18 April 2018
EMA/406203/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alsitek

International non-proprietary name: masitinib

Procedure No. EMEA/H/C/004398/0000

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
ALS	Amyotrophic lateral sclerosis
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
Bid	bis in diem/twice a day
CAFS	Combined Assessment of Function and Survival
C-Findings	Clinical Findings
CRF	Case Report Form
CR	Clinical Research
CSF1R	Colony-stimulating factor 1 receptor
CYP	Cytochrome P450
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FVC	Forced Vital Capacity
ECG	Electrocardiogram
HDPE	High Density Polyethylene
HHD	Handheld Dynamometer
IC50	Inhibitory Concentration 50
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
MAR	Missing at Random
NMJ	neuromuscular junctions
OS	Overall Survival
IRB	Institutional Review Board
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
SRC	Steroid Receptor Coactivator
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AB Science submitted on 12 September 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Alsitek, through the centralised procedure falling within the 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 15 September 2016.

Alsitek was designated as an orphan medicinal product EU/3/16/1722 on 29 August 2016 in the following condition: treatment of amyotrophic lateral sclerosis.

The applicant applied for the following indication:

Masitinib is indicated for the treatment of adult patients with probable or definitive amyotrophic lateral sclerosis (ALS).

Masitinib is administered as dual oral therapy in combination with riluzole.

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 applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14(7) of Regulation (EC) No 726/2004.

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.

Protocol assistance

The applicant did not seek Protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bruno Sepodes Co-Rapporteur: Eleftheria Nikolaidi

The application was received by the EMA on	12 September 2016
The procedure started on	29 September 2016
The Rapporteur's first Assessment Report was circulated to all CHMP members on	22 December 2016
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	29 December 2016
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 January 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 January 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 August 2017
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	27 September 2017
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2017
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	12 October 2017
The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– A GCP inspection at 2 sites: investigator sites in Spain and in Argentina between 18 December 2017 and 22 December 2017, and 8 January 2018 and 12 January 2018 respectively. The outcome of the inspection carried out was issued on	7 February 2018
The applicant submitted the responses to the CHMP List of Outstanding	20 February 2018

Issues on	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	12 and 14 March 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	21 March 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued via written procedure a negative opinion for granting a marketing authorisation to Alsitek on	18 April 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

This Marketing Authorisation Application concerns the use of Masitinib Mesilate in combination with riluzole for the treatment of adult patients with probable or definitive amyotrophic lateral sclerosis (ALS).

Amyotrophic lateral sclerosis (ALS) is a fatal motor neuron disorder that is characterized by progressive loss of the upper and lower motor neurons (LMNs) at the spinal or bulbar level [Rowland LP and Shneider NA, 2001]. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. Motor neurons are nerve cells located in the brain, brain stem, and spinal cord that serve as controlling units and vital communication links between the nervous system and the voluntary muscles of the body. Messages from motor neurons in the brain (called upper motor neurons) are transmitted to motor neurons in the spinal cord (called lower motor neurons) and from them to particular muscles. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, and stop sending messages to muscles. Unable to function, the muscles gradually weaken, waste away (atrophy), and have very fine twitches (called fasciculations). Eventually, the ability of the brain to start and control voluntary movement is lost.

2.1.2. Epidemiology and risk factors, screening tools / prevention

Population-based studies have established that the incidence of ALS in Europe is fairly uniform at 2·16 per 100 000 person-years. Although ALS affects people worldwide, an exact incidence of this disease is not yet known. Men have a higher incidence of disease (3·0 per 100 000 person-years; 95% CI 2·8–3·3) than do women (2·4 per 100 000 person-years; 95% CI 2·2–2·6), although the incidence between men and women is about the same in familial disease. The overall population-based lifetime risk of ALS is 1:400 for women and 1:350 for men. Peak age at onset is 58–63 years for sporadic disease and 47–52 years for familial disease. Incidence decreases rapidly after 80 years of age.

ALS is categorized in two forms: familial and sporadic, with the latter being the most common (90–95%) which has no obvious genetically inherited component. In general about 5–10% of ALS is familial, with a Mendelian dominant inheritance pattern, although regional variations have been observed underscoring the complicated epidemiology of ALS. Numerous genes and loci of major effect have been identified. The remaining 90% of people diagnosed with ALS are classified as having sporadic disease. For these patients, results from family aggregation studies have identified an overlap between ALS and common neurodegenerative disorders, suggesting the existence of susceptibility genes that might increase the overall risk of neurodegeneration among relatives. Results from candidate gene studies have identified several susceptibility genes, although the relative contribution of every identified "at risk" gene rarely exceeds an odds ratio of 2.0, and the mechanism by which risk is conferred is not known

The first onset of symptoms is usually between the ages of 50 and 65. The most common symptoms that appear in both types of ALS are muscle weakness, twitching, and cramping, which eventually can lead to the impairment of muscles. In the most advanced stages, ALS patients will develop symptoms of dyspnea and dysphagia. When muscles in the diaphragm and chest wall fail, people lose the ability to breathe without ventilator support. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10% of those with ALS survive for 10 or more years.

Although the disease usually does not impair a person's mind or intelligence, it has been suggested that some persons with ALS may have depression or alterations in cognitive functions involving decision-making and memory [NINDS, 2013].

2.1.3. Biologic features, aetiology and pathogenesis

Motor neurons are nerve cells located in the brain, brain stem, and spinal cord that serve as controlling units and vital communication links between the nervous system and the voluntary muscles of the body. Messages from motor neurons in the brain (called upper motor neurons) are transmitted to motor neurons in the spinal cord (called lower motor neurons) and from them to particular muscles. In ALS, both the upper motor neurons and the lower motor neurons degenerate or die, and stop sending messages to muscles. Unable to function, the muscles gradually weaken, waste away (atrophy), and have very fine twitches (called fasciculations). Eventually, the ability of the central nervous system to initiate and control voluntary movement is lost.

The exact molecular pathway causing motor neuron degeneration in ALS is unknown, but as with other neurodegenerative diseases, it is likely to involve a complex interplay between multiple pathogenic cellular mechanisms that may not be mutually exclusive. These may include: genetic factors, excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, neurofilament aggregation, protein aggregation, inflammatory dysfunction and contribution of non-neuronal cells.

The scientific rationale for the use of masitinib in the treatment of ALS is based on the following features:

As a proposed primary mechanism of action, masitinib acts on neuroglia through the inhibition of a receptor found on glial cells called CSF1R (colony-stimulating factor 1 receptor). There exists robust evidence in the scientific literature to link neuronal damage in ALS with microgliosis, in particular the emergence of aberrant glial cells; a process regulated by the CSF1/CSF1R signaling pathway. Through targeting this pathway, masitinib is able to inhibit glial cell proliferation, including aberrant microglial cells that are strongly associated with motor neuron degeneration, and also retard microglia cell migration.

As a secondary mechanism of action downregulating deleterious inflammation in glial cells, masitinib appears to act on mast cells through inhibition of the c-Kit/SCF and LYN/FYN signaling pathways. Consequently, masitinib is capable of regulating mast cell activity including mast cell–microglia cross-talk, leading to a reduction in the release of inflammatory mediators. There is putative evidence in the literature to suggest that inhibition of mast cell activity, and thus a reduction in the release of proinflammatory and vasoactive mediators may contribute to masitinib's overall therapeutic effect in ALS by regulating the neuroinflammatory network and modulating blood-brain barrier (BBB) and blood-spinal cord barrier permeability.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

ALS causes weakness with a wide range of disabilities. Eventually, all muscles under voluntary control are affected, and individuals lose their strength and the ability to move their arms, legs, and body. When muscles in the diaphragm and chest wall fail, people lose the ability to breathe without ventilator support. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10% of those with ALS survive for 10 or more years.

Although the disease usually does not impair a person's mind or intelligence, it has been suggested that some persons with ALS may have depression or alterations in cognitive functions involving decision-making (frontal executive functions) and memory.

ALS Symptoms

Many individuals first see the effects of the disease in a hand or arm as they experience difficulty with simple tasks requiring manual dexterity such as buttoning a shirt, writing, or turning a key in a lock. In other cases, symptoms initially affect one of the legs, and people experience awkwardness when walking or running or they notice that they are tripping or stumbling more often. When symptoms begin in the arms or legs, it is referred to as "limb onset" ALS. Other individuals first notice speech problems, termed "bulbar onset" ALS. Regardless of the part of the body first affected by the disease, muscle weakness and atrophy spread to other parts of the body as the disease progresses. Individuals may develop problems with moving, swallowing (dysphagia), and speaking or forming words (dysarthria). Symptoms of upper motor neuron involvement include spasticity and exaggerated reflexes (hyperreflexia) including an overactive gag reflex. An abnormal reflex commonly called Babinski's sign (the large toe extends upward as the sole of the foot is stimulated in a certain way) also indicates upper motor neuron damage. Symptoms of lower motor neuron degeneration include muscle weakness and atrophy, muscle cramps, and fasciculations.

To be diagnosed with ALS, people must have signs and symptoms of both upper and lower motor neuron damage that cannot be attributed to other causes. Although the sequence of emerging symptoms and the rate of disease progression vary from person to person, eventually individuals will not be able to stand or walk, get in or out of bed on their own, or use their hands and arms. Difficulty swallowing and chewing impair the person's ability to eat normally and increase the risk of choking. Maintaining weight will then become a problem. Because cognitive abilities are relatively intact, some people are aware of their progressive loss of function and may become anxious and depressed. In later stages of the disease, individuals have difficulty breathing as the muscles of the respiratory system weaken. They eventually lose the ability to breathe on their own and must depend on ventilator support for survival. Affected individuals also face an increased risk of pneumonia during later stages of ALS.

2.1.5. Management

No cure has yet been found for ALS. However, the first drug treatment for the disease, riluzole (Rilutek), was approved in 1995. Riluzole is believed to reduce damage to motor neurons by decreasing the release of glutamate. Clinical trials with ALS patients showed that riluzole modestly prolongs survival and also extends the time before an individual needs ventilation support. Riluzole does not reverse the damage already done to motor neurons, and persons taking the drug must be monitored for liver damage and other possible side effects. However, this first disease-specific therapy offers hope that the progression of ALS may one day be slowed by new medications or combinations of drugs.

Other treatments for ALS are designed to relieve symptoms and improve the quality of life for individuals with the disorder. This supportive care is best provided by multidisciplinary teams of health care professionals such as physicians; pharmacists; physical, occupational, and speech therapists; nutritionists; and social workers and home care and hospice nurses. Working with patients and caregivers, these teams can design an individualized plan of medical and physical therapy and provide special equipment aimed at keeping patients as mobile and comfortable as possible. Physicians can prescribe medications to help reduce fatigue, ease muscle cramps, control spasticity, and reduce excess saliva and phlegm. Drugs also are available to help patients with pain, depression, sleep disturbances, and constipation. Physical therapy and special equipment can enhance an individual's independence and safety throughout the course of ALS. People may begin using suction devices to remove excess fluids or saliva and prevent choking. When individuals can no longer get enough nourishment from eating, doctors may advise inserting a feeding tube into the stomach.

When the muscles that assist in breathing weaken, use of nocturnal ventilatory assistance (intermittent positive pressure ventilation [IPPV] or bilevel positive airway pressure [BIPAP]) may be used to aid breathing during sleep. Individuals may eventually consider forms of mechanical ventilation (respirators) in which a machine inflates and deflates the lungs. To be effective, this may require a tube that passes from the nose or mouth to the windpipe (trachea) and for long-term use, an operation such as a tracheostomy, in which a plastic breathing tube is inserted directly in the patient's windpipe through an opening in the neck. Although ventilation support can ease problems with breathing and prolong survival, it does not affect the progression of ALS.

The cause of death in ALS is normally of a respiratory nature. Approximately 60 % of patients have a predictable decline in function while the remainders die suddenly, sometimes from other causes.

The only registered treatment option is riluzole [Miller, 2012]. However, clinical improvement is very modest with deterioration slowed by approximately 2 months with respect to placebo.

According to the EMA website listing of European public assessment reports there are two medications specifically authorised in Europe for the treatment of ALS (see Table 1).

Table 1 Drugs authorized in Europe for the treatment of ALS

Active substance	Drug	Authorization	Population indicated
Riluzole	Rilutek	10/06/1996	Amyotrophic lateral sclerosis. Rilutek is used to extend the patient's life, or the time before they need to use mechanical ventilation
	Riluzole Zentiva	07/05/2012	
Nuedexta	Dextromethorphan / quinidine	24/06/2013	Neurobehavioral Manifestations: treats the symptoms of pseudobulbar affect (PBA) in adults. PBA is a condition where damage to certain areas of the brain results in sudden and uncontrollable episodes of crying or laughing that do not relate to the patient's real emotional state. Efficacy has only been studied in patients with underlying amyotrophic lateral sclerosis or multiple sclerosis.

This information is taken from the EMA website listing of European public assessment reports. See http://www.ema.europa.eu/ema/ - Find Medicine - Human Medicine - Keyword Search (enter {amyotrophic lateral sclerosis} with option of 'Therapeutic indication' selected).

Many symptomatic treatments, which do not slow disease progression but affect quality of life, appear helpful to individuals in clinic (Table 2 lists the various symptomatic treatments commonly used for management of ALS [Jenkins 2014]). However, evidence of significant benefit is generally weak and further randomized clinical trials are required to provide a more robust evidence base. This opinion is reflected in a Cochrane systematic review of treatments for spasticity in ALS by Ashworth and colleagues (published in 2006 with update in 2011) [Ashworth 2006]. The authors identified only one randomized controlled trial in the scientific literature pertaining to interventions for treating spasticity in ALS that met their inclusion criteria. That trail was on the use of individualized moderate intensity endurance type exercise; no other medical or surgical alternative treatment had been evaluated in randomized trials. The authors concluded that this trial was too small to determine benefit and recommended that further research was needed to test whether anti-spasticity medication (for example baclofen or dantrolene) is beneficial or causes harm by worsening muscle weakness and function.

One exception to this lack of supporting evidence for symptomatic treatment in ALS is the use of non-invasive ventilation at the time of respiratory failure. A single randomized trial of non-invasive ventilation suggests that it significantly prolongs survival and improves or maintains quality of life in people with ALS and without severe bulbar symptoms [Radunovic 2013]. The Sponsor notes however that since this is not a drug intervention then there is no reason why it should not be concomitantly administered. A patient would therefore be expected to still receive the benefits associated with non-invasive ventilation for the symptom of respiratory failure in addition to additional functional and survival benefits offered by masitinib.

Table 2 Summary of symptomatic treatments commonly used in patients with ALS [adapted from Jenkins 2014]

Drug	Population indicated / Common usage
Baclofen (Lioresal)	Indicated for the relief of spasticity of voluntary muscle resulting from such disorders, for example, multiple sclerosis. In patients 0 to <18 years it is indicated for the symptomatic treatment of spasticity of cerebral origin, including ALS.
Hyoscine	Hypersalivation
Carbocisteine	Difficulty expectorating secretions
Amitriptyline	Neuropathic pain
Gabapentin	Neuropathic pain
Citalopram	Depression and emotional lability
Venlafaxine	Depression
Nortriptyline	Depression

Hence, ALS is a debilitating and life-threatening disease that leads to a progressive inability to move, respiratory function insufficiency, and poor prospects of long-term survival.

2.1.6. Pharmacologic properties

Masitinib is a small molecule drug that selectively inhibits specific tyrosine kinases such as colony-stimulating factor 1 receptor (CSF1R), c-Kit, LYN, FYN, and platelet-derived growth factor receptor (PDGFR) α and β, in the submicromolar range [Dubreuil, 2009; Davis, 2011]. At the cellular level, masitinib is a potent inhibitor of CSF1R-dependent cell proliferation (IC_{50} 90 nM), of wild-type (WT) 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). Two large-scale independent studies have shown masitinib to have the highest selectivity from a wide range of protein kinase inhibitors, including all those approved or under clinical development at the time of publication [Anastassiadis, 2011; Davis, 2011]. In particular, it was shown that from a panel of 178 compounds, masitinib was the most selective protein kinase inhibitor tested [Anastassiadis, 2011]. Selectivity generally indicates how safe a given targeted treatment will be, the greater the number of kinases inhibited (i.e. lower selectivity) the greater the potential for off-target effects and toxicity.

2.1.7. Mode of action

The exact molecular pathway causing motor neuron degeneration in ALS is unknown, but as with other neurodegenerative diseases, it is likely to involve a complex interplay between multiple pathogenic cellular mechanisms that may not be mutually exclusive. These include: genetic factors, excitotoxicity, oxidative stress, mitochondrial dysfunction, impaired axonal transport, neurofilament aggregation, protein aggregation, inflammatory dysfunction and contribution of non-neuronal cells. The scientific rationale for the use of masitinib in the treatment of ALS is based on the following features.

As a primary mechanism of action, masitinib is proposed to act on neuroglia through the inhibition of a receptor found on glial cells called CSF1R (colony-stimulating factor 1 receptor). There exists some evidence in the scientific literature to link neuronal damage in ALS with microgliosis, in particular the emergence of aberrant glial cells; a process regulated by the CSF1/CSF1R signaling pathway. Through targeting this pathway, masitinib is able to inhibit glial cell proliferation, including aberrant microglial cells that are strongly associated with motor neuron degeneration, and also retard microglia cell migration. Most of the relevant evidence on the pathogenesis has been provided by the Applicant and has not been considered so far a major pathophysiology path to clinical ALS progression.

