
Primary analysis–- mLOCF	7.54 [0.76;14.32]	0.0296
MI	6.43 [-0.71; 13.57]	0.0772
MI+JTR	5.85 [-1.11;12.81]	0.0993
CIR	5.85 [-0.98;12.67]	0.0931

Argument 4.15: Secondary analysis were not controlled for alpha but all variables except TFS showed benefit of trends towards benefit, supporting evidence of efficacy

Table 126: Normal Progressor Masitinib 4.5 mg/kg/day –Overview of main efficacy endpoints

Differential treatment effect (M4.5 vs placebo)		**Primary analysis population (Normal Progressors)**
ΔALSFRS-R (CIR)	Diff. of mean	2.68
	p-value	0.0462
CAFS	Relative benefit	14.8%
	P-value	0.0776
ALSAQ-40 (CIR)	Diff. of mean	-6.04
	p-value	0.0305
FVC (CIR)	Diff. of mean	5.85
	p-value	0.0931
Median PFS	Gain	+ 4 months
	Median [95% CI]	20 [14; 30] vs 16 [11; 19]
	p-value log rank	0.0159
Median OS (Long-term) (censoring of placebo at time of switch to masitinib)	Gain	+ 6 months
	Median [95% CI]	46 [33; 69] vs 40 [30; 49]
	p-value log rank	0.0761

Argument 4.16: Time to event PFS, pre planned in SAP, showed benefit

EMA guidance on ALS requires for registration that in addition to a significant effect on ALSFRS, there is at least a trend on a time to event endpoint.

Choice of a 9-point cut-off for progression was based on information from the scientific literature [Gordon 2007]. This research suggests that a 9-point decline in ALSFRS-R represents a clinically meaningful change in functionality. Hence, the 9-point threshold is appropriate for two reasons:

- Provides a well-matched and sensitive endpoint for detecting treatment-effect over a 48-week period (with an anticipated active control decline of around 1 point/month). For example,

thresholds of 6 or 12 points are likely to be insensitive because the survival-to-event condition is, respectively, reached too soon with loss of sensitivity or is not reached by a sufficient number of patients in the treatment-arm.

- Represents a clinically meaningful change in functionality reported to be discernible by patients [Gordon, 2007].

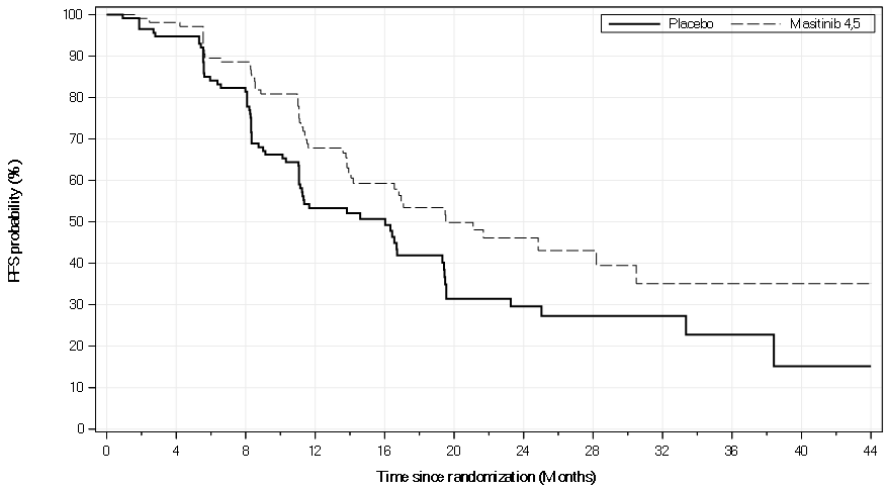
Study AB10015 showed a significant improvement in PFS (+4 months, P=0.0159) defined as the earliest of a decline of 9 points in ALSFRS-R or death.

Table 127: Normal Progressor Masitinib 4.5 mg/kg/day – PFS

Treatment group	Total	Median months [95% CI]	Wilcoxon p-value
Placebo	113	16 [11; 19]	0.0159
Masitinib 4.5	105	20 [14; 30]	

model based on post baseline data as per sap

Figure 12: Normal Progressors – KM analysis of PFS - Masitinib 4.5 mg vs Placebo



Argument 4.17: Tracheotomy, ventilation and gastrostomy occurred mainly after progression, making PFS robust

To make sure that PFS was not potentially biased by ventilation and gastrostomy and tracheostomy, we looked at the occurrence of those events as compared to progression.

Table 128: Summary of Interventions with respect to time of progression

Event Type	Treatment	Total(n)	(n%)< Progression	(n%) >= Progression
Tracheostomy	Placebo (N=114)	5	0	5(100.0)
	Masitinib 4.5 (N=106)	11	0	11(100.0)
Ventilator	Placebo (N=114)	21	0	21(100.0)
	Masitinib 4.5 (N=106)	24	2(8.3)	22(91.7)
Gastrostomy	Placebo (N=114)	20	3(15.0)	17(85.0)
	Masitinib 4.5 (N=106)	22	6(27.3)	16(72.7)

As seen in table above, all tracheotomy and most of the ventilation or gastrostomy events occurred after progression which is an earlier event.

Argument 4.18: When accounting for progression, tracheotomy, ventilation and gastrostomy or death in EFS, EFS showed benefit

Even when integrating those events, in an Event Free Survival (EFS), with Event being the earlier event between progression, tracheotomy, ventilation or gastrostomy, the EFS test remains statistically significant (p=0.01) showing a benefit of 3 months in median for masitinib as presented below.

Table 129: Analysis of PTVGFS - Masitinib 4.5 mg/kg/day –Normal Progressor

Treatment group	Total	No. of Events	Median [95% CI]	Wilcoxon p-value
Placebo	113	76	11 [10; 17]	
Masitinib 4.5	105	66	14 [12; 20]	0.0162

PTVGFS: Progressor, Tracheostomy, Ventilator, Gastrostomy free survival

Table 130: Analysis of PTVGFS – Masitinib 4.5 mg/kg/day – mITT Population (Normal Progressor prior to any loss of function)

Treatment group	Total	No. of Events	Median [95% CI]	Wilcoxon p-value
Placebo	104	69	11 [10; 19]	0.0106
Masitinib 4.5	84	47	17 [14; 25]	

PTVGFS: Progressor, Tracheostomy, Ventilator, Gastrostomy free survival

EFS in the subgroup described in the next section, normal progressors prior to any loss of function showed an even larger benefit of 6 months in median (p=0.0106)

Argument 4.19: Survival of placebo who switched to masitinib in Open Label Extension showed benefit versus the ones who did not switch

As requested by the Rapporteur, new long-term OS analysis was performed, censoring placebo patients at the time they switched to masitinib treatment in the NPP program.

This retreatment is essential because OS was significantly improved for placebo patients who switched to masitinib 4.5 mg/kg/day as compared with placebo patients who did not switch.

Table 131: Normal Progressor- Analysis of overall survival in the NPP program (placebo switch vs no switch to masitinib)

Treatment group	Total	No. of Events	Median [95% CI]	Log Rank
Placebo	48	20	62 [49; NE]	0.0367
Masitinib 4.5	23	10	69 [44; NE]	

Argument 4.20: Censoring placebo who switched to masitinib at the time of the switch showed trend towards benefit of OS from randomization

OS showed a trend in the population normal progressor with the censoring of placebo when they switched to masitinib in the open label extension, since this switch provided a significant benefit.

Table 132: Normal Progressor- Masitinib 4.5 mg/kg/day – OS (censoring of placebo patients at time of switch to masitinib)

Treatment group	Total	No. of Events	Median [95% CI]	Log Rank
Placebo	114	63	40 [30; 49]	0.0761
Masitinib 4.5	106	60	46 [33; 69]	

Argument 4.21: Strength was not measured but according to guideline this is a necessity only for treatment which are purely symptomatic, whereas masitinib targeting mast cells and microglia acts as a disease modifying

As per EMA Guidance on ALS, muscle strength is a required efficacy endpoint for symptomatic treatment,

for disease modifying treatment like masitinib.

For disease modifying treatment, EMA Guidance required either time to death including other end of life measures that prolong life or function, or both, or alternatively, time-to-event endpoint with the event defined as death or a predefined deterioration on the ALSFRS-R scale, or CAFS.

In addition, the EMA guidance became effective after the initiation of AB10015 study.

EMA Scientific advice for phase 3 confirmatory study (EMA/CHMP/SAWP/596883/2018) was first provided in 2018. AB Science diligently implemented the recommendation from the CHMP regarding measuring muscle strength.

However, this advice was provided after the completion of AB10015 study.

Argument 4.22: TFS showed no benefit because Tracheostomy was not measured systematically after discontinuation and because there were several biased against masitinib

CHMP has a concern that TFS shows no benefit. However, the following considerations need to be taken into account:

- The number of tracheostomies are limited and tracheostomy is known to be biased due to personal decision or cultural factors.

- Tracheotomy has been followed until discontinuation. Long-term follow-up of tracheostomy was not planned and has not therefore been monitored in the same manner as OS was, the latter of which was followed for 75.6 months.

- The rate of tracheostomy has been impacted by multiple disbalances against masitinib, in particular by a greater proportion of patients with a loss of function at baseline (i.e., very severe ALS), a cohort with longer duration of disease at baseline, and also a cohort that had a longer treatment duration in the extension period.

- All tracheotomy occurred after the protocol defined progression of ALSFRS-R and PFS was statistically significant when integrating any earlier event than tracheotomy.

- Potential confounding factors such as ventilation, gastrostomy and tracheostomy events, have been assessed and had no impact on PFS.

- Ventilation and gastrostomy occurred mostly after ALSFRS-R progression and even when taken into account via an event free survival (EFS) analysis, with progression, tracheostomy, ventilation gastrostomy or death, the EFS showed a statistically significant benefit in favor of masitinib.

- No drug registered for treatment of ALS or investigational drugs for ALS have demonstrated survival benefit with the exception of riluzole, which is used in combination with masitinib.

■ Tracheostomies are limited up to week 48 and tracheostomy events in extension are impacted by several imbalances in disfavor of masitinib, more very severe patients, longer duration in extension, longer time from disease or time from onset to randomization

There was no statistically significant difference (p=0.7382) observed between masitinib (4.5 mg/kg/day) and placebo for time to tracheostomy free survival (TFS) in the Normal Progressor population.

Table 133: Analysis of TFS–- Masitinib 4.5 mg/kg/day – Normal Progressor

Treatment group	**Total**	**No. of Events**	**Percentage censored**	**Median [95% CI]**	**p-value using Wilcoxon test**
Placebo	113	34	69.9	32 [23; .]	0.7382
Masitinib 4.5 + R	105	35	66.7	30 [22; .]	

During the main study period, in there were few (4) tracheostomy events the primary analysis population, 3 events in the masitinib 4.5 mg/kg/arm versus 1 in the placebo arm.

During the extension period, there were 12 tracheostomy events the primary analysis population, 8 events in the masitinib 4.5 mg/kg/arm versus 4 in the placebo arm.

Table 134: Summary of Tracheotomy patients in Normal progressor

	Masitinib 4.5 mg/kg				**Placebo**			
Cumulative Events	All	Very severe ALS	Severe ALS	Moderate ALS	All	Very severe ALS	Severe ALS	Moderate ALS
Week 48	**3**	**0**	**2**	**1**	**1**	**0**	**0**	**1**
Extension	8	3	3	2	4	1	2	1
Total	11	3	5	3	5	1	2	2

This disbalance was essentially visible in the extension phase between the two treatment arms

There were multiple reasons to explain the disbalance in tracheotomy:

- Time under treatment in extension which we know is not the same for masitinib 4.5mg/kg, 25 weeks in median, versus 15 weeks for placebo.

- Severity of patients at baseline.

    - there is a disbalance of number of very severe patients (20% of very severe patients with masitinib 4.5mg/kg versus 9% with placebo),

    - but also, a disbalance against masitinib in number of functions lost within the very severe patients

    - and also, a disbalance against masitinib in time from diagnostic to baseline or time from onset of symptoms to baseline

    - and also a disbalance against masitinib in median duration of treatment in the extension phase

    - despite these disbalances, tracheotomy occurred later and death after tracheotomy also

In addition, the study was not designed to record the tracheostomy as a long term efficacy endpoint.

By contrast, survival has been followed as a key secondary endpoint after discontinuation and very long term and all data have been monitored. As such, when it comes to analyzing the long-term time to event time point that includes a large part of the data post discontinuation, survival is a more robust measure, based on the design of the protocol.

- Imbalance at baseline that impacted tracheotomy

TFS has been impacted by multiple imbalances that could affect the masitinib arms, in particular the masitinib 4.5 mg/kg/day treatment arm.

i. Greater severity at baseline in patients under masitinib group 4.5 mg/kg/day as compared to patients in placebo group

Table 135: Disposition of patients by ALS severity status at baseline

	Placebo		Masitinib 4.5	
Severity Status	N	%	N	%
Moderate ALS	62	54.4%	45	42.4%
Severe ALS	42	36.8%	40	37.7%
Very Severe ALS	10	8.8%	21	19.8%
Total	114	100%	106	100%

- more very severe patients (score of zero on any ALSFSR-R score) being randomized in the masitinib arm (19.8%) than in the control arm (8.8%).

- The severity in this subset of very severe patients was higher in the masitinib arm, with a disbalance in favour of placebo in terms of number of items with ALSFSR-R score=zero (see response to MO2B).

ii. Longer median duration of treatment in the extension phase

The number of tracheotomy events that occurred in the extension phase were also impacted by a longer duration of treatment in the masitinib arm relative to the placebo arm, with a median of 25 versus 15 weeks, respectively.

Table 136: Summary of time on treatment (extension period) according to treatment arm

	Placebo	Masitinib 4.5
Time on treatment (weeks)		
n	80	73
Median	15.4	25.0

iii. Median time to tracheostomy free was extended in patients from the masitinib 4.5 mg/kg/day arm as compared with the placebo arm, despite the fact that patients from the masitinib 4.5 mg/kg/day arm had a longer disease duration. Death occurred also later post tracheotomy with masitinib.

It is important to note that patients treated by masitinib 4.5 mg/kg/day underwent tracheostomy later than patients treated by placebo. The overall mean time to tracheostomy from symptoms onset was 28.5 versus 39.4 months for placebo and masitinib arms, respectively. This delay in tracheostomy was also seen in terms of overall mean time to tracheostomy from baseline; i.e., 24.7 versus 38.5 months, respectively. Furthermore, this masitinib related delay in tracheostomy was independent of baseline disease severity, as evidenced by it being seen across moderate, severe and very severe subgroups. Indeed, the largest difference was associated with the very severe subgroup, with a delay of approximately 10 months, despite the fact that their disease was already at an advanced stage at baseline and that there were more very severe patients in the masitinib arm than the placebo arm.

After tracheostomy, patients treated with masitinib 4.5 mg/kg/day survived longer than those treated with placebo, as evidenced by an overall mean time to death from tracheostomy of 24.7 versus 38.5 months for placebo and masitinib arms, respectively.

Table 137: Time to tracheostomy from onset and from baseline, time to death/last follow-up from tracheostomy (in months, population Normal Progressors)

Patients with tracheostomy	Placebo (n=5)	Masitinib 4.5 (n=11)
Mean time to tracheostomy from symptoms onset (months)		
Moderate	27.38 (±2.21)	30.37 (±9.69)
Severe	25.74 (±3.74)	37.20 (±13.17)
Very Severe	36.47 (± n/a)	46.06 (±21.95)
Mean time to tracheostomy from baseline (months)		
Moderate	15.44 (±10.27)	21.34 (±16.73)
Severe	12.07 (±0.67)	14.99 (±8.14)
Very Severe	12.91 (± n/a)	20.10 (±7.27)
Mean time to death/last follow-up tracheostomy (months)		
Moderate	18.91 (±3.46)	44.46 (±13.69)
Severe	22.09 (±28.23)	38.23 (±26.05)
Very Severe	41.56 (±n/a)	32.88 (±29.74)
Total mean time to tracheostomy from symptoms onset	28.54 (±5.0)	39.39 (±14.25)
Total mean time to tracheostomy from baseline	13.59 (±5.43)	18.11 (±10.11)
Total mean time to death from tracheostomy	24.71 (±17.13)	38.47 (±22.50)

n= number of tracheostomy. Values shown a Mean (± standard deviation)

- Other potential bias affecting TFS

In addition to the above factors, the TFS analysis may have been confounded by the fact that:

- Criteria for tracheostomy and continuous assisted ventilation dependence were not pre-specified or standardized in the protocol and furthermore, the study enrolled patients from multiple countries where the standard of care for end-of-life situations may vary.

- Tracheostomy is invasive is highly subject to patient personal choice.

- The use of tracheostomy in ALS patients is therefore controversial and varies from one country to another. In Switzerland, for example, it remains used only exceptionally.

Argument 4.23: Objection regarding TFS was considered resolved by the CHMP

During the procedure, that Rapporteurs had the following question (D120 - Q119)

SAP includes secondary endpoint "Survival defined as the time from randomization to the date of documented death or first tracheotomy" which is not presented elsewhere. The Applicant is asked to clarify this and present results for this endpoint.

Data as reported in Section 4.22 above were presented to the Rapporteurs.

In the Rapporteurs Day 150 Joint Assessment Report, the CHMP concluded that the issued is resolved

Argument 4.24: OS was followed for the very long term and is a robust long term time to event measure

Because median OS analysis remains the gold standard for demonstration of a drug's therapeutic benefit in ALS, long-term OS assessment represents a valuable complement to the study's primary analysis.

All investigational sites from study AB10015 were contacted with a request for an update on each patient's vital (survival) status. Overall survival was defined as the time elapsed between randomization and death from any cause. Overall survival P values were calculated via the multivariate log-rank test using the covariates of age and ALSFRS-R score at randomization, site of onset (spinal versus bulbar), geographical region, and post-onset ALSFRS-R progression rate (ΔFS). All covariates were prespecified in the AB10015 protocol as randomization stratification factors [Mora 2020]. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated via the Cox proportional-hazards model using the abovementioned covariates.

Vital status (i.e., survival status of alive or dead, including date of death) of all patients originally randomized to study AB10015 was collected from each participating investigational site. As such, three patient groups were defined long-term high-dose (4.5 mg/kg/day) masitinib, long-term low-dose (3.0 mg/kg/day) masitinib, and long-term placebo. Long-term assessment for study AB10015 encompassed the prospectively declared 48-week treatment period with associated double-blind extension (commencing in April 2013 until data readout), and a post study (unblinded) follow-up period (from November 2017 until June 2020). Patients still alive at the time of analysis were censored at the date of last contact. 95% of patients had status verified <7 months prior to cut-off.

These entirely new long-term OS data is based on average follow-up of 75.6 months since diagnosis and 66.1 months since randomization and included cross-over from placebo to masitinib treatment.

Period (Start-End)	Week 48 LPLV Period (Apr 2013–Dec 2016)	Extension Period (Dec 2016–Nov 2017)	Cross-over Period (Nov 2017-June 2020)
Blinding status	Blinded	Blinded up to Apr 2017 Open label from Apr 2017	Open-label
M3.0	131*		30* **Enter NPP** 37* **No NPP (discontinue)**
M4.5	130*		29* **Enter NPP** 41* **No NPP (discontinue)**
Control	133*		25* **Cross-over to NPP** 53* **No NPP (discontinue)**

Argument 4.25: OS remains the gold standard and cannot be biased

In accordance with "Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS)" (EMA/531686/2015, Corr.1) *criteria for tracheostomy and continuous assisted ventilation dependence as a study endpoint event should be carefully pre-specified and standardised since patient management varies considerably between countries and regions. Where these endpoints are used, an additional analysis using only time to death as the endpoint should also be provided to allow evaluation of the consistency of the results*.

OS remains the gold standard variable in ALS. In study AB10015, OS was followed long term for 83.5 month from diagnosis.

Survival has been the only event that was followed post discontinuation and very long term.

Therefore, when it comes to a long-term analysis only OS can be used

Argument 4.26: Consistency between ALSFRS, PFS, and OS

Study AB10015 showed a robust consistency between the significant benefit on ALSFRS-R calculated with a non LOCF conservative methodology, the significant benefit in PFS which is unbiased and the trend towards benefit in OS which is the gold standard, in the primary population of the study, normal progressors.

These benefits did not come at the expense of toxicity since there was also a significant benefit in quality of life on ALSAQ using non LOCF methodology.

The consistency of the benefit on key variables is a justification in favor of the demonstration of efficacy.

Argument 4.27: There is no treatment that can extend life, investigational or registered, except riluzole which was given add on

Failure of numerous phase 2 or 3 programs in ALS have recently been reported, including confirmatory phase 3 studies of registered drugs such as Albrioza (Amylyx) and oral edaravone (Ferrer), as well as studies from investigational drugs such as TUDCA (the TUDCA-ALS consortium), reldesemtiv (Cytokinetics) and the RIPK1 inhibitor SAR443820 (Sanofi).

Tofersen is registered for use in SOD1 familial forms, which represent approximately 2% of patients.

For sporadic ALS, riluzole therefore remains the only reference treatment with a proven modest effect on survival and no effect on motor function, which is a key dysfunctional impairment in ALS.

Argument 4.28: The lag time of efficacy is compatible with masitinib MoA being a disease modifying

Published non-clinical data indicate that the reduction of CNS and PNS neuroinflammation of masitinib in ALS animal models is observed in few days or weeks after treatment onset [Trias 2020; Trias 2016]. However, one must consider that the final therapeutic effect of masitinib on ALS patients' neurological deficits is not only dependent on neuroinflammation, but rather on the preservation or repair of the anatomy and functionality of central and peripheral motor pathways.

Most motor neurons bear long myelinated axons that establish neuromuscular junctions (NMJ) to control skeletal muscle. In ALS, motor axons develop axonopathy in the CNS and PNS, followed by demyelination and accumulation of myelin debris. Any therapeutic agent that stops or reduces the inflammatory cellular microenvironment around the damaged motor neurons, is expected to take time to normalize the function of motor neuron cell bodies and subsequently improve the structure and physiology of motor axons. The length of time this takes can be significant.

Because masitinib ameliorates the neurodegenerative cellular microenvironment that surrounds motor neuron cell bodies and the peripheral projections, it is expected that the therapeutic effect on motor symptoms is observed after a period of several weeks or months.

Examples of similar delayed response to therapeutic agents, also referred to as 'therapeutic lag', is seen in the treatment of multiple sclerosis and depression.

- Roos and colleagues calculated the duration of therapeutic lag for numerous immunomodulatory therapies used in the treatment of multiple sclerosis (for example, alemtuzumab, natalizumab, mitoxantrone, rituximab, fingolimod, dimethyl fumarate, teriflunomide, and glatiramer acetate) [Roos 2020]. Results showed that the duration of therapeutic lag for relapses (defined as occurrence of new symptoms or the exacerbation of existing symptoms) ranged between 12 and 30 weeks, whereas the duration of therapeutic lag for disability progression (defined as 6-month confirmed EDSS progression) ranged between 30 and 70 weeks.

- In order to eliminate the effects of therapeutic lag, Kalincik and colleagues disregarded EDSS events within 6 months from treatment start for their study on MS prediction modelling [Kalincik 2022].

- Giovannoni and colleagues discuss the concept of a therapeutic lag in progressive MS being supported by the observation of randomised placebo-controlled study of interferon-beta-1b in primary progressive MS [Giovannoni 2017]. The authors state that 'therapeutic lag may manifest as a delay for a specific treatment in the slowing down, or a plateauing out, in the rate of progression in a particular pathway.