The applicant claimed as a secondary mechanism of action downregulating deleterious inflammation in glial cells, masitinib acts on mast cells through inhibition of the c-Kit/SCF and LYN/FYN signaling

pathways. Consequently, masitinib is capable of regulating mast cell activity including mast cell–microglia cross-talk, leading to a reduction in the release of inflammatory mediators. There is putative evidence in the literature to suggest that inhibition of mast cell activity, and thus a reduction in the release of proinflammatory and vasoactive mediators, is likely to contribute to masitinib's overall therapeutic effect in ALS by regulating the neuroinflammatory network and modulating blood-brain barrier (BBB) and blood-spinal cord barrier permeability.

The development of masitinib in ALS is therefore primarily based on its pharmacological action in microglia cells and mast cells, including a population of glial cells displaying aberrant phenotypes and increased proliferation. This dual therapeutic approach in potently targeting both microglia and mast cell activity, thereby modulating neuroinflammation and slowing microglial-related disease progression, provides a strong medical plausibility for the use of masitinib in ALS. It is through this multifaceted mechanism of action that masitinib appears capable of generating the beneficial treatment effects observed in relevant preclinical animal studies (SOD1G93A rats 7 days after paralysis onset, i.e. in the therapeutic setting) and in ALS clinical trials (as evidenced from interim analysis of a randomized, placebo-controlled, phase 3 study AB10015).

Type of Application and aspects on development

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest, for the reasons detailed below.

Indeed, the request would have been justified with regards to the target population for the indication and the relevance of the disease. Although a very rare disease, ALS impacts on general public health as most patients belong to late adulthood, with family and professional responsibilities, and the speed of progression is widely feared among the general population. A new truly effective agent will be of major interest.

However, the CHMP concluded that the strength of evidence presented in the request for accelerated assessment prevented the granting of a positive decision from the Committee. The presented interim analysis data were not considered sufficiently compelling to justify this approach, and in addition it was considered unlikely that the applicant could have their database cleared and locked at the time of planned CHMP assessment.

Based on the assessment of the request provided by the applicant, the draft CHMP guideline on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) no 726/2004, the CHMP did not accept the accelerated assessment procedure pursuant to Article 14 (9) of Regulation (EC) No 726/2004 for Masitinib mesilate.

The applicant also requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14(7) of the above mentioned Regulation. The applicant requested a conditional marketing authorisation based on the following claims:

- Masitinib aims at the treatment of seriously debilitating diseases and life-threatening disease (ALS).

Amyotrophic lateral sclerosis (ALS) is a progressive, incurable and fatal neurodegenerative disease. ALS is a serious neurological disease that causes muscle weakness, disability and eventually death. Median survival for ALS is 2 to 4 years from onset; only 5–10% of patients survive beyond 10 years [Chio, 2013]. The disease is heterogeneous, but most patients die less than 3 years from symptom-onset [Gordon, 2013].

The cause of death in ALS is normally of a respiratory nature. Approximately 60 % of patients have a predictable decline in function while the remainders die suddenly, sometimes from other causes.

The only registered treatment option is riluzole [Miller, 2012]. However, clinical improvement is very modest with deterioration slowed by approximately 2 months with respect to placebo.

- Masitinib satisfies the requirements laid down in Article 4 of Commission Regulation (EC) No 507/2006.

The position of the CHMP on the above claims is expressed in the sections of the report below, but a key aspect of this position is that the Committee did not consider the presented data sufficient to conclude on the positive B/R ration of Alsitek in the intended indication.

2.2. Quality aspects

2.2.1. 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 high density polyethylene (HDPE) bottles with child resistance closures.

2.2.2. 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.

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:

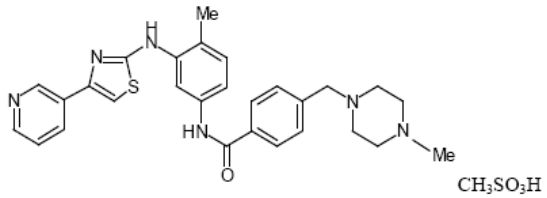

Figure 1 Structure of masitinib mesilate

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.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.

During the procedure it was noted that the correct spelling of the salt is “mesilate” rather than “mesilate”. The applicant should correct this in throughout the CTD and application documents.

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.

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.

The proposed starting materials comply with the general principles for selection of the starting materials as outlined in ICH Q11 and the EMA reflection paper 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 new 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 these impurities.The active substance is packed in double LDPE bags which comply with EC 10/2011 and with the Ph. Eur. monograph 3.1.4.

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 assay mesilate ion (titration).

In addition, tests for the metal impurities and tests for a number of potential mutagenic impurities (GC - UPLC/MS) are included.

The analytical methods used have been adequately described and the non-compendial methods appropriately mostly validated in accordance with the ICH guidelines. Some additional validation and system suitability data is required.

The specifications and their limits are considered to be acceptable and have been appropriately justified. The potential formation of impurities has been investigated and appropriate specifications have been set, however the specification limits for some impurities need to be updated.

Batch analysis data on 3 production scale batches of the active substance 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.

Stability

Stability data on three production scale batches of the active substance from the proposed manufacturer) stored for 12 months under long term conditions at 25 ºC / 60% RH and for 6 months under accelerated conditions at 40 ºC / 75% RH were provided. These batches were tested according to the specifications and with the analytical methods. No trend was observed and no significant differences between room temperature and accelerated conditions occurred.

A forced degradation study was conducted on one batch of masitinib mesilate in solid state (at high temperature) and in aqueous solution (at high temperature, UV, acidic, alkaline and oxidative conditions). The impurity test method used for release testing was used. In oxidative conditions masitinib showed nearly complete degradation. Some degradation was observed at aqueous high temperature (80 °C) UV and acidic conditions. There was no significant degradation in solid state at high temperature (120°C) or in aqueous alkaline conditions.

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.

Additional stability data on six batches of the active substance manufactured before certain changes to the manufacturing process of the active substance were implemented were also provided. These batches were tested according to the specifications and using the analytical methods in force at the time of the studies (). The results from long-term stability studies at 25 ºC / 60% RH (3 batches x 60 months and 3 batches x 48 months) as well as from the accelerated stability studies at 40 ºC / 75% RH (6 batches x 6 months) show that the active substance is stable, all parameters comply with the established specification limits; no trend is observed and no significant differences between room temperature and accelerated conditions occurred.

Overall the batch data provided justify the retest period of 48 months for the masitinib mesilate active substance.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product was proposed as light-orange, capsule-shape, film-coated tablets containing 100 mg or 200 mg of masitinib (as mesilate) as active substance.

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

The proposed container closure system was an HDPE bottles, 30 tablets per bottle, closed with a childproof closure system.

The pharmaceutical development for masitinib 100 mg and 200 mg film-coated tablets has been adequately described. The aim was to develop an immediate release dosage form of masitinib.

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.

A major objection was initially raised relating to the discriminatory power of the dissolution method proposed for quality control testing. The applicant subsequently submitted additional experimental data justifying the selection of the dissolution test conditions (i.e. paddle speed, medium, pH) and demonstrating the discriminatory power of the dissolution test and proposed specification limits (by testing batches of uncoated tablets formulated without disintegrant and testing batches manufactured with variable granulation parameters (equipment, granulation times, blade speed, water content and subsequent hardness). The major objection was considered to be resolved.

The primary packaging is HDPE bottles closed with a polypropylene child-resistant closure with an induction sealed aluminium/polyethylene liner. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The material complies with Ph.Eur. and EC requirements. During storage the tablets are in contact with the protective polyethylene liner, however after opening, the polyethylene liner is removed and the tablets are in contact with a waxed white pulp board attached to the polypropylene closure. A specification for the waxed white pulp board liner has not been provided by the applicant at the time of opinion.

Manufacture of the product and process controls

The manufacturing process consists of 8 main steps: weighing, preparation of binder solution, granulation, drying, milling, compression, tablet coating and packaging. 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 some steps only. In response to questions from CHMP, the applicant updated the process validation protocol to include all relevant steps in the manufacturing process. The updated process validation protocol is considered acceptable.

Product specification

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

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

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 three batches of 100 mg tablets and six batches of 200 mg tablets manufactured at the proposed commercial manufacturing site, at commercial scale, confirming the consistency of the manufacturing process.

Stability of the product

Stability data of two batches of the 100 mg tablets and six batches of the 200 mg tablets (all at commercial scale) stored under long term conditions at 25 ºC / 60% RH for up to 48 months and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Samples were tested for appearance, moisture content, hardness, assay, impurity content, dissolution and microbial testing.

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 are acceptable.

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.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. These are listed below as recommendations for future quality development.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the proposed SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Some information is missing from, or needs to be updated, in the quality part of the dossier. This has no impact on the benefit/risk of the product.

2.2.6. Recommendation for future quality development

The applicant should correct spelling of the salt to “mesilate” rather than “mesylate” throughout the CTD and application documents.

The active substance specification limits for impurities should be updated.

The requested additional validation and system suitability data for active substance test procedures should be provided.

A specification for the liner consisting of waxed white pulp board should be established. The specifications should include a test for identification of the material, which is in contact with the finished product after removal of the protective liner.

2.3. Non-clinical aspects

2.3.1. Pharmacology

The exact molecular pathway causing motor neuron degeneration in ALS is unknown, but as with other neurodegenerative diseases, it is likely to involve a complex interplay between multiple pathogenic cellular mechanisms that may not be mutually exclusive.

As a primary mechanism of action, masitinib acts on neuroglia through the inhibition of a receptor found on glial cells called CSF1R (colony-stimulating factor 1 receptor). There exists robust evidence in the scientific literature to link neuronal damage in ALS with microgliosis, the emergence of aberrant glial cells; a process regulated by the CSF1/CSF1R signaling pathway. Through targeting this pathway both in vitro and in vivo, masitinib was shown to be able to inhibit glial cell proliferation, including aberrant microglial cells that are strongly associated with motor neuron degeneration, and retard microglia cell migration.

Excessive inhibition of CSF1 has been shown to result in complete microglia ablation, which might be deleterious by compromising otherwise normal microglia brain function. On the other hand, Trais and colleagues showed that prolonged dosing of masitinib did not inhibit microglial survival [Trias, 2016]. The rationale for such specific beneficial effect of masitinib, in contrast to other studies showing microglia ablation with CSF1, has high clinical relevance and was further discussed and clarified by the applicant. The applicant claims to have demonstrated that masitinib inhibits excessive microglial proliferation and emergence of aberrant glial cells without resulting in depletion of all microglia cells.

Secondary pharmacodynamics studies have shown that masitinib has a potential modulatory role on proinflammatory and vasoactive mediators released by mast cells, by sustaining the neuroinflammatory network and modulating BBB permeability, as well as mast cell–microglia cross-talk, inhibition of mast cell activity via targeting of c-Kit/SCF and Lyn/Fyn signaling pathways. These effects are likely to contribute to masitinib’s overall therapeutic effect in ALS.

Safety pharmacology studies in rats revealed no treatment-related effect on the central nervous system or respiratory system at single oral doses up to 150 mg/kg. Masitinib induced a concentration-dependent reduction in hERG tail current over the concentration range 0.1 to 30 µM. The lowest concentration tested (0.1 µM) gave rise to a hERG current inhibition of 8% while the IC50 value was 8.3 µM. This effect was only partially reversed after the washout period and was significant compared to the spontaneous run-down observed in the control group. No effect was observed on electrocardiogram parameters in telemetered dogs (n=3) receiving 50 mg/kg and clinical studies do not suggest risk of QT prolongation with masitinib (Only one QTc elevation was observed among the 53

ECG performed after a period of treatment of patients with masitinib of at least 3 months, and the increased QTc was less than 480 msec). The free plasma Cmax of masitinib which is about 0.08µmol/L, for a single dose of 400mg (for 800mg, the free plasma Cmax is about 0.13µM), is far lower than the IC50 measured in the hERG channel inhibition test. It is agreed that, at therapeutic doses in humans, masitinib is unable to inhibit hERG channel. No pharmacodynamic drug interaction studies were performed for masitinib.

2.3.1. Pharmacokinetics

Preclinical pharmacokinetic and toxicokinetic investigations have been conducted in mice, rats and dogs in order to characterize the pharmacokinetic behaviour of masitinib mesilate.

Absorption

In vitro studies in Caco-2 cells, indicate that masitinib may be a substrate of P-gp mediated transport at concentrations <10 µM. At higher concentrations (≥10 µM), masitinib appears to be an inhibitor of P-gp mediated transport which is likely to be due to saturation of P-gp-mediated efflux. It was not possible to establish an exact IC50, however approximated IC50 values were calculated, and in the range of 63.24 to 154.22 µM. The free concentration of masitinib in plasma is well below this range, hence inhibition of systemic P-gp is considered unlikely, whereas the concentration of masitinib in the gut is much higher than the approximated IC50 values, and inhibition of P-gp in the gut is a potential risk.

The absorption of masitinib was studied after single i.v. (5 mg/kg) and p.o (10 mg/kg) administration of 14C-masitinib to Beagle dogs and Sprague-Dawley rats. No gender differences were observed. Tmax following p.o. dosing was 2.2 h in dogs and 4 h in rats. Elimination half-life (T½) following oral administration was 4.6 h and 10.4 h in rats and dogs, respectively. The bioavailability was relatively high with a mean value of 83% in dogs and 72% in rats. Masitinib had a relatively large volume of distribution (Vd) with values of 10.2 and 6.38 L/kg for male and female Sprague-Dawley rats, respectively. The plasma clearance for male and female rats was 19.8 and 14.8 mL/min/kg, respectively.

In male Swiss mice after oral administration of AB1010 at four doses: 30, 125, 250 and 500 mg/kg, the tmax was reached 0.5 or 1 hour after oral (gavage) administration. Systemic exposure (as measured by the Cmax and AUC0-24h) increased with dose-level. Repeated dosing to rats revealed higher exposure in females. However, exposure to the major metabolite AB3280 was approximately two times higher in male rats. AB3280 Tmax was in the range from 3-4 h while the elimination half-life varied from 3.55 to 4.23 h. No gender differences were observed with respect to masitinib absorption in dogs following repeated oral administration. Results from TK analysis in rats revealed a supra-linear increase in exposure at lower dose levels (between 10 and 30 mg/kg).

Distribution

The binding of ^{14}C-Masitinib mesilate was determined on human blood cells, human plasma proteins and isolated human plasma proteins as well as on rat, mouse, dog and rabbit blood cells and plasma. The results indicate that for the ^{14}C-Masitinib mesilate concentration used, 100-3000 ng/mL the binding to human, rat, mouse, dog and rabbit plasma proteins was high 93.93%, 92.15%, 86.12%, 93.33% and 97.50%, respectively and constant within the tested concentration range.

Following intravenous injection and oral gavage, the test item distributed throughout the body. Higher concentration was observed in the *adrenals, kidneys, spleen and intestines*. However, rapid elimination was observed from all tissues as only trace amount was observed after 24 hours and 7 days respectively. A new in vivo study in rats has been performed to further investigate the passage of masitinib to the brain. It was shown that masitinib indeed crosses the blood brain barrier in rats and Cmax levels appear to be sufficiently high to inhibit c-Kit kinase directly in the brain tissues. Albeit, no appreciable treatment-related CNS adverse events were observed in *in vivo* preclinical models and in human patients in the non-oncology clinical development program of masitinib. These results suggest that masitinib is unlikely to elicit CNS toxicity in humans despite its ability to cross the blood brain barrier.

Metabolism

The Phase I metabolism of masitinib was investigated in hepatic microsomes from CD-1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs, Cynomolgus monkeys and humans. While the identical five metabolites were detected in mice and rabbits (AB3280, MET1, MET2, MET3 and AB1187.3), four metabolites were seen in rats, monkeys and humans (AB3280, MET1, MET2, MET3). While AB3280 was the major metabolite in hepatic microsomes derived from mice, rats, monkeys and humans (≥18%), AB3280 was not formed in dog hepatocytes in vitro. Hence, the dog microsomes formed MET1, MET2 and MET3. No human specific metabolites were detected.

In addition, the Phase I and II metabolism of masitinib was studied in hepatocytes from CD-1 mice, Sprague-Dawley rats and humans. While AB3280 was the major metabolite in hepatocytes from rats and humans AB2436 was the major metabolite in mice hepatocytes in vitro (>47%). AB2436 was less abundant in rats (16%) and it was not found in human hepatocytes. Moreover, MET1/AB5235, which is genotoxic in the presence of S9 fraction in vitro, was only detected in mouse hepatocytes. Again, no human specific metabolites were observed.

In initial in vivo i.v. and p.o. metabolite studies conducted in rats and dogs, no masitinib plasma metabolites were detected. With a more sensitive method, it was shown that the aniline metabolite AB2436 is present in plasma in mice and rats. In mice, it is present at high levels (AUC for AB2436 is 4x AUC for AB1010) while in rats the levels are low (AUC for AB2436 is 0.005x AUC for AB1010). In humans the AUC for AB2436 at steady state is <3% of the AUC for AB1010.

The major metabolite AB3280 was quantified during the course of repeat-dose studies in mice, rats and dogs. Based on the sum of in vitro data, plasma, urinary and faecal data, an overview of the expected metabolism of masitinib in mice, rats, dogs and humans has been gathered. N-demethylation of masitinib to AB3280 takes place in mice, rats, dogs as well as humans and AB3280 represents the major masitinib metabolite in plasma. Based on the presence of AB3280 and/or AB1187.3 in urine, the cleavage of the amide bond leading to the formation of AB1187.3 and the aniline AB2436 occurs in all species tested. N-oxidation and hydroxylation appear to be minor metabolic pathways. N-oxides of either masitinib or AB3280 or both, were found as minor metabolites in urine and faeces of rats and dogs and were not specifically searched for in plasma of any species. Hydroxylated derivatives of masitinib were identified as minor metabolites in urine and faeces of rats and dogs. To conclude, the major metabolites detected in humans are also formed in animals and as such the species used for toxicity testing are considered valid animal models.

Excretion

Masitinib was predominantly excreted via the faeces (*around 90% of the administered dose*) following p.o. and i.v. administration to rats and dogs.

Pharmacokinetic Drug Interactions

In line with the recommendations in the draft guideline on the investigation of drug interactions (CPMP/EWP/560/95 Rev 1), the CYP450 inhibitory properties of masitinib and AB3280 towards CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 were investigated in human liver microsomes. The results revealed:

1) AB1010 was a weak to moderate inhibitor of the CYP3A4/5 and CYP2C9, as well as CYP2D6 with IC50 values of 14 µM, 20 µM and > 30 µM, respectively. This inhibition is partly reversible.

2) AB1010 does not increase the activity of CYP3A4/5, CYP2C9 and 2C19 but slightly increase CYP1A2 activity. AB1010 does not affect the mRNA of CYPs 1A2, 2B6 and 3A4/5.

3) At lower concentrations (<10 µM), AB1010 appears to be a substrate of P -gp mediated transport while at higher concentrations (≥10 µM), AB1010 appears to be an inhibitor of P-gp mediated transport which is likely to be due to competitive inhibition of P-gp-mediated efflux.

4) AB1010 is not an inhibitor of OATP1B1 (IC50 not reached) and a weak inhibitor of OATP1B3 (IC50 of 130µM).

5) It is agreed that the human potential impact of AB2436 on DDI is negligible.

2.3.2. Toxicology

Single-dose toxicity studies conducted in rats showed that the approximately lethal dose in rats is 2000 mg/kg following p.o. administration and higher than 100 mg/kg following i.v. dosing.

Repeat dose toxicity studies have been conducted of 4, 13 and 26 weeks duration in the rat and 4, 13 and 39 weeks duration in the dog. Repeated dose toxicity studies were performed in the mouse up to 3 months duration.

In these studies the principal target organ toxicity findings attributed to treatment with masitinib concerned the bone marrow, the liver and the kidney in dogs and rats, gastrointestinal tract intolerance in dogs, the heart, 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.

Bone marrow toxicity observed in mice, rats and dogs was characterized 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. Considering the important role of c-Kit during haematopoiesis, the bone marrow toxicity represents an expected finding. Hence, anaemia, lymphopenia, leucopenia and neutropenia are either common or very common findings in patients treated with masitinib.

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 (ALT/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. Since masitinib appears to be primarily eliminated via biliary excretion, this finding is considered treatment-related.

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. The applicant hypothesized that the renal disorders 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.

Masitinib exerted gastrointestinal toxicity in the dog in the form of vomiting, regurgitation and soft/liquid faeces. In addition, reddish or greenish coloured faeces was observed in dogs administered 150 mg/kg/day for 4 weeks.

In all toxicity studies in rats, female genital organs showed morphological changes indicative of estrous cycle disturbance from 100 mg/kg/day. The ovaries had moderate to large number of luteal and/or follicular hematocysts, no or few corpora lutea, and very few or few follicular developments. Depending on the ovarian stage, this was associated with endometrial epithelial cell atrophy or hypertrophy together with hyaline droplet deposit in the endometrial stroma, and vaginal epithelial cell atrophy, hyperplasia or mucification. Partial reversibility was noted in the 4-week toxicity in rats, although not confirmed in the 13-week toxicity in rats. The mechanism of action and clinical significance has subsequently been sufficiently discussed by the Applicant.

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). In the male reproductive tract there was vacuolation of the seminiferous epithelium and oligospermia in the epididymides in 2/4 dogs at the top dose of the 39 week study.

Slight to moderate hyperostosis were observed in the bones of rats administered 100 mg/kg/day for 6 months. The related tyrosine kinase inhibitors imatinib and sunitinib have been associated with a low and moderate risk for cardiotoxicity in the clinical setting, respectively.

One of the factors reported to lead to cardiotoxicity is the inhibition of the tyrosine kinase Abl which serves a maintenance function in cardiac-muscle cells. The Applicant points to that masitinib displays a lower affinity towards c-Abl than imatinib and sunitinib, however based on the publication from Davis et al (2011), the affinity of masitinib and imatinib was similar towards nonphosphorylated and phosphorylated c-Abl, while sunitinib displayed no significant affinity towards either nonphosphorylated and phosphorylated c-Abl.

The repeated dose toxicity studies revealed myocardial degeneration and fibrosis in the rat 26 week study and pericardial oedema in 1/4 female dogs at the top dose in the 39 week study. In the 2 year rat carcinogenicity study cardiomyopathy/atrial fibrosis occurred in both sexes at the mid-and top-dose levels and was considered to be a contributing factor to death in 5/50 males and 2/50 females at the top dose level. The severity of the cardiomyopathy appeared to be dose dependent, however, the frequency was not increased compared to the control group. Masitinib treatment in this study increased the severity of the underlying cardiomyopathy. Preclinical cardiac findings are stated in section 5.3 of the SmPC. Warnings regarding patients presenting with long QT interval or with cardiac failure is included in section 5.2, and lastly, cardiac toxicity, hypertension and hypotension are identified as potential important risks in the RMP. Since the bioanalysis conducted in the 26-week study in rats and the 39-week study in dogs were not performed under GLP conditions, the toxicokinetic data from these studies are only considered indicative.

No safety margins were presented in the initial non-clinical dossier that compares the exposure in animals (based on NOAEL values) to exposure in humans, i.e. to establish safety margins to observed toxicities. During the procedure the Applicant provided a comprehensive and elaborated discussion on the non-clinical data concerning the observed renal, reproductive organs- and cardiovascular toxicities. It appears that the toxicities observed in animals may be considered to be species specific, and this is supported by clinical data where lack of signals in these target organs prevails. The risk minimization measures suggested by the Applicant are therefore endorsed.

No treatment-related effect on mating parameters, the reproductive organs or seminology was noted at doses up to 100 mg/kg/day in male Sprague-Dawley rats treated p.o. from 29 days prior to mating.

Female Sprague-Dawley rats were treated p.o. with 10, 30 or 100 mg/kg/day masitinib from 29 days prior to mating until day 7 post-coitum. There were no effects on mating behaviour, whereas the fertility of females given 100 mg/kg/day was affected, as indicated by the number of non-pregnant females (3/24, compared to 0/24 in the vehicle), the low number of corpora lutea and implantation sites and the high pre-implantation loss. At 100 mg/kg/day, the increased number of early resorptions in addition to the increased number of dead concepti resulted in a low number of live concepti. The microscopic examination of the ovaries showed haemocysts in many corpora lutea in all the females given 100 mg/kg/day. Cystic degeneration of corpora lutea (with accumulation of fibroblasts and a few erythrocytes) was seen at 100 and 30 mg/kg/day (respectively, 17/24 and 6/24 females).

The adverse effects on female fertility appeared reversible hence acyclic oestrous cycle was the only finding in female Sprague-Dawley rats were given p.o. 15 and 50 mg/kg/day masitinib for 28 days followed by a recovery period of two weeks before mating.

Overall, the NOAEL for male and female fertility is considered 100 mg/kg/day and 10 mg/kg/day, respectively.

The potential effects of masitinib on embryo-fetal development were evaluated in rats and rabbits. In the rat study, a lower (-10%) mean fetal body weight was observed in the high-dose group (100 mg/kg/day). While visceral or skeletal malformations were not observed, masitinib-treatment was associated with variations in the form of unossified or incompletely ossified bones of the head, sternebrae and ribs. The incomplete ossifications were observed at doses ≥ 30 mg/kg/day. 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.

Cases of unossified fetal bone (5th and 6th sternebra) were observed in the rabbit embryo-fetal development study at doses ≥ 30 mg/kg/day. Maternal toxicity was observed at 100 mg/kg/day in the form of a 74% reduction in overall body weight gain relative to control animals. Moreover, all pregnant females experienced a mean net body weight loss (body weight change adjusted for gravid uterus weight) from day 6 post-coitum, but this was markedly greater than control at 100 mg/kg/day.

Since the skeletal variation observed (cases of unossified bone) are reversible and as such not adverse to the animal, the NOAEL for developmental toxicity is considered 30 mg/kg/day based on the reduced fetal weight observed in rats. The NOAEL for maternal toxicity (reduced body weight/macroscopic findings) is considered < 10 mg/kg/day.

No study on pre- and postnatal toxicity has been performed. A study on pre- and postnatal toxicity is expected to accompany an MAA unless there is a strong justification for omitting such data. Cautious recommendations in the SmPC are not a sufficient argument for waiving studies on developmental and reproductive toxicity. These studies are needed to make well-educated decisions in those rare cases where exposure occurs during early or late pregnancy. A decision to waive or postpone a study on pre- and postnatal toxicity must be justified by that fertile women are rare in the patient population or that data from the embryo-fetal toxicity study suggest such pronounced embryotoxicity that a pre- and postnatal toxicity study is unlikely to provide data of additional value. In absence of such justification, a decision to allow for a post-approval commitment must be based on the demonstration of an important clinical benefit and an agreement that the access to patients should not be delayed.

According to the Non-Clinical review of the Applicant for masitinib *"There was no evidence of teratogenicity in the rat or the rabbit, over a range of dose-levels that included doses causing maternal toxicity"*. The Applicant having performed a reproductive toxicity study in rats observed toxicity in the female reproductive system, which consisted of haematocysts and corpus luteum cysts in the ovaries only. According to the Applicant's view *"the hormone-dependent toxicity observed in female rats with masitinib is unlikely to occur in humans"*. However, this is not considered an accurate conclusion. It is considered that a sufficient number of well-designed studies, that would further investigate detrimental teratogenic effects of masitinib, have not been performed with masitinib.

Masitinib induced delayed contact hypersensitivity in the murine Local Lymph Node Assay. Moreover, masitinib was identified as slightly irritating and severely irritating to rabbit skin and eyes, respectively.

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

The Applicant has submitted long-term carcinogenicity studies conducted with mastinib 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 5/52 male CD-1 administered 500/300/80 mg/kg/day masitinib for 80 weeks, while transitional papillomas 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 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 hypothesized 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 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. 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.

The Applicant was asked to determine 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 1/105 cancer risk is to take the dose resulting in a 50% tumour incidence (TD50) and divide by 50000. As an alternative one may use the benchmark dose lower confidence limit 10% (BMDL10, an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodent). The company has chosen this approach which is understandable, since tumour incidence was clearly below 50%. While the data do not allow a clear calculation of BMDL10, the applicant has presented an interval which is agreed. It is however not agreed to make the calculation separately for the transitional carcinomas and papillomas. These tumours are likely to be related in terms of mechanism. It would be most appropriate to make the calculation on the sum. This would however not change the conclusion that BMDL10 would 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. It is concluded that the BDML10 value falls between 80 mg/kg and 140 mg/kg. This conclusion is endorsed.

To make a risk estimate based on exposure to the aniline metabolites, the Applicant refers to data showing about 500 times higher exposure in mice versus humans when comparing at a human equivalent dose. This factor is based on PK data submitted earlier and is agreed.

The inclusion of this factor in the ICH M7 formula results in an acceptable daily intake (AI) of masitinib between 4 – 12 mg/kg/day. The applicant argues that no transitional cell carcinomas were seen at the mid dose, and proposes 8 mg/kg to be the AI. However, the papillomas should be considered why a higher AI than 4 mg/kg is not agreed. This is just below the maximum daily dose. However, 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 program (as proposed by the applicant).

The masitinib metabolite AB3280 was devoid of a genotoxic potential in tests for gene mutations in bacteria (Ames test) and in mammalian cells (cultured human lymphocytes). Moreover, AB3280 at doses up to 600 mg/kg only gave rise to minor findings in a 2-week repeat-dose toxicity study in rats.

However, the metabolite AB2436 gave rise to gene mutations in both bacteria and human lymphocytes in the presence of S9. The metabolites AB5235 and AB6465 also showed mutagenic activity with a rat liver metabolic activation system

2.3.3. Ecotoxicity/environmental risk assessment

The legal basis for the current submission (Masitinib 100 mg film-coated tablets) is Article 3 (1) of Regulation (EC) No 726/2004, an orphan medicinal product status. It contains a new developed active substance masitinib, which will be used for the treatment of adult patients with probable or definitive amyotrophic lateral sclerosis (ALS). The recommended dose is 4.5 mg/Kg/day taken orally in the morning and evening. Masitinib may be administered until patients are no longer benefiting from treatment.

The applicant performed an ERA in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use (EMEA/CHMP/SWP/4447/00).

A PEC surface water (0.00824 mg/L) based on a DOSEAI of 329.76 mg/inhabitant/day and a fraction market penetration of 5x10-5 (orphan drug designation for ALS), resulted very low and did not trigger the action limit calculation. The log Kow has been performed for masitinib according to the OECD guideline No. 117, the resulted value of 1.44±0.003 demonstrated to be below 4.5 (action limit for PBT screening). However, taking into account that masitinib is an ionisable substance (pKa =7.5 - quality dossier - 3.2.S.1.3), for which the solubility is pH dependent, an ion-corrected log Dow was performed, covering the environmentally relevant pH-range.

Table 3 Summary of main study results

Substance (INN/Invented Name): Masitinib			
CAS-number (if available): 790299-79-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	Study performed according to a non-OECD method.	3.75 (neutral form at pH 9)	not B according to screening criteria
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	3.75 (pH 9)	Not B according to screening criteria
	BCF	no data	
Persistence	DT50 or ready biodegradability	no data	
Toxicity	NOEC or CMR	no data	
PBT-statement :	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	0.008	µg/L	< 0.01 µg/L (threshold)
Other concerns (e.g. chemical class)			no

2.3.4. Discussion on non-clinical aspects

The exact molecular pathway causing motor neuron degeneration in ALS is unknown, but as with other neurodegenerative diseases, it is likely to involve a complex interplay between multiple pathogenic cellular mechanisms that may not be mutually exclusive.

As a primary mechanism of action, masitinib possibly acts on neuroglia through the inhibition of a receptor found on glial cells called CSF1R (colony-stimulating factor 1 receptor). The applicant claims to have demonstrated that masitinib inhibits excessive microglial proliferation and emergence of aberrant glial cells without resulting in depletion of all microglia cells.

Secondary pharmacodynamics studies have shown that masitinib has a potential modulatory role on proinflammatory and vasoactive mediators released by mast cells, by sustaining the neuroinflammatory network and modulating BBB permeability, as well as mast cell–microglia cross-talk, inhibition of mast cell activity via targeting of c-Kit/SCF and Lyn/Fyn signaling pathways. These effects may also contribute to masitinib's overall therapeutic effect in ALS.

The major human metabolite, AB3280 was present in animals to an extent allowing toxicological qualification. The mutagenic aniline metabolite AB2436 was shown to be a minor circulating metabolite in humans (<3% if the AUC for masitinib) but was present in high levels in mouse (4x AUC for AB2436). As discussed below, the genotoxic metabolite may be associated with a carcinogenic risk.

In a long-term carcinogenicity study in CD-1 mice after repeated administration of masitinib 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.

In the long-term carcinogenicity study in Sprague-Dawley rats 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 the current 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). 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 and therefore was considered to be induced by masitinib. 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.

Studies on developmental and reproductive toxicity are needed to make well-educated decisions in those rare cases where exposure occurs during early or late pregnancy. A decision to waive or postpone a study on pre- and postnatal toxicity must be justified by the fact that fertile women are rare in the patient population, or that data from the embryo-foetal toxicity study suggest such pronounced embryotoxicity that a pre- and postnatal toxicity study is unlikely to provide data of additional value. In absence of a valid justification, only in the case of a major clinical benefit it would be acceptable for such data to be provided as a post–approval commitment.

There were tumour findings in both the mouse and the rat carcinogenicity study. Based on the findings of the carcinogenicity study in mice, uncertainties 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. However, it is anticipated that further nonclinical evaluation will not clarify this risk. Should the product be found to be of important clinical benefit in the target population, these findings would be described in the product information and proposed to be managed in the context of the risk management program (See discussion on benefit- risk).

2.3.5. Conclusion on the non-clinical aspects

Uncertainties in the non-clinical information submitted in support of the application of Alsitek are related to the lack of developmental and reproductive toxicity studies and carcinogenic findings in rats. Should a significant clinical benefit be proven (see discussion on Clinical efficacy, Clinical Safety and Benefit / Risk) it can be concluded that such uncertainties could be managed with appropriate warnings in the PI and measures in the RMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

A triggered GCP inspection was requested by the Committee for Medicinal Products for Human Use, on the conduct of the clinical study AB10015, in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and article 15 of Directive 2001/20/EC. Specific concerns have been identified by the assessors during the assessment of the data submitted. Inspectors confirmed these concerns during the inspection. The two centres inspected accounted for more than 40% of the overall study population. Several findings were detected. Four (4) critical, seven (7) major and two (2) minor findings have been observed. Critical findings were related to inadequate conduct of the trial, management of the trial by sponsor/CRO, failing to communicate protocol deviations to the Spanish Medicines or Medical Devices Agency and clinical monitoring. Major findings were observed at qualification and training, TMF, clinical conduct of the trial, safety reporting, IMP, source data verification and Clinical Study Report. Minor findings were addressed to archiving and equipment used in the trial.