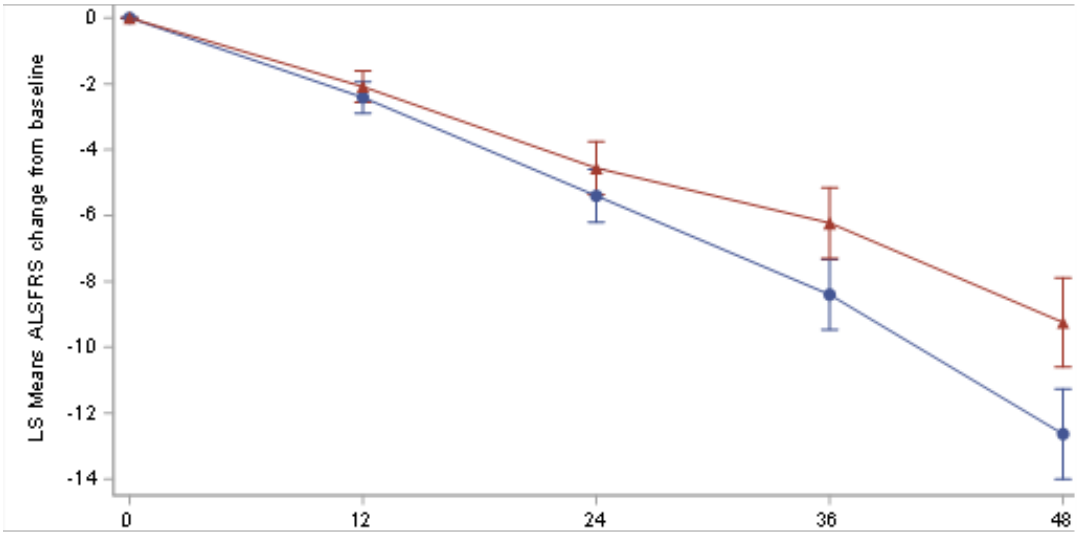
Argument 4.29: A lag time to detect a treatment effect in ALS is expected since ALSFRS is not a responsive endpoint to give a reliable result before week 24

A trend towards separation of the treatment-arms is evident as early as week-12, especially for the secondary endpoints, and becomes more apparent by week-24. The separation between treatment-arms is then maintained or continues to increase (as is the case for ALSFRS-R) through to the week-48 timepoint for all endpoints.

Gordon and colleagues have previous stipulated that "6 months are needed to detect changes in the ALSFRS-R because of variability, due principally to differing rates of progression among patients" [Gordon 2006].

This is therefore perfectly consistent with the treatment-effect of masitinib only clearly manifesting itself at week-24 of study AB10015.

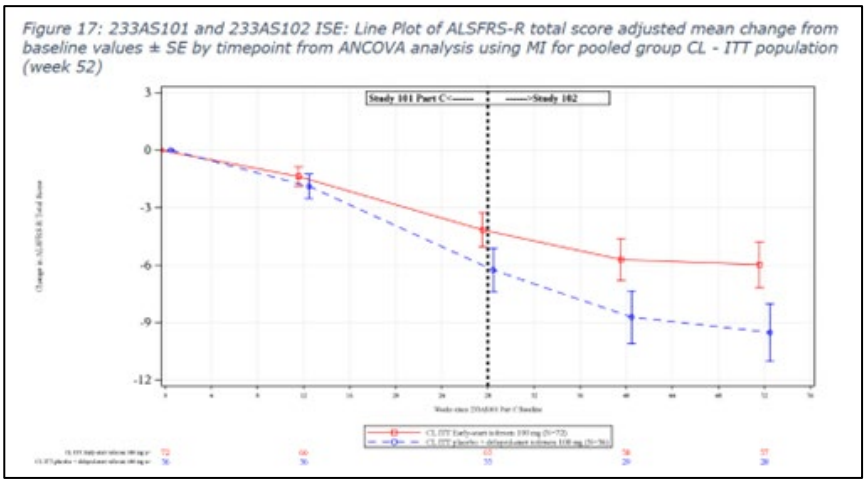
Figure 13: Time series plots of least-squares mean difference in ALSFRS-R from baseline in Normal Progressor patients receiving Masitinib AB Science 4.5 mg/kg/day versus placebo (primary efficacy population)



Reference

Argument 4.30: Qalsody exhibited similar lag time, if effective

Figure 17: 233AS101 and 233AS102 ISE: Line Plot of ALSFRS-R total score adjusted mean change from baseline values ± SE by timepoint from ANCOVA analysis using MI for pooled group CL - ITT population (week 52)



Source: EMA/276404/2024

Argument 4.31: The position adopted by the CHMP for Qalsody shows that full JTR is not the single and absolute requirement to be fulfilled since it failed for Qalsody

The position adopted by the CHMP for Qalsody shows that JTR is not the single and absolute requirement to be fulfilled.

Indeed, the EMA registered Qalsody with the EPAR showing that the JTR for the preplanned analysis had a p-value of 0.5, and a p-value of 0,2 when introducing *post hoc* the NfL biomarker covariate.

Qalsody showed no benefit in any efficacy variables at week 28.

Nevertheless, and despite these statistical results, the CHMP concluded that there was a benefit because NfL reduction has been considered predictive of a clinical benefit.

Argument 4.32: Other supportive evidences show a perceived strong efficacy of masitinib from practitioners having relevant clinical experience with masitinib in ALS patients

Two testimonies, based on real life evidence over a long period of time and numerous patients treated, show a perceived strong efficacy of masitinib on control of functional score and survival.

Argument 4.33: Support from patient associations

We wish to inform the Rapporteurs that EUpALS has close ties (including financial) with TRICALS, which is committed to other projects than masitinib clinical development. As such, we consider that there might be a potential conflict of interest and we recommend the Rapporteurs/ SAG to consult with (or to add in their consultation) other ALS patients associations or representatives, such as:

-ARSLAN (France)

-APELA (Portugal)

-ConALSncio (Italy)

-Post Fata Resurgo (Italy)

-ZsALSa (Czech Republic)

- EUpALS patients and carers expert board (PCEB).

4. The strategies to post hoc identify new target populations ("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version of 4.1) are considered as data driven decisions and are, therefore, not acceptable.

The Applicant presented first some statements included in section 2.6.6 of this CHMP AR.

The CHMP considers that the compelling evidence of efficacy on all clinically relevant endpoints including PFS and OS was not demonstrated. The long-term assessment of the available data encompassed five distinct periods. Notably, the categorization of patients into normal and fast progressions were conducted with third amendment, while the open label post study follow-up period from November 2017 until June 2020 was added as the fifth the amendment. During the open label period patients were followed for overall survival, however, the PFS and OS results generated in the open label conditions inherit potential biased information on survival events, because of impact of various factors, which occurred under unrandomized conditions (i.e. used medicines in the post pivotal study period, tracheostomy events, needs for the non-/invasive ventilation etc.). Therefore, the long-term survival data presented by the Applicant is derived from a highly selected patients' population defined *post hoc* therefore, can be considered only as descriptive not confirmatory of Masitinib AB Science efficacy in the proposed indication. Further, in order to address the concern of CHMP regarding an indication for ALS treatment that excludes fast progressors, the Applicant has presented a modified indication, based on up-dated efficacy and safety analyses, to the "treatment of ALS patients prior to any loss of function" (wherein loss of function is defined as a score of zero on any item of the ALSFRS-R). However, the strategies to *post hoc* identify new target populations ("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version of section 4.1 of the SmPC) are considered as data driven decisions and are, therefore, not acceptable. In the response, the Applicant has reiterated previously assessed data and justifications. The *post hoc* subgroup analysis may be performed at the initiative of the Applicant according to the guidelines EMA/CHMP/539146/2013. However, the guideline Scenario 2 criteria "*Replication of subgroup findings from other relevant trials or if not available the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally strong*" is considered not fulfilled, as the effect observed in the subgroup is not replicated across trials by the time of opinion.

AB Science Response

Argument 5.1: CHMP stated there is no new data but Applicant showed a major disbalance against masitinib with the subset of patients with at least one loss of function (20% vs 8%) and more functions lost in masitinib subset. This has not been taken into consideration so far, including in the CHMP final opinion

- The preplanned primary analysis population of Normal progressors was disbalanced in favour of the control arm

Indeed, upon further analysis, it appears that the preplanned primary analysis population of Normal progressors was disbalanced in favour of the control arm in a subset of patients with 'very severe' ALS (i.e. patients having at least a zero on any the 12 ALSFRS-R item).

- more very severe patients (score of zero on any ALSFSR-R score) being randomized in the masitinib arm (20%) than in the control arm (8%).

- The severity in this subset of very severe patients was higher in the masitinib arm, with a disbalance in favour of placebo in terms of number of items with ALSFSR-R score=zero

- This disbalance could occur because ALSFRS-R score was minimized but not stratified by category of severity

Table 138: Distribution of subset of very severe patients in primary analysis population

Population	Statistic	Placebo N=113 n (%)	Masitinib 3 mg N=110 n (%)	Masitinib 4.5 mg N=105 n (%)
Normal Progressor all patients	n (%)	113 (100)	110 (100)	105 (100)
Normal Progressor (Moderate/Severe ALS) patients	n (%)	104 (92)	94 (85.5)	84 (80)
Excluded patients (Very severe ALS) patients	n (%)	9 (8)	16 (15.5)	21 (20)
1 Question (item) with score 0	**n [Q]**	**8 [8]**	**10 [10]**	**10 [10]**
Within Bulbar subdimension	n [Q]	2 [1]	1 [1]	1 [1]
Within Fine motor subdimension	n [Q]	0	0	1 [1]
Within Gross motor subdimension	n [Q]	6 [1]	8 [1]	7 [1]
Within Respiratory subdimension	n [Q]	0	1 [1]	1 [1]
2 Questions (item) with score 0	**n [Q]**	**0**	**3 [6]**	**7 [10]**
Within Bulbar subdimension	n [Q]	0	0	1 [2]
Within Fine motor subdimension	n [Q]	0	3 [4]	2 [3]
Within Gross motor subdimension	n [Q]	0	2 [2]	3 [5]
Within Respiratory subdimension	n [Q]	0	0	
3 Questions (item) with score 0	**n [Q]**	**0**	**3 [9]**	**3 [9]**
Within Bulbar subdimension	n [Q]	0	1 [2]	0
Within Fine motor subdimension	n [Q]	0	3 [5]	3 [8]
Within Gross motor subdimension	n [Q]	0	1 [2]	1 [1]
Within Respiratory subdimension	n [Q]	0	0	0
4 Questions (item) with score 0	**n [Q]**	**1 [4]**	**0**	**1 [4]**
Within Bulbar subdimension	n [Q]	0	0	0
Within Fine motor subdimension	n [Q]	1 [2]	0	1 [2]
Within Gross motor subdimension	n [Q]	1 [2]	0	1 [2]
Within Respiratory subdimension	n [Q]	0	0	0

Note: The bracketed [Q] within the number represents the number of questions with scores, and some patients are very severe in more than one subdimension.

The efficacy profile of masitinib, as well as the safety profile of masitinib, are improved when analysed without this disbalanced subset of patients, as justified in the section below.

- When excluding this subset of very severe patients (i.e. score of 0 on at least one ALSFRS-R item), the baseline characteristics in the subgroup are balanced and unlikely to create a bias in favour of masitinib

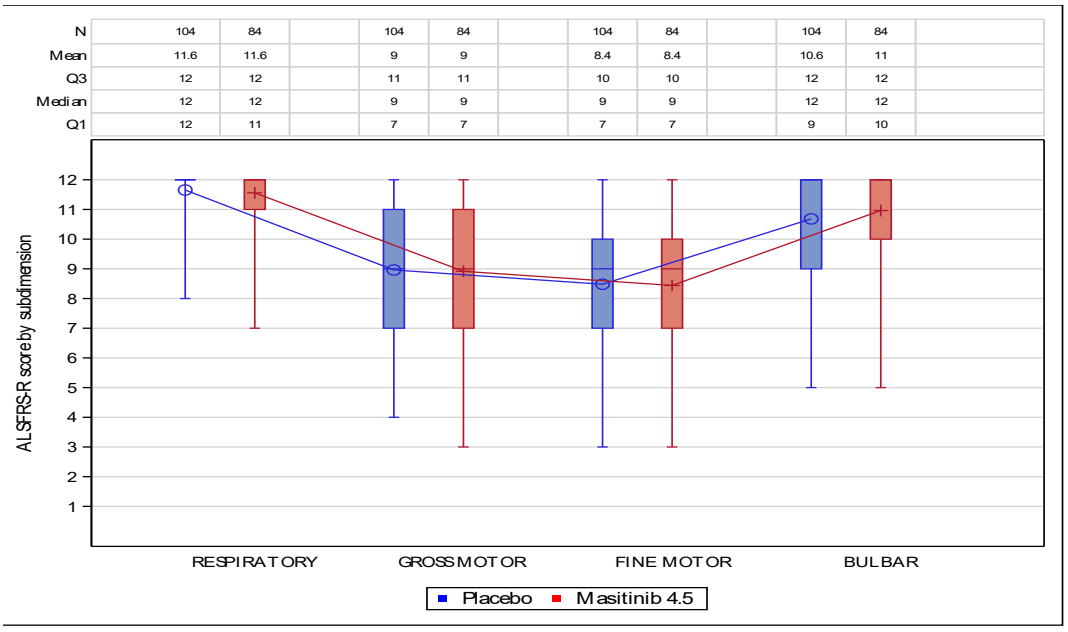
Baseline characteristics in the subgroup were balanced between treatment-arms.

Table 139: Baseline characteristics – Subjects prior to any loss of function

		Placebo (N=104)	Masitinib 3.0 (N=94)	Masitinib 4.5 (N=84)
Sex; n (%)	Male	64 (61.5%)	62 (66.0%)	57 (67.9%)
Average ΔFS (pts/month)	Mean ± SD	0.49 +/- 0.25	0.45 +/- 0.24	0.45 +/- 0.25
	Range	0.05 ; 1.07	0.09 ; 1.04	0.03 ; 1.08
ALSFRS-R score at baseline	Mean ± SD	39.8 +/- 4.3	39.8 +/- 3.9	39.9 +/- 4.2

		Placebo (N=104)	Masitinib 3.0 (N=94)	Masitinib 4.5 (N=84)
	Range	29.0 ; 47.0	28.0 ; 46.0	30.0 ; 47.0
Age (years)	Mean ± SD	55.4 +/- 10.8	54.4 +/- 10.7	54.3 +/- 10.7
	Range	27.0 ; 75.0	33.0 ; 75.0	24.0 ; 78.0
Time from first symptom to randomization (months)	Mean ± SD	18.9 +/- 8.3	19.6 +/- 7.6	20.4 +/- 8.7
	Range	3.0 ; 36.0	7.0 ; 35.0	4.0 ; 36.0
Time from diagnosis to randomization (months)	Mean ± SD	9.4 +/- 7.1	10.1 +/- 7.4	9.9 +/- 7.8
	Range	1.1 ; 31.3	1.3 ; 30.1	1.0 ; 33.9
FVC (% predicted)	Mean ± SD	90.9 +/- 18.4	89.2 +/- 18.4	91.8 +/- 16.0
	Range	37.0 ; 131.0	51.0 ; 149.0	60.0 ; 131.0
Site of onset; n (%)	Spinal	81 (77.9%)	80 (85.1%)	68 (81.0%)
	Bulbar	23 (22.1%)	14 (14.9%)	16 (19.0%)
Region; n (%)	North America & West. Europe	66 (63.5%)	59 (62.8%)	49 (58.3%)
	Eastern Europe	7 (6.7%)	3 (3.2%)	7 (8.3%)
	Other Countries	31 (29.8%)	32 (34.0%)	28 (33.3%)

Figure 14: ALSFRS-R Score (Descriptive statistics and per dimension - patients prior to any loss of function - Normal Progressor)



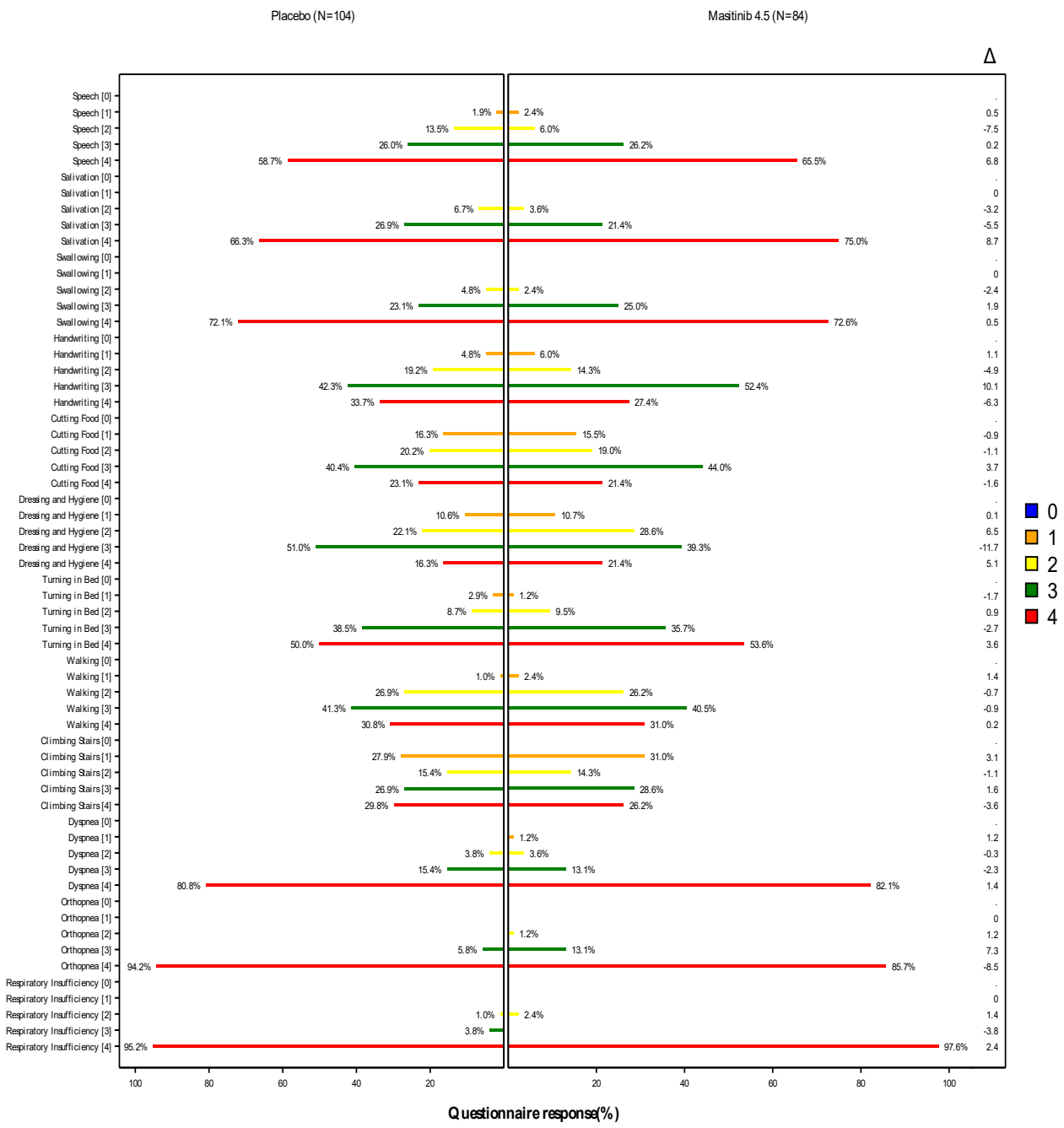
Descriptive statistics showed balanced baseline ALSFRS-R score across each of the four dimensions.

Table 140: Baseline ALSFRS-R score per dimension – Subgroup of patients prior to any loss of function

		Placebo N=104	Masitinib 3 mg/kg/d N=94	Masitinib 4.5 mg/kg/d N=84
Bulbar (Q1 to Q3)	Mean +/- SD	10.68 +/- 1.75	10.73 +/- 1.81	10.96 +/- 1.54
	Median	12	12	12
	Min, Max	5 , 12	5 , 12	5 , 12
	Q1 , Q3	9 , 12	10 , 12	10 , 12
Fine moror	Mean +/- SD	8.48 +/- 2.41	8.54 +/- 2.68	8.44 +/- 2.31

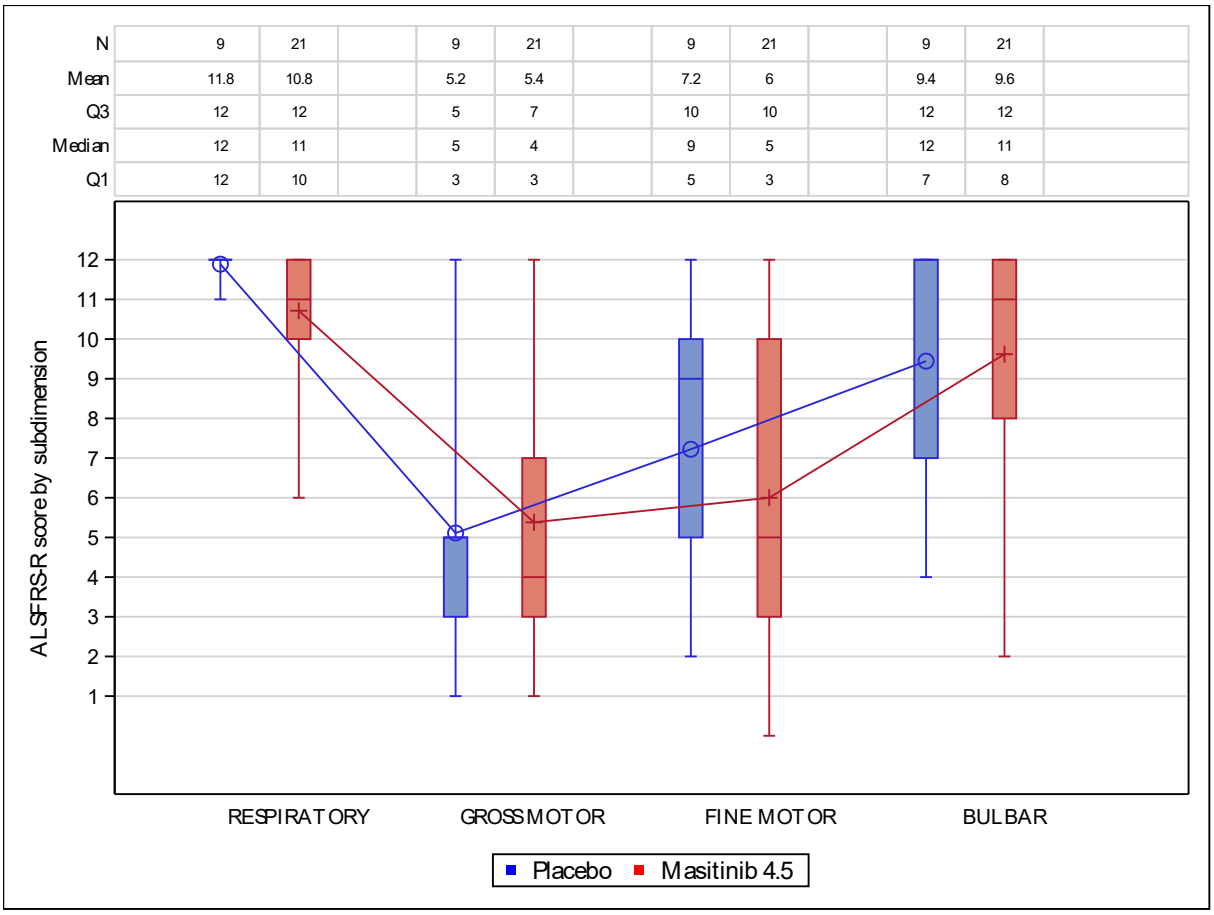
(Q4 to Q6)	Median	9	9	9
	Min, Max	3 , 12	3 , 12	3 , 12
	Q1 , Q3	7 , 10	7 , 11	7 , 10
Gross motor (Q7 to Q9)	Mean +/- SD	8.96 +/- 2.29	8.99 +/- 2.12	8.92 +/- 2.33
	Median	9	9	9
	Min, Max	4 , 12	5 , 12	3 , 12
	Q1 , Q3	7 , 11	7 , 11	7 , 11
Respiratory (Q10 to Q12)	Mean +/- SD	11.65 +/- 0.76	11.51 +/- 1.03	11.56 +/- 0.92
	Median	12	12	12
	Min, Max	8 , 12	7 , 12	7 , 12
	Q1 , Q3	12 , 12	12 , 12	11 , 12

After removing the patients with prior loss of function, the distribution of the ALSFRS-R items in the remaining population of patients without prior loss of function is well balanced between groups as visible in the figure below:



The use of 'ALS patients prior to any loss of functions' allows to have a more balanced population excluding more extreme cases hence a lower variability and does not favour the active group.