The nature and of the findings, the systematic deficiencies observed, the massive number of protocol deviations which translated into a general lack of adherence to the protocol, the lack of global investigator meetings to harmonise procedures, and the suboptimal quality of management by the sponsor and CROs involved, all have a negative impact on data reliability. Inspectors are of the opinion that the data obtained at the sites inspected and represented in the CSR, are not trustworthy enough to support the application authorisation submitted to the Agency for Alsitek.

- **Tabular overview of clinical studies**

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
BA (food-effect)	AB1010-PIHV05031	evaluate the food intake influence on pharmacokinetic	Cross over	Masitinib, Tablet, 200mg, oral	12	healthy volunteers	Single dose	Complete, Full
Comparative BE	AB1010-PIHV04015	compare the relative BA of AB1010 from two formulations	Cross over	Masitinib, Tablet, Capsules, 100mg, oral	12	healthy volunteers	Single dose	Complete, Full
Analytical Methods	AB1010-03005	validation of analytical method of AB1010 and AB3280 in human plasma	Not applicable (not a clinical study)					
PK (HV)	AB1010-PIHV03001	determine safety / tolerability and PK parameters of AB1003	Double blind, placebo-controlled	Masitinib, powder for solution, ascending doses (40, 100, 200, 400 and 800	40	healthy volunteers	Dose escalations, single dose	Complete, Full

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
PK (HV)	AB1010-PIHV03003	determine safety / tolerability and PK parameters of AB1003	Double blind, placebo-controlled	Masitinib, Capsule, ascending doses (40, 100, 200, 400 and 800	32	healthy volunteers	7 days	Complete, Full

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
PK (patients)	AB03002	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 tumors	12 weeks + extension phase	Complete, Full
Extrinsic PK (HV)	AB14004 (DDI part)	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

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
Population PK	N/A	To perform a PK-POP modeling and to estimate the PK parameters of masitinib. - To evaluate the	Not applicable (more than one clinical study). the report include patients from the following studies: AB03001, AB03003, AB04013, AB05013 and AB03002					

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
		possible influence of different covariates and baseline characteristic on the PK parameters of masitinib,						
Population PK	AB14004	To perform a POP-PK modeling and to estimate the PK parameters of masitinib. - To evaluate the possible influence of different covariates and baseline characteristic on the PK parameters of masitinib. - To assess the risk of inhibition of CYP3A3 on masitinib pharmacokinetics.	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

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
Efficacy	AB10015	assess the efficacy and safety of masitinib in combination with riluzole in adult	Prospective, multicenter, randomized, double blind, placebo-controlled,	Masitinib,Tablet, 3mg/kg/day, oral Masitinib,Tablet, 4.5 mg/kg/day, oral	381 planne d (study on-going)	patients with amyotrophic lateral sclerosis	48 weeks + extension phase	Study Ongoing, Interim report based on interim

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administratio	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
		amyotrophic lateral sclerosis	**parallel groups (masitinib versus**					**analysis is available**
Safety	AB14004 (QT study)	evaluate the cardiotoxic potential of masitinib	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	15	healthy volunteers	28 days	Complete, Full

Type of study	Study number	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administratio	N	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
Safety	AB06006 (ECG safety report)	Analysis of ECGs from the phase III study AB06006 with the investigational drug masitinib in patients with smouldering systemic, indolent systemic or cutaneous mastocytosis with handicap	prospective, multicenter, randomized; double blinded, placebo-controlled, 2-parallel group with a randomization 1:1	masitinib at 6 mg/kg/day	150 (in study AB06006). 117 patients with ECG	patients with smouldering systemic, indolent systemic or cutaneous mastocytosis with handicap	24 weeks + extension	Complete, Full

2.4.2. Pharmacokinetics

The pharmacokinetics of masitinib has been investigated in three studies, including a mass-balance study, in healthy subjects. Additionally, three studies have been conducted to bridge PK data from the early formulation used (capsules) to the to-be-marketed formulation (tablets), to investigate the effect of food on masitinib PK and to evaluate the effect of CYP3A4/P-gp inhibition on masitinib PK (using itraconazole), respectively. The PK in the target group has also been investigated in 18 patients with ALS. 17 in vitro studies using human biomaterial have been performed.

The absorption profile of masitinib demonstrates a relatively slow absorption with tmax 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 have been adequately demonstrated in vivo for the tablet formulation intended for the market versus the formulation used in phase I. Following a high fat meal, masitinib Cmax and AUC0-∞ increased by 19% and 23%, respectively.

Masitinib 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 in healthy subjects is non-linear. The apparent volume of distribution (Vd/F) is high, indicating an extensive tissue distribution and perhaps a low bioavailability.

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 were approximately 13 h and 17 h, respectively. Urinary recovery rates were low with less than 2% recovery for masitinib 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.

CYP3A4 catalyses the metabolism of masitinib 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. AB3280 steady state plasma concentration in healthy subjects corresponded to roughly 20-30% of the steady state masitinib plasma concentration. The transformation of masitinib to AB3280 appears to be rapid, indicating that masitinib undergoes first-pass conversion to AB3280. Several masitinib 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 (AUC0-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.

The PK of plasma masitinib 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 CL was not affected by dose, and that AUC thus behaves in a dose-proportional manner. AUC-based accumulation ratios for masitinib in healthy subjects was 1.8-2.3 at therapeutic doses.

PK in adult patients with probable or definitive amyotrophic lateral sclerosis was similar to healthy subjects. However, Masitinib is administered concomitantly with Riluzole and no DDI study was presented.

The PK of masitinib in special populations has not been satisfactorily investigated. A product specific waiver for a paediatric investigational plan (PIP) in accordance with the paediatric regulation has been granted. No information is available on how race may affect the PK of masitinib. Gender does not appear to influence PK of masitinib. There are no data on renal impairment, but the applicant has commited to performe such a study as a PAM. Hepatic impairment may affect the masitinib PK and the Applicant also considered to perform a clinical study of masitinib PK in patients with impaired hepatic function as PAM. At the time, no recommendations on the use of masitinib in patients with impaired hepatic or renal function can be made.

The potential for drug interaction 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. A number of questions are raised that require further discussion and additional studies. Studies investigating masitinib as a substrate of OCT2, OAT1, OAT3 are lacking, and the potential for inhibition of the transporter bile salt export pump (BSEP) 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 investigated. The Applicant has conducted a study investigating the effect of inhibition of CYP3A4 and has committed to conduct a study investigating the effect of induction of CYP3A4 on masitinib PK. The need to conduct other in vivo studies investigating the potential for clinically relevant drug-drug interactions should be further discussed. Since the solubility of masitinib mesilate is pH dependent in the physiological pH range, there is a potential for an interaction with medicinal products that moderate pH in the gut which needs to be further investigated. Masitinib is proposed to be contraindicated to pregnant women and women of child bearing potential are proposed to take effective contraception. This is in contradiction with the absence of a DDI study with oral contraceptives and a DDI study with an oral contraceptive is requested as a PAM. Overall, at the current time, a total of 9 additional in vitro and in vivo studies are requested for elucidating the PK of masitinib in special populations and its DDI potential.

2.4.3. Pharmacodynamics

Pre-clinical evidence obtained in SOD1G93A rat models showed a therapeutic benefit of masitinib at the dose of 30 mg/kg/day, which is close to a Human Equivalent Dose of 4.5 mg/kg/day.

The applicant stated that: “No studies having a primary objective of determining PD effects of masitinib have been performed during the clinical development of masitinib.” The Sponsor notes, however, that auxiliary PK/PD studies have been included as sub-studies in several clinical trials for masitinib.

Healthy Subject PD: PK studies have been carried out in healthy volunteers but no PD data have been collected in these subjects. Therefore, study reports related to PD and PK/PD analyses in healthy subjects were not provided in this dossier.

Oral administration of masitinib to SOD1G93A rats starting after paralysis onset showed that masitinib decreased the emergence/expansion of aberrant glial cells thereby controlling microgliosis and motor neuron pathology in the degenerating spinal cord, when compared with vehicle-treated rats. Masitinib treatment initiated 7 days after paralysis onset prolonged post-paralysis survival by 40%.

The pre-clinical evidence in SOD1G93A rat model thus indicated that the administration of masitinib at 30 mg/kg/day provided therapeutic benefit in an advanced therapeutic setting.

The dose used in rats corresponds to the Human Equivalent Dose (HED) of 4.8 mg/kg/day (factor of 6.2), which is close to the dose-level of 4.5 mg/kg/day.

The relevance of the animal model and relation to MoA of masitinib in ALS has been discussed as a concern. The SOD1G93A rat model was considered the most relevant model. Unfortunately, neither SOD(H46R) transgenic rat model nor the sporadic ALS Wobbler mouse model, which have been used to identify MoA targeting proof of concept by the recent concurrent agents used in clinical trials for ALS have been discussed. As for the newly identified action of masitinib in mast cell involvement in NMJ pathology, which is claimed by the applicant as a complementary mechanism of action, there are comments to be expressed. If indeed masitinib would significantly act on NMJ, then endpoints directly related to this action should have been better studied or registered. In fact, this MoA should be reflected in muscle strength or muscular respiratory stability or improvement, and should have shown clear results in forced vital capacity, fatigue and HHD. HHD has not been studied, but the other strength / respiratory endpoints did not show clear results.

2.4.4. Discussion on clinical pharmacology

The data provided for pharmacodynamics only marginally addresses the potential effect of masitinib on the underlying mechanisms of disease in ALS. Only one classical model has been used, and it appears that the data was produced a posteriori once the trial was already ongoing.

As expressed in the ALS guideline (EMA/CHMP/40105/2013 Page 10/21), section 7.2. Pharmacodynamics: At present the best studied animal model to evaluate Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) candidate drugs is transgenic rodents overexpressing the gene encoding superoxide dismutase 1 (SOD-1) (Gurney 1994; Robertson 2002; Danzeisen 2006; van den Bosch 2011). However, as SOD-1 mutations account only for the hereditary type of ALS this animal model might have little relevance to human sporadic ALS. For this reason, consideration should be also given to the applicability of other animal models of ALS, which have been recently developed (examples include but are not limited to models with mutations in TDP-43, FUS/TLS, C90RF72, EPhA4 etc.; Wegorzewska 2009; De Jesus-Hernandez 2011; Renton 2011; Van Hoecke 2012). Animal data and the appropriateness of the model should be evaluated carefully (Ludolph 2010). The mechanism of action and PD effect could also be supported by in vitro data in human cells (Dimos 2008; Coatti 2015).

The use of a single model, using the specified doses in the symptomatic period 1-7 days, is far from sufficient to demonstrate the MoA, especially when the proposed MoA does not act directly on the apoptotic motor neuron cells, but through an indirect glia-based action.

Secondary PD issues have also not been adequately responded to. The MAA did not specifically address how the action of masitinib on other system organs like bone marrow, calcium / phosphorus metabolism would impact on the progression of the disease on the preclinical models. The explanation focused on the CNS effects – which are the ones for whom animal models are less sensitive. In fact, nausea was frequent or very frequent in the highest 4.5 mg/Kg dose, and was not identified in the animal model. It would have been interesting to provide data on weight loss / anaemia / bone lesions of animals and how it impacted survival or paralysis.

Unlike the Applicant's claim that in a classical SOD1 rat model masitinib exerts several mechanisms of action and that this aspect is remarkable, it is argued that all strategies based in the SOD1 rat model response in the past 20 years have failed in humans, and this is the reason why masitinib results with this model must be interpreted cautiously, independently of the number of potential mode of action on a single classical model. Should a single MoA be present in three animal models, and the likelihood that this MoA would be present in humans would be higher, and the robustness of data would be increased.

The Applicant has failed to respond in any of the requests for information, on the issues concerning the secondary pharmacodynamics and several off target effects. Given the fact that masitinib has been studied in several pathologies and animal models, this also creates concerns on the reasoning which led to the clinical program on ALS.

2.4.5. Conclusions on clinical pharmacology

The mode of action of the compound has not been convincingly demonstrated, and the fact that the preclinical studies which are presented to support the MoA in ALS have been published after the start of the trial is of concern.

The only preclinical model that was presented has been the SOD1G93A rat model, which as stated in the ALS guideline is supportive for congenital SOD1 related ALS, and for sporadic ALS this model should be supplemented and confirmed with other published models. Moreover the best target dose in ALS has also not been addressed a priori.

2.5. Clinical efficacy

2.5.1. Main study(ies)

The development program of masitinib in amyotrophic lateral sclerosis (ALS) was based on the following pivotal phase 2/3 study:

A Phase 2/3 study AB10015: A prospective, multicenter, randomized, double-blind, placebocontrolled, parallel groups, phase 2/3 study to compare the efficacy and safety of masitinib versus placebo in the treatment of patients suffering from ALS.

The applicant initially submitted the results from an interim analysis, and later in the procedure these were supplemented by the results of the final analysis.

Study AB10015 is a prospective, placebo controlled study that followed the recommendations set in the EMA guideline on clinical investigation of medicinal products for the treatment of ALS (EMA/531686/2015, Corr.1) and in the draft Guidance for Industry Drug Development for ALS.

Patients were randomly allocated to one of the three following groups:

Group 1: masitinib at 4.5 mg/kg/day + riluzole

Group 2: masitinib at 3 mg/kg/day + riluzole

Group 3: placebo of masitinib + riluzole

Patients received treatment for 48 week, with possible extension.

The design of study AB10015 effectively compares masitinib plus riluzole in association with standard of care symptomatic treatments against placebo plus riluzole in association with standard of care symptomatic treatments. The study protocol states that: "All medications taken by the patients at the onset of study and all medication given in addition to the Investigational Medicinal Product during the study are regarded as concomitant medications", and "All concomitant medications and/or therapies should be documented in the patient file and reported in the electronic Case Report Form". Hence, there was no restriction placed on the investigator's choice of standard of care symptomatic treatments (for example, physical therapy, surgical interventions, and alternative therapies).

Four amendments were implemented while the study remained blinded, and the primary analysis hypothesis on the treatment effect (Δ3.3 points) never changed.

- The study was initiated as a phase 2 study in April 2013. However, considering that patient recruitment was extremely fast, it was decided to transform the phase 2 directly into a phase 3, without reviewing the phase 2 data. Protocol Version 1.0 (including amendment No. 1, dated 02 July 2013) incorporated the modification of the sample size (passage from phase 2 to phase 2/3 study with 210 patients).
- Protocol Version 2.0 (including amendment No. 2, dated 21 March 2014) primarily incorporated the split of the two masitinib treatment-arms and the planning for a futility test and an interim analysis. The sample size was modified as a result of the changes in the study design (change from 210 patients to 300 patients).
- Protocol Version 3.0 (including amendment No. 3, dated 08 October 2014) introduced a distinction between "Normal Progressor" patients and "Fast Progressor" patients. This amendment was indicated to be not data driven and was mandatory to avoid the risk of bias. A switch from repeated measures to absolute change from baseline to week 48 was also introduced in the primary analysis, with Last Observation Carried Forward (LOCF) as primary method for missing data handling at week 48. The sample size was modified taking into consideration the change from repeated measure to LOCF method (change from 300 patients to 381 patients).
- Protocol Version 4.0 (including amendment No. 4, dated 16 March 2015) introduced minor changes, including modification in the LOCF method.

The most relevant protocol amendment was No. 3 when the distinction between patient populations of "Normal Progressor" and "Fast Progressor" was made. This was justified by the Applicant by the fact that it has been observed in clinical practice that ALS patients experience different rates of disease progression. It is hypothesized by the Applicant that different rates of disease progression reflect differing pathogenesis of ALS, with ramifications as to the efficacy of therapies directed towards any specific mechanism of disease. That is to say, heterogeneity within the overall ALS population in terms of disease progression can be explained by distinct subpopulations of ALS patients. The applicant states that there are at least two highly distinct populations of ALS patient within the overall ALS population, which can be distinguished from one another in terms of "Fast Progressor" patients who progress at a relatively fast rate as measured via progression of a suitable clinical marker of disease burden (such as ALSFRS-R), and "Normal Progressor" patients who progress at a relatively slower rate. The former population represents a more aggressive and heterogeneous form of disease with patients at higher risk of death (significantly shorter median survival time) or tracheostomy [Kimura, 2006].

Kimura and colleagues have proposed that progression of the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score (i.e. the rate of change in ALSFRS-R score prior to treatment initiation expressed in points per unit of time) provides a prognostic measure of ALS [Kimura, 2006]. ALSFRS-R is a clinical marker of disease burden with a score of zero representing the worst outcome and a score of 48 the least serious outcome. Briefly, 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 = cannot 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 as measured by the Sickness Impact Profile, indicating that the quality of function is a strong determinant of quality of life in ALS [Cedarbaum, 1999].

In order to determine at diagnosis slowest and fastest progressors, Kimura [2006] suggests the use of progression rate (ΔFS) calculated as: ΔFS =[48−score ALSFRS-R at diagnosis] / [date of onset− date of diagnosis].