Figure 15: ALSFRS-R Score (Descriptive statistics - very severe ALS patients (prior to any loss of function) from Normal Progressor)



In very Severe ALS patients those with any loss of function only, when considering from the Normal Progressor population, descriptive statistics (mean, median, Q1, and Q3) with box plots across all sub-dimensions clearly demonstrate that both treatment groups are disbalance.

Argument 5.2: EMA guidance EMA/CHMP/539146/2013 states that there is an interest to apply the guideline on subgroup when there is a disbalance

Scenario 2 of the guidance refers to a situation where the clinical data are statistically persuasive in the primary analysis population, but where it might be of interest to identify a subgroup that has not been pre-specified as part of the confirmatory testing strategy, where efficacy and risk-benefit would be convincing.

However, as stated under option 3 of this scenario 2, there are "*risks and uncertainties are present in a subset of the population to the extent that a positive risk-benefit cannot be concluded in that subset*".

In the case of AB10015, the third option listed is applicable because, although statistically and clinically persuasive data is presented in the primary analysis population, there are risks and uncertainties present in a subset of the population to the extent that a positive risk-benefit cannot be concluded in that subset.

Argument 5.3: EMA guidance applies to *post hoc* analyses initiated by the Applicant

This EMA guidance makes clear reference to situation where "[…] *it is of interest to identify post hoc a subgroup, where efficacy and risk-benefit is convincing"*.

Such *post hoc* subgroup analysis may be performed at the initiative of the Applicant, as the guidance states that the applicable principles on which to build a credible subgroup analysis applies " […] *irrespective of whether it is the company or the regulator that is specifying additional investigations of interest*".

Argument 5.4: EMA guidance on subgroup is applicable to single pivotal study where confirmatory evidence is not yet available

This EMA guidance is applicable to trials that are presented in a Marketing Authorisation Application, in particular in phase III confirmatory clinical trials, but not exclusively. This guidance makes specific reference to applications based on a single pivotal study and quotes the EMA guidance on this matter (CPMP/EWP/2330/9).

The EMA guidance further states that "*A particular challenge exists in applications based on a single pivotal study since replication is a key component of credibility. In this instance the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally stro*ng".

It therefore applies to AB10015, which is a phase 3 study presented for marketing authorization as a single pivotal study.

Argument 5.5: Masitinib study fits scenario 2 of the guidance, where the study is a success on its predefined primary analysis but the outcome is not compelling enough

Scenario 2 of the guidance refers to a situation where the clinical data are statistically persuasive in the primary analysis population, but where it might be of interest to identify a subgroup that has not been pre-specified as part of the confirmatory testing strategy, where efficacy and risk-benefit would be convincing.

In the case of AB10015, the third option listed is applicable because, although statistically and clinically persuasive data is presented in the primary analysis population, there are risks and uncertainties present in a subset of the population to the extent that a positive risk-benefit cannot be concluded in that subset.

- Statistically persuasive efficacy in the primary analysis population

According to AB Science, assessment scenario 2 of the guidance is applicable because the condition "*The clinical data presented are statistically persuasive in the primary analysis population"* is met.

Indeed, as presented is response to Q.8.2.iii, there are sufficient statistically persuasive evidences to consider that masitinib generated efficacy in the primary analysis population.

- The quantity of missing data is in line with other ALS studies of 48-week duration.
- The study results are based on a large number of patients above 100 per arm, providing more accurate estimation of treatment effect.
- The primary analysis based on ANCOVA test and LOCF was positive.
- The sensitivity analyses based on conservative non LOCF methods show a positive and treatment effect, in particular preplanned cluster imputation, multiple imputation, jump to reference for prespecified discontinuation MNAR.
- The jump to reference methodology for any discontinuation is extreme, because not all reasons of discontinuation are because patients who withdraw may retain some of the benefit accrued during the treatment period. But even in this extreme case, the tipping point is 76% meaning

24% remaining efficacy from treatment is enough for the study to be successful, meaning treatment effect remain relevant

- The methodology Copy Increment, less brutal that JTR and recommended by EMA is positive
- The primary endpoint analysis is supported by multiple key secondary endpoints.
- The primary endpoint analysis is supported by a trend towards overall survival (OS) benefit (+6 months) based on the sensitivity analysis recommended by the Rapporteurs, i.e., censoring placebo patients at the time they switched to masitinib treatment.

■ Clinically persuasive efficacy in the primary analysis population

- The magnitude of the functional benefit ranges from 2.8 to 3.4 depending on the sensitivity analysis applies and always remains above the threshold of 2 considered are clinically relevant by the majority of EMA experts.
- The functional benefit was associated with a gain of +4 months of median PFS.
- There was trend in survival benefit of + 6 months in median overall survival.
- The improvement in decline in ALSFRS-R was not at the expense of quality of life, as there was a significant benefit on quality of life.

■ Risks and uncertainties have been identified in a subset of the population

As presented in section 5.1 above, there are "*risks and uncertainties are present in a subset of the population to the extent that a positive risk-benefit cannot be concluded in that subset*".

Argument 5.6: The 5 additional conditions to apply guideline are fulfilled

Irrespective of whether it is the company or the regulator that is specifying additional investigations of interest, the guidance lists five criteria that would usually apply for a subgroup to be considered credible.

1) External evidence should exist that the subgroup of interest is a well-defined and clinically relevant entity.
2) A pharmacological rationale or a mechanistically plausible explanation.
3) The treatment effect observed in the subgroup would usually be larger.
4) Replication of subgroup findings from other relevant trials or if not available the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally strong.
5) Whenever a treatment recommendation is to be based on a subgroup, it is mandated that risk-benefit should be carefully inspected.

According to AB Science, the criteria are fulfilled in the context of AB10015 trial.

1. Subgroup of interest is a well-defined and clinically relevant

■ The subgroup is well defined and clinically relevant

The subgroup is well-defined and clinically relevant, based on the following considerations.

- Loss of function is well-characterized and fits guidance definition (§4.1).

  Loss of function is based on ALSFRS-R score, which is a validated and widely used scale in ALS. ALSFRS-R score at baseline was a stratification factor. Furthermore, Loss of function is stable once reached.

- The analysis to identify the subgroup is based on a credible number of patients ((104+84)/(113+105))≈86% of primary analysis population).

■ External evidence is available to support the subgroup

Severity is defined in terms of remaining functionality on items of the ALSFRS-R score, as opposed to the total ALSFRS-R score. A drawback of this latter global approach, is that it assumes a uniform deterioration across all items, and does not therefore adequately take into consideration that a complete loss of functionality may have occurred in one item, even though the global functionality may remain relatively high (i.e., a consequence of the scale's multidimensionality).

Hence, the following categories have been defined (note that various documents may use different wording to describe these subgroup thresholds, however, the cohorts defined are identical):

- Very severe ALS: Patient has a score of zero (i.e., loss of function) on at least one individual item of the ALSFRS-R.

- Severe ALS: Patient has a score of 1 (i.e., severe impairment of function) on at least one of the individual ALSFRS-R items and a score of greater than zero on all individual ALSFRS-R items.

- Moderate (or non-severe) ALS: Patient has a score of 2 (i.e., moderate impairment of function) on at least one of the individual ALSFRS-R items and a score of greater than 1 on all individual ALSFRS-R items.

- Mild ALS: Patient has a score of 3 (i.e., mild impairment of function) on at least one of the individual ALSFRS-R items and a score of greater than 2 on all individual ALSFRS-R items.

The origin of this patient enrichment categorization is found in the edaravone MCI 186-16 trial *post hoc* analysis "p*atients with 2 points or better, on each of the individual items of the ALSFRS-R*" [Takahashi 2017], which was later incorporated as an inclusion criterion of the pivotal MCI 186-19 trial "*eligible patients had scores of at least 2 on all 12 items of ALSFRS-R*" [Writing Group 2017].

Given the structure of the ALSFRS-R scoring system, i.e., 12 items scored from 4 to 0 with higher scores indicating less severity, it is a logical progression of thought to also categorize patients with 3 points or better, 1 point or better, etc.

To facilitate the description and clinical interpretation of such severity categories it is common practice to adopt terminology such as 'mild', 'moderate' and 'severe', and this was also the case for the edaravone study populations mentioned above. An example of this is found in press releases issued by the study sponsor, Mitsubishi Tanabe Pharma Corporation, dated May 8th, 2017 [mitsubishimay82017] and also May 5th, 2023 [https://www.mt-pharma-de.com/aktuelles/pressemitteilungen.html], in which the population of study MCI 186-19 is described as 'patients with comparatively moderate ALS'.

Hence, it logically follows from this 'moderate ALS' anchor point descriptor, that patients with scores of at least 3 on all 12 items of ALSFRS-R would be designated as 'mild ALS', whereas patients with scores of at least 1 on all 12 items of ALSFRS-R (but who do not meet the criteria for mild or moderate ALS) would be designated as 'severe ALS'. To this we can also add the category of 'very severe ALS' for any patient with any complete loss of function (score of zero) on at least one individual item of the ALSFRS-R.

Beyond the terminology introduced by the Mitsubishi Tanabe Pharma Corporation for describing its

edaravone study population, i.e., moderate ALS, Maier and colleagues have more recently developed a new revision of the ALSFRS-R, which they described as a "disease-specific severity score that reflects motor impairment and functional deterioration in people with ALS" [Maier 2022]. They go on to highlight the following aspects of this scale:

- The ALSFRS-R is a functional scale that measures deviations from unrestricted or "normal" motor functioning as caused by ALS.

- To ordinally scale the loss of functionality, anchor points grade functionality from 0 to 4 for each item. To determine an ordinal score, the scale considers whether there is an increased need for assistance or assistive devices.

    - Scores of 4 designate unrestricted functionality.

    - Scores of 3 designate *mild* impairment, reflecting a condition that does not yet require compensatory help.

    - Scores of 2 are characterized by intermittent use of compensatory measures

    - Scores of 1 are given if assistive procedures or devices are needed in all instances and independence is *severely* reduced but not entirely lost

    - Scores of 0 designate a complete loss of functionality

Hence, it is further established in this article that a score of 3 on an individual component of the ALSFRS-R is associated with *mild impairment of function*, that a score of 1 on an individual component of the ALSFRS-R is associated with *severely* reduced function, and that a score of 0 on an individual component of the ALSFRS-R is associated with complete loss of functionality. Although the anchor-point descriptors of 'moderate' and 'very severe' are not explicitly used by Maier, it is obvious that the pattern of 'mild', 'moderate'; 'severe' and 'complete loss of function (very severe)' are associated with the above scores of 3, 2, 1, and 0, respectively.

Hence, there are precedence in the literature for the ALSFRS-R severity-based patient categorization and terminology used for AB10015 subgroup analyses (i.e., the edaravone trials and related Mitsubishi Tanabe Pharma communications), and also evidence that the terminology and concepts used for this categorization are known and acceptable for clinical use in practice (i.e., as evidenced by the MND-NET consensus group).

2) Pharmacological rationale and mechanistically plausible explanation exist for differential efficacy

The subgroup "prior to any loss of function" fits masitinib's mechanism of action because masitinib does not regenerate motor-neurons but slows down disease progression through modulation of mast cell and microglia activity.

Masitinib acts by slowing the progression of the disease by acting on the innate immune systems, reducing macrophage infiltration, preventing terminal Schwann cells loss, and improving reinnervation in partially denervated plantaris muscles [Harrison 2020]. These results suggested that pharmacological interventions maintaining terminal Schwann cells at denervated endplates is a viable treatment strategy to attenuate the loss of motor function in ALS.

It is therefore expected that masitinib would provide better outcomes if administered when the larger motoneurons innervating type IIb fibers are still functioning and capable of sprouting terminal branches to reinnervate previously denervated endplates.

Hence, preserved or improved sprouting capacity would maintain motor function longer and slow the ALSFRS-R decline This is entirely consistent with masitinib's clinical findings, which showed that treatment-effect was greatest when masitinib treatment was initiated at a less severe stage of the disease, i.e., prior to any loss of function.

3) The treatment effect is larger in the subgroup

There is clear increased benefit in the subgroup across all clinical endpoints at week 48, as presented in the table below.

The exclusion of the most severe patients, more frequent in the Masitinib 4.5 mg group led to significant improvement in survival. This shows that severe patients have major contribution to OS analysis.

Table 141: Differential treatment effect in the subgroup

		Subgroup	Primary analysis Population (Normal Progressors)
ΔALSFRS-R (CIR)	Diff. of mean	3.13	2.68
	p-value	0.0308	0.0462
CAFS	Relative benefit	**20.2%**	14.8%
	P-value	0.0290	0.0776
ALSAQ-40 (CIR)	Diff. of mean	-6.22 [-12.27;-0.17]	-6.04 [-11.51;-0.57]
	p-value	0.044	0.0305
FVC (CIR)	Diff. of mean	7.59 [0.41;14.77]	5.85 [-0.98;12.67]
	p-value	0.0384	0.0931
Median PFS	Gain	**+ 9 months**	+ 4 months
	Median [95% CI]	25 [17, NE] vs 16 [11, 19]	20 [14; 30] vs 16 [11; 19]
	p-value log rank	0.0057	0.0159
Median OS (Long-term) (censoring of placebo at time of switch to masitinib)	Gain	**+ 12 months**	+ 6 months
	Median [95% CI]	53 [36; NE] vs 41 [30; 54]	46 [33; 69] vs 40 [30; 49]
	p-value log rank	0.0192	0.0761

Figure 16: Normal Progressors- prior to any loss of function – KM analysis of PFS – Masitinib 4.5 mg vs Placebo

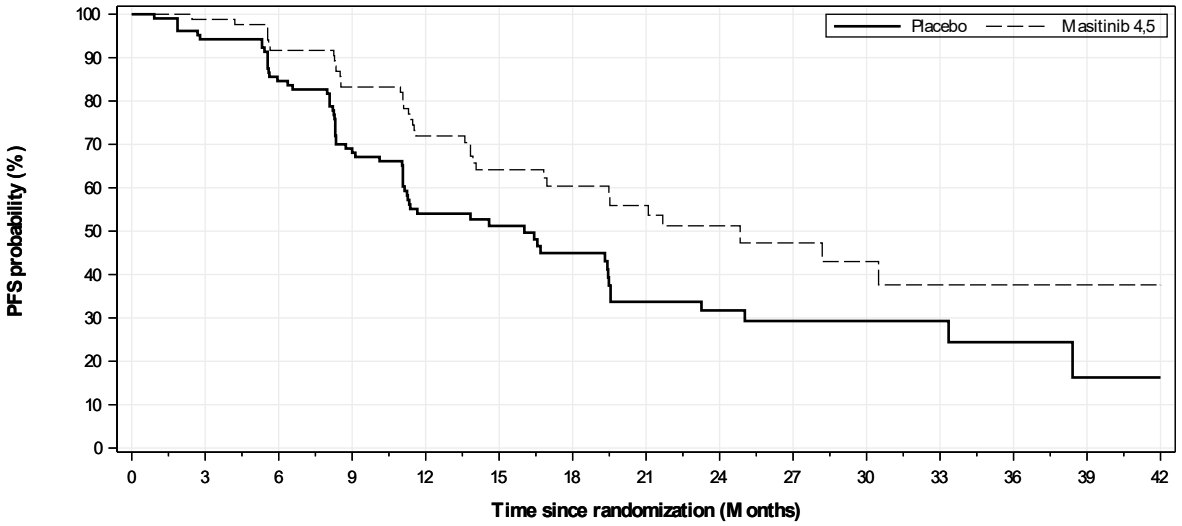
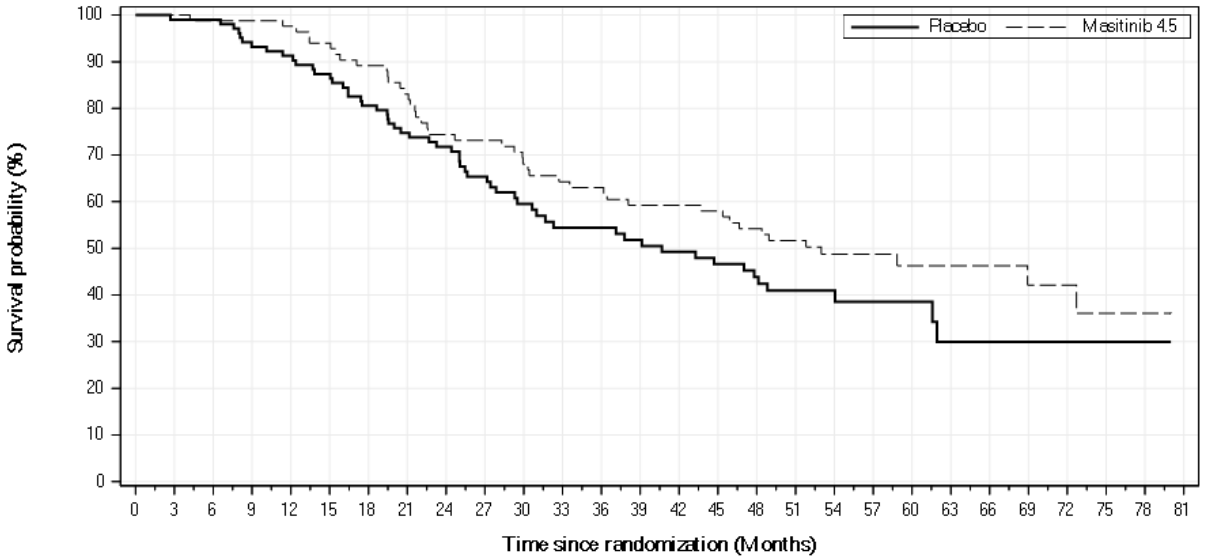


Figure 17: Normal Progressors- prior to any loss of function – KM analysis of OS – Masitinib 4.5 mg vs Placebo



4) Replication of subgroup findings from other relevant trials or if not available the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally strong

a) The effect observed in the subgroup is not replicated by any masitinib trial at the time of conditional approval. However, the biological plausibility and the clinical trial data from the subgroup are exceptionally strong.

- CHMP previously concluded (EMA/CHMP/171026/2019) that the mechanism of action and biological plausibility of using masitinib for treatment of ALS could be considered as demonstrated in preclinical animal models. The assumption that a similar effect could be translated into human disease is feasible. Masitinib's mechanism of action in ALS has been well-demonstrated in the preclinical setting using a relevant model that recapitulates the complexity of a multicomponent immune response with concomitant evidence of neurodegeneration [Kovacs 2021; Trias 2020; Harrison 2020; Trias 2018; Trias 2017; Trias 2016].

  The clinical trial data from the subgroup are exceptionally strong, for example:

  - Benefit on CAFS

There is a significant effect on CAFS. There is a relative benefit of +20.2% (p=0.0290) in the subgroup. CAFS is a robust statistical measure to assess the superiority of the active treatment arm versus the control.

  - Benefit on PFS

There is a statistically significant and clinically relevant improvement in PFS with masitinib in the subgroup, with median increase in PFS of + 9 months (p=0.0057). It is also clinically relevant endpoints and an endpoint in line with EMA guidance on ALS that requires a time to event endpoint.

  - Benefit on overall survival

This survival benefit reported in AB10015 study is obtained in add-on to riluzole, which has been reported to provide a survival benefit of (~3-6 months).

Although the study was not powered for survival, with a follow-up of 75 months, there was in the subgroup further enlarged (+12 months, p=0.0192) when censoring as recommended by the Rapporteurs the 25 placebo patients who switched to masitinib in open label extension.

A survival benefit of greater than 4-5 months is considered in principle as clinically significant by the CHMP (EMA/CHMP/487533/2023).

The exclusion of the most severe patients, more frequent in the Masitinib 4.5 mg group led to significant improvement in survival. This shows that severe patients have major contribution to OS analysis.

b) The replication of subgroup findings has been observed for other relevant clinical trials that have used similar patient enrichment strategies.

Edaravone is approved outside of the EU for the treatment of ALS and has been shown to slow the rate of functional decline. Edaravone was not approved by the EMA, but, as indicated in the EMA documentation (EMA/293450/2019 https://www.ema.europa.eu/en/documents/medicine-qa/questions-and-answers-withdrawal-marketing-authorisation-application-radicava-edaravone_en.pdf)

- Reasons from not approving edaravone were not related to the choice of the study population, in particular the exclusion of patients prior to loss of any function
- Given the clear need for further evidence of edaravone's effectiveness, the CHMP considered the possibility of a conditional approval. However, there was not agreement between CHMP and the Applicant regarding confirmatory evidence to be provided

The FDA approval of edaravone was based on the outcomes from Study 19 (MCI186-19; clinicaltrials.org, NCT01492686), which was a 24-week, randomized, double-blind, placebo-controlled study.

Conversely, the initial randomized trials of edaravone in ALS (studies MCI-186-16, MCI-186-17, and MCI-186-18) all failed to demonstrate a significant difference between treatment arms.

A key difference between the success and failure of these trials was that Study 19 introduced an inclusion criterion stipulating that patients must have a score above 1 on each item of the ALSFRS-R scale. This population has close similarities to that which has been defined for masitinib subgroup analysis, i.e., 'ALS patients prior to any loss of function'. On the contrary, patient cohorts for the failed edaravone studies did not include any eligibility criteria based on disease severity according to remaining functionality on each ALSFRS-R item (see table below).

Study 16 showed a decreased rate of decline in ALSFRS-R score in the edaravone group versus the placebo group, but the difference was not statistically significant. The statistically significant findings in Study 19, which had a more homogeneous population with less severe disease at baseline, indicates that heterogeneity in patients' baseline characteristics were major factors for the initial study failures. Put another way, the lack of significance treatment effect in Study 16 appears to have been due to the broader range in disease characteristics in that study cohort, and particularly the inclusion of patients with more severe disease (i.e., ALSFRS-R item scores ≤1).

Hence, the exclusion of patients with more severe disease, for example, patients with complete loss of function on at least one item of ALSFRS-R, has been a critical factor for successful demonstration of edaravone treatment effect. Subgroup analysis from masitinib study AB10015 has shown the same pattern, highlighting the importance of such patient enrichment strategies for neuroprotective therapies in ALS.

Table 142: Details of edaravone studies eligibility criteria [CADTH 2019]

	Study 16 (MCI186-16)	**Study 17 (MCI186-17)**	**Study 18 (MCI186-18)**	**Study 19 (MCI186-19)**
Study Design	Phase III, DB, parallel-group RCT	Extension phase III study, two arms DB, one arm OL, RCT	Phase III, DB, parallel-group RCT	Phase III, DB, parallel-group RCT
Locations	Japan	Japan	Japan	Japan
Randomized (N)	206 (one excluded from FAS)	206 randomized, 181 participated	25	137

	Study 16 (MCI186-16)	Study 17 (MCI186-17)	Study 18 (MCI186-18)	Study 19 (MCI186-19)
Inclusion Criteria	At enrolment: • definite ALS, probably ALS, or "probable ALS – laboratory supported" according to the El Escorial revised Airlie House diagnostic criteria • grade 1 or 2 ALS according to the Japanese ALS severity classification • FVC of ≥ 70% • ≤ 3 years since onset of ALS • age of 20 to 75 years At randomization: • a change in ALSFRS-R score of −1 to −4 points during the 12-week pre-observation period	Completion of Study 16	At enrolment: • definite ALS, probably ALS, or "probable ALS – laboratory supported" according to the El Escorial revised Airlie House diagnostic criteria • grade 3 ALS according to the Japanese ALS severity classification • FVC of ≥ 60% • ≤ 3 years since onset of ALS • age of 20 to 75 years At randomization: • a change in ALSFRS-R score of −1 to −4 points during the 12-week pre-observation period	At enrolment: • definite ALS or probable ALS according to the El Escorial revised Airlie House diagnostic criteria • grade 1 or 2 ALS according to the Japanese ALS severity classification • **score of ≥ 2 points on each item of the ALSFRS-R (on each side for "handwriting" and "eating motion")** • FVC of ≥ 80% (using actual values) • ≤ 2 years since onset of ALS • age of 20 to 75 years At randomization: • a change in ALSFRS-R score of −1 to −4 points during the 12-week pre-observation period
Exclusion Criteria	• Comorbidities that could affect efficacy evaluation (e.g., Parkinson's disease, schizophrenia, or dementia) • Renal impairment in the 28 days prior to the start of treatment • Judged by the investigator to be ineligible due to general condition deterioration due to complications requiring hospitalization or concomitant infections requiring antibiotic treatment • History of hypersensitivity to edaravone • Participation in another clinical study within 12 weeks of enrolment • Otherwise judged by the investigator to be ineligible		• Decreased respiratory function and a complaint of dyspnea (≤ 3 points on any of the following ALSFRS-R items under "respiration": dyspnea, orthopnea, or respiratory insufficiency • Comorbidities that could affect efficacy evaluation (e.g., Parkinson's disease, schizophrenia, or dementia) • Renal impairment in the 28 days prior to the start of treatment • Otherwise judged by the investigator to be ineligible	
	• Decreased respiratory function and a complaint of dyspnea (≤ 3 points on any of the following ALSFRS-R items under "respiration": dyspnea, orthopnea, or respiratory insufficiency • History of treatment for malignancy	• Undergoing treatment for a concomitant malignancy	• Judged by the investigator to be ineligible due to general condition deterioration due to complications requiring hospitalization or concomitant infections requiring antibiotic treatment • History of treatment for malignancy • History of hypersensitivity to edaravone	• History of spinal surgery after ALS onset or plans for spinal surgery during the study period • Current symptoms may be of a disease requiring differential diagnosis (e.g., cervical spondylosis, multifocal motor neuropathy) • Treatment for concomitant malignancy • Previously administered edaravone • Significant complication (grade 3 adverse drug reaction used as reference) • Administered an investigative product within 12 weeks of enrolment

5) Safety data in the population in the subgroup is improved

The safety of masitinib in ALS is deemed acceptable by the CHMP.

The safety of masitinib is further improved in the claim, as presented in the table below.

- Reduction of serious AEs from 27.6% to 22.6% vs 16.3% with control arm
- Reduction of AEs leading to death from 2.9% to 1.2% vs 6.7% with control arm
- Reduction of severe AEs from 24.8% to 22.6% vs 17.3% with control arm

Table 143: Differential safety overview – Subgroup versus primary analysis population

[W0 – W48]	**Subgroup**		Primary analysis Population (Normal Progressors	
	Placebo (N=104)	Masitinib 4.5 (N=84)	Placebo (N=114)	Masitinib 4.5 (N=105)
At least one AE	80 (76.9%)	72 (85.7%)	88 (77.2%)	92 (87.6%)
At least one serious AE (non fatal)	17 (16.3%)	19 (22.6%)	19 (16.7%)	29 (27.6%)
Death	7 (6.7%)	1 (1.2%)	8 (7.0%)	3 (2.9%)
At least one severe AE	18 (17.3%)	19 (22.6%)	20 (17.5%)	26 (24.8%)

Argument 5.7: In particular the data in the subgroup prior to any complete loss of function are extremely compelling including a +12 months benefit

In particular, there is a clear benefit increase in the subgroup, in particular on JTR analysis and OS

- Primary endpoint: Difference of means =3.13 (p=0.0308)
- Survival: +12 months median long-term OS (p=0.0192) when censoring placebo patients at the time they switch to masitinib as recommended by the Rapporteurs.

Argument 5.8: Even when accounting for fast progressors, in patients prior to any complete loss of function, data remain very compelling

The efficacy in the subgroup remains persuasive when adding fast progressors.

The proportion of fast Progressor was higher in the Masitinib 4.5 group (13/97 = 13.4%) than in the placebo group (11/115 = 9.6%). Other baseline characteristics were balanced between treatment-arms.

A positive differential treatment effect was still observed in this patient population.

In particular, when adding fast progressors, the ALSFRS-R calculated with CAFS, the ALSAQ, the FVC and the PFS showed a statistically significant benefit. The OS benefit remained substantial (+7 to 8 months), and close to significance (p=0.0684) in line with requirements stated on ALS in terms of OS benefit.

Table 144: Differential treatment effect in patients prior to any loss of function (Normal + Fast Progressors

		Patients prior to any loss of function (Normal + Fast)	Primary analysis Population (Normal Progressors)
ΔALSFRS-R (CIR)	Diff. of mean	2.76	2.68
	p-value	0.0538	0.0462

CAFS	Relative benefit	18.4%	14.8%
	P-value	0.0346	0.0776
ALSAQ-40 (CIR)	Diff. of mean	-6.74 [-12.57;-0.91]	-6.04 [-11.51; -0.57]
	p-value	0.0235	0.0305
FVC (CIR)	Diff. of mean	7.79 [0.47;15.11]	5.85 [-0.98;12.67]
	p-value	0.0369	0.0931
Median PFS	Gain	+ 5 months	+ 4 months
	Median [95% CI]	20 [14; 30] vs 15 [11; 19]	20 [14; 30] vs 16 [11; 19]
	p-value log rank	0.0183	0.0159
Median OS (Long-term) (censoring of placebo at time of switch to masitinib)	Gain	+ 8 months	+ 6 months
	Median [95% CI]	46 [30; 69] vs 38 [29; 49]	46 [33; 69] vs 40 [30; 49]
	p-value log rank	0.0684	0.0761

The safety of masitinib was also improved in this population of patients prior to any loss of function including fast progressors.

- Reduction of serious AEs from 31.0% to 26.0% vs 17.4% with control arm
- Reduction of AEs leading to death from 7.8% to 5.2% vs 7.0% with control arm
- Reduction of severe AEs from 30.2% to 26.0% vs 17.4% with control arm

Table 145: Differential safety overview – Subgroup versus primary analysis population

[W0 – W48]	**Patients prior to any loss of function (Normal + Fast)**		Primary analysis Population (Normal Progressors	
	Placebo (N=115)	Masitinib 4.5 (N=96)	Placebo (N=133)	Masitinib 4.5 (N=129)
At least one AE	91 (79.1%)	83 (86.5%)	104 (78.2%)	114 (88.4%)
At least one serious AE (non fatal)	20 (17.4%)	25 (26.0%)	24 (18.0%)	40 (31.0%)
Death	8 (7.0%)	5 (5.2%)	12 (9.0%)	10 (7.8%)
At least one severe AE	20 (17.4%)	25 (26.0%)	26 (19.5%)	39 (30.2%)

Argument 5.9: The Applicant proposes to use label that maximized benefit/risk: in patients prior to any complete loss of function, which might provide a solution not to exclude fast progressors from the label

- Normal progressors

The Normal progressor population is the primary analysis population.

A claim based on Normal progressors only is acceptable because the study was positive in the preplanned primary analysis population and because:

- ΔFS is a clinically relevant, independent predictor of survival, capable of distinguishing patient subgroups that have a different course of disease progression.
- The ΔFS cut-off has a large margin of error of ±20% compatible with clinical practice.
- ΔFS is a simple-to-use instrument for patient selection, the components of which are measured as part of routine clinical practice.

■ Patients prior to any loss of function

The distribution of the ALSFRS-R score were unbalanced at baseline on normal progressor, with more severe cases in the active groups, particularly in the Masitinib 4.5 mg group (20%) than in the placebo group (8%).

The exclusion of the most severe patients, more frequent in the Masitinib 4.5 mg group, led to significant improvement across all efficacy endpoints, including survival. Importantly, the safety profile was also improved in these patients. As a result, the benefit -risk balance is improved in this claim.

In addition, treating patients with masitinib prior to any loss of function is more in line with masitinib mechanism of action.

The claim prior to any loss of function is easy to use in clinical practice based on ALSFRS-R assessment and is stable over time

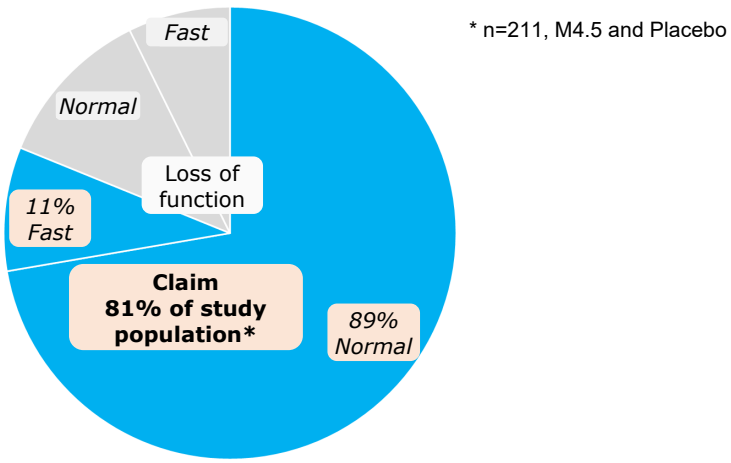
Finally, initiating results in patients prior to any loss of function does not alter generalizability of the trial results, and a claim is this patient population is not expected to restrict access to the treatment. Indeed, once the drug is commercially available, it is expected that patients will receive treatment shortly after diagnosis. The median time from first symptom to diagnosis being around 12 months [Mitchell 2010; Paganoni 2014], it can be expected that, at the time of treatment start, patients would have 24 months or less of disease duration. In addition, as previously discussed, it is also reasonable to expect at the time of treatment start, most patients would have a score of at least 1 on each of the 12 ALSFRS-R individual component items.

- The average deterioration on ALSFRS-R score is around 1 point per month [Atassi 2014]
- The deterioration in ALSFRS-R is approximately linear for each domain over the timeframe of interest, especially for the spinal cohort [Rooney 2017].

Results in patients prior to any loss of functions accounted for 81% of the study population and Fast progressors accounted for 11% of the patients prior to any loss of function, which is in line with the general ALS population.

This claim has therefore greater generalizability than a claim in Normal progressors only and provided greater clinical efficacy together with improved safety.

Figure 18: Disposition of patients in the claim and outside of the claim (M4.5 and placebo)



■ Conclusion

AB Science would like to discuss the most appropriate claim with the agency.

AB Science considers that a claim prior to any loss of function should be favoured because it is more in line with masitinib mechanism of action and because there is an improved benefit/risk in these patients.

In the Scientific advice procedure regarding the design of AB23005 phase 3 masitinib confirmatory study (EMADOC-360526170-1973369), the scientific advice working party (SAWP) confirmed that: "*The Applicant intends to include patients with definite or probable diagnosis of ALS (defined by the revised El Escorial criteria), prior to complete loss of function in any individual component of the ALSFRS-R at baseline in study AB23005 […]. Such population restriction is in principle acceptable*".

Argument 5.11: Qalsody introduced *post hoc* covariates to optimize statistical data and CHMP registered Qalsody

The position adopted by the CHMP for Qalsody shows that *post hoc* analysis can be acceptable.

EMA registered Qalsody with the EPAR showing that the sponsor amended its SAP once data were unblinded and introduced new covariates, NfL and riluzole/edaravone interactions, leading to an improvement in statistics data on which EMA relied to conclude that NfL predicts some clinical benefit.

CHMP position on the Ground for re-examination

Overall, the Applicant's responses to the grounds for refusal are excessive and unfocused , presented results lack methodological description and respective data sources are unclear. Several arguments are not deemed relevant for addressing the respective ground for refusal. Arguments relevant to the grounds for refusal are discussed in more detail, whereas arguments not deemed relevant are listed for completeness.

The following assessment concerns Ground #2.2: […] the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS.

1. A statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population.

The third amendment of study AB10015 dating from 8 October 2014 introduced a hierarchical testing scheme with change in ALSFRS-R in the subset of 'normal progressors' as primary analysis. It is understood that the main concern of this part of the ground for refusal is the *post hoc* nature of the subgroup analysis of normal progressors, which confers exploratory character to the analysis termed as primary by the Applicant.

An analysis is pre-specified if it is described before any data is seen and preferably (at least in its crucial aspects such as the definition of the primary endpoint and/or the primary population) before the first patient is enrolled. The change of primary analysis population was made after the study was already ongoing (1.5 years after study commencement) when 46 patients including 8 fast progressors could have reached study week 48 (Argument 2.10). According to the GCP Inspection Report, there was a lack of monitoring plan from the beginning of study until 2016, and the amendment in question was done in 2014.Therefore it can be said that the validity (including blinding) and timing of this amendment is questioned, as it was done during an essentially unmonitored part of the study. Functional unblinding cannot be excluded if changes are done after the study is already ongoing. In this particular case, functional unblinding cannot be ruled out in the view of the different safety profiles of Masitinib AB Science and placebo arms. The considerable impact of the change in study population on the study outcomes (i.e. on the formal 'success' of the study) raises further concerns. It should be noted that, when a submission is based on only one pivotal (ie. confirmatory) study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality and internal consistency (CPMP/EWP/2330/99).

Reducing heterogeneity of the study population was given as a justification for this approach in the initial

assessment. Indeed, the guideline on the investigation of subgroups in confirmatory trials, EMA/CHMP/539146/2013, clearly outlines that consideration on the heterogeneity within a target population should be done but also outlines that this should be done during the planning of a clinical trial. Thus, it is expected that the choice of the study population for a confirmatory trial is made before study begin based on data from prior studies.

Consequently, the change in primary analysis population is deemed *post hoc*, and the ITT population (normal + fast progressors) is viewed as a primary efficacy analysis population.

For the question of prespecification, discussion of

- the approval of the investigators and ALS experts on the change of primary endpoint (Arguments 2.2 and 2.3),
- the expected amount of missing values in the excluded patients (Argument 2.4),
- the feasibility of the initially defined analysis in terms of statistical power (Argument 2.5),
- the validation of the third amendment by the competent authorities (Argument 2.6),
- the commonness of protocol amendments during the enrolment period (Arguments 2.7, 2.8),
- whether excluding the patients who had reached study week 48 at the time of the third amendment changed the results for the population of normal progressors (Argument 2.11) and
- whether the interim analysis was positive in the total study population (normal + fast progressors) (Argument 2.12)

is considered irrelevant for the acceptability of the change in the primary efficacy population. Whether the change was recommended / endorsed by investigators, ALS experts or competent authorities does not affect acceptability of the change in the primary efficacy population (Arguments 2.2, 2.3 and 2.6). The expected amount of missing values in the excluded patients and the *un*feasibility of the initially defined analysis in terms of statistical power and sample size (Arguments 2.4 and 2.5) do not imply that this change in the primary efficacy population is acceptable (although it may trigger a more careful definition of target population in a future trial). The commonness of protocol amendments during the enrolment period as illustrated by examples of other drug development programs (Arguments 2.7 and 2.8) does also not justify the acceptability of the amendment. Furthermore, it is reiterated that each MAA is evaluated on its own merits. Results from subgroup analysis (Argument 2.11) or interim results (Argument 2.12) cannot justify the acceptability of a change in the primary efficacy population.

Study AB10015 used a group-sequential design with one interim analysis to be performed at significance level 0.0311 (Pocock spending function) when about 50% of patients were randomized. Results from the interim analysis had been submitted for the preceding MAA (EMEA/H/C/004398/0000). The current submission focuses on the results from the last planned analysis. The Applicant reports that as the interim analysis was successful in their opinion, the updated analysis was performed at 5% level of significance. This approach is not agreed to. Effect estimates from the updated analysis should be accompanied by repeated confidence intervals, assuring that the simultaneous coverage probability is maintained at 95%. These repeated confidence intervals would be wider than the currently provided naïve 95% confidence intervals. Moreover, it remains unclear from the submitted data, whether the interim analysis can be confirmed to have been successful.

To conclude, the *post hoc* change in the primary efficacy population from full study population to normal progressors only is not acceptable. The ITT full study population (normal + fast progressors) is viewed as a primary efficacy analysis population.

2. The approach to categorize the population into normal and fast progressors is not supported.

Reference to other clinical trials (Argument 3.1) in ALS is not considered supportive of the use of ΔFS to define normal and fast progressors, as they either do not constitute regulatory precedence in the treatment of ALS (beta hydroxybutyrate ester, bosutinib, edaravone, high-caloric fatty diet, lenzumestrocel, methylcobalamin, nitrazine, NurOwn, rasagiline, ravulizumab) or in the case of Qalsody (tofersen) (also Argument 3.8) use different parameters for the categorization of patients (different cutoff: ΔFS of 0.9 per month, plus mutation type and SVC cutoff) as compared to study AB10015. In general, reference to the assessment of study conduct in other procedures is inappropriate, as each product's benefit-risk needs to be assessed individually and comparative assessment of different applications cannot be done as there are multiple factors affecting the benefit-risk evaluation for each application. In any case, the table provided by the Applicant for Argument 3.1 illustrates that the criteria for categorization of progressors in clinical trials vary widely across the trials in terms of cut-offs, periods of observation (n-weeks period, from onset) and definition of categories (normal, intermediate, fast). The selected cut-off of 1.1 points/month appears arbitrary and has not even been used in any other study presented by the Applicant.

The Applicant presented studies evaluating the utility of the ΔFS as a prognostic factor, mainly referring to Requardt et al 2021 and Kollewe et al 2008 (Argument 3.2). Both have limitations in terms of defining cut-off values and time measurements. It cannot be agreed that the definition of fast progressors measured from onset of symptoms is a highly robust, independent prognostic predictor of survival. More importantly, as shown by Requardt et al 2021, (Arguments 3.2+3.4) ΔFS is not stable throughout the course of disease. This was also not disputed by the Applicant, stating that ΔFS is a timeframe dependent parameter and patients frequently switch between ΔFS categories over time, hence the use of post-onset (early slope) ΔFS (as opposed to interval/late slope ΔFS). However, CHMP's concerns of previous assessments are upheld due uncertainties regarding the retrospective determination of exact timing of symptom onset, despite a new publication by Ludolph et al 2024, claiming that post-onset ΔFS is derived from information routinely collected as part of standard patient care and monitoring (Argument 3.7). It can still not be excluded that items on the ALSFRS-R may not be recorded at all, and/or that the exact timing of symptom onset cannot be reliably determined retrospectively at some centers. The timeframe dependency of ΔFS is also highlighted by Kollewe et al 2008, as varying median ΔFS are calculated, depending on the timeframe considered: 1.0, 1.185 and 0.65 for ΔFS calculated from first symptom to time of diagnosis, ΔFS calculated over the whole course of disease (i.e., from first assessment until last assessment prior to death or tracheotomy), and ΔFS calculated within a defined period of 100 days, respectively. While the ethical concerns of an untreated lead-in period to assess the ΔFS within a defined period of 100 days are understood, rejecting this option due to 0.65 being very dissimilar to 1.185 (Argument 3.3) is considered arbitrary.

Sensitivity analyses showed that the difference in ALSFRS-R (ΔLSM) between Masitinib AB Science 4.5 mg/kg/d vs placebo was statistically significant ($p<0.05$) up to a ΔFS cut-off of 1.4, and that the difference tends to increase by lowering the ΔFS cut-off (Argument 3.5). The relevance of this observation for applying the proposed 1.1 cutoff remains unclear. In fact, this observation may rather suggest there is no scientifically sound rationale for the selected 1.1 cutoff. Based on further analyses investigating the margin of error associated with accuracy on the date of first symptoms the Applicant concludes that the possibility of misclassification is marginal (Argument 3.6). Again, the relevance of these exploratory analyses, which use arbitrary cut-offs throughout, is unclear.

Taken together, none of the Applicant's arguments can alleviate the concern to categorize the population into normal and fast progressors. The previous CHMP opinion is upheld.

3. Considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data including statistical assumptions on missingness and the definition of intercurrent events in J2R strategy are not considered acceptable.

The SAP dating from 16 March 2017 was finalized after performing the interim analysis on 10 March 2016 and after submitting this interim analysis in the course of the MAA for Alsitek (EMEA/H/C/004398/0000). In particular, only the methods listed in the protocol can be considered to have been prespecified.

When thinking about how to handle missing values due to treatment discontinuation there are two aspects which need to be discussed. First, the estimand of primary interest needs to be defined, including the strategy for handling the intercurrent event of treatment discontinuation. Subsequently, it needs to be decided which analysis methods best approximate this estimand.

It is agreed with the previous view of the CHMP that for study AB10015 an estimand using a treatment policy strategy for treatment discontinuation is of primary interest from the regulatory perspective as it represents the treatment difference observed in practice. In contrast, applying a hypothetical strategy would result in an estimand not reflecting clinical practice, assuming that patients do not discontinue treatment (see the ICH E9 R1 addendum, EMA/CHMP/ICH/436221/2017). Ideally, all patients discontinuing treatment would have stayed in the study and data would have been collected also after treatment discontinuation, allowing to target the estimand of primary interest by an analysis using all observed data. It is agreed with the CHMP that the jump-to-reference (JTR) approach is suitable for approximating the values after treatment discontinuation if they had not been observed. As cited by the Applicant, JTR might be seen as extreme in some situations (Argument 4.6), but is considered plausible in the present context. Moreover, all other employed methods are considered to be potentially anticonservative.

The mLOCF approach defined as primary analysis by the Applicant (Argument 4.2) imputes missing values due to discontinuation for toxicity or lack of efficacy as the last observed change from baseline. Given the progressive nature of ALS, this strategy is suspected to strongly overestimate the unobserved outcome of patients and consequently gives an overly optimistic estimate for the treatment effect as there were substantially more discontinuations due to toxicity or lack of efficacy in the masitinib arms compared to the placebo arm. The Applicant acknowledged that the mLOCF approach is not the most appropriate method to address missing data (Argument 4.2).

The cluster-based imputation relying on copy-increment from ‘similar’ patients does not target the estimand of primary interest but might approximate a hypothetical strategy for the intercurrent event discontinuation (Argument 4.3), which is of minor relevance as pointed out above.

It is understood from the SAP that the tipping point analysis applies a similar type of penalty to all discontinued patients, independent of the treatment arm. Thus, it does not even seem to be clear that a larger penalty necessarily leads to a smaller estimated treatment effect, as would generally be expected from a tipping point analysis. Consequently, the tipping point analysis provided by the Applicant (Argument 4.11) is considered of little value. The Applicant cited the SAWP to have stated that 'a tipping point analysis is a valid approach to handle missing data'. While this statement can be agreed to in general, it could not be found in the final letter of the cited procedure.

The copy-increment in reference approach (Argument 4.11) would approximate the estimand based on the treatment policy strategy if it could be assumed that after discontinuation the deterioration speed will become similar to that of the reference arm but that the patient will still benefit from the initial slower deterioration and that loss of that treatment effect after discontinuation is unlikely. However, the action of Masitinib as disease modifying agent is not considered sufficiently substantiated. The argument that the observed lag time of efficacy is compatible with Masitinib AB Science being a disease modifying medicinal product (Arguments 4.28 and 4.30) is not considered convincing.

In addition to the listed shortcomings, the mLOCF approach, the cluster-based imputation and the tipping point analysis are implemented as single imputation methods, which might bias the standard error

downwards by ignoring the uncertainty of imputed values. As explained in the Guideline on Missing Data in Confirmatory Clinical Trials (EMA/CPMP/EWP/1776/99 Rev. 1) confidence intervals for the treatment effect calculated using single imputation methods may be too narrow and give an artificial impression of precision that does not really exist. There is not enough information on the copy-increment in reference approach to know whether it was implemented as single or multiple imputation approach. Generally, the documentation lacks details on the multiple imputation methods.