Because at time of diagnosis the ALSFRS-R score was not available, the Applicant convened experts to propose a method to estimate progression, which has been to distinguish at randomization "Normal Progressors" and "Fast Progressors" relating "Progression of ALSFRS-R score before randomization (point/month)" (thereafter called ΔFS_r) calculated in the following way: ΔFS_r=[48 (ALSFRS-R score at date of first symptom supposed to be 48) – score ALSFRS-R at baseline] / [date of randomization – date of first symptom]. This best estimator of progression, supposed to be similar to the published estimator ΔFS, would be a strong predictor of "Normal Progressor" and "Fast Progressor" patient status at the time of randomization. To differentiate "Fast Progressors" and "Normal Progressors", a cut for ΔFS_r between 1.0 (as for ΔFS) and 1.2 was suggested. Consequently, "Fast Progressors" were defined as ALS patients whose ΔFS_r is more than or equal to 1.1 points per month.

Hence, for study AB10015 two distinct ALS patient populations have been defined. The population of "Normal Progressors" is defined as ALS patients whose progression of ALSFRS-R score before randomization is less than 1.1 points per month. The population of "Fast Progressors" is defined as ALS patients whose progression of ALSFRS-R score before randomization is more than or equal to 1.1 points per month.

2.5.1.1. Methods

- **Study participants**

At the time of the interim analysis a total of 192 patients diagnosed with a laboratory supported, clinically "probable" or "definite" ALS according to the El Escorial criteria were randomized. The “Normal Progressor” population included 161 randomized patients: 53 patients in the 4.5 mg/kg/day masitinib treatment-arm, 54 patients in the 3 mg/kg/day masitinib treatment-arm and 54 patients in the placebo arm. The “Normal + Fast Progressor” population included 192 randomized patients: 64 patients in the 4.5 mg/kg/day masitinib treatment-arm, 63 patients in the 3 mg/kg/day masitinib treatment-arm and 65 patients in the placebo arm.

At the time of the final analysis with a cut-off date 05 December 2016 a total of 394 patients were randomized in one of the three treatment groups:

- 133 patients received placebo + riluzole, including 114 Normal Progressors

- 130 patients received masitinib at 4.5 mg/kg/day + riluzole, including 106 Normal Progressors

- 131 patients received masitinib at 3 mg/kg/day + riluzole, including 110 Normal Progressors

Study inclusion / exclusion criteria

The inclusion and exclusion criteria of study AB10015 followed the recommendation of EMA guidance EMA/531686/2015, Corr.1 and were representative of the general ALS population. The inclusion and exclusion criteria of the study are displayed below:

INCLUSION CRITERIA

1. Female or male patient aged between 18 and 75 years of age, with a weight > 50 kg and BMI between 18 and 35 kg/m².
2. Familial or sporadic ALS
3. Patient diagnosed with laboratory supported, clinically probable or definite ALS according to the World Federation of Neurology Revised El Escorial criteria (Brooks, 1994)
4. Disease duration from symptoms onset no longer than 36 months at the screening visit
5. Patient treated with a stable dose of riluzole (100 mg/day) for at least 30 days prior to screening
6. Patient with a FVC (Forced Vital Capacity) equal to or more than 60% predicted normal value for gender, height, and age at the screening visit
7. Patient with life expectancy ≥ 6 months
8. Patient with adequate organ function at screening and baseline:
   - Absolute Neutrophils Count (ANC) ≥ 2 x 109/L
   - Hemoglobin ≥ 10 g/dL
   - Platelets (PTL) ≥ 100 x 109/L
   - AST/ALT ≤ 3 ULN
   - Bilirubin ≤ 1.5 ULN
   - Albuminemia > 1 x LLN
   - Creatinine clearance > 60 mL/min (Cockcroft and Gault formula)

- 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

9. Female patient of childbearing potential (entering the study after a menstrual period and who have a negative pregnancy test), who agrees to use two highly effective methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake.
10. Male patients must use medically acceptable methods of contraception if your female partner is pregnant, from the time of the first administration of the study drug until three months following administration of the last dose of study drug.
11. Male patients must use two highly effective methods (one for the patient and one for the partner) of medically acceptable forms of contraception during the study and for 3 months after the last treatment intake.
12. Female patient of childbearing potential must have a negative pregnancy test at screening and baseline
13. Patient able and willing to comply with study procedures as per protocol
14. Patient able to understand, and willing to sign, and date the written informed consent form at screening visit prior to any protocol-specific procedures
15. Patient able to understand, and willing to follow the safety procedures mentioned on the patient card in case of signs or symptoms of severe neutropenia or severe cutaneous toxicity, during the first 2 months of treatment

EXCLUSION CRITERIA:

1. Patient with history of hematologic, hepatic, respiratory disorder that is clinically significant for his/her participation in the study
2. Patient who underwent tracheostomy and /or gastrostomy
3. Patient with a diagnosis of cancer or evidence of continued disease within 5 years before starting study treatment
4. Patient with significant sensory abnormalities, dementia, other neurologic diseases, uncompensated medical illness and psychiatric illness
5. Patient who have participated in a clinical trial within 3 months prior to screening
6. Pregnant, or nursing female patient
7. Patient with a known diagnosis of human immunodeficiency virus (HIV) infection
8. Patient with known hepatitis B, hepatitis C or tuberculosis
9. Patient with any severe and/or uncontrolled medical condition
10. Patient having cardiac disorders defined by at least one of the following conditions:

- Patient with recent cardiac history (within 6 months) of:
  - Acute coronary syndrome
  - Acute heart failure (class III or IV of the NYHA classification)
  - Significant ventricular arrhythmia (persistent ventricular tachycardia, ventricular fibrillation, resuscitated sudden death)
- Patient with cardiac failure class III or IV of the NYHA classification
- Patient with severe conduction disorders which are not prevented by permanent pacing (atrio-

ventricular block 2 and 3, sino-atrial block)
- Syncope without known etiology within 3 months
- Uncontrolled severe hypertension, according to the judgment of the investigator, or symptomatic hypertension

11. Patient with history of poor compliance or history of drug/alcohol abuse, or excessive alcohol beverage consumption that would interfere with the ability to comply with the study protocol, or current or past psychiatric disease that might interfere with the ability to comply with the study protocol or give informed consent

- **Treatments**

Patients were to be enrolled into one of three groups as per study synopsis:

- Group 1: patients on masitinib at 4.5 mg/kg/day and riluzole
- Group 2: patients on masitinib 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, or a matching placebo, to be taken during meals.

Masitinib or placebo were administered orally in two daily doses over 48 weeks with a possibility of double-blind extension period.

The randomization procedures included a minimization process aimed at reducing any difference in the distribution of these stratification factors:

- ALS patient populations ("Normal Progressor" (progression before randomization<1.1) versus "Fast Progressor" (progression before randomization≥1.1).
- Progression of ALS functional rating scale Revised (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 populations "Normal Progressor" and "Fast Progressor".
- Site of onset (bulbar versus other).
- ALSFRS-R score at baseline.
- Age at baseline.
- Region (North America and West Europe versus Eastern Europe versus Other Countries).

An interim analysis was pre-planned in AB10015 study protocol, with 50% of randomized patients potentially having reached the 48-week time point.

Study treatment administration

Study treatment daily dose of 4.5 mg/kg were administered in divided doses as indicated in Table 8

Table 4 Dose of study treatment (mg) to be administered according to patient's weight (4.5 mg/kg/day)

		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 should be taken during breakfast. In case of nausea, the administration can take place during lunch.

**Evening: the tablets should be taken during dinner.

Study treatment daily dose of 3 mg/kg will be administered in divided doses as indicated in Table 9.

Table 5 Dose of study treatment (mg) to be administered according to patient's weight (3 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

*Morning: the tablets should be taken during breakfast. In case of nausea, the administration can take place during lunch.

**Evening: the tablets should be taken during dinner.

Concomitant treatments

- ***Mandatory concomitant medication: riluzole***

Patients must have been treated for a minimum of 1 month with a stable dose of riluzole at baseline.

Safety issues related to riluzole should be managed according to usual practice.

- Prohibited concomitant treatment
    - Live attenuated vaccines
    - Benzodiazepine
    - Amiodarone
    - Chemotherapies
    - Any hepatotoxic agent (e.g. allopurinol, methyldopa, sulfasalazine)
    - Any investigational treatment (other than study treatment) related or not to ALS
    - Drugs known to be at high risk of Stevens-Johnson syndrome: allopurinol, lamotrigine, carbamazepine,phenytoine, phenobarbital, sulfasalazine, sulfamide, oxicam and nevirapine; or to be at high risk of DRESS syndrome: minocycline, modafenil, dapsone
    - Treatments to be given with high caution

- Drugs known to interact with the same CYP450 isoenzymes (3A4) than study treatment, whetherinducers, inhibitors or substrates
- Therapeutic anticoagulation with warfarin
- Any nephrotoxic drug
- Treatments to be given with caution
- Drugs known to interact with the same CYP450 isoenzymes (2C9 and 2D6) than study treatment,whether inducers, inhibitors or substrates

- **Objectives**

The objective of AB10015 was to compare the efficacy and safety of masitinib combined with riluzole versus placebo combined with riluzole in the treatment of patients suffering from Amyotrophic Lateral Sclerosis (ALS).

Hypothesis: Superiority: compare the efficacy and safety of masitinib at 4.5 or 3 mg/kg/day in combination with riluzole versus placebo in combination with riluzole

- **Outcomes/endpoints**

Table 6 Endpoints and definitions

Primary endpoint	ALSFRS-R	Absolute change from baseline to week 48 in Amyotrophic Lateral Sclerosis functional rating scale-Revised.
Secondary endpoints	FVC	Absolute change from baseline to week 48 in Forced Vital Capacity.
	CAFS	Combined Assessment of Function and Survival, which takes into account changes in ALSFRS-R) total scores and time to death up to week 48.
	Quality of life (measured by ALSAQ-40)	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
	OS	Trend on Overall Survival, defined as the time from randomization to the time of the documented death.
	Tracheostomy free survival	Tracheostomy-free survival defined as the time from randomization to the date of documented death or first tracheotomy

No further methods were described to refine the outcome measures, besides the training of investigators for the primary endpoint.

- **Sample size**

The objective of the study was to compare each “masitinib + riluzole” group (ie. 3 mg/kg/day masitinib + riluzole and 4.5 mg/kg/day masitinib + riluzole) to “placebo + riluzole” group. Therefore sample size was calculated in a 1:1 randomisation ratio for the comparison of each masitinib group to the placebo group making the same hypothesis for each masitinib group.

Sample size calculation is based on absolute change from baseline to Week 48 in Amyotrophic Lateral Sclerosis functional rating scale Revised (ALSFRS-R).

Primary analysis:

ALSFRS-R change from baseline to W48 is supposed to be higher in “Normal progressors + faster progressors” population (with a standard deviation equal to 9) than in “Normal progressors” population (with a standard deviation equal to 7.5) notably because patients have more tracheotomy and death in “Normal progressors + faster progressors” than in “Normal progressors” population.

Primary analysis was to be performed using an ANCOVA model.

“Normal progressors” population

An ancova model on the ALSFRS-R change from baseline to week 48 is used with the following hypotheses:

- Alpha set to 5% 2-sided test
- Power set to 80%
- Difference in mean change of ALSFRS-R between placebo group and masitinib group equal to 3.3
- Standard deviation of the change from baseline to W48 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 spendingfunction.

Comparison of the ‘4.5 mg/kg/day masitinib + riluzole’ group to the ‘placebo + riluzole’ group:

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

Comparison of the ‘3 mg/kg/day masitinib + riluzole’ group to the ‘placebo + riluzole’ group:

Same calculation as for the comparison of the ‘4.5 mg/kg/day masitinib + 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 group and 100 treated in placebo group) are enough to detect a 3.3(+/-7.5) point difference between groups (each of the masitinib groups vs placebo group) in order to achieve a power of 80% with a significance level for a two-sided test of 5% in “normal progressor” population.

“Normal progressors + faster progressors” population

An ancova model on the ALSFRS-R change from baseline to week 48 is used with the following hypotheses:

- Alpha set to 5% 2-sided test
- Power set to 80%
- Mean change from baseline for placebo group equal to -11(from 38 to 27)
- Mean change from baseline for masitinib groups equal to -7.7(from 38 to 30.3)
- Difference in mean change of ALSFRS-R between placebo group and masitinib group equal to 3.3
- Standard deviation of the change from baseline to W48 from all groups equal to 9
- Effect size = 0.36
- Allocation ratio : 1:1

354 patients (118 in each masitinib group and 118 in placebo group) should be included to detect a 3.3(+/-9) point difference between groups (each of the masitinib groups vs placebo group) in order to achieve a power of 80% with a significance level for a two-sided test of 5%.

Taking into account around 5% of non evaluable patient, 381 patients (127 in each masitinib group and 127 in placebo group) should be included to detect a 3.3(+/-9) point difference between groups (each of the masitinib groups vs placebo group) in order to achieve a power of 80% with a significance level for a two-sided test of 5%.

Table 7 Summary table of sample size in each population of ALS patient – primary analysis

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

Secondary analysis:

"Normal progressors" population:

186 patients are enough to detect a difference between a masitinib group to the placebo group for the following secondary analysis:

Combined Assessment of Function and Survival (CAFS)

A total of 186 patients (93 in Masitinib group and 93 in Placebo group) will provide a > 80% power with a two-sided 5% alpha in order to compare CAFS score between a masitinib group to the placebo group (Mann-Whitney Test (Uniform Distribution) with a difference of 24+/-53.8).

Change of Forced Vital Capacity (FVC) from baseline to W48

A total of 186 patients (93 in Masitinib group and 93 in Placebo group) are necessary to detect a 11(+/-25) mean change difference from baseline to W48 in FVC between a masitinib group and placebo group with a > 80% power and a type-I error of 5%.

"Normal + faster progressors" population:

236 patients are enough to detect a difference between a masitinib group to the placebo group for the following secondary analysis:

Combined Assessment of Function and Survival (CAFS)

A total of 236 patients (118 in Masitinib group and 118 in Placebo group) will provide a > 80% power with a two-sided 5% alpha in order to compare CAFS score between a masitinib group to the placebo group (Mann-Whitney Test (Uniform Distribution) with a difference of 26+/-68.3).

Change of Forced Vital Capacity (FVC) from baseline to W48

A total of 236 patients (118 in Masitinib group and 118 in Placebo group) are necessary to detect a 10(+/-25) mean change difference from baseline to W48 in FVC between a masitinib group and placebo group with a > 80% power and a type-I error of 5%.

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

A total of 236 patients (118 in Masitinib group and 118 in Placebo group) or 83 events will provide a > 80% power with a two-sided 5% alpha in order to compare Time to first tracheotomy at W48 between a masitinib group to the placebo group (exponential maximum likelihood test of equality of survival curves) with an hazard ratio of 0.54 (74% of patients alive without tracheotomy at W48 in placebo group (Bensimon & Al) and 85% alive without tracheotomy at W48 in a masitinib group). Planned duration of inclusions is 24 months and planned analysis around 12 months after last inclusion (total follow-up 36 months).

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

A total of 236 patients (118 in Masitinib group and 118 in Placebo group) or 56 events will provide a > 80% power with a two-sided 5% alpha in order to compare survival at W48 between a masitinib group to the placebo group (exponential maximum likelihood test of equality of survival curves) with an hazard ratio of 0.47 (80% of patients alive at W48 (L.Lacomblez, G.Bensimon & Al) in placebo group and 90% alive at W48 in a masitinib group). Planned duration of inclusions is 24 months and planned analysis around 12 months after last inclusion (total follow-up 36 months).

- **Randomisation**

Randomisation was performed with a minimization algorithm on:

- ALS patients population ("Normal progressors"(progression before randomization<1.1) VS "Faster progressors" (progression before randomization>=1.1))
- Progression of ALSFRS-R score (point/month) from date of first symptom to baseline (ALSFRS-Rscore at date of first symptom supposed to be 48) , Balanced between treatment groups in each of ALS patients population "Normal progressors" and "Faster progressors"
- Site of onset (Bulbar vs Others)
- ALSFRS-R score at baseline
- Age at baseline
- Region (North America and West Europe versus Est Europe versus Other Countries)

- **Blinding (masking)**

This study was a double-blind study.

The investigator was provided with technical options and password information to selectively break the code for an individual patient by telephone, facsimile transmission, or through electronic message transfers.

The premature breaking of the code had to be confined to emergency cases in which knowledge of the administered drug is necessary for adequate treatment. Whenever possible, the sponsor should be contacted before breaking the blinded emergency code. Should any code be broken, the respective patient was withdrawn from further participation in the study and a written explanation had to be given by the investigator; the sponsor must be notified immediately.

- **Statistical methods**

Primary analysis:

Primary analysis was to be performed in mITT “Normal progressors” population.

This analysis was to be done on patients randomized at an initial masitinib dose of 4.5mg/kg/day (Group 1) versus placebo patients (Group 3) at a 5% alpha-level. Missing values of ALSFRS-R at study visit were to be replaced based on the Modified Last Observation Carried Forward (mLOCF) method.

mLOCF is 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 imputationwill be done (Observed Cases).