The Applicant's reasoning that the tipping point analysis and the copy-increment in reference approach were recommended in this form by the CHMP cannot be followed (Argument 4.12). The final letter for the protocol assistance procedure from September 2018 does neither discuss the tipping point analysis nor the copy-increment approach. Furthermore, the applicant refers to the D150 JAR of the preceding MAA ('Alsitek'), but D150 JAR are not consolidated by the CHMP and there was no recommendation with regard to tipping point analysis or copy-increment in reference approach in the respective consolidated D180 LoOI.

The Applicant suggests that missing values associated with discontinuation due to travel, cancer, death, non-compliance, being fed up with study procedures and protocol deviations should be assumed to be missing at random (Argument 4.5, Argument 4.10), which can be understood to reflect a hypothetical strategy assuming that these events had not occurred. However, an estimand based on the treatment policy strategy for discontinuation due to any reason is considered to better reflect what to expect in clinical practice and is thus of primary interest from a regulatory perspective. Moreover, it is considered infeasible to reliably decide whether a patient’s discontinuation was related to the study drug or not. A statistical approach based on model fit is not an appropriate method for deciding on the missing data mechanism or selecting strategies to address intercurrent events (Argument 4.7). Further, the details and purpose of the model-fit analysis are unclear. Typically, the AIC is used to compare models with different covariate sets. In the analysis presented by the Applicant the models seem to differ in the definition of the dependent variable. It is unclear how the AIC can be used for a comparison of models with different dependent variables.

Besides, death should have been handled as a separate intercurrent or rather terminal event. Neither the treatment policy strategy nor the hypothetical strategy can be reasonably applied to death. One option might be to use a composite strategy, for instance setting the ALSFRS-R values at study week 48 for deceased patients to zero as implemented for the mLOCF approach. However, as there is no single adequate approach for the handling of the terminal event death, it is difficult to decide *post hoc* which method to apply. The number of deaths was similar between the treatment arms in the main study period.

Consequently, applying the JTR approach to all values which were missing due to discontinuation of treatment independent of the underlying reason is considered the most relevant analysis. The Applicant argues that this 'full JTR' approach in the normal progressors exhibits a trend towards benefit (Argument 4.8) but fact is that this approach did not demonstrate superiority of Masitinib AB Science against placebo with a point estimate of 2.31 and 95% confidence interval of (-0.17; 4.80). Of note, repeated confidence intervals should have been provided which would be even wider. Further, when a submission is based on only one pivotal (ie. confirmatory) study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality and internal consistency (CPMP/EWP/2330/99).

As discussed above, applying the JTR approach only to a subset of discontinued patients (Argument 4.9) is not considered to provide relevant information.

The Applicant clarified that in the JTR analysis provided with the last responses, imputation of missing data after discontinuation for reasons other than lack of efficacy or toxicity did not rely on the mLOCF approach but on copy increment from 'similar' patients (cluster-based imputation) (Arguments 4.3, 4.4).

However, cluster-based imputation is not considered to give a realistic estimate for the disease course after discontinuation, i.e. is not considered suitable for targeting the treatment policy strategy.

The Applicant also provided additional analyses using different imputation strategies for the secondary variables ALSAQ-40 and FVC (Argument 4.14). Again, using JTR for all missing values caused by discontinuation ('full JTR' termed by the Applicant) is considered the most appropriate strategy. It is unclear whether this method is among the provided analyses, as 'MI+JTR' might as well refer to applying JTR to all missing observations or only to the missing values considered to be MNAR. Regardless, both secondary endpoints are of supportive nature and cannot compensate for a failed primary endpoint.

The precedent of the marketing authorisation for Qalsody discussed by the Applicant (Argument 4.31) is acknowledged however it should be noted that every MAA is assessed on its own merit, based on the totality of the data presented in the application, in support of the claimed indication.

The focus of this ground for reexamination was the handling of missing values. Thus, a discussion of

- whether the quantity of missingness is in line with other studies (Argument 4.1),
- the relevance of a p-value of 0.07 observed for CAFS (Argument 4.13),
- the results of secondary endpoints independent of imputation strategies (Arguments 4.15, 4.16, 4.18, 4.19, 4.20),
- the robustness of progression-free survival (Argument 4.17),
- the reasons for unavailability of measurements of muscle strength within trial AB10015 and the level of importance of this parameter (Argument 4.21),
- why there was no effect observed for tracheostomy-free-survival (Argument 4.22),
- the resolution of the issue of unavailability of results for tracheostomy-free-survival at D120 (Argument 4.23),
- the robustness, relevance and unbiasedness of overall survival (Arguments 4.24 and 4.25),
- the consistency between ALSFRS, PFS and OS (Argument 4.26),
- the lack of treatment alternatives for ALS (Argument 4.27),
- the plausibility of the delayed treatment effect (Argument 4.29),
- the general experience of practitioners with masitinib (Argument 4.32) and
- the general opinions of patient associations with regard to masitinib (Argument 4.33)

is considered to be out of the scope of this ground because none of the above arguments discuss the Applicant's strategy for handling the intercurrent event of treatment discontinuation including the approach(es) to handle missing data and the appropriateness of the underlying assumptions on missingness patterns inherent to the chosen methods.

Regarding Argument 4.1, whether the quantity of missingness is in line with other studies is not relevant for the discussion on the strategies for handling the intercurrent event of treatment discontinuation and methods to handle missing data. However, the high discontinuation rates and large amount of missing data makes inference very sensitive to imputation assumptions and techniques used. In other words, the impact of an inappropriate selection of methods on handling missing data on the validity of the results is higher due to the large amount of missing data.

The discussions on the results of secondary endpoints independent of imputation strategies (Arguments 4.13, 4.15, 4.16, 4.17, 4.18, 4.19, 4.20, 4.22, 4.26), overall survival (Arguments 4.24, 4.25, 4.26) are

not discussing the Applicant's strategy for handling the intercurrent event of treatment discontinuation including the approach(es) to handle missing data and the appropriateness of the underlying assumptions on missingness patterns inherent to the chosen methods. Thus, are not relevant for the assessment on whether this ground for refusal is solved or not.

Same applies to the other arguments potentially relevant for the efficacy in the context of this MAA (Arguments 4.21, 4.23, 4.29) or completely out of the scope of a discussion of a B/R balance (Arguments 4.27, 4.32, 4.33).

In summary, the estimand based on the treatment policy strategy for missing values caused by discontinuation due to any reason is the preferred one from a regulatory perspective. Furthermore, it is agreed with the previous assessment that this estimand is best implemented using the jump-to-reference approach. Based on this approach already the provided naive 95% confidence interval included zero for the analysis population of 'normal progressors'. As discussed above, repeated confidence intervals should have been provided, maintaining the simultaneous coverage probability taking into account the interim and the final analysis. The repeated confidence interval would be even wider than the provided confidence interval. The previous CHMP opinion is upheld.

4. The strategies to post hoc identify new target populations ("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version of 4.1) are considered as data driven decisions and are, therefore, not acceptable.

The Applicant showed an imbalance of distribution and baseline data in the subset of patients of normal progressors (for a discussion on the subgroup of normal progressors see Ground #2.2. above) with at least one loss of function ('very severe' ALS, i.e. score of 0 on at least one ALSFRS-R item), and presented modified baseline data excluding this subset as 'new data' (Argument 5.1). However, the observed imbalance is not surprising, as no stratification was implemented to account for this *post hoc* identified predictive factor, which was also pointed out by the Applicant, and does not justify the *post hoc* modification of the analysis population. In principle, since these results are *post hoc* analyses and derived from a highly selected patient population, they have a high probability of being chance findings and not deemed confirmatory. Nevertheless, even if the definition of the new target population was deemed appropriate (which it is not), the efficacy in the proposed severity subgroup (prior to any loss of function) is only improved for OS (Argument 5.7), but not for the primary endpoint, for which the efficacy is similar to the normal progressors analysis population, questioning the biological plausibility. The Applicant provided further *post hoc* analyses compiling yet another subgroup, claiming that with fast progressors included, the proposed severity subgroup still shows a treatment effect and improved safety (Argument 5.8). Only the *post hoc* exclusion of 'very severe' ALS patients allows – in the view of the Applicant – an extrapolation from normal to fast progressors (Argument 5.9). These analyses suffer from similar shortcomings as the subgroup analysis of patients prior to any loss of function and are thus not considered relevant for the overall conclusion.

Even if the proposed population restriction may be acceptable to enrich a population in a future clinical trial, the *post hoc* analyses in study AB10015 are at best exploratory and would need confirmation in another RCT. Moreover, the proposed indication to only include ALS patients prior to any loss of function may not be practicable in clinical routine, as treatment with Masitinib AB Science would have to be stopped in a patient with any loss of function while on treatment. However, no stopping rules are foreseen in the proposed SmPC for Masitinib AB Science.

For a subgroup to be considered credible within the scope of Section 5.3. Assessment scenario 2 of EMA/CHMP/539146/2013 (Arguments 5.2-5.6), several criteria need to be fulfilled (see below). However, there is no convincing external evidence that the subgroup of interest is well-defined and clinically relevant, and there is no replication of subgroup findings from other relevant trials. Furthermore, the biological plausibility is not considered exceptionally strong. The fact that there is only one pivotal trial,

which is not considered to yield compelling results, only adds to the uncertainties related to efficacy results, hampering a conclusion of true benefit.

The Applicant provided detailed explanations (Argument 5.6) why the five criteria apply for the subgroup to be considered credible, which is not agreed by CHMP, since not all criteria are fulfilled: (1) The subgroup definition of very severe ALS is of debatable clinical relevance, as the external evidence is based on *post hoc* analyses of the edaravone MCI 186-16 trial, incorporated as inclusion criteria in the MCI 186-19 trial. Both trials used LOCF as imputation method, which may be considered overly optimistic. Furthermore, the analysis population differed in other aspects from study AB10015 (%FVC, disease duration). The main focus of Meier et al 2022 was to facilitate assessment of the ALSFRS-R, rather than demonstrating clinical relevance or predictive value of individual scores. (2) The pharmacological rationale for differential efficacy in less severely affected patients appears plausible. Masitinib acts on the innate immune system and not on neuronal function per se. Therefore, neuronal loss cannot be reversed by treatment with masitinib. (3) The larger treatment effect in the subgroup cannot be confirmed from the provided tables and figures with certainty as the details of the underlying analyses are insufficiently described. However, the previous opinion that the *post hoc* enrichment strategy based on survival data is deemed inappropriate, is upheld. (4) Replication of subgroup findings from other relevant trials (i.e. trials investigating the efficacy of masitinib) is currently not available. The biological plausibility is not exceptionally strong as it is only established in preclinical studies. Therefore, clinical trial data from AB10015 suggesting improved efficacy in some endpoints in the subgroup is considered a circular argument. (5) Whether the safety data in the subgroup is improved cannot be concluded with certainty, as the safety data may not be of sufficient quality due to reporting issues (see Ground #2.1).

It is reiterated that reference to other procedures (Argument 5.11) is inappropriate, as each product's benefit-risk needs to be assessed individually and comparative assessment of different applications cannot be done as there are multiple factors affecting the benefit-risk evaluation for each application.

Taken together, the *post hoc* identification of the target population 'ALS patients prior to any loss of function' as proposed in the latest version of 4.1 of the SmPC, is considered data driven and exploratory. Moreover, the proposed indication to only include ALS patients prior to any loss of function may not be practicable in clinical routine, as treatment with masitinib would have to be stopped in a patient with any loss of function while on treatment. The previous CHMP opinion is upheld and no amendments to the B/R are necessary.

In the latest stage of the assessment, the Applicant proposed a new claimed indication as follows: "*Masitinib, in combination with riluzole, is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS)*". Therefore, in light of the latest claimed indication, this subitem of the ground 2.2 becomes obsolete and is not further pursued.

Overall conclusion of Ground 2.2

The overarching ground for refusal (#2.2) was that the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS. It is not agreed that normal progressors constitute the primary analysis population, the ITT full study population (normal + fast progressors) is considered the primary efficacy population. The categorization of the population between normal and fast progressors is not agreed. The approach to handle missing data due to the intercurrent event treatment discontinuation is not agreed as it does not address the estimand of primary interest from regulatory perspective. The *post hoc* identification of the target population initially proposed for section 4.1 of the SmPC is considered data driven and not acceptable. However, in light of the latest claimed indication, this last point is not further pursued.

Given that all the other points of ground 2.2 remain unsolved, the overarching ground 2.2 remains

unsolved.

Point not resolved

5.1.4. Ground #3

A CMA requires that all requirements as described in Article 4 of Commission Regulation (EC) No. 507/2006 are met. In addition to not fulfilling the first criterion, which relates to the positive benefit / risk balance, also other CMA criteria are not considered fulfilled: it is considered unlikely that the Applicant will be in a position to provide comprehensive clinical data post-authorisation, the Applicant has not sufficiently justified that Masitinib AB Science would provide a major therapeutic advantage versus tofersen and, taking all the above into account, it is considered that the benefits to public health of the immediate availability of Masitinib AB Science do not outweigh the risks inherent in the fact that additional data are still required.

Applicant´s position on the for re-examination

The Applicant presented first some statements included in section 2.6.6 of the CHMP AR.

1. It is considered unlikely that the Applicant will be in a position to provide comprehensive clinical data post-authorisation

As per the requested CMA, the Applicant initially presented study AB19001 as proposed specific obligation that would provide comprehensive evidence on efficacy and safety of Masitinib AB Science post approval. […].

During the procedure, the Applicant stated that the enrolment in study AB19001 has been slow due to the restrictive design features of that study (i.e. long 3 months run-in period, with no control of FVC at baseline / Moderate ALS only / approved treatment in the USA - Edaravone, Relyvrio – not allowed / blinded extension at week 48). Consequently, the Applicant proposed to conduct a new confirmatory study post approval - AB23005 study- and presented the AB19001 study as an exploratory study.

Study AB23005 is a multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase 3 Trial to evaluate the efficacy and safety of masitinib as add-on therapy in ALS patients treated with standard of care. Patients will be randomized (1:1) to receive Masitinib AB Science 4.5 mg/kg/day or matching placebo and Masitinib AB Science 6 mg/kg/day will not be pursued further in the study AB23005. The primary endpoint is the absolute change in ALSFRS-R from baseline to week 48. In this study, the secondary endpoints include measurements of muscle strength, progression free survival and overall survival. According to the synopsis of the study provided during the procedure, the primary efficacy population will be the ITT (all randomized full study population). The Applicant specifies two measures of ALSFRS-R progression rate (point/month) will be evaluated at screening to categorize ALS patient as slow, moderate, or fast progressor. As per the inclusion criteria, only patients with a ALSFRS-R progression rate between > 0.3 and <1.1 point/month as measured between onset of the disease and screening AND as measured by any available ALSFRS-R assessment during the period ranging from 7 months to 2 months prior to screening and screening, reassessed and documented by certified rater performing ALSFRS-R assessment from screening visit onward will be enrolled (synopsis of AB23005 protocol). Further restriction is included as per the baseline ALSFRS-R scores as a total score of at least 15 points of ALSFRS-R at baseline and screening [at least 3 in item3; at least 2 in item12; at least 1 in each of the other items] is also requested as inclusion criterion. All aforementioned considerations on using delta FS to select study population are also applicable here. While no further categorization is proposed to be done after enrolment (i.e. primary efficacy population is full study population), it is considered that the mentioned inclusion criteria could lead to the inclusion of a restricted ALS population. Moreover, it is considered that a duration of the study AB23005 (48 weeks) might not be long enough

to generate sufficient data on survival events, which are necessary to support the primary endpoint and considering that the positive data on survival or survival equivalent are expected.

Besides to the above considerations on the study design features and the potential impact on the ability of Study AB23005 to provide comprehensive evidence, the CHMP was concerned about the feasibility to properly conduct that study if Masitinib AB Science is authorised in the EU. It needs to be bear in mind that ALS is a fatal condition for which the only therapeutic options in the EU are symptomatic treatment and riluzole for all ALS patients except those with SOD1-ALS. Hence, the CHMP is concerned that the authorisation of Masitinib AB Science will impact the recruitment and the conduction of the AB23005 study in the EU sites as ALS patients will likely start (i.e. impact on recruitment) or shift (i.e. impact on conduction) to the commercial Masitinib AB Science when available. The new confirmatory AB23005 study is expected to enrol 408 patients. The Applicant presented a feasibility analysis and concluded that a total of 855 patients could be enrolled over a 12-month period including 583 patients in non-EU countries and US. The Applicant claimed that Study AB23005 can be completed within 2.5 years with involvement of site from USA and other non-EU countries or within 3 years with involvement of site only from other non-EU countries. These figures assume the study starts in Q2 2024. Thus, the Applicant position is that confirmatory study AB23005 is feasible outside of the EU and further facilitated since Relyvrio is withdrawn from market in USA and Canada. However, considering the numerous changes undertaken in the protocol of the pivotal study during its execution as well as the slow enrolment in the study AB19001, which became an exploratory study later on, the Applicant capability of properly conduct this study is still unclear, despite the Applicant's declared commitment.

In view of the above, high uncertainties remain with regard to the possibility to provide comprehensive clinical data, should a CMA have been granted.

AB Science Response

Argument 6.1: Confirmatory study will enroll 408 patients and feasibility shows enrolment of 583 patients from 62 sites per 12 month period outside of EU countries

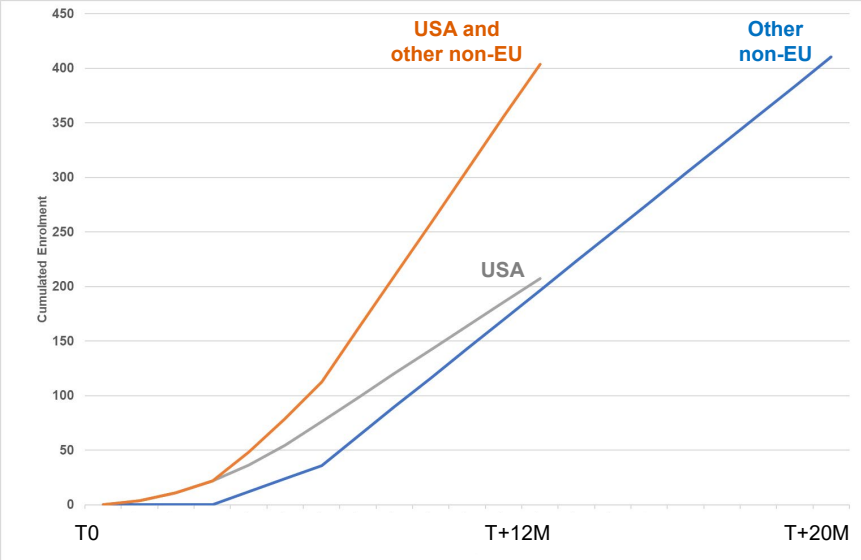
Table 146: AB23005 feasibility study for non-EU sites

Country	Sites	Planned enrolment per 12-month period
USA	**36**	**262**
Other non-EU countries	**26**	**321**
Argentina	5	47
Australia	4	24
Brazil	1	48
China	3	75
Israel	2	20
Japan	2	11
Russia	1	24
Saudi Arabia	1	12
Serbia	1	10
South Korea	5	43

Ukraine	1	7
Total Non-EU countries	**62**	**583**

Argument 6.2: Study AB23005 can be completed within 2.5 years with involvement of site from USA and other non-EU countries or within 3 years with involvement of site only from other non-EU countries

Figure 19: AB23005 planned enrolment based on feasibility study



Argument 6.3: Albrioza is not marketed anymore and other obstacles to enrolment in study AB19001 are removed with AB23005 study design

AB Science identified several delaying factors in the study AB19001 that are responsible for this the slow enrolment, and are circumvented with AB23003 study design, namely

- Absence of 12-week run-in period
- Enrolment of moderate and severe (ALSFRS≥1) ALS patients, as opposed to moderate (ALSFRS≥2) ALS only
- Albrioza is no longer marketed, whereas AB19001 study did not authorized concomitant treatment with Albrioza
- Edaravone will be eligible in the country where it is registered, whereas AB19001 study did not authorized concomitant treatment with Edaravone
- Authorization of an Open Label Extension beyond week 48, whereas its absence in AB19001 study led certain advocacy groups and patients to boycott study AB19001
- Absence of investigation of Masitinib 6.0 mg/kg/day group treatment group

Argument 6.4: The design of the confirmatory study AB23005 has been endorsed by the SAWP

In the Scientific advice procedure regarding the design of AB23005 phase 3 masitinib confirmatory study (EMADOC-360526170-1973369), the scientific advice working party (SAWP) indicated, overall that the

study design was acceptable from the high-level point of view.

The endorsement of the study design by the SAWP will facilitate the rapid initiation of study AB23005

2.The Applicant has not sufficiently justified that Masitinib AB Science would provide a major therapeutic advantage versus tofersen.

The Applicant presented first some statements included in section 3.7.3 of the CHMP AR.

The third criterion requires that unmet medical needs will be fulfilled. As other medicinal products for the treatment of ALS are authorised in EU, the Applicant should justify that Masitinib AB Science provides a major therapeutic advantage (MTA) over each existing authorised medicinal products in an overlapping indication, in case a CMA would be granted. The currently authorised medicinal products for ALS are riluzole and tofersen (the latter, only for SOD1-ALS).

The pivotal study AB10015 of this CMA is a prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase II/III study to compare the efficacy and safety of Masitinib AB Science versus placebo in ALS patients. The study objective was to evaluate efficacy and safety of Masitinib AB Science as add-on therapy to riluzole. Indeed, all patients included in this pivotal study received riluzole. Hence, this pivotal trial is designed to measure causal effects (efficacy) of Masitinib AB Science on top of Riluzole. If efficacy was demonstrated for Masitinib AB Science on top of riluzole in this pivotal trial, the differences in ALSFRS-R score and survival equivalent (PFS) estimates observed in the pivotal trial in favor of Masitinib AB Science arms in principle could have been considered as meaningful improvements of morbidity or mortality of the disease and thus supporting that Masitinib AB Science provides MTA versus riluzole. However, as efficacy was not demonstrated, it cannot be concluded whether Masitinib AB Science provides a MTA versus riluzole.

On the other hand, the Applicant provided a succinct justification of an MTA over tofersen during the oral explanation. The Applicant claimed that Masitinib AB Science and tofersen have different mechanisms of action. This is agreed; however, a different mechanism of action does not automatically justify for MTA, it needs to be justified that the new mechanism of action provides a significant clinical advantage versus the existing therapies. In accordance with the Guideline on the scientific application and the practical arrangements necessary to implement Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 MTA would normally be based on meaningful improvement of efficacy or clinical safety or, in exceptional cases, on major improvements to patient care. Furthermore, the Applicant claimed that SOD1-ALS represents approximately 2% of people living with ALS. This is also correct, but the MTA needs to be justified in the overlapping indication. Hence, in view of the claimed indication for Masitinib AB Science, it is still the case that the Applicant has to demonstrate that Masitinib AB Science provides MTA versus tofersen in the SOD1-ALS subpopulation. Finally, the Applicant claimed during the oral explanation that Masitinib AB Science makes a major contribution to patient care with a benefit on ALSFRS, QOL, and PFS, OS (+ 12 months).

Based on the above, it is understood the Applicant is claiming MTA based on improved efficacy and major contribution to patient care. With regard to the first claim (i.e. improved efficacy), it needs to be considered that the pivotal trial did not enroll any patient treated with Qalsody. It is unclear whether SOD1-ALS patients were enrolled at all in the pivotal trial. The Applicant has not sufficiently justified that the claimed benefits– if finally accepted by the CHMP- could be extrapolable to the SOD1-ALS subpopulation who could benefit from a more targeted therapy (Tofersen addressed overexpression of SOD1 as a key pathological mechanism of damage in SOD1-ALS) and thus, provides meaningful improvement of efficacy versus tofersen in this ALS sub-population. With regard to the third claim (i.e. major contribution to patient care), the Applicant has not sufficiently justified which is exactly the contribution to the patient care.