- Case 3: death for related disease progression before W48:

If patient was treated when he died, score ALSFRS-R is replaced by 0

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

- ALS patients population (“Normal progressors”(progression before randomization<1.1) VS

“Faster progressors” (progression before randomization>=1.1)) *

*only for analysis in “Normal progressors + faster progressors” population

- Progression of ALSFRS-R score (point/month) from date of first symptom to baseline (ALSFRS-Rscore at date of first symptom supposed to be 48)
- ALS patients population (“Normal progressors”(progression before randomization<1.1) VS
- “Faster progressors” (progression before randomization>=1.1))
- ALSFRS-R score at baseline
- Site of onset (Bulbar vs Others)
- Age at baseline
- Region (North America and West Europe versus Est Europe versus Other Countries)

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

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

One of the remarked issues in GCP inspection was the fact that similar reasons for withdrawal were registered differently, thus leading to different imputations in the final analysis.

The primary analysis uses a rerandomization 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 randomized patient

- Maintenance of the real order (=observed) of arrival of the patients (e.g. patient 00101 randomized 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 randomized patients (ITT). For the population of interest (mITT), the analysis of covariance 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 analysis ofcovariance (ANCOVA) adjusted on following factors: treatment (masitinib/placebo) and stratificationcriteria (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 analysis of covariance (ANCOVA) adjusted on the following factors: treatment (masitinib/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-Rscore 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% confidence interval 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 formissing data

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

Secondary analysis:

Combined Assessment of Function and Survival (CAFS)

Combined Assessment of Function and Survival (CAFS) on rank data will be analyzed 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.Combined Assessment of Function and Survival (CAFS) will be analyzed with an ANCOVA modelwith 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 ITTand PP populations.

Change of Forced Vital Capacity (FVC) from baseline to week 48

Absolute change from baseline to week 48 in FVC will be estimated using a model of analysis of covariance (ANCOVA) adjusted on following factors: treatment (masitinib/placebo) and stratification criteria. Missing values of FVC at study visit will be replaced based on the Modified Last Observation Carried Forward (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 model of analysis ofcovariance (ANCOVA) adjusted on following factors: treatment (masitinib/placebo) and stratificationcriteria (no re-randomization test). Missing values of FVC at study visit will be replaced based on theModified Last Observation Carried Forward (mLOCF).

2.Primary analysis corresponding to FVC and sensitivity analysis 1- will be repeated using ObservedCases 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 ITTand 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 analyzed with a rerandomization test using stratified log-rank test as statistical test.

Sensitivity analyses:

1.Time to first tracheotomy will be analyzed using stratified log-rank test (no re-randomization test).

2.Multivariate Cox proportional hazards regression model will be constructed to compare hazard ratesbetween treatment groups if the basic assumption that hazard ratio is constant through time is verified

3.Primary analysis corresponding to time to first tracheotomy and sensitivity analysis 1- and 2- will berepeated 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 ratesbetween treatment groups if the basic assumption that hazard ratio is constant through time is verified

3.Primary analysis corresponding to overall survival and sensitivity analysis 1- and 2- will be repeated onthe ITT and PP populations.

Futility analysis

For each dose group (3mg /kg/day and 4.5mg/kg/day) and each population (“Normal progressors” and “Normal progressors + faster progressors”), the IDMC will review the different efficacy criteria about 48 weeks after the [60th - 75th] patient randomized.

In case of lack of efficacy, the IDMC will recommend 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” population

OR

- Conditional power is less than a prespecified threshold for “Normal progressors + faster progressors”population

Full details will be prespecified in the interim statistical analysis plan (iSAP).

Interim analysis

One interim analysis was planned for this study with around 50% of patients randomized.

Interim analysis performed in “Normal progressors” population.

The efficacy criteria will be tested at a significance level determined with the Pocock alpha spending method, approximated by the following Hwang-Shi-Decani function:

$$\alpha^*(t,\gamma) = \alpha \frac{1 - e^{-\gamma t}}{1 - e^{-\gamma}}$$

with a global alpha level set to 5%, a gamma parameter equal to +1, and the information fraction t defined as the proportion of evaluable patients at the time of analysis.

For each of the two planned analysis (interim and final), the significance levels $\alpha_{i,i=1,2}$ 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 $\alpha^*(t,\gamma)$ level.

The interim analyses was 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 to stop or continue 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 Reestimation (SSR), 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.

Control of overall familly-wise type I error at the study level

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 at the $\alpha^*(t,\gamma)$ level.

Safety Analysis

Based on the occurrence of AEs in each group of masitinib (3mg or 4.5mg) or other clinically significant safety evaluations, it was to be decided which dose of masitinib had the best risk/benefit ratio to conclude for further studies.

2.5.2. Results

- **Recruitment**

At the time of the interim analysis total of 192 patients were randomized from a total of 12 sites in Spain, Argentina, and Slovakia.

At the time of the final analysis with a cut-off 05 December 2016, a total of 394 patients were randomized from a total of 34 sites in 9 countries.

Table 8 Overall patient disposition by center

Site n.	Country	Placebo	Masitinib 4.5	Masitinib 3	Total (N=3
001-	CANADA	0 (0%)	1 (0.8%)	0 (0%)	1 (0.3%)
001-	CANADA	2 (1.5%)	0 (0%)	0 (0%)	2 (0.5%)
001-	CANADA	0 (0%)	1 (0.8%)	0 (0%)	1 (0.3%)
001-	CANADA	2 (1.5%)	1 (0.8%)	1 (0.8%)	4 (1%)
031-	NETHERLANDS	3 (2.3%)	3 (2.3%)	4 (3.1%)	10 (2.5%)
034-	SPAIN	33	37	36	106
034-	SPAIN	0 (0%)	1 (0.8%)	0 (0%)	1 (0.3%)
034-	SPAIN	8 (6%)	5 (3.8%)	9 (6.9%)	22 (5.6%)
034-	SPAIN	10 (7.5%)	8 (6.1%)	7 (5.4%)	25 (6.3%)
034-	SPAIN	0 (0%)	0 (0%)	1 (0.8%)	1 (0.3%)
039-	ITALY	4 (3%)	3 (2.3%)	2 (1.5%)	9 (2.3%)
039-	ITALY	6 (4.5%)	10 (7.6%)	2 (1.5%)	18 (4.6%)
039-	ITALY	7 (5.3%)	5 (3.8%)	4 (3.1%)	16 (4.1%)
039-	ITALY	1 (0.8%)	2 (1.5%)	0 (0%)	3 (0.8%)
039-	ITALY	2 (1.5%)	0 (0%)	4 (3.1%)	6 (1.5%)
039-	ITALY	1 (0.8%)	0 (0%)	2 (1.5%)	3 (0.8%)
039-	ITALY	6 (4.5%)	4 (3.1%)	4 (3.1%)	14 (3.6%)
039-	ITALY	0 (0%)	0 (0%)	2 (1.5%)	2 (0.5%)
039-	ITALY	1 (0.8%)	2 (1.5%)	1 (0.8%)	4 (1%)
351-	PORTUGAL	0 (0%)	1 (0.8%)	2 (1.5%)	3 (0.8%)
421-	SLOVAKIA	1 (0.8%)	0 (0%)	1 (0.8%)	2 (0.5%)
421-	SLOVAKIA	1 (0.8%)	1 (0.8%)	1 (0.8%)	3 (0.8%)
421-	SLOVAKIA	1 (0.8%)	1 (0.8%)	0 (0%)	2 (0.5%)
421-	SLOVAKIA	1 (0.8%)	1 (0.8%)	0 (0%)	2 (0.5%)
421-	SLOVAKIA	2 (1.5%)	0 (0%)	2 (1.5%)	4 (1%)
030-	GREECE	1 (0.8%)	1 (0.8%)	3 (2.3%)	5 (1.3%)
030-	GREECE	1 (0.8%)	1 (0.8%)	1 (0.8%)	3 (0.8%)
052-	MEXICO	1 (0.8%)	1 (0.8%)	1 (0.8%)	3 (0.8%)
054-	ARGENTINA	22	14	17	53
054-	ARGENTINA	0 (0%)	3 (2.3%)	6 (4.6%)	9 (2.3%)
054-	ARGENTINA	8 (6%)	14	8 (6.2%)	30 (7.6%)
054-	ARGENTINA	2 (1.5%)	2 (1.5%)	3 (2.3%)	7 (1.8%)
054-	ARGENTINA	6 (4.5%)	5 (3.8%)	5 (3.8%)	16 (4.1%)
054-	ARGENTINA	0 (0%)	3 (2.3%)	1 (0.8%)	4 (1%)

Table 9 Patients' disposition by treatment-arm and status – Normal Progressor – [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	75 (65.8%)	69 (65.1%)	71 (64.5%)
Prematurely discontinued before W48	39 (34.2%)	37 (34.9%)	39 (35.5%)

Reason of discontinuation main part			
N	39	37	39
AE Related	1 (2.6%)	11 (29.7%)	7 (17.9%)
Non compliance	0 (0.0%)	2 (5.4%)	1 (2.6%)
Lack of Efficacy	12 (30.8%)	17 (45.9%)	20 (51.3%)
Travel	12 (30.8%)	3 (8.1%)	1 (2.6%)
Procedure	2 (5.1%)	0 (0.0%)	0 (0.0%)
Death	7 (17.9%)	2 (5.4%)	7 (17.9%)
Protocol Deviation	2 (5.1%)	1 (2.7%)	2 (5.1%)
Cancer not related	2 (5.1%)	1 (2.7%)	0 (0.0%)
Prohibited Concomitant treatment	1 (2.6%)	0 (0.0%)	1 (2.6%)

Table 10 Patients' disposition by treatment-arm and status – Normal + Fast Progressor – [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	81 (60.9%)	76 (58.5%)	80 (61.1%)
Prematurely discontinued before W48	52 (39.1%)	54 (41.5%)	51 (38.9%)
Reason of discontinuation main part			
n	52	54	51
AE Related	1 (1.9%)	12 (22.2%)	7 (13.7%)
Lost to Follow-up	0 (0.0%)	1 (1.9%)	0 (0.0%)
Non compliance	0 (0.0%)	3 (5.6%)	2 (3.9%)
Lack of Efficacy	21 (40.4%)	26 (48.1%)	28 (54.9%)
Travel	13 (25.0%)	4 (7.4%)	1 (2.0%)
Procedure	3 (5.8%)	0 (0.0%)	0 (0.0%)
Death	9 (17.3%)	6 (11.1%)	9 (17.6%)
Protocol Deviation	2 (3.8%)	1 (1.9%)	2 (3.9%)

Cancer not related	2 (3.8%)	1 (1.9%)	0 (0.0%)
Prohibited Concomitant treatment	1 (1.9%)	0 (0.0%)	2 (3.9%)

- **Conduct of the study**

The applicant stated that:

The study was conducted in compliance with the Good Clinical Practices (GCP), as described in the following documents:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
- Directive BPC 2001/20/CE 04PR2002, The Rules Governing Medicinal Products in the European Community.
- Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, plus note of clarification paragraph 29 added by the WMA General Assembly, Washington, 2002).

There were serious concerns raised by the inspectors, during the triggered inspection requested by the EMA in the course of the assessment. For more information see GCP section.

- **Baseline data**

The baseline characteristics of the two populations were comparable, except for the deterioration in ALSFRS-R before randomization.

Disease characteristics

The main disease characteristics of ALS patients included in study AB10015 are displayed below:

Table 11 Disease characteristics of the study patients (Normal Progressors)

	Placebo	Masitinib 4,5	Masitinib 3	Total (N=3
ALSFRS_R Baseline				
n	114	106	110	330
Mean +/- SD	39.3 +/-	38.3 +/-	38.6 +/-	38.7 +/-
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 +/-	89.0 +/-	88.1 +/-	89.2 +/-
Median	87.0	92.0	88.0	89.0
Range	37.0 ;	60.0 ;	51.0 ;	37.0 ;

Table 12 Disease characteristics of the study patients (modified Normal Progressors)

	Placebo	Masitinib 4,5	Masitinib 3	Total (N=2
ALSFRS_R Baseline				
n	101	92	97	290
Mean +/- SD	39.6 +/-	38.8 +/-	39.2 +/-	39.2 +/-
Median	40.0	39.0	40.0	40.0
Range	27.0 ; 47.0	25.0 ; 47.0	25.0 ; 46.0	25.0 ; 47.0
FVC Baseline				
n	101	92	97	290
Mean +/- SD	90.4 +/-	89.0 +/-	88.4 +/-	89.3 +/-
Median	88.0	92.0	88.0	89.5
Range	37.0 ;	60.0 ;	51.0 ;	37.0 ;

Table 13 Disease characteristics of the study patients (Normal + Faster Progressors)

	Placebo	Masitinib 4,5	Masitinib 3	Total (N=3
ALSFRS_R Baseline				
n	133	130	131	394
Mean +/- SD	38.1 +/- 5.5	37.5 +/- 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	87.5	85.0	87.0
Range	37.0 ; 136.0	45.0 ; 131.0	51.0 ; 149.0	37.0 ; 149.0

Prior medical history

Prior medical history of ALS patients included in study AB10015 was comparable between the 2 populations. The percentage of patients with at least one medical history was 91.9% in the “Normal Progressor” population, versus 92.1% in the “Normal + Fast Progressor” population.

Exposure.

In the “Normal Progressor” population 105 patients received masitinib at a dose of 4.5 mg/kg/day, 110 patients received masitinib at a dose of 3 mg/kg/day, and 114 patients received placebo. The mean treatment duration was 9.5 months (ranging from

0.3 to 11.7 months) in the masitinib 4.5 mg/kg/day arm, 9.1 months (ranging from 0.7 to 12.8 months) in the masitinib 3 mg/kg/day arm, and 9.8 months (ranging from 0.2 to 14.5 months) in the placebo arm.

In the “Normal + Fast Progressor” population 129 patients received masitinib at a dose of 4.5 mg/kg/day, 131 patients received masitinib at a dose of 3 mg/kg/day, and 133 patients received placebo. The mean treatment duration was 9.1 months (ranging from 0.3 to 11.7 months) in the masitinib 4.5 mg/kg/day arm, 9.0 months (ranging from 0.7 to 12.8 months) in the masitinib 3 mg/kg/day arm, and 9.6 months (ranging from 0.2 to 14.5 months) in the placebo arm.

- **Numbers analysed**

ANALYSIS DATASETS

Intention-To-Treat (ITT) dataset

The ITT population was defined as all randomised patients with probable or definite amyotrophic lateral sclerosis, 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 290 “modified Normal Progressor” patients.

Modified Intent-To-Treat (mITT) dataset

The mITT (modified Intent-To-Treat) population included all ITT patients with at least one post baseline efficacy assessment who took at least one dose of study treatment (masitinib/placebo). The actual number of patients in the final analysis mITT population was 391 patients, including 328 “Normal Progressor” patients and 288 “modified Normal Progressor” patients.

Per Protocol (PP) dataset

The PP population consisted of 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 randomized and who took at least one dose of study medication (masitinib or placebo).

PRIMARY EFFICACY EVALUATION ON (ALSFRS-R)

The primary analysis was to demonstrate a statistically significant difference between the treatment-arms of masitinib + riluzole and placebo + riluzole on the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R).

In accordance with the fixed sequence method to control the global family-wise error rate, the first step was to demonstrate a statistically significant difference between masitinib 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 population.

Missing values of ALSFRS-R were replaced based on the mLOCF method. Sensitivity analyses were carried out based on the reasons for discontinuation and on multiple imputation.

- **Outcomes and estimation**

The primary efficacy analysis was performed on the modified Intention-to-Treat (mITT) population, which included all randomised patients with at least one post baseline efficacy assessment who took at least one dose of study treatment (masitinib/placebo). The actual number of patients in the final analysis mITT population was 391 patients, including 328 "Normal Progressor" patients and 288 "modified Normal Progressor" patients.

Efficacy analyses were conducted in a stepwise manner (fixed sequence method) to control the global family-wise error rate at the 0.05 level for the primary analysis.

The primary analysis was performed first in the "Normal Progressor" population, testing patients randomized at an initial masitinib dose of 4.5 mg/kg/day (Group 1) versus placebo patients (Group 3).

If the analysis is conclusive at a 0.05 significance level, then the primary analysis was performed in the "Normal Progressor" population, testing patients randomized at an initial masitinib dose of 3 mg/kg/day (Group 2) versus placebo patients (Group 3).

If this analysis was conclusive, then the same sequence was repeated, but in the "Normal + Fast Progressor" population.

The cut-off date for the efficacy analysis is 15 December 2016.

Demographics of patients in the Normal + Fast Progressor population are displayed in the Table 18 below.

Table 14 Demographics of the study patients (Normal + Faster Progressors)

	Placebo (N=133)	Masitinib 4,5 (N=130)	p -	Masitinib 3	p-value
Country			0.6		0.9875
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			0.5		0.7794
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	
No	19 (14.3%)	24 (18.5%)		21 (16.0%)	
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 +/-	
Median	0.53	0.55		0.53	
Range	0.05 ; 5.00	0.03 ; 3.69		0.09 ; 2.24	

In general, the baseline characteristics of patients evaluated in study AB10015 are representative of the ALS population who usually are included in clinical trials.

Results for masitinib 4.5 mg/kg/day – Normal Progressor

PRIMARY EFFICACY EVALUATION ON (ALSFRS-R)

The primary analysis was to test a statistically significant difference between the treatment-arms of masitinib + riluzole and placebo + riluzole on the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R). In accordance with the fixed sequence method to control the global family-wise error rate, the first step was to demonstrate a statistically significant difference between masitinib 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 population. Missing values of ALSFRS-R were replaced based on the mLOCF method. Sensitivity analyses were carried out based on the reasons for discontinuation and on single imputation. The Table 19 below summarizes the datasets for the primary and sensitivity analyses on ALSFRS-R absolute change from baseline to week 48.

Table 15 Number of patients analysed for the primary and sensitivity analyses on ALSFRS-R – Masitinib 4.5 mg/kg/day – Normal Progressor

	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

The result of the primary efficacy analysis is presented below.

Table 16 Absolute change from baseline to week 48 in ALSFRS-R - Primary efficacy analysis – masitinib 4.5 mg/kg/day – Normal Progressor

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

The primary analysis used a re-randomization test. A statistically significant difference in the ALSFRS-R score was observed between masitinib and placebo (Difference of least-square means=3.39; p=0.0158), with an improvement of 27%, which is in line with the 25% threshold considered for a clinically meaningful benefit in publications [Castrillo-Viguera, 2010].

Sensitivity analyses presented

SENSITIVITY ANALYSES BASED ON REASONS OF DISCONTINUATION FOR MASITINIB 4.5MG/KG/DAY IN THE NORMAL PROGRESSOR POPULATION

The sensitivity analyses on the primary endpoint, based on reasons of discontinuation, were all positive. Overall, the benefit remained significant regardless of the method retained for treating missing data based on reasons for discontinuation (p-value ranging from 0.019 to 0.029).

The result of the sensitivity analyses on the primary endpoint are presented in the Table 21 below.

Table 17 Absolute change from baseline to week 48 in ALSFRS-R – First Sensitivity analyses - Masitinib 4.5 mg/kg/day – Normal Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence	p-value
mLOCF Rule 2:				
Placebo	103	-12.53	3.28 [0.55;6.01]	0.0190
Masitinib 4.5 mg	99	-9.25		
mLOCF Rule 3:				
Placebo	107	-12.09	3.06 [0.39;5.73]	0.0248
Masitinib 4.5 mg	102	-9.03		
mLOCF Rule 4:				
Placebo	108	-12.00	2.96 [0.31;5.62]	0.0289
Masitinib 4.5 mg	102	-9.04		
mLOCF Rule 5:				
Placebo	111	-11.82	2.86 [0.29;5.43]	0.0291
Masitinib 4.5 mg	104	-8.96		

- The first sensitivity analysis (Rule 2) was based on the mLOCF method for imputation of missing data in case of premature discontinuation due to lack of efficacy, toxicity, and withdrawal of consent-related to study procedures. No imputation (Observed Cases) was done for other causes of discontinuation. A statistically significant difference in terms of ALSFRS-R was observed between masitinib and placebo treatment-arms (Difference of means = 3.28, p-value=0.0190).
- The second sensitivity analysis (Rule 3) was based on the mLOCF method for imputation of missing data in case of premature discontinuation due to lack of efficacy, toxicity, and withdrawal of consent-related to any travel issue. No imputation (Observed Cases) was done for other causes of discontinuation. A statistically significant difference in terms of ALSFRS-R was observed between masitinib and placebo treatment-arms (Difference of means = 3.06, p-value=0.0248).
- The third sensitivity analysis (Rule 4) was based on the mLOCF method for imputation of missing data in case of premature discontinuation due to lack of efficacy, toxicity, and withdrawal of consent-related to study procedures or any travel issue. No imputation (Observed Cases) was done for other causes of discontinuation. A statistically significant difference in terms of ALSFRS-R was observed between masitinib and placebo treatment-arms (Difference of means = 2.96, p-value=0.0289).
- The fourth sensitivity analysis (Rule 5) was based on the mLOCF method for imputation of missing data in case of premature discontinuation due to lack of efficacy, toxicity, and withdrawal of consent-related to study procedures or any travel issue. No imputation (Observed Cases) was done for other causes of discontinuation. A statistically significant difference in terms of ALSFRS-R was observed between masitinib and placebo treatment-arms (Difference of means = 2.96, p-value=0.0289).

SENSITIVITY ANALYSES BASED ON SINGLE IMPUTATION FOR MASITINIB 4.5MG/KG/DAY IN THE NORMAL PROGRESSOR POPULATION

Another sensitivity analysis was used to calculate differently the ALSFRS-R. Absolute change from baseline to week 48 in ALSFRS-R was estimated using two different single imputation analyses to deal with missing data.

- Imputation was done by clustering of “similar patients” by Site of Onset at baseline, Region and treatment group and then using the average increment within group.
- Imputation was done by clustering of “similar patients” by Site of Onset at baseline, Region and treatment group and imputation using mean increment within group + penalty of 50% to those patients who discontinued early due to lack of efficacy.

The result of these sensitivity analyses on the primary endpoint is presented in the Table 22 below.

Overall, the benefit remained significant when using the single imputation model (p-value ranging from 0.0176 to 0.0182).

Table 18 Absolute change from baseline to week 48 in ALSFRS-R – Second sensitivity analyses - Masitinib 4.5 mg/kg/day – Normal Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence	p-value
Single imputation : Rule 6				
Placebo	111	-13.96	3.01 [0.53;5.49]	0.0176
Masitinib 4.5 mg	104	-10.95		
Single imputation : Rule 7				
Placebo	111	-14.43	3.03 [0.52;5.54]	0.0182
Masitinib 4.5 mg	104	-11.40		

- The fifth sensitivity analysis (Rule 6) was based on the single imputation method using the average increment within each cluster of patient. A statistically significant difference in terms of ALSFRS-R was observed between masitinib and placebo treatment-arms (Difference of means = 3.01, p- value=0.0176).
- The sixth sensitivity analysis (Rule 7) was based on the single imputation method using the

average increment within each cluster of patient, with a 50% penalty on patients discontinuing for lack of efficacy. A statistically significant difference in terms of ALSFRS-R was observed between masitinib and placebo treatment-arms (Difference of means = 3.03, p-value=0.0182).

SENSITIVITY ANALYSIS BASED ON TIPPING ANALYSIS FOR MASITINIB 4.5 MG/KG/DAY IN NORMAL PROGRESSOR POPULATION (POST-HOC ANALYSIS NOT DETAILED IN THE SAP)

Since it is difficult to check the validity of the assumption of missing at random (MAR), some sensitivity analyses need to be performed assuming some missing data is NMAR. The tipping point analysis is introduced to assess how severe departures from MAR must be in order to overturn conclusions from the primary analysis.

The following methods were used as tipping point analyses:

It is assumed that the patients who discontinue in the treatment arm (Masitinib 4.5) perform worse than those in the Placebo arm. So the imputed values will be shifted by a certain additive shift.

The formula is: P-> P

M-> P+ (M-P) x (1-penalty)

So, if penalty is 100% i.e. 1 then M = P and if penalty is 0% then M = M

1. With 100% penalty (ie. Replacing the Masi 4.5 avg by placebo avg for Masi patients)

Treatment group	N	LS Mean	Difference of means [95% confidence	p-value
Placebo	111	-14.09	2.31 [-0.17;4.80]	0.0678
Masitinib 4.5 mg	104	-11.79		

2. With 76% penalty

Treatment group	N	LS Mean	Difference of means [95% confidence	p-value
Placebo	111	-14.06	2.48 [0.01;4.96]	0.0498
Masitinib 4.5 mg	104	-11.58		

3. With 77% penalty

Treatment group	N	LS Mean	Difference of means [95% confidence	p-value
Placebo	111	-14.06	2.47 [-0.01;4.95]	0.0504
Masitinib 4.5 mg	104	-11.59		

SENSITIVITY ANALYSES FOR MASITINIB 4.5 MG/KG/DAY IN THE MODIFIED NORMAL PROGRESSOR POPULATION

The sensitivity analyses were reproduced on the modified Normal progressor population (progression of < 0.8 points per month) to account for the uncertainty in the date of presentation of the first symptoms. The result of these sensitivity analyses on the primary endpoint is presented in the table below.

Overall, the benefit was increased when considering patient with lower disease progression at baseline. A statistically significant difference in terms of ALSFRS-R was observed between masitinib and placebo treatment-arms (Difference of means ranging from 3.07 to 3.50).

Table 19 Absolute change from baseline to week 48 in ALSFRS-R – Sensitivity analyses on primary endpoint - Masitinib 4.5 mg/kg/day – modified Normal Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
mLOCF Rule 1:				
Placebo	90	-12.29	3.50 [0.62;6.37]	0.0174
Masitinib 4.5 mg	85	-8.80		
mLOCF Rule 2:				
Placebo	91	-12.17	3.36 [0.51;6.22]	0.0214
Masitinib 4.5 mg	85	-8.81		
mLOCF Rule 3:				
Placebo	94	-11.74	3.18 [0.37;5.99]	0.0266
Masitinib 4.5 mg	88	-8.55		
mLOCF Rule 4:				
Placebo	95	-11.64	3.07 [0.28;5.86]	0.0315
Masitinib 4.5 mg	88	-8.57		
mLOCF Rule 5:				
Placebo	98	-11.45	2.97 [0.28;5.66]	0.0308
Masitinib 4.5 mg	90	-8.48		
Single imputation : Rule 6:				
Placebo	98	-13.54	3.26 [0.64;5.88]	0.0149
Masitinib 4.5 mg	90	-10.27		
Single imputation : Rule 7:				
Placebo	98	-14.03	3.33 [0.69;5.98]	0.0139
Masitinib 4.5 mg	90	-10.70		

SECONDARY EFFICACY EVALUATION

PROGRESSION FREE SURVIVAL (PFS)) FOR MASITINIB 4.5 MG/KG/DAY IN THE NORMAL PROGRESSOR POPULATION

Treatment group	Total patients	Median time (months) [95%	p-value using Wilcoxon test
Placebo	113	16 [11; 19]	0.0159
Masitinib 4,5	105	20 [14; 30]	

In the Normal progressor population, median PFS was increased by 4 months with masitinib (4.5 mg/kg/day) as compared with placebo treatment-arms, and this improvement was significant (p-value=0.0159), corresponding to a 25% increase. Of note, the number of patients that have withdrawn from masitinib 4.5 mg arm was higher, and many in the beginning of the study. With the loss to follow up, the patients likely to remain in study were the more resistant.

QUALITY OF LIFE

Results of secondary analysis based on ALSAQ-40 are presented in the Table 24 below.

Table 20 ALSAQ-40 score – Masitinib 4.5 mg/kg/day – Normal Progressor

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

A statistically significant difference was observed between masitinib (P=0.0078) and placebo treatment-arms in the Quality of life for the Normal Progressor population (improvement between 42% and 46%). Of note, the number of patients that have withdrawn from masitinib 4.5 mg arm was higher, and many in the beginning of the study. With the mLOCF imputation, the patients which were withdrawn from the study were assigned a better ALSAQ40 score than the ones who complete the study.

FORCED VITAL CAPACITY (FVC) FOR MASITINIB 4.5 MG/KG/DAY IN THE NORMAL PROGRESSOR POPULATION

Absolute change from baseline to week 48 in FVC between masitinib 4.5 mg/kg/day and placebo in Normal Progressors is presented in the Table 25 below.

Table 21 Absolute change from baseline to week 48 in FVC –Masitinib 4.5 mg/kg/day – Normal Progressor population

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

A statistically significant difference was observed between masitinib (4.5 mg/kg/day) and placebo treatment-arms in the absolute change from baseline to week 48 in FVC for the Normal Progressor population (improvement between 25% and 29%).

COMBINED ASSESSMENT OF FUNCTION AND SURVIVAL (CAFS) FOR MASITINIB 4.5 MG/KG/DAY IN THE NORMAL PROGRESSOR POPULATION

Results of secondary analysis based on CAFS is presented in the Table 26 below.

Table 22 CAFS score – Masitinib 4.5 mg/kg/day – Normal Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
Placebo	111	104.73	8.91 [-6.73;24.56]	0.2626
Masitinib 4.5 mg	104	113.64		

A non-statistically significant difference was observed between masitinib (4.5 mg/kg/day) and placebo treatment-arms in the CAFS score for the Normal Progressor population (difference = 8.91, p-value=0.2626). The CAFS, which translates withdrawing patients into severed patients, and thus more conservative than mLOCF, did not reach statistical difference.

OVERALL SURVIVAL FOR MASITINIB 4.5 MG/KG/DAY IN THE NORMAL PROGRESSOR POPULATION

There was no benefit on survival with masitinib 4.5 mg/kg/day as compared with placebo in the Normal progressor population.

Table 23 Analysis of OS - Masitinib 4.5 mg/kg/day – Normal Progressor

Treatment group	Total	Median [95% CI]	p-value using Wilcoxon test
Placebo	113	Not reached [25; .]	0.3727
Masitinib 4.5 mg	105	Not reached [30; .]	

RESULTS FOR MASITINIB 3 MG/KG/DAY - "NORMAL PROGRESSOR" POPULATION

PRIMARY EFFICACY EVALUATION ON (ALSFRS-R)

Because analysis was conclusive at a 0.05 significance level for the first step of the fixed sequence method, it was permissible to move onto the next, second step of the sequence. Hence, the primary analysis was performed in the "Normal Progressor" population, to demonstrate a statistically significant difference between masitinib at a dose of 3 mg/kg/day + riluzole versus placebo + riluzole on ALSFRS-R after a 48 week treatment period.

The Table 28 below summarizes the datasets for the primary and sensitivity analyses on ALSFRS-R absolute change from baseline to week 48.

Table 24 Number of patients analysed for the primary and sensitivity analyses on ALSFRS-R – Masitinib 3 mg/kg/day – Normal Progressor

	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

The result of the primary efficacy analysis is presented below.

Table 25 Absolute change from baseline to week 48 in ALSFRS-R - Primary efficacy analysis – masitinib 3 mg/kg/day – Normal Progressor

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		

A difference close to statistical significance was observed in the ALSFRS-R score between masitinib and placebo (Difference of least-square means=2.73; p=0.0661), with an improvement of 24%, which is in line with the 25% threshold defined for a clinically meaningful benefit [Castrillo-Viguera, 2010].

The result of the sensitivity analyses on the primary endpoint are presented in the Table below.

Table 26 Absolute change from baseline to week 48 in ALSFRS-R – First Sensitivity analyses - Masitinib 3 mg/kg/day – Normal Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
mLOCF Rule 2:				
Placebo	103	-11.24	2.61 [-0.29;5.51]	0.0774
Masitinib 3 mg	106	-8.63		
mLOCF Rule 3:				
Placebo	107	-10.83	2.26 [-0.59;5.11]	0.1194
Masitinib 3 mg	107	-8.57		
mLOCF Rule 4:				
Placebo	108	-10.75	2.16 [-0.68;4.99]	0.1356
Masitinib 3 mg	107	-8.59		
mLOCF Rule 5:				
Placebo	111	-10.53	2.37 [-0.33;5.07]	0.0854
Masitinib 3 mg	110	-8.16		

Table 27 Absolute change from baseline to week 48 in ALSFRS-R – Second sensitivity analyses - Masitinib 3 mg/kg/day – Normal Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
Single imputation : Rule 6				
Placebo	111	-13.08	2.23 [-0.47;4.92]	0.1049
Masitinib 3 mg	110	-10.85		
Single imputation : Rule 7				
Placebo	111	-13.65	2.11 [-0.62;4.84]	0.1297
Masitinib 3 mg	110	-11.55		

The secondary analysis based on Quality of Life measure with ALSAQ-40 yeilded the following outcome:

Table 28 ALSAQ-40 score – Masitinib 3 mg/kg/day – Normal Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
mLOCF Rule 1				
Placebo	102	23.65	-8.04 [-13.71;-2.37]	0.0057
Masitinib 3 mg	106	15.60		
mLOCF Rule 5				
Placebo	111	22.09	-6.96 [-12.27;-1.65]	0.0104
Masitinib 3 mg	110	15.12		

A statistically significant difference was observed between masitinib (p=0.0057) and placebo treatment-arms in the Quality of life for the Normal Progressor population (improvement between 32% and 34%).

RESULTS FOR MASITINIB 4.5 MG/KG/DAY - "NORMAL + FAST PROGRESSOR" POPULATION

Table 29 Number of patients analysed for the primary and sensitivity analyses on ALSFRS-R – Masitinib 4.5 mg/kg/day – Normal + Fast Progressor

	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	119/132	121/132	125/132	127/132	130/132	130/132	130/132
Masitinib 4.5 mg + riluzole	120/128	120/128	124/128	124/128	126/128	127/128	127/128

The result of the primary efficacy analysis is presented below.

Table 30 Absolute change from baseline to week 48 in ALSFRS-R - Primary efficacy analysis – masitinib 4.5 mg/kg/day – Normal + Fast Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
Placebo	119	-12.9743	2.09 [-0.55;4.73]	0.1202
Masitinib 4.5 mg	120	-10.8865		

In terms of survival, in this population masitinib failed to show an effect (Figure 4).