AB Science Response

Argument 7.1: Alsitek (masitinib) would provide a major therapeutic advantage versus Qalsody (tofersen) in terms of improvements to patient care

Following the recent approval of Qalsody (tofersen), there is an overlap between Qalsody and masitinib indications, namely, the SOD1-ALS subpopulation, which comprises just 2% of the overall ALS population. Because there is no data available for direct, or indirect, comparison of efficacy between masitinib and Qalsody, we must instead consider other relevant aspects, such as patient burden associated with route of administration, procedural complications and safety concerns.

- *Tofersen is administered directly into the cerebrospinal fluid through intrathecal lumbar puncture and is absorbed by the central nervous system.*

A lumbar puncture involves using a long, thin needle to puncture the skin and its underlying structures in the lower back, allowing access to the space surrounding the spinal cord for drug delivery. Antisense oligonucleotide drugs do not readily pass through the blood-brain barrier and, as a result, must be administered directly into the central nervous system (CNS). Before administering a dose of tofersen, it is recommended to extract 10 mL of cerebrospinal fluid (CSF) from the patient [Cerillo 2023]. This procedure prevents fluid overload and reduces the potential risk of increased intracranial pressure. To administer tofersen in patients, it is recommended to inject the medication slowly for 1 to 3 minutes using the same lumbar needle previously employed for the removal of the CSF.

The recommended dosage of tofersen for adults is 100 mg (per 15 mL) per administration. The administration of tofersen begins with 3 loading doses, followed by a monthly maintenance dose. The first 3 doses of 100 mg are administered to patients at 14-day intervals, with subsequent doses provided at 28-day intervals after that [Qalsody SmPC].

Patients may be given a sedative if tofersen administration causes them severe distress [Cerillo 2023]. Lumbar punctures can be uncomfortable procedures and often lead to lower back discomfort, headaches, and dizziness. Imaging techniques, such as computed tomography and ultrasound guidance, may also be used to ensure accurate needle placement and depth during the tofersen administration; however, both measures add further complexity and expense to the procedure or will simply not be available options for all physicians.

The most common adverse effects of tofersen are headache, injection-site pain, fatigue, arthralgia (joint pain), pleocytosis (increase in CSF white blood cells), and myalgia (muscle pain) [Miller 2020; Miller 2022]. Tofersen may also cause more serious adverse events, including:

- inflammation and damage of the spinal cord and nerve roots (i.e., myelitis and radiculitis)
- swelling and increased pressure in the optic nerve and brain (i.e., papilledema and elevated intracranial pressure)
- inflammation of the membranes covering the brain and spinal cord (i.e., aseptic meningitis, also called chemical meningitis or drug-induced aseptic meningitis).

These adverse effects may arise due to direct drug effects or complications related to administering the drug through a lumbar puncture, which introduces foreign materials into the sterile CNS cavity [Cerillo 2023].

The aforementioned clinical trial safety concerns have been reproduced in the real-world setting, with pleocytosis, elevated protein levels and intrathecal immunoglobulin synthesis being common findings in the CSF [Wiesenfarth 2024]. In a cohort of 24 patients with SOD1-ALS from ten German ALS reference centers, pleocytosis was observed in 73% of patients (11 of 15) and an intrathecal immunoglobulin synthesis (IgG, IgM, or IgA) was seen in 9 out of 10 patients. Pleocytosis and Ig synthesis in CSF with

clinical symptoms related to myeloradiculitis in two patients, indicates the potential of an autoimmune reaction. The authors concluded that such alterations in the CSF are suggestive of an autoimmune inflammation of the CNS, which necessitates special attention when treating patients with tofersen.

In conclusion, tofersen treatment comes with considerable patient burden that is primarily related to the monthly intrathecal administration of the drug. This is turn raises questions of patient compliance over the longer-term. Furthermore, adverse effects related to this route of administration can be severe and potentially life-threatening, necessitating an immediate diagnostic workup and prompt medical treatment (if applicable) to aide recovery, with cessation of tofersen dosing thereafter.

For those SOD1-ALS patients that experience serious complications related to administration of the drug, or who find the burden/risk of regular intrathecal lumbar puncture procedures unacceptable, or who are unresponsive to tofersen, there remains an urgent unmet medical need.

- *Masitinib is an orally administered, CNS-penetrative drug, with minimal patient burden or risks associated with its route of administration*

Masitinib is an orally administered, film coated tablet formulation, which can penetrate the CNS at therapeutically relevant concentrations. In contrast to tofersen, masitinib carries none of the safety complications or patient burden associated with invasive intrathecal lumbar puncture administration. Moreover, masitinib is comparatively simple to take, allowing for convenient, safe and inexpensive self-administration, outside of the hospital setting, all of which are beneficial for improved patient compliance. Indeed, in the primary efficacy population of study AB10015, mean treatment compliance was 97.9% for masitinib 4.5 mg/kg/day versus 95.6% for active control. This excellent rate of compliance was also seen in the study's overall population, with a mean treatment compliance of 96.8% for masitinib-treated patients versus 95.5% for active control.

Masitinib therefore provides a major therapeutic advantage for all those patients unable or unwilling to take tofersen, for whom, riluzole remains the only available treatment option.

Argument 7.2: Safety Profile and Autoimmune Reactions

Autoimmune reactions were a significant safety concern in the VALOR study, with approximately 6% of patients experiencing these events. These reactions included:

1. Pleocytosis (10-12%): An increase in white blood cells in the cerebrospinal fluid, sometimes asymptomatic but indicative of central nervous system inflammation.
2. Skin Rashes (4-5%): Mild to moderate erythematous or urticarial lesions.
3. Autoantibody Elevations (3%): Indicative of generalized immune activation, potentially leading to autoimmune conditions.
4. Systemic Inflammatory Syndromes (<2%): Symptoms like fever, fatigue, and joint pain, requiring immunosuppressive treatment.

During post-marketing surveillance under conditional approval, the frequency of autoimmune reactions remained consistent with VALOR study findings, indicating a persistent risk.

- Autoimmune reactions are a significant safety concern for several reasons:
- Chronicity: Autoimmune reactions can be persistent and difficult to manage, potentially leading to chronic conditions that could outweigh the benefits of ALS treatment.
- Severity: In some cases, autoimmune responses can lead to severe, life-threatening conditions, particularly if they involve the CNS or other vital organs.

Impact on ALS Patients: ALS patients are already in a fragile health state, and the added burden of an autoimmune condition could accelerate disease progression or reduce the quality of life.

In conclusion, while tofersen shows potential benefits for SOD1-related ALS, the occurrence of autoimmune reactions, such as pleocytosis and systemic inflammatory syndromes, raises significant safety concerns while no significant effect on disease progression has been provided so far.

Argument 7.3: Masitinib has shown clinical and survival benefits that have not been demonstrated for Qalsody

Despite there being no head-to-head trial of masitinib against Qalsody, masitinib has demonstrated both clinical benefit (e.g., ΔALSFRS-R, ΔFVC and ΔQoL) and survival benefit (e.g., OS, CAFS and PFS) to an extent that has not been demonstrated to date with Qalsody (see table below).

The efficacy of Qalsody has been predominately established on a significant reduction of SOD1 protein in cerebral spinal fluid, a marker of target engagement, and significant reduction of neurofilament light chain (NfL) in plasma, a potential marker of disease-modifying effect. However, clinical progression parameters such as ALSFRS-R, respiratory function, and quality of life did not reach statistical significance after 6 months. No survival benefit over placebo has been demonstrated for Qalsody.

	Masitinib (AB1010)	Qalsody (tofersen)
Study Code	AB10015 (NCT02588677)	VALOR (NCT02623699)
Number of patients	N = 394 (ITT) Placebo = 132 masitinib 3.0 mg/kg/day = 131 masitinib 4.5 mg/kg/day = 128 Patients assessable for the primary endpoint Placebo = 102 masitinib 4.5 mg/kg/day = 99	N = 108 (ITT) Tofersen = 72 Placebo = 36 Patients included in primary efficacy population (mITT) Tofersen = 39 Placebo = 21
ALSFRS-R (Primary endpoint)	Between group difference at W48 = 3.39 points/mo 95%CI(0.65–6.13); P = 0.016 (masitinib 4.5 mg/kg/d vs placebo)	- mITT Adjusted mean difference at W24 = 1.2 points/mo (95%CI[-3.2,5.5]); P = 0.9689 - ITT Adjusted mean difference at W24 = 2.1 points/mo (95%CI[-0.3,4.5]); P = 0.5015
CAFS (Secondary endpoint)	Between group difference = 14.95; P = 0.0776 (masitinib 4.5 mg/kg/d vs placebo)	Not done
ALSAQ (Secondary endpoint)	ALSAQ-40 LMS Difference = -7.8 [-13.5 ; -2.1], p=0.008 (masitinib 4.5 mg/kg/d vs placebo)	ALSAQ-5 - mITT Adjusted mean difference at W24 = -5.6 95%CI[-15.6,4.4]); P = 0.2715 - ITT Adjusted mean difference at W24 = -5.7 (95%CI[-11.8,0.4]); P = 0.0668
FVC (Secondary endpoint)	FVC LMS Difference = 7.5 [0.8 ; 14.3]; p=0.03 (masitinib 4.5 mg/kg/d vs placebo)	SVC - mITT Adjusted mean difference at W24 = 7.9 95%CI[-3.5,19.3]); P = 0.3233 - ITT Adjusted mean difference at W24 = 8.5 (95%CI[1.8,15.2]); P = 0.0689
HHD Megascore (Secondary endpoint)	Not done	- mITT Adjusted mean difference at W24 = 7.9 95%CI[-0.21,0.26]); P = 0.8390 - ITT Adjusted mean difference at W24 = 0.1 (95%CI[-0.04,0.23]); P = 0.1547
TIME-TO-EVENT (Secondary endpoint)	PFS Median[95%CI] PBO = 16 months [11;19] M4.5 = 20 months [14;30] Difference = 4 months; p = 0.016 (masitinib 4.5 mg/kg/d vs placebo)	Time to Death or PV Not estimable due to limited number of events
Overall survival (months) (Secondary endpoint)	OS (Long-term analysis) LT-M4.5 (≥2 each baseline ALSFRS-R item, any ΔFS) - Masitinib median OS = 69 [44;NE] - Placebo median OS = 44 [31;62] - Survival benefit = 25 months; p = 0.037 - HR = 0.56 (95%CI [0.33–0.97]);	OS Not estimable due to limited number of events

	Masitinib (AB1010)	Qalsody (tofersen)
	P=0.037 - 44% reduced risk of death LT-M4.5 (≥2 each baseline ALSFRS-R item, ΔFS<1.1) - Masitinib median OS = 69 [47;NE] - Placebo median OS = 44 [31;62] - Survival benefit = 25 months; p = 0.037 - HR = 0.53 (95%CI[31–92]); P=0.025 - 47% reduced risk of death (masitinib 4.5 mg/kg/d vs placebo)	

Argument 7.4: Preclinical evidence based on the SOD1^{G93A} model has strongly established masitinib's biological plausibility in ALS, with its clinical benefits therefore extrapolatable to SOD1-ALS patients

The Applicant confirms that no head-to-head data exist that would permit a direct comparison of masitinib versus Qalsody efficacy in the SOD1-ALS subpopulation. Indeed, no clinical data is available for masitinib in the SOD1-ALS subpopulation as ALS genotypes were not assessed as part of study AB10015. There is, however, a wealth of preclinical evidence based on the SOD1^{G93A} model, which has strongly established masitinib's biological plausibility in ALS.

The SOD1 model recapitulates the complexity of a multicomponent immune response with concomitant evidence of neurodegeneration [Kovacs 2021; Trias 2020; Harrison 2020; Trias 2018; Trias 2017; Trias 2016]. Of significance, these data also provide a direct link between SOD1 model-derived evidence and human ALS pathology (with data being derived from ALS patient autopsied quadriceps femoris muscles) [Kovacs 2021; Trias 2018]. This clearly implies that cell targets identified in masitinib preclinical studies are also implicated in ALS human pathology and supports the relevance of masitinib SOD1 model data to human pathology.

Recently generated preclinical evidence further support the mechanism of action of masitinib in ALS. masitinib has been shown to limit neuronal damage in a model of neuroimmune-driven neurodegenerative disease [Hermine 2024], the results of which can be extrapolated to ALS. Neuronal damage, or prevention thereof, can be rapidly assessed by measuring serum neurofilament light chain (NfL) concentration in EAE-induced mice. Results showed that masitinib can significantly lower serum NfL levels in this neurodegenerative disease model, with concomitant reduction in pro-inflammatory cytokines and slowing of clinical (EAE) symptoms. The observed NfL treatment response indicates that masitinib has a neuroprotective effect under conditions of chronic neuroinflammation and therefore plausible disease-modifying activity in ALS.

Taken together these preclinical findings establish the biological plausibility for using masitinib in ALS and support the hypothesis that masitinib may provide a neuroprotective effect in the clinical setting for both SOD1-ALS and sporadic ALS patients. Likewise, the clinical benefits observed in study AB10015, which was undoubtedly performed in a predominantly sporadic ALS population, are extrapolatable to SOD1-ALS patients.

- Based on the results from study AB10015, there is evidence of clinical effectiveness in the treatment of ALS patients, with Masitinib AB Science 4.5 mg/kg/day providing a significant increase in efficacy in terms of slowing disease progression such that the overall benefit profile is improved over marketed ALS therapies in Europe. Data also presented an acceptable clinical safety profile in these patients who require effective new therapies for this progressive, life-threatening medical condition.
- Based on the long-term survival results from study AB10015, there is promising evidence of clinical effectiveness in the treatment of ALS patients (prior to any complete loss of functionality), with masitinib 4.5 mg/kg/day providing a significant increase in efficacy in terms of reduced mortality when compared to riluzole alone.

Key findings from the rodent SOD1 model studies are briefly described below.

- Masitinib treatment in post-paralytic SOD1G93A rats [Trias 2016] was shown to modulate the functionality of microglia cells in terms of: preventing microglia proliferation, migration, and

transformation into neurotoxic aberrant glial cells; reducing the number of aberrant glial cells in the degenerating spinal cord; inhibiting microgliosis along the degenerating spinal cord; inhibiting microglia proinflammatory phenotype; and improving motor neuron pathology.

- This modulation of microglia activity was also shown to translate into a significant survival advantage [Trias 2016]. Masitinib treatment initiated at the time of paralysis onset or 7 days after paralysis onset prolonged post-paralysis survival by 35% and 50%, respectively, with respect to the control group.
- There is massive infiltration and accumulation of mast cells around degenerating motor axons and neuromuscular junctions in SOD1G93A rats with degranulation of mast cells correlating with paralysis progression. This indicates that mast cells may be deleterious for the maintenance of functional neuromuscular junctions. Because neuromuscular junctions serve as a critical link between skeletal muscles and the nervous system, this finding represents a novel pathogenic mechanism in ALS that can be therapeutically targeted by masitinib [Trias 2017].
- Masitinib-induced mast cell inhibition significantly reduced the rate of neuromuscular junction denervation and motor deficits in SOD1G93A rats [Trias 2017].
- Post-paralysis administration of masitinib to SOD1G93A rats, reduced the loss of 2B myofibers isotype in the EDL muscle [Trias 2018], slowing motor function decline [Trias 2017].
- Masitinib preserved muscle strength as evidenced by a significantly improved latency-to-fall time (inverted screen test) from 5–15 days after onset [Trias 2017].
- Massive mast cell infiltration was observed in sciatic nerve and ventral roots of SOD1G93A rats during paralysis progression [Trias 2018].
- Mast cells infiltrate into the degenerating spinal cord of both murine models of ALS and ALS patients [Kovacs 2021]. This phenomenon is accompanied by marked blood spinal cord barrier pathology, characterized by frequent morphological abnormalities such as basal membrane interruptions, strings, and sprouts, allowing the extravasation of cells from blood, including c-Kit+ mast cell precursors. Post-paralysis treatment with masitinib for 10 days significantly reduced the number of c-Kit+ and chymase+ mast cells in the lumbar motor neuron-vascular niche, with respect to the vehicle-treated mice. Also, masitinib-treated animals showed a 30-40% reduction in microvascular abnormalities relative to vehicle- treated mice and a 50% reduction in the number of c-Kit+ mast cell precursors infiltrating the spinal cord parenchyma. These results are consistent with a masitinib protective effect via c-Kit inhibition, preventing the trafficking of mast cell precursors and mast cell local differentiation in the motor neuron-vascular niche.
- Neutrophil infiltration and neutrophil extracellular traps (NET) formation was observed in the extensor digitorum longus (EDL) muscle of SOD1G93A rats during paralysis progression [Trias 2018]. Post-paralysis masitinib administration to SOD1G93A rats significantly reduced both mast cell and neutrophil accumulation, as well as motor pathway degeneration [Trias 2018].
- Schwann cell proinflammatory phenotype is present in both sporadic human ALS subjects and an animal model of ALS. Masitinib treatment in post-paralytic SOD1G93A rats sharply decreased Schwann cell reactivity, immune cell infiltration and proliferation along the peripheral motor pathways [Trias 2020].
- Masitinib also prevented morphological changes (degeneration) in Schwann cells and capillary networks that are typically observed in advanced paralysis [Trias 2017].
- Treating SOD1G93A mice with masitinib significantly reduced macrophage infiltration, prevented terminal Schwann cells loss, and improved reinnervation in partially denervated plantaris muscles [Harrison 2020]. Results suggested that pharmacological interventions maintaining terminal Schwann cells at denervated endplates is a viable treatment strategy to attenuate the loss of motor function in ALS.

Argument 7.5: Significant differences exist between masitinib and Qalsody in terms of mechanism of action and principal molecular structure, therefore, masitinib is not a similar medicinal product to Qalsody

As demonstrated in the Alsitek (masitinib mesilate) Assessment Report on Similarity, significant differences exist between masitinib and Qalsody in terms of mechanism of action and principal molecular structure, therefore, in accordance with Article 3 of Commission Regulation (EC) No 847/2000, masitinib is not a similar medicinal product to Qalsody, even though there is overlap between the therapeutic

indications. Accordingly, the existence of any market exclusivity for Qalsody in the treatment of amyotrophic lateral sclerosis should not prevent the granting of the marketing authorisation of masitinib. Briefly,

- The active substance of Qalsody is tofersen, another nervous system drug (ATC code: N07XX22). Qalsody is an antisense oligonucleotide that binds to the mRNA of the superoxide dismutase 1 (SOD1) gene to reduce the production of SOD1 protein. By reducing the amount of defective SOD1 protein, this medicine is expected to improve the symptoms of ALS. Qalsody will be available as a 100 mg solution for injection and will be given intrathecally by lumbar puncture. Regarding molecular structure, Tofersen, an antisense oligonucleotide, is a 20-base residue (20-mer) 5-10-5 MOE gapmer mixed backbone oligonucleotide. Of the nineteen internucleotide linkages, fifteen are 3′-O to 5′-O phosphorothioate diesters, and four are 3′-O to 5′-O phosphate diesters. Ten of the twenty sugar residues are 2-deoxy-D-ribose and the remainder are 2′-O-(2-methoxyethyl)-D-ribose (MOE). The residues are arranged so that there are five MOE nucleosides at the 5′ and 3′-ends of the molecule flanking a gap of ten 2′-deoxynucleosides. The cytosine and uridine bases are methylated at the 5-position. The molecular formula is C230 H317 N72 O123 P19 S15 and the molecular weight is 7127.86 atomic mass units (amu).

- The active substance of Alsitek is masitinib mesilate, an antineoplastic or immunomodulating agent, other protein kinase inhibitor drug (ATC code: L01EX06). Masitinib inhibits the activity of specific tyrosine kinases such as colony-stimulating factor 1 receptor (CSF1R), c-Kit, LYN, FYN, and platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR- beta), in the sub-micromolar range. Masitinib can also inhibit cellular events mediated by activation of these receptor kinases. It is suggested that masitinib is capable of exerting neuroprotection via selective kinase inhibition that modulates the functionality of different cells implicated in ALS pathogenesis including microglia and mast cells. Masitinib Alsitek is proposed to act by slowing microglial-related disease progression, reducing neuro-inflammation, and modulating the degenerative neuronal microenvironment in both central and peripheral nervous systems. Regarding molecular structure, masitinib is a small molecule drug, selectively inhibiting specific tyrosine kinases. Masitinib is a 2-aminoarylthiazole derivative, which is a compound characterized by the presence of a thiazolyl group substituted on position 2 (i.e., between the heterocyclic nitrogen and sulphur atoms) by a secondary or tertiary amine, wherein the nitrogen atom of the amine is substituted by at least one aryl group. The chemical name for masitinib is 4-(4-methyl-piperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl-thiazol-2-ylamino)-phenyl]-benzamide, methane sulfonic acid salt. The molecular formula is C28 H30 N6 OS and the molecular weight (free base of masitinib) is 498.66 g/mol.

Argument 7.6: Concluding statements on major therapeutic advantage over existing treatments

The efficacy of Alsitek (masitinib) has been demonstrated as an add-on to riluzole, therefore establishing that masitinib provides a major therapeutic advantage over riluzole.

Qalsody treatment comes with considerable patient burden that is primarily related to the monthly intrathecal administration of the drug. Adverse effects related to this route of administration can be severe and potentially life-threatening, with myelitis, radiculitis, papilledema, elevated intracranial pressure and aseptic meningitis being established risks for Qalsody treated ALS patients.

Pleocytosis and Ig synthesis in CSF are suggestive of an autoimmune inflammation of the CNS, which necessitates special attention when treating patients with tofersen.

For those SOD1-ALS patients that experience serious complications related to administration of Qalsody (tofersen), or who find the burden/risk of regular intrathecal lumbar puncture procedures unacceptable, or who are unresponsive to tofersen, there remains an urgent unmet medical need.

Masitinib would provide a major therapeutic advantage versus Qalsody in terms of improvements to patient care. In particular, masitinib addresses serious existing issues with Qalsody treatment

compliance, allowing ambulatory treatment instead of hospital treatment, and removes the safety complications and patient burden associated with monthly intrathecal administration of that drug. Furthermore, masitinib has shown no signs of causing autoimmune-related complications.

Despite there being no head-to-head trial against all marketed ALS therapies, masitinib has shown both clinical benefit (e.g., ΔALSFRS-R, ΔFVC and ΔQoL), and survival benefit (e.g., OS, CAFS and PFS) to an extent that has not been demonstrated to date with other marketed ALS therapies. Moreover, preclinical findings support the hypothesis that masitinib may provide a neuroprotective effect for both SOD1-ALS and sporadic ALS patients. It follows therefore, that the aforementioned clinical benefits observed in study AB10015 should be extrapolatable to SOD1-ALS patients.

Finally, it is also pertinent to emphasis that approximately 98% of the overall ALS population are not eligible for Qalsody.

CHMP position on the Ground for re-examination

1. It is considered unlikely that the Applicant will be in a position to provide comprehensive clinical data post-authorisation.

The Applicant is proposing confirmatory study AB23005 where 408 patients are expected to be enrolled and provided a feasibility analysis which shows potential enrolment of 583 patients from 62 sites over a 12-month period outside of EU countries (USA and non-EU countries) [Argument 6.1]. It is noted that feasibility assessment for some sites appears overambitious having in mind actual enrolment numbers of sites from study AB10015 where most of the 34 sites recruited less than 20 patients. Moreover, the Applicant claimed that study AB23005 can be completed within 2.5 years with involvement of sites from the USA and other non-EU countries or within 3 years with involvement of sites only from other non-EU countries [Argument 6.2]. Obviously, completion of the study depends on recruitment speed, hence, given the ambitious recruitment numbers, this timeline might be challenging. Nevertheless, it is the Applicant's position that recruitment for study AB23005 is facilitated compared to previously planned confirmatory study AB19001, which has been declared supportive due to recruitment issues [Argument 6.3]. Modifications from study AB19001 to AB23005 based on their potential responsibility for the slow enrolment in study AB19001 (i.e. absence of 12-week run-in period, enrolment of moderate and severe (ALSFRS≥1) ALS patients, Albrioza/Relyvrio is no longer marketed but was back then not allowed as ConMed in study AB19001, Edaravone was also not permitted as ConMed ins study AB19001 but will be allowed in study AB23005, authorization of an open label extension beyond week 48 and omission of Masitinib 6.0 mg/kg/day treatment group) appear principally plausible to facilitate recruitment. However, as already outlined in the previous CHMP AR, considering the numerous changes undertaken in the protocol of the pivotal study during its execution as well as the slow enrolment in study AB19001, the Applicant's capability to properly conduct study AB23005 is still questionable. Hence, despite the Applicant's declared commitment, high uncertainties remain with regard to the possibility to provide comprehensive clinical data.

Furthermore, the Applicant's claim that the design of study AB23005 has been endorsed by the SAWP [Argument 6.4] cannot be confirmed. There have been two scientific advice procedures and one clarification on the design of AB23005, EMA/SA/0000156604 from December 2023, EMA/SA/0000164743 from April 2024 and EMA/SA/0000182621. There, it was repeatedly discouraged, for several reasons, to only enroll patients with an initial disease progression rate of >0.3<1.1 ALSFRS-R points per month (i.e. normal progressors).

Moreover, the study duration of study AB23005 of 48 weeks was not considered long enough to provide meaningful information on overall survival. In addition, the advice to avoid using a minimisation algorithm for randomization was not adhered to. Imputation strategies were only discussed at high level, but are expected to be of particular importance at the time of assessment.

2. The Applicant has not sufficiently justified that Masitinib AB Science would provide a major therapeutic advantage versus tofersen.

The Applicant's argument [Argument 7.1] that Masitinib AB Science would provide a MTA versus Qalsody (tofersen) in terms of improvements to patient care is agreed to. This is mainly based on the route of administration which, in case of a positive B/R balance, would be expected to provide major improvements to patient care. While tofersen treatment comes with considerable patient burden that is primarily related to the monthly invasive intrathecal lumbar puncture administration and bears risks of severe and potentially life-threatening adverse effects, Masitinib AB Science is an orally administered, CNS-penetrative drug, with minimal patient burden or risks associated with its route of administration. It is further agreed with the Applicant that Masitinib AB Science is comparatively simple to take, allowing for convenient, safe and inexpensive self-administration, outside of the hospital setting, all of which are beneficial for improved patient compliance. This is reflected in the high compliance rate in the primary efficacy population and the overall study population of study AB10015.

As further outlined by the Applicant, autoimmune reactions were detected in about 6% of patients treated with tofersen [Argument 7.2]. While this is acknowledged and it is agreed that autoimmune reactions bear additional patient burden, this argument is considered less relevant in terms of the MTA discussion, as the majority of these events are linked to the invasive administration route. Indeed, concerning the overall safety profile, AEs related to the administration of tofersen via intrathecal lumbar puncture can be prevented/diminished through oral administration of Masitinib AB Science, which is considered an improvement of patient care (see above).

Since the clinical benefit and survival benefit have not been demonstrated for Masitinib AB Science in the intended target population (see GfR#2.2), the Applicant's argumentation [Argument 7.3], that Masitinib AB Science has demonstrated both clinical benefit and survival benefit to an extent that has not been demonstrated to date with tofersen is obsolete. Even if deemed positive, there was no head-to-head trial of Masitinib AB Science against tofersen and results are not comparable across trials (e.g. PEP/benefit assessed at W48 with Masitinib AB Science vs. W24 with tofersen; no data on OS for tofersen).

The Applicant argues [Argument 7.4] that pre-clinical data from SOD1G93A and EAE models support the hypothesis that Masitinib AB Science may provide a neuroprotective effect in the clinical setting for both SOD1-ALS and sporadic ALS patients. However, this argument is deemed irrelevant for the question of whether efficacy results in all ALS patients are extrapolatable to ALS patients with SOD1 mutations. In fact, no clinical data are available for Masitinib AB Science in the SOD1-ALS subpopulation, as ALS genotypes were not assessed as part of study AB10015. Thus, no confirmation that Masitinib AB Science provides improved efficacy versus tofersen in the SOD1-ALS subpopulation is available.

The Applicant's claim [Argument 7.5] that Masitinib AB Science and tofersen have a different mechanism of action and different principal molecular structure is agreed to and justify the non-similarity overall conclusion in the similarity assessment versus Qalsody that has been already agreed by the CHMP. The concept of MTA in the CMA differs from the requirements to assess similarity with authorised orphan medicinal products. Indeed, difference in the mechanism of action and principal molecular structure are relevant arguments for the assessment of similarity versus Qalsody, However, as already stated, a different mechanism of action does not automatically justify for MTA, it needs to be substantiated that the new mechanism of action provides a significant clinical advantage versus the existing therapies. Indeed, as stated above, an MTA of Masitinib AB Science over tofersen is considered justified solely based on its route of administration which would be expected to provide major improvements to patient care.

The final argument [Argument 7.6] reiterates previous arguments, claiming an MTA of Masitinib AB Science over tofersen, based on the route of administration, patient burden, safety profile and efficacy

profile. Please see assessments above. The claim, that efficacy of Masitinib AB Science has been demonstrated as an add-on to riluzole, therefore masitinib's MTA over riluzole is established, is not agreed to. The study design of AB10015 does not allow a conclusion on MTA of Masitinib AB Science over riluzole, as patients in both study arms received riluzole. MTA as add-on to riluzole over riluzole alone would only apply, if GfR #2.2 was resolved and efficacy of Masitinib was established (please refer to GfR #2.2).

Overall conclusion

In conclusion, it can be agreed that Masitinib AB Science could have provided a MTA versus tofersen, based on the route of administration which would be expected to provide major improvements to patient care, but only if an overall positive benefit/risk had been concluded. Furthermore, it is considered unlikely that the Applicant will be in a position to provide comprehensive clinical data post-authorisation (see also below 'Report from the SAG' and the question on feasibility of proposed study), and, taking all the above into account, it is considered that the benefits to public health of the immediate availability of Masitinib AB Science do not outweigh the risks inherent in the fact that additional data are still required. Thus, the overall conclusion is that none of the other (i.e. second, third and fourth) criteria for a CMA as described in Article 4 of Commission Regulation (EC) No. 507/2006 are met.

5.2. Report from the SAG

Following a request from the Applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the specific clinical questions in relation with the grounds of refusal.

1. **The Applicant has proposed the following indication: "Masitinib AB Science in combination with riluzole is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS) prior to any loss of function", i.e. excluding very severe ALS patients (that have a score of zero on at least one individual item of the ALSFRS-R).**

- **Is this subgroup easily identifiable in clinical practice and are the criteria to obtain the ALSFRS-R score well-documented in clinical practice?**

The SAG-N experts considered that the ALSFRS-R scale is widely used in the clinical practice and criteria for administration are available for health care professionals. Hence, this subgroup can be easily identifiable in the clinical practice.

From a patient's representative's perspective, the above statement is fully agreed.

The experts noted that the definition should be "prior to any TOTAL loss of function" as 0 subscore represents a total loss function while the other subscores (1-3) represents partial loss of function

As a side note, the SAG-N experts questioned that severity phenotyping (as proposed in the indication) could be done using solely a single scale.

- **Do you consider that the presented data can support a treatment effect in the proposed target population?**

The SAG-N experts did not consider that the data can support a treatment effect in the proposed target population. The target population in the proposed indication is not aligned with the claimed primary efficacy analysis population (i.e. normal progressors/full study population regardless of the total ALSFRS-R). The presented data is *post hoc* derived and hence, cannot render confirmatory evidence of a treatment effect.

From a patient's representative's perspective, the above statement is fully agreed.

2. **The Applicant has proposed to categorize the study population into normal and fast progressors using an average rate of change in ALSFRS-R from onset to randomization lower than 1.1 points per month as cut-off for normal progressors.**

   Is this categorization clinically relevant?

The SAG-N experts agreed that categorization of study population in a trial could reduce heterogeneity of study population. However, few SAG-N experts questioned the utility of ALFRS-R scale as a single instrument to predict the progression of the condition. Further, the chosen single cut-off of 1.1 per month was also questioned based on the non-linearity of the decline (i.e. the cut-off may be different across the different stages of the condition). It was also questioned that as currently proposed the observation period (denominator) over which the average decline in ALFRS-R scale is calculated, is different across the participants in the trial. Finally, the SAG-N experts noted that the categorization was done while the study was ongoing. Nevertheless, while the majority of SAG-N experts acknowledged the above limitations, they still agreed with the proposed categorization approach and the meaningfulness of the cutoff for a trial. Therefore, the SAG-N experts views were split on this aspect with a majority of views supporting the categorization proposal (use of ALSFRS-R, the period of observation from onset and the 1.1 points per month as cut-off) if properly pre-specified which is agreed by consensus that is not applicable to this particular trial.

From a patient's representative's perspective, stratification is considered to be clinically relevant and the cut-off point of 1.1 month is reasonable and in line with expected evolution of the condition. So, if properly planned (which is not the case for this trial), it would have been acceptable.

   Considering the non-linear pattern in the ALSFRS-R decline, is the approach to use change from onset and the proposed cutoff meaningful?

The experts referred to the prior subquestion where the non-linearity and cutoff have been discussed.

3. **As part of a conditional marketing authorisation commitment, the Applicant proposes to conduct study AB23005. The Applicant has presented a plan to enrol 583 patients from 62 sites per 12-month period outside of EU countries. The experts are invited to comment on the feasibility of this proposal?**

The SAG-N experts including the patient's representatives agreed by consensus that the feasibility of the proposal is highly questionable based on the prior experience on recruitment in other trials conducted by the Applicant, the inclusion of certain countries (Russia, Ukraine) and the possibility to access the medicinal product (even if not authorised in their jurisdictions) by patients in the proposed countries which could limit the willingness to participate (limitation for recruitment) or to continue (limitation for conduction) in a trial.

5.3. Oral Explanation

The Applicant was invited to present its position during an oral explanation. On 16 October 2024, a presentation to address the grounds for refusal as made in front of the CHMP plenary meeting.

However, after this OE, the Committee concluded that the grounds for refusal, with the uncertainties and concerns regarding the quality and efficacy of Masitinib AB Science as expressed above, still remained.

5.4. Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the Applicant and considered the views of the Scientific Advisory Group.

In the latest stage of the assessment, the Applicant proposed a new claimed indication as follows: "*Masitinib, in combination with riluzole, is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS)*".

The CHMP concluded that none of the grounds for refusal have been solved by the Applicant. However, the subitem number four of the ground 2.2 for refusal (i.e. *The strategies to post hoc identify new target populations ("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and "ALS patients prior to any loss of function" as proposed in the latest version of 4.1) are considered as data driven decisions and are, therefore, not acceptable*) becomes obsolete in light of the latest claimed indication and is not further pursued as ground for refusal notwithstanding the other points of ground 2.2 (*Beside the data not being reliable, the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS*) remain unsolved and therefore, ground 2.2 remains unsolved.

After the oral explanation, the Applicant submitted a clarification note claiming that the following points were adequately addressed by the Applicant (1) ALSFRS-R could not be relied upon according to inspection; (2) dichotomization between normal and fast progressors is not supported and (3) the only statistical analysis retained for missing data is full JTR with a penalty on all discontinuations. The action of Masitinib as disease modifying agent is not considered sufficiently substantiated. The arguments included in the note were assessed and it is concluded that no new information was provided that impacts the assessment of the grounds for refusal. Therefore, the grounds for refusal remain unsolved.

Immediately prior to the Oral Explanation the Applicant submitted a clarification note on quality aspects. The arguments included in the note were assessed and it is concluded that no new information was provided that impacts the assessment of the ground for refusal. Therefore, the quality ground for refusal remains unsolved.

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

ALS is a neurodegenerative disorder affecting primarily the motor system, but in which extra-motor manifestations are increasingly recognized. The loss of UMN and LMN in the motor cortex, the brain stem nuclei and the anterior horn of the spinal cord gives rise to progressive muscle weakness and wasting. ALS often has a focal onset but subsequently spreads to different body regions, where failure of respiratory muscles typically limits survival to 2–5 years after disease onset.

6.1.2. Available therapies and unmet medical need

Riluzole is currently the only medical product specifically authorised in the EU for ALS. Tofersen has recently been authorised for the treatment of SOD1-ALS, representing 2% of ALS. The cornerstone of disease management for ALS patients remains multidisciplinary care which has a positive effect on patient satisfaction and outcome. Several discomforting symptoms of ALS can be managed by symptomatic treatment options, including pharmacological and non-pharmacological interventions. Non-invasive ventilation is the preferred life-prolonging treatment for respiratory insufficiency. Currently, there is no cure for ALS, and it is agreed that the unmet medical need remains substantial for the majority of the ALS patients.

6.1.3. Main clinical studies

The main efficacy study was a phase IIb/III, randomised, double-blind, placebo-controlled study (AB10015). The study was initially planned as a phase 2 dose-finding study and only after an amendment it was upgraded to a phase 3 pivotal study for this application. The primary objective of study AB10015 was to evaluate the efficacy of Masitinib AB Science in combination with riluzole based on the change in the ALSFRS-R (ΔALSFRS-R) from baseline to week 48 in adult patients with ALS. While the study was ongoing, the applicant amended the protocol to redefine the primary efficacy population as the "normal progressors" subpopulation, i.e. patients with ΔFS<1.1. A total of 394 patients from 34 sites in 9 countries were randomised (133, 131, and 130 patients in the placebo, Masitinib AB Science 3 mg/kg/day [M3.0], and Masitinib AB Science 4.5 mg/kg/day [M4.5] treatment-arms, respectively). A total of 267 patients completed the week 48 main protocol period at week 48. A long-term survival follow-up analysis of this study has been provided.

6.2. Favourable effects

The analysis of the primary endpoint in the full study population comprising normal + fast progressors in the Masitinib AB Science 4.5 mg/kg/day group showed a difference of 2.09 95%CI (-0.55-4.73) $p_{nominal}$=0.1202.

The difference in PFS in the full study population comprising normal + fast progressors was 3 months gain in favour of Masitinib AB Science 4.5 mg/kg/day group ($p_{nominal}$ 0.1389).

Analysis of ALSAQ-40 (mLOCF Rule 1) showed difference of means -6.59, $p_{nominal}$ 0.0148 in the full study population including normal + fast progressors.

In analysis of FVC in the full study population comprising normal + fast progressors difference of means was 5.63, ($p_{nominal}$ 0.0914).

In the latest stage of the assessment, the applicant proposed a new claimed indication as follows: "*Masitinib, in combination with riluzole, is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS)*". The above estimates are derived from analyses including the full study population regardless of any ALSFRS-R. Thus, they are applicable for the new claimed indication.

A summary of long-term median OS results (cut off June 2020) for various patient cohorts of the AB10015 study population has been submitted. No estimates for the OS were provided for the full study population comprising normal + fast progressors during the re-examination. During the procedure, the applicant claimed that the median OS was 36 months (95% CI 28, 48) for patients receiving Masitinib AB Science 4.5 mg/kg/day (n=130) versus 37 months (95% CI 28,44) for patients receiving placebo (n=133).

6.3. Uncertainties and limitations about favourable effects

A triggered GCP inspection (GCP/2017/001) was requested by the CHMP on the conduct of the clinical study AB10015 in the previous MAA for the same medicinal product as a treatment for ALS. Major and critical findings were identified, and GCP inspection concluded that the data obtained at the sites inspected are not trustworthy. In accordance with the GCP inspection report conclusion, after the evaluation of the responses submitted by the applicant in response to the GCP inspection findings (EMA Inspection report, *Addendum 1: Response form the sponsor or inspectee* for both sites; dated 30 Jan 2018 site 1, and 01 Feb 2018 site 2), the Inspection Team considered that in view of the observed departures from GCP, it cannot be ensured that the data inspected are trustworthy and the aforementioned deficiencies are likely to have an impact on the final results. Data integrity is highly likely

to be impaired as several protocol deviations were identified at eligibility, conduct and in other aspects inspected. The applicant claims that the GCP findings were addressed with implementation of preventive actions across study and functions within AB Science. The applicant also claims that for study AB10015, corrective actions were implemented wherever feasible. It is noted that the measures specified by the applicant have been assessed in the current marketing authorisation procedure and were not found sufficient to recommend the use of data. These measures were also re-assessed as part of the re-examination. (See also section 5.1.2 of this report).

Given the nature of the findings, the systematic deficiencies observed (i.e. massive number of protocol deviations) and the fact that some findings such as the deficiencies during inclusion/exclusion criteria verification and subjects' follow up (Critical finding 1 in the inspection report) cannot be corrected retrospectively, the corrective actions presented are not considered adequate to address all the concerns raised.

The deviation impact analysis, conducted by the applicant as corrective measure, was performed after the data base lock when data was already unblinded. Moreover, it was implemented by the applicant and therefore, objectivity of this analysis is questionable. Additionally, during the inspection, data was deemed untrustworthy not solely due to protocol deviations but also due to broader concerns such as lack of training, lack of monitoring, lack of proper record keeping, suboptimal trial management, data entry changes and other deviations.

Data from clinical study AB10015 cannot be relied upon. Thus, the CHMP maintains the position that the internal validity of the clinical study AB10015 is highly compromised in light of the outcome of the CHMP triggered GCP inspection, GCP/2017/001 and that the clinical study data are not deemed trustworthy.

In a study amendment while the study was already ongoing, the applicant introduced division of enrolled participants in two subgroups: fast and normal progressors. Normal progressors were re-defined as the population for the primary analysis with aim to reduce heterogeneity in study population. This approach is not supported as the categorization was not pre-specified but performed once the study was already ongoing. Functional unblinding could not be ruled out in this context. The full study population is considered the primary efficacy population. Furthermore, the dichotomisation leads to a selective subgroup that is not representative of general ALS population. Additionally, the chosen cut-off point (ΔFS 1.1) is of questionable clinical relevance and is not based on pathophysiology of ALS or mechanism of action of Masitinib AB Science. Furthermore, ΔFS alone has relatively low predictive value of progression (Thakore et al, 2017) and is not stable throughout the course of disease (Requardt, 2021) thus, a linear assumption for the ΔFS decline (average rate of change from onset to randomization) might lead to misclassification of patients. Moreover, randomization was unsuccessful, which undermines the quality of the results of this pivotal study.

It is unclear whether formal success of the trial could indeed already be concluded from the interim analysis as claimed by the applicant. During the re-examination, the applicant presented results from the interim analysis but only for the normal progressors subpopulation. In any case, performing the updated analysis at significance level of 5% is considered overly optimistic. Repeated confidence intervals should have been provided, maintaining the simultaneous coverage probability taking into account the interim and the final analysis. The repeated confidence interval would be even wider than the provided confidence interval.

There was a substantial number of early dropouts across study arms. Due to the high proportion of missing data, handling of missing data has a significant impact on the study results. To account for missing data, the applicant used mLOCF method and provided various sensitivity analysis. The approach is not supported, because in the context of progressive ALS it overestimates effect. Considering the progressive nature of ALS and that the effect of treatment will not be maintained after discontinuation of medication, applying the J2R method to all missing values independent of whether considered related

or unrelated to treatment is considered the most appropriate approach. Based on the J2R approach already the provided naive 95% confidence interval included zero for the treatment effect in the analysis population of 'normal progressors'. The repeated confidence interval would be even wider. Hence, the results of the primary efficacy analysis when using appropriate methods for accounting for missing data did not render statistically significant results for the primary endpoint, even if the normal progressor would have been considered as prespecified (which is not supported by the CHMP). For the full study population already the 95% confidence interval based on mLOCF included zero and it is assumed that the J2R approach would result in an even smaller estimated treatment effect. Thus, there is insufficient evidence to support efficacy in this single pivotal trial.

As per the data on survival or survival equivalents that is requested as per the EMA guideline for ALS, the applicant provided data on long-term overall survival. A limitation of this analysis is that no information on the post-study use of invasive ventilation was collected, nor was information regarding which drugs were taken following withdrawal from study AB10015 or its associated named patient programme. Also, more than 20% of participants have discontinued the treatment before the open-label extension phase due to the lack of efficacy. Therefore, due to this discontinuation, analysis of long-term overall survival could cause bias in favour to Masitinib AB Science treatment arms. Further, the effect in the long-term survival claimed by the applicant is derived from a highly selected patients' population defined *post hoc* therefore can be considered only as descriptive not confirmatory of Masitinib AB Science efficacy in the proposed indication. The OS analysis was largely underpowered and inadequate. In addition, inconsistency in the reporting of OS analysis was noted, increasing uncertainty and concern about how this study was conducted and analysed. When the analysis was conducted in a population that corresponds to the primary analysis population of pivotal study and hence, full study population regardless of (any) baseline ALSFRS-R item, significant benefit in OS was not observed.

Based on up-dated efficacy and safety analyses, the applicant presented a proposal for a modified indication to the "treatment of ALS patients prior to any loss of function" (wherein loss of function is defined as a score of zero on any item of the ALSFRS-R). However, the strategies to *post hoc* identify new target populations (M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1 for analyses of survival and subsequently only including "ALS patients prior to any loss of function) are considered as data driven decisions and are, therefore, not acceptable. The study has no basis to define the target population *post hoc*. This trial does not fall under the exception rule for the *post hoc* definition of a target subgroup because the study did not show an effect in the overall population and does not fulfil the credibility criteria as outlined in the guideline EMA/CHMP/539146/2013 for scenario 2. In the latest stage of the assessment, the applicant proposed a new claimed indication as follows: "*Masitinib, in combination with riluzole, is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS)*". In light of the latest claimed indication, this concern is not further pursued.

6.4. Unfavourable effects

In study AB10015 during main study protocol period (48 weeks), at least 1 AE was reported by 83.7% of patients in the full study population. Of them, 78.2% in placebo, 84.7% in the 3.0 mg/kg, 88.4% in the 4.5 mg/kg Masitinib AB Science arm.

More frequently reported AEs in one of the Masitinib AB Science versus placebo arms were maculo-papular rash, nausea, peripheral oedema, iron deficiency anaemia, respiratory failure, and dyspnoea.

The most frequently reported non-fatal SAEs in Masitinib AB Science patients under MedDRA SOC were Gastrointestinal Disorders, then Respiratory, Thoracic and Mediastinal Disorders, Infection and Infestations, Injury Poisoning and Procedural Complications, and Investigations. The most frequent PTs

were Dysphagia, Respiratory Failure, Dyspnoea, Lower Respiratory Tract Infection, Bronchitis, Fall, Transaminases Increased, Weight Decreased, and Neutropenia.

According to the applicant, respiratory failure, dysphagia, and dyspnoea were associated with ALS disease progression and were not reported as drug related.

The most common AEs with reported more than > 5% higher incidence in ALS patients were in the blood and lymphatic system disorders (8.4% in Masitinib AB Science 3mg/kg/day group and 14.7% in Masitinib AB Science 4.5 mg/kg/day group versus 1.5% in placebo group); nausea (6.9% in 3 mg/kg/day group and 12.45 in Masitinib AB Science 4.5 mg/kg/day group versus 4.5% in placebo group); diarrhoea (8.4% in Masitinib AB Science 3 mg/kg/day group and 7.8% in Masitinib AB Science 4.5 mg/kg/day group versus 3.8% in placebo group); dyspepsia (7% in Masitinib AB Science 4.5 mg/kg/day group versus 2.3% in placebo group); peripheral oedema (5.3% in Masitinib AB Science 3 mg/kg/day group and 7% in Masitinib AB Science 4.5 mg/kg/day group versus 0.8% in placebo group); nervous system disorders (18.6% in Masitinib AB Science 4.5 mg/kg/day group versus 9.8% in placebo group); respiratory and thoracic disorders (27.1% in Masitinib AB Science 4.5 mg/kg/day group versus 12% in placebo group including reported respiratory failure in 10.1% patients in Masitinib AB Science 4.5 mg/kg/day group vs 4.5 % in placebo group and dyspnoea 6.2% in Masitinib AB Science 4.5 mg/kg/day group versus 0.8% in placebo group); skin and subcutaneous tissue disorders (20.6% in Masitinib AB Science 3 mg/kg/day group and 30.2% in Masitinib AB Science 4.5 mg/kg/day group versus 12% in placebo group); infections and infestations (34.9% in Masitinib AB Science 4.5 mg/kg/day group versus 21.15 in placebo group).

Cardiovascular disorders were identified as an important potential risk and patients with current or history of severe cardiovascular disease were excluded from the study. Nonetheless, 3 severe cardiac events were reported in masitinib exposed patients including 2 death events. Although none of them was reported as study drug related, potential cardiotoxicity remains as a significant and not properly addressed safety risk.

ALS is a disease, which leads to death mainly from respiratory complications; however, also has underestimated cardiovascular effects, like increased heart rate variability, malignant arrhythmias, and sudden death (Orsini et al, 2021). Furthermore, cardiac symptoms in ALS patients may develop at any stage of the disease and initial cardiac symptoms if not closely monitored may go unnoticed in ALS patients.

6.5. Uncertainties and limitations about unfavourable effects

Important uncertainty of unfavourable effects is also related to the reliability of data. Many deviations from the protocol have been found during the inspections of the study centres. As part of this marketing authorization Applicant presented implemented preventive actions across study and functions within AB Science. Given the nature of the findings, the systematic deficiencies observed (i.e. massive number of protocol deviations) and the fact that some findings such as the deficiencies during inclusion/exclusion criteria verification and subjects' follow up (Critical finding 1 in the inspection report) cannot be corrected retrospectively, the corrective actions presented are not considered adequate to address all the concerns raised. Data from clinical study AB10015 cannot be relied upon, increasing the uncertainties and limitations also regarding unfavourable effects.

The uncertainties and limitations regarding reliability of safety data of the pivotal clinical trial are alleviated by the safety data from the trials in non-oncological conditions. It is considered that the safety concerns could have been manageable with risk minimization measures as outlined in the RMP.

6.6. Effects Table

Table 147: Effects table for Masitinib AB Science

Effect	Short Description	Unit	Masitinib 4.5 mg	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Difference in ALSFRS-R	Normal + Fast progressors	score	-10.89	-12.97	Difference 2.09 (-0.55-4.73) p=0.1202	(1)
Median PFS	Normal + Fast progressors		17	14	3 months, p-value 0.1389	(1)
Quality of Life (ALSAQ-40)	Normal + Fast progressors		21.58	28.17	difference of means -6.59, p-value 0.0148	(1)
FVC	Normal + Fast progressors		-30.81	-36.45	difference of means 5.63, p-value 0.0914	(1)
Survival OS	Normal + Fast progressors		36	37	p-value 0.1778	(2)
Unfavourable Effects						
Deaths	Number (and Percent of Patients)	Number	10 (7.8)	12 (9.0)	Up to week 48 SoE: longer duration of treatment and more severe patients in masitinib arm	(3)
Gastrointestinal Disorders	Number (and Percent of Patients)	Number	14 (10.9)	10 (7.5)	Up to week 48 Unc: cumulative effect of riluzole and masitinib in terms of GI events.	(3)
Respiratory, Thoracic and Mediastinal Disorders	Number (and Percent of Patients)	Number	13 (10.1)	4 (3.0)	Up to week 48 SoE: larger # of very severe patients in masitinib arm	(3)
Infections and Infestations	Number (and Percent of Patients)	Number	10 (7.8)	7 (5.3)	Up to week 48 SoE: larger # of very severe patients in masitinib arm	(3)
Transaminases Increased	Number (and Percent of Patients)	Number	2 (1.6)	0	Up to week 48	(3)

Abbreviations: ALSFRS-R - Amyotrophic lateral sclerosis functional rating scale-revised, ALSAQ-40 - Amyotrophic Lateral Sclerosis Assessment Questionnaire, long form, 40 questions, FP - Fast Progressors, FVC - Forced vital capacity, LS-Difference of least-square means, median PFS – median progression-free survival, TD - Treatment Difference M vs P, M = ALSITEK + Riluzole; P = Placebo + Riluzole.
Notes: (1) Clinical Study Report Protocol No. AB10015, (2) Supplemental Clinical Study Report (Long-term Survival Analysis of Masitinib in Amyotrophic Lateral Sclerosis (ALS) from Study AB10015) (3) 2.7.4 Summary of Clinical Safety

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

ALS is a neurodegenerative disease with limited treatment options with overall survival of 2–5 years after disease onset.

The current application is based on one pivotal study (AB10015); prospective, multicentre, randomised, double-blind, placebo controlled, parallel groups, phase 2/3 study to compare the efficacy and safety of

two doses of Masitinib AB Science versus placebo in the treatment of patients suffering from ALS. The primary endpoint was originally the change from baseline to week 48 in the ALSFRS-R in patients with ALS. The clinical study protocol had multiple amendments including change from Phase 2 to Phase 2/3 and change of the primary efficacy analysis population (see below).

A triggered GCP inspection was requested by the CHMP on the conduct of the clinical study AB10015 in the previous MAA for masitinib use in ALS. Major and critical findings were identified during the inspection. The critical and major issues are overarching and impact all study-related activities, from staff training to trial monitoring, data collection process, data entry and, finally, data interpretation. The GCP report concluded that the data obtained at the sites inspected are not trustworthy. As part of this submission the applicant claims that the GCP findings were addressed with implementation of preventive actions across study and functions within AB Science. The applicant also claims that for study AB10015, corrective actions were implemented wherever feasible. It is noted that the measures specified by the applicant in this application have been thoroughly re-assessed and were not found sufficient to reassure the CHMP to recommend the use of data. Therefore, data from clinical study AB10015 cannot be relied upon. See also section 5.1.2 of this report.

In 2014, an amendment to the study protocol introduced a distinction between "normal progressor" patients and "fast progressor" subpopulations while the study was ongoing, and the primary efficacy analysis was to be done in the normal progressor subpopulation randomised to an initial Masitinib AB Science dose of 4.5mg/kg/day versus placebo patients at a 5% alpha-level. This is not agreed by the CHMP. The change was done 1.5 years after study commenced while considerations about heterogeneity and the decision of the study population should be done before starting a confirmatory study. The validity (including blinding) and timing of this amendment is questioned, as it was done during an essentially unmonitored part of the study as indicated by the GCP reports, which suggest that there was no monitoring plan from the start of the study until 2016

The functional unblinding cannot be ruled out in this context since safety profiles of placebo and Masitinib AB Science obviously differed. Finally, this change is not accepted because of its considerable impact on the study outcomes (ie. on the formal 'success' of the study).

Furthermore, the categorization itself is not considered acceptable for the following reasons: the use of ALSFRS-R score as the only variable to inform the progression of ALS, the linear assumption of ALSFRS-R decline being unreliable for long time periods (i.e. change from disease onset), the use of arbitrary cut-offs for the categorization that are not based on clinically relevant thresholds, ALS pathology or mechanism of action of Masitinib AB Science. Nevertheless, it should be highlighted that the majority of the SAG-N experts could have considered the categorization approach (i.e. use of a single scale, the time from onset and the cutoff point) as acceptable had it been prespecified in the study protocol. Considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results.
In order to account for missing data after treatment discontinuation, the applicant used the mLOCF method for the first and secondary endpoints. A mLOCF approach assumes that the benefit experienced until the time of missing data is also retained thereafter. This is a strong assumption for imputing data after treatment discontinuation. This approach of handle missing data is prone to overestimate the effects of Masitinib AB Science. The applicant provided more conservative approaches such as J2R that assumes that the benefit experienced until the point of missing data is not retained and instead the outcome would correspond to the outcome in the reference group. The CHMP is of the opinion that J2R is the preferred option in the view of the progressive nature of ALS.
The primary statistical analysis in the phase 2/3 main efficacy study revealed an estimated difference in the change in ALSFRS-R score between Masitinib AB Science 4.5 mg/kg/day and placebo of 2.09 (95% CI -0.55, 4.73; p=0.1202) in "normal + fast progressor" population. These results are based on the mLOCF method and it is expected that the preferred J2R approach would result in an even smaller

treatment difference as discussed above. Moreover, repeated confidence intervals should have been provided, maintaining the simultaneous coverage probability taking into account the interim and the final analysis. The repeated confidence interval would be even wider than the provided confidence interval.

A summary of long-term median OS results for various patient cohorts of the AB10015 study population has been provided (cut-off date 14 June 2020). No statistically significant long-term survival advantage was observed for the full study population for Masitinib AB Science 4.5 mg/kg/day cohort. The results indicating prolonged survival in a *post hoc* selected, enriched population (cohortLT-M4.5 with ≥2 on each baseline ALSFRS-R item, and ΔFS<1.1) is not considered robust and is not representative for the population intended to be treated.

The proposed indication (*ALS patients prior to any loss of function* [i.e. cohortLT-M4.5 with **>0** on each baseline ALSFRS-R item, and ΔFS<1.1]) based on *post hoc* analyses is not acceptable as it is considered data driven. This is also the position from the SAG-N experts. As described in the document EMA/CHMP/539146/2013 and in line with the ICH principles, the definition of a new target population should be done in a separate study. The exception to the rule of defining a new target population in a separate study cannot be not applied to AB10015 as the study results were not statistically persuasive. However, in light of the latest claimed indication, this concern becomes obsolete and is not further pursued.

Dose dependent respiratory and thoracic disorders were reported in 4.5 mg/kg/day Masitinib AB Science group with more than twice higher incidence compared to placebo group, including 10.1% severe AEs in Masitinib AB Science group compared to 6% in placebo group. Furthermore, it is a concern that data reliability issues identified in the triggered GCP inspection also affects proper reporting of safety data. Nevertheless, the safety profile was further characterised based on safety data of trials conducted in non-oncological conditions. It is considered that the safety profile is reasonably characterised for a CMA (i.e. based on non-comprehensive data).

6.7.2. Balance of benefits and risks

The provided analyses of the single pivotal study are not considered to establish efficacy in the target population of patients with ALS. In addition, a triggered GCP inspection has concluded that the data from clinical study AB10015 are not trustworthy. Data cannot be relied upon, and the corrective measures and actions presented by the applicant (including re-monitoring and impact analysis) have not resolved this issue. Hence, efficacy of Masitinib AB Science in the treatment of ALS is not established and there is therefore nothing to outweigh any unfavourable effects.

6.7.3. Additional considerations on the benefit-risk balance

Quality

Based on an unresolved Ground for refusal, several deficiencies and the lack of an acceptable explanation for the observed significant intra-batch and inter-batch variability of the dissolution results still remain. The root cause of this variability has not been convincingly identified by the applicant.

Furthermore, the observed significant inter-batch and intra-batch variability in dissolution profiles between the tested drug product batches may indicate that the manufacturing process is not under sufficient control. Namely, based on the presented dissolution profile data, it is concluded that the dissolution profiles of the drug product batches manufactured according to the proposed manufacturing process are not similar, i.e. the presented dissolution profiles do not demonstrate reproducibility of the proposed manufacturing process. The differences in dissolution behaviour between the two strengths further underline the lack of understanding of the potential causes related to high variability of the

dissolution results.

In conclusion, the suitability of the proposed dissolution method to ensure adequate control of the drug product during the drug product lifecycle has not been sufficiently demonstrated. Furthermore, it has not been demonstrated that the proposed manufacturing process is robust and reproducible and that it ensures adequate batch to batch consistency in order to obtain a medicinal product with the intended high quality.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation (CMA) was requested by the applicant in the initial submission and maintained during the re-examination phase. The CHMP agrees that the data is not comprehensive. The application is based on a single pivotal trial, study AB10015, which was designed as a phase 2 dose-finding trial. Only upon a protocol amendment, it was upgraded to a phase 3 pivotal trial. The study population of AB10015 study is not considered fully representative of the overall ALS population and the efficacy endpoints did not include any measures of muscle strength. These features could have been acceptable for a phase 2 dose-finding trial but are considered serious limitations for a phase 3 pivotal study intended to provide comprehensive evidence of efficacy and safety. Moreover, a triggered GCP inspection has concluded that the data from clinical study AB10015 are not trustworthy. Data cannot be relied upon, and the corrective measures presented by the applicant have not resolved this issue.

The CHMP considers that the product cannot be recommended for a CMA as the benefit-risk balance is negative (as discussed), the applicant is unlikely to be able to provide comprehensive data after authorisation, it has not been demonstrated that the product will address an unmet medical need, and the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required.

1. Positive benefit/risk balance:

The applicant argued that results from Study AB10015 are valid and demonstrate efficacy of Masitinib AB Science for patients with ALS with an adequate safety profile. The CHMP position is that a positive benefit/risk balance of Masitinib AB Science for the treatment of patients with ALS cannot be established because the data from the pivotal clinical study AB10015 cannot be relied upon. Despite the applicant's arguments and corrective measures, the re-assessment concluded that the deficiencies identified during previous GCP inspection cannot be resolved by performing re-monitoring and retrospective analyses at the study sites and cannot be corrected retrospectively. Beside the data not being reliable, the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS, because a statistically significant difference compared to placebo was not demonstrated for the primary efficacy population (i.e. full study population encompassing normal and fast progressors); the approach to categorise the population into normal and fast progressors is not supported (the use of ALSFRS-R score as the only variable to inform the progression of ALS, the linear assumption of ALSFRS-R decline being unreliable for long time periods, the use of arbitrary cut-offs for the categorization that are not based on clinical relevant thresholds, ALS pathology or mechanism of action of Masitinib AB Science); considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data in the primary analysis is not considered acceptable. In light of the latest claimed indication, the concern about the *post hoc* identification of new target population *("M4.5 with ≥2 on each baseline ALSFRS-R item and ΔFS<1.1" for analyses of survival and subsequently only including "ALS patients prior to any loss of function" as proposed in the latest version of 4.1 of the SmPC*) is not further pursued.

2. It is likely that the applicant will be able to provide comprehensive data

As per the requested CMA, the applicant initially presented Study AB19001 as the one that would lead to comprehensive evidence on efficacy and safety of Masitinib AB Science. Study AB19001 is a multicenter, randomised, double-blind, placebo-controlled, parallel group, phase 3 study to evaluate the efficacy and safety of masitinib as add-on therapy in Amyotrophic Lateral Sclerosis (ALS) patients treated with riluzole (further details can be found in section 3.7.3).

During the procedure, the applicant stated that the enrolment in study AB19001 has been slow due to the restrictive design features of that study (i.e. long 3 months run-in period, with no control of FVC at baseline / Moderate ALS only / by that time approved treatment in the USA - Edaravone, Relyvrio (no longer marketed) – not allowed / blinded extension at week 48). Consequently, the applicant proposed a new confirmatory study - AB23005 study- and presented the previously proposed confirmatory AB19001 study as an exploratory one.

Study AB23005 is a multicenter, randomised, double-blind, placebo-controlled, parallel group, phase 3 Trial to evaluate the efficacy and safety of masitinib as add-on therapy in ALS patients treated with standard of care. Patients will be randomised (1:1) to receive Masitinib AB Science 4.5 mg/kg/day or matching placebo.

Besides some considerations on the study design features and the potential impact on the ability of Study AB23005 to provide comprehensive evidence, as already discussed in section 3.7.3 and grounds for re-examination (n.3), the CHMP was concerned about the feasibility to properly conduct that study if Masitinib AB Science is authorised in the EU. It needs to be bear in mind that ALS is a fatal condition for which the only therapeutic options in the EU are symptomatic treatment and riluzole for all ALS patients expect those with SOD1-ALS. Hence, the CHMP is concerned that the authorisation of Masitinib AB Science will impact the recruitment and the conduction of the AB23005 study in EU sites as ALS patients will likely start (i.e. impact on recruitment) or shift (i.e. impact on conduction) to the commercial Masitinib AB Science when available. In response to this concern, the applicant presented a feasibility analysis and concluded that 583 patients in non-EU countries and US could be enrolled over a 12-month period. The applicant claimed that Study AB23005 can be completed within 2.5 years with involvement of site from USA and other non-EU countries or within 3 years with involvement of site only from other non-EU countries. Thus, the applicant position is that confirmatory study AB23005 is feasible outside of the EU and further facilitated since Relyvrio is withdrawn from market in USA and Canada. However, considering the numerous changes undertaken in the protocol of the pivotal study during its execution as well as the slow enrolment in the study AB19001, which became an exploratory study later on the applicant's capability to properly conduct this study is still unclear, despite the applicant's declared commitment.

The SAG-N experts considered that the feasibility of the proposal is highly questionable based on the aforementioned reasons (see SAG-N minutes above). In the late phase of the procedure, the applicant presented a new feasibility analysis including some modifications (e.g. no sites proposed to be included in Ukraine, Russia, Japan, Saudi Arabia, and Israel and fewer patients as initially proposed will be recruited in Brazil and China) and concluded that 466 patients in non-EU countries and US could be enrolled over a 12-month period. Then, the applicant proposed to enrol 408 patients in 1.5 years. However, it is still considered unlikely that the applicant provides comprehensive clinical data post-authorisation based on the prior experience and the concerns about the possibility to access the medicinal product (even if not authorised in their jurisdictions) by patients in the proposed countries which could limit the willingness to participate (limitation for recruitment) or to continue (limitation for conduction) in a trial.

In view of the above, it is considered unlikely that the applicant will be in a position to provide comprehensive clinical data post-authorisation.

3. Fulfilment of unmet medical need

The third criterion requires that unmet medical needs will be fulfilled. As other medicinal products for the treatment of ALS are authorised in EU, the applicant should justify that Masitinib AB Science provides a MTA over each existing authorised medicinal products in an overlapping indication, in case a CMA would be granted. The currently authorised medicinal products for ALS are riluzole and tofersen (the latter, only for SOD1-ALS).

The pivotal study AB10015 of this CMA is a prospective, multicenter, randomised, double-blind, placebo-controlled, parallel groups, phase II/III study to compare the efficacy and safety of Masitinib AB Science versus placebo in ALS patients. The study objective was to evaluate efficacy and safety of Masitinib AB Science as add-on therapy to riluzole. Indeed, all patients included in this pivotal study received riluzole. Hence, this pivotal trial is designed to measure causal effects (efficacy) of Masitinib AB Science on top of riluzole. If efficacy was demonstrated for Masitinib AB Science on top of riluzole in this pivotal trial, the differences in ALSFRS-R score and survival equivalent (PFS) estimates observed in the pivotal trial in favour of Masitinib AB Science arms in principle could have been considered as meaningful improvements of morbidity or mortality of the disease and thus, supporting that Masitinib AB Science provides MTA versus riluzole. However, as efficacy was not demonstrated, it cannot be concluded whether Masitinib AB Science provides an MTA versus riluzole.

Regarding the MTA over tofersen, the applicant claimed that Masitinib AB Science and tofersen have different mechanisms of action. This is agreed; however, a different mechanism of action does not automatically justify for MTA, it needs to be justified that the new mechanism of action provides a significant clinical advantage versus the existing therapies. In accordance with the Guideline on the scientific application and the practical arrangements necessary to implement Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 MTA would normally be based on meaningful improvement of efficacy or clinical safety or, in exceptional cases, on major improvements to patient care. The applicant's claim that Masitinib AB Science would provide a MTA over tofersen in terms of improvements to patient care based on the route of administration is agreed to. While tofersen treatment comes with considerable patient burden that is primarily related to the monthly invasive intrathecal lumbar puncture administration and bears risks of severe and potentially life-threatening adverse effects, Masitinib AB Science is an orally administered, CNS-penetrative drug, with minimal patient burden or risks associated with its route of administration. It is further agreed with the applicant that Masitinib AB Science is comparatively simple to take, allowing for convenient, safe and inexpensive self-administration, outside of the hospital setting, all of which are beneficial for improved patient compliance. Concerning the overall safety profile, AEs related to the administration of tofersen via intrathecal lumbar puncture can be prevented/diminished through oral administration of Masitinib AB Science, which is considered an improvement of patient care, as stated above.

The applicant´s argumentations on superior efficacy are not relevant because the CHMP considers that efficacy of Masitinib AB Science in ALS has not been demonstrated.

In conclusion, it could have been agreed that Masitinib AB Science could have provided a MTA versus tofersen, in terms of improvements to patient care based on the route of administration. However, as an overall positive benefit/risk is not established, it cannot be concluded whether Masitinib AB Science provides an MTA versus tofersen.

4. The benefit of immediate availability outweighs the risks

The applicant position is that benefit associated with the immediate availability of Masitinib AB Science based on number of deaths avoided and total gain in life-years as estimated based on study AB10015 (pivotal study for this CMA) outweighs the risk of adverse events.

However, taking all above into account, especially since the benefit risk balance has not been determined

as positive, the benefits to public health of the immediate availability of Masitinib AB Science do not outweigh the risks inherent in the fact that additional data are still required

Third Party Intervention

The CHMP received, during the assessment of the re-examination of this application, one correspondence from ALS patients organisations (hereinafter referred to as "third parties") expressing the third parties' views about the efficacy and safety profile of Masitinib AB Science and the unmet medical need of ALS patients. The permission to share was granted for all.

The CHMP considered the intervention and concluded that the arguments put forward by the third-party did not impact the CHMP conclusions.

6.8. Conclusions

The overall benefit/risk balance of Masitinib AB Science is negative.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the quality and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated and therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- The suitability of the proposed dissolution method to ensure proper control of the medicinal products during the lifecycle of the medicinal product, especially for the 200 mg strength, and therefore to ensure batch to batch consistency has not been sufficiently demonstrated. Several deficiencies and the lack of an acceptable explanation for the significant differences of dissolution data between the 100 mg strength and the 200 mg strength, as well as differences in dissolution profiles between different batches of the 200 mg strength remain at the time of opinion. The applicant has not convincingly demonstrated that tablet hardness and film-coating are the main issues for differences in dissolution results between 100 mg and 200 mg tablets as dissolution results do not correlate with these parameters. Moreover, the potential reasons of different dissolution results between 200 mg batches (intra-batch and inter-batches) were not discussed in order to ensure that, e.g., the manufacturing process is adequate to obtain a product with the intended high quality.
- A positive benefit/risk balance of Masitinib AB Science for the treatment of patients with ALS cannot be established based on the following:
    - The data from the pivotal clinical study AB10015 cannot be relied upon. Despite the applicant's arguments and the implementation of corrective measures, the deficiencies identified during previous GCP inspection cannot be resolved by performing re-monitoring and retrospective analyses at the study sites and cannot be corrected retrospectively.
    - Beside the data not being reliable, the results from the pivotal study AB10015 do not demonstrate efficacy of Masitinib AB Science in the treatment of patients with ALS, because:
        - A statistically significant difference compared to placebo was not demonstrated for the primary endpoint in the full study population.
        - The approach to categorise the population into normal and fast progressors is not supported.

    - Considering that there were approximately 30% of missing data in each Masitinib AB Science arm, handling of missing data can have a significant impact on the results. The approach to handle missing data including statistical assumptions on missingness and the definition of intercurrent events in J2R strategy are not considered acceptable.

- A CMA requires that all requirements as described in Article 4 of Commission Regulation (EC) No. 507/2006 are met. In addition to not fulfilling the first criterion, which relates to the positive benefit / risk balance, also the other CMA criteria are not considered fulfilled. It is considered unlikely that the applicant will be in a position to provide comprehensive clinical data post-authorisation. Further in the view of the negative benefit / risk balance, it cannot be agreed that Masitinib AB Science provides a major therapeutic advantage versus the already authorised medicinal products and that the benefits to public health of the immediate availability of Masitinib AB Science outweighs the risks inherent in the fact that additional data are still required.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as discussed during the procedure cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in Appendix 8.2.