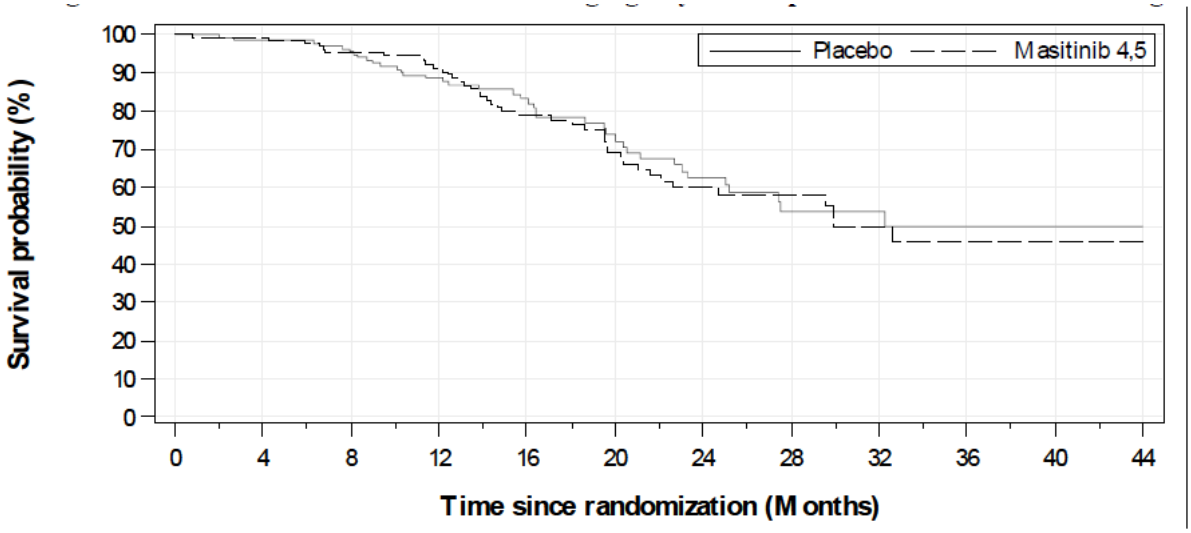

Figure 2 Overall Survival: Masitinib 4.5 mg/kg/day versus placebo – Normal + Fast Progressors

RESULTS FOR MASITINIB 3 MG/KG/DAY - "NORMAL + FAST PROGRESSOR" POPULATION

Table 31 Number of patients analysed for the primary and sensitivity analyses on ALSFRS-R – Masitinib 3 mg/kg/day – Normal + Fast Progressor

	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	119/132	121/132	125/132	127/132	130/132	130/132	130/132
Masitinib 3 mg +	126/131	126/131	127/131	127/131	131/131	131/131	131/131

The result of the primary efficacy analysis is presented below.

Table 32 Absolute change from baseline to week 48 in ALSFRS-R - Primary efficacy analysis – masitinib 3 mg/kg/day – Normal + Fast Progressor

Treatment group	N	LS Mean	Difference of means [95% confidence	p-value
Placebo	119	-12.07	1.80 [-0.91;4.51]	0.1918
Masitinib 3 mg	126	-10.27		

A small numerical difference in favor of masitinib was observed in the ALSFRS-R score (Difference of least-square means=1.80; p=0.1918), with an improvement of 15%.

Clinical studies in special populations

No special studies were performed in special populations.

2.5.3. Discussion on clinical efficacy

The development program of masitinib in amyotrophic lateral sclerosis (ALS) was based on the pivotal phase 2/3 study (Study AB10015): A prospective, multicentre, randomized, 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.

In the pivotal trial patients were randomly allocated to one of the three following groups: Group 1: masitinib at 4.5 mg/kg/day + riluzole; Group 2: masitinib at 3 mg/kg/day + riluzole; Group 3: placebo of masitinib + riluzole. Patients received treatment for 48 weeks, with possible extension.

The design of study AB10015 compares masitinib in combination with riluzole and in association with standard of care symptomatic treatments against placebo in combination with riluzole and in association with standard of care symptomatic treatments. There was no restriction placed on the investigator's choice of standard of care symptomatic treatments (e.g., physical therapy, surgical interventions, and alternative therapies). The patient population included mild to moderate ALS patients, with few co-morbidities and co-medications, and excluded patients on gastrostomy.

The primary analysis was performed on the subset of 'normal progressor' patients randomized at an initial masitinib dose of 4.5 mg/kg/day versus placebo patients. The decision to target 'normal progressors' for the primary analysis and the choice of mLOCF as the imputation method of choice was made in the third protocol amendment after the study had started. The primary endpoint was the absolute change from baseline to week 48 in ALSFRS-R. The results of the primary analysis (as per Clinical Study Report AB10015 v 1.0 dated 11AUG2017) are reported below:

- ALSFRS-R: Masitinib 4.5 mg/kg/day-Normal Progressors

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			

Progression free survival (PFS), Overall survival (OS), ALSAQ-40, Forced vital capacity (FVC) and Combined Assessment of Function and Survival (CAFS) were pre-specified secondary endpoints. Results are presented below (as per Clinical Study Report AB10015 v 1.0 dated 11 AUG 2017).

- Progression Free Survival: Masitinib 4.5 mg/kg/day versus placebo – Normal Progressors

Treatment group	Total	Median [95% CI]	p-value using Wilcoxon test
Placebo	113	16 [11; 19]	0.0159
Masitinib 4,5	105	20 [14; 30]	

Of note, as per definition criteria of PFS, patients who have withdrawn and not reached progression (death or increase of 10 points or more in ALSFRS-R) are not included in the analysis. Patients withdrawing due to adverse events in the first 6 to 9 months favour PFS results in the arm.

- Overall survival: Masitinib 4.5 mg/kg/day versus placebo – Normal Progressors

Treatment group	Total	Median [95% CI]	p-value using Wilcoxon test
Placebo	113	Not reached [25; .]	0.3727
Masitinib 4.5 mg	105	Not reached [30; .]	

- QoL ALS scale: ALSAQ-40 score (40 items score 0 to 3 each)– Masitinib 4.5 mg/kg/day – Normal Progressor (imputation rules mLOCF related 1 and 5 only:

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

- FVC: Masitinib 4.5 mg/kg/day – Normal Progressor (imputation rules mLOCF related 1 and 5 only):

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

- CAFS (Combined Assessment of Function and Survival): Masitinib 4.5 mg/kg/day – Normal Progressor:

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value
Placebo	111	104.73	8.91 [-6.73;24.56]	0.2626
Masitinib 4.5 mg	104	113.64		

The CHMP expressed serious concerns about the conduct of the trial, the applied methodology and the robustness of the data used to support the claim for efficacy for masitinib in ALS. As discussed, the mLOCF approach to missing data handling tends to favour the active treatment arm.

The first major concern on the conduct is related to the fact that the findings of the triggered inspection of two sites that were major enrollers, contributing to over 40% of the recruitment in the study, posed strong doubts on the data integrity. The inspection findings were considered to have a negative impact on data reliability. Inspectors presented to the CHMP their opinion that the data obtained at the sites inspected and represented in the CSR were not trustworthy enough to support the application authorisation submitted to the Agency for masitinib.

The trial went through a number of significant protocol amendments, and for the CHMP the reasoning and drivers for some of those remain unclear. A significant change was that the target population for the primary analysis of the trial was changed from the wider ALS population initially included, to a restricted 'normal progressor' population. Others amendments included multiple changes to the planned statistical analysis and the sequence of testing to handle the multiple dose groups. The presence of multiple major amendments made after the start of the study in a single pivotal trial is of concern

Apart from the concerns about the trial conduct, there were also issues related to the methodology for data acquisition. Although it is recognized that ALS represents an area with a severe unmet medical need, where in principle a single pivotal trial could be sufficient for a marketing authorization application following the requirements of the EMA guideline (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf), and applying appropriate scientifically justified methodology, , the presented development programme suffers from significant deficiencies. The population in a confirmatory trial should represent the population indicated for treatment. In a confirmatory trial, and especially in a scenario with a single pivotal trial, surrogate endpoints could be accepted if they have been validated, and when their translation into clinical endpoints is undisputable.

The most relevant concern raised by the CHMP in relation to the analytical approach was the methodology used for dealing with missing data. It was noted that there were a significant number of dropouts in the trial, and the reasons for dropping out differedt significantly between patients on active treatment and placebo, with more patients discontinuing due to lack of efficacy / adverse events on the active treatment arms. The primary and most of the so-called sensitivity analyses excluded some patients and employed LOCF to impute endpoint values for others. Exclusion of patients from analysis in a progressive disease like ALS, with the use of LOCF as imputation method introduces significant bias that may seriously overestimate the effects of the active treatment vs placebo. Other sensitivity analyses include all patients but impute within treatment-group based on observed responses. This is also a potential source of bias since patients remaining in the study are a selected subgroup of those initially randomised. The use of patients remaining on treatment to impute values for those who have discontinued treatment is also questionable.

The definition of the term ‘normal progressor’ is subject of discussion in the ALS field: being a retrospective concept requiring long previous follow-up, does not represent clinical practice and would affect negatively the possibility to extrapolate the observed findings on the broad ALS population. Although this retrospective version of ALSFRS-R has been published, it should rely on previous top quality clinical records. The quality of past clinical records could not be confirmed on the inspected study centres. The modification of the primary endpoint with the trial ongoing raised additional concerns related to the validity of approach to prove efficacy of the compound in this condition. There was no scientific justification based on the suspected mechanism of action for masitinib that would justify such a dichotomisation of the ALS population. This becomes even more relevant as the primary endpoint on the “normal progressor” population is not followed by clinically significant results in the secondary endpoints, particularly those more robust such as overall survival, ALSAQ40, CAFS or FVC. Of note, for the "normal + fast progressor" population the absolute change from baseline to week 48 in ALSFRS-R between masitinib 4.5 mg/kg/day and placebo is 2.09 [-0.55;4.73], not reaching statistical significance (P = 0.1202). In addition, the lack of specific criteria to classify withdrawing patients led to similar reasons for discontinuation being classed and analysed differently.

Unfortunately, muscle strength has not been studied to potentially corroborate masitinib’s effect on muscle power. The lack of data on muscle strength combined with the fact that OS and time to tracheostomy have not shown benefits, increases the level of uncertainty about the claimed efficacy of masitinib. In spite of the claim being disease modification rather than symptomatic effect, a slowness of muscle strength decrease would be present under an efficacious disease modifying agent, and therefore a difference between active treatment and placebo should be apparent by week 48.

Additionally, some further limitations remain:

- Three study centres from two countries have enrolled 48% of the trial sample, thus making study external validity lower; The Applicant considered that the EU countries which refused the trial forced the sponsor strategy to restrict centres and involved countries, but this does not increase study validity and reinforces the concerns.

- ALSFRS R score at baseline and at wk48 varied significantly from study centre to study centre. The Applicant justified the asymmetries of enrolment in centres with the number of citizens per country. This cannot be acceptable since these centres are not unique in the country and are not the single ALS specialized centres in the country. Final data analysis showed less variability among recruiting centres - as far as study population baseline characteristics are concerned, than what was observed in the interim analysis where the initial and fast study centres enrolled a more heterogeneous population.

- The efficacy results of the patients allocated to 3mg/kg/day of masitinib were not initially analysed. Upon request the MAA performed a partial analysis. The 3mg/kg/day arm data show that there is a smaller trend of effect in ‘normal progressors’ than the 4.5 mg dose. Like the 4.5 mg dose, most endpoints did not reach statistical significance and even less clinical significance. Similar to the 4.5 mg dose, the 3.0 mg dose did not show a difference from placebo on the QoL parameter. There is a reference that the safety profile was similar to the placebo arm, but no further data were explored.

In summary, a clear chain of evidence has not been created, providing supportive data in a logical stepwise manner, starting with a clear pre-clinical proof-of-principle, moving into a justified dose- selection strategy and proof-of-concept, before finally generating sufficient confirmatory data from a properly designed clinical programme. The efficacy data provided are insufficient to justify a positive benefit/risk profile of masitinib in ALS.

Additional discussion in the context of a conditional MA

The Applicant applied for conditional Marketing authorisation (CMA), basing the claim for positive B/R balance on the results from the interim analysis. As described above, these were not considered comprehensive and compelling. As a condition of the CMA the Applicant initially proposed the final results from the pivotal study to be presented, and claimed that should CHMP be requesting a second study as a condition, the granting of a conditional marketing authorization would not affect the ability to complete this second study in a timely manner. The CHMP disagreed with the proposed strategy despite agreeing with the claim for an unmet medical need in ALS. For the Committee, the available data, from both interim and final analyses were not sufficient to establish a positive B/R for Alsitek in ALS, thus failing to fulfil condition 1 of Article 4 of Commission Regulation (EC) No 507/2006, and not allowing a CMA to be granted.

2.5.4. Conclusions on the clinical efficacy

While CPMP/EWP/2330/99 indicates that a single pivotal study can be an acceptable basis for licensing where certain prerequisites are met, data from the single pivotal trial of Alsitek are not adequate to establish efficacy. Study AB10015 does not meet the criteria concerning data quality and absence of indications of potential bias. Multiple crucial protocol amendments have been implemented during the course of the study. Thus, a reliable estimate of efficacy has not been presented.

2.6. Clinical safety

Patient exposure

The Table 37 below presents the duration of patient exposure in the Normal Progressor population.

Table 33 Exposure to study drug – Normal Progressors

	Placebo	**Masitinib 4,5**	**Masitinib 3**
exposure main part(days)			
n	114	105	110
Mean +/- SD	299.6 +/- 86.7	288.2 +/- 89.2	277.2 +/-
Median	336.0	335.0	335.5
Range	7.0 ; 442.0	9.0 ; 357.0	22.0 ; 390.0
exposure main part(weeks)			
n	114	105	110
Mean +/- SD	42.8 +/- 12.4	41.2 +/- 12.7	39.6 +/- 14.6
Median	48.0	47.9	47.9
Range	1.0 ; 63.1	1.3 ; 51.0	3.1 ; 55.7
exposure main part(months)			
n	114	105	110
Mean +/- SD	9.8 +/- 2.8	9.5 +/- 2.9	9.1 +/- 3.4
Median	11.0	11.0	11.0
Range	0.2 ; 14.5	0.3 ; 11.7	0.7 ; 12.8

105 patients received masitinib at a dose of 4.5 mg/kg/day, 110 patients received masitinib at a dose of 3 mg/kg/day, and 114 patients received placebo. The mean treatment duration was 9.5 months (ranging from

0.3 to 11.7 months) in the masitinib 4.5 mg/kg/day arm, 9.1 months (ranging from 0.7 to 12.8 months) in the masitinib 3 mg/kg/day arm, and 9.8 months (ranging from 0.2 to 14.5 months) in the placebo arm.

Table 38 below presents the duration of patient exposure in the Normal + Fast Progressor population.

Table 34 Exposure to study drug – Normal + Faster Progressors

	Placebo	Masitinib 4.5	Masitinib 3
exposure main part(days)			
n	133	129	131
Mean +/- SD	293.4 +/- 90.7	276.7 +/- 98.8	273.9 +/-
Median	336.0	335.0	335.0
Range	7.0 ; 442.0	9.0 ; 357.0	22.0 ; 390.0
exposure main part(weeks)			
n	133	129	131
Mean +/- SD	41.9 +/- 13.0	39.5 +/- 14.1	39.1 +/- 15.0
Median	48.0	47.9	47.9
Range	1.0 ; 63.1	1.3 ; 51.0	3.1 ; 55.7
exposure main part(months)			
n	133	129	131
Mean +/- SD	9.6 +/- 3.0	9.1 +/- 3.2	9.0 +/- 3.4
Median	11.0	11.0	11.0
Range	0.2 ; 14.5	0.3 ; 11.7	0.7 ; 12.8

129 patients received masitinib at a dose of 4.5 mg/kg/day, 131 patients received masitinib at a dose of 3 mg/kg/day, and 133 patients received placebo. The mean treatment duration was 9.1 months (ranging from

0.3 to 11.7 months) in the masitinib 4.5 mg/kg/day arm, 9.0 months (ranging from 0.7 to 12.8 months) in the masitinib 3 mg/kg/day arm, and 9.6 months (ranging from 0.2 to 14.5 months) in the placebo arm.

Adverse events

During the protocol period, the frequency of AEs was moderately increased with masitinib 4.5 mg/kg/day and was comparable with masitinib 3 mg/kg/day as compared with placebo, regardless of the population.

- In the “Normal Progressor” population, the frequency of AEs was 87.6% and 84.5% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 78.1% for placebo (delta with respect to placebo = +9.5% and +6.5%, respectively).
- In the “Normal + Fast Progressor” population, the frequency of AEs was 88.4% and 84.7% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 78.9% for placebo (delta with respect to placebo = +9.4% and +5.8%, respectively).

The frequency of suspected or not assessable AEs was increased with masitinib 4.5 and 3 mg/kg/day as compared with placebo. The frequency of suspected or not assessable AEs was higher with masitinib 4.5 mg/kg/day than with masitinib 3 mg/kg/day.

- In the “Normal Progressor” population, the frequency of suspected or not assessable AEs was 63.8% and 45.5% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 28.1% for placebo (delta with respect to placebo = +35.7% and +17.4%, respectively).
- In the “Normal + Fast Progressor” population, the frequency of suspected or not assessable AEs was 60.5% and 45.0% at the masitinib doses of 4.5 and

- 3.0 mg/kg/day, respectively, as compared with 27.1% for placebo (delta with respect to placebo = +33.4% and +18.0%, respectively).

The acquisition of data related to adverse events and adequate narratives was not of very good quality. This has impaired the discrimination between disease and masitinib related AEs. This is also relevant in "AEs leading to death", where no audit on these cases has been performed shortly after the event, to obtain data that otherwise has been lost henceforth.

During the extension period, the frequency of AEs was increased with masitinib 4.5 mg/kg/day and was comparable with masitinib 3 mg/kg/day as compared with placebo, regardless of the population.

- In the "Normal Progressor" population, the frequency of AEs was 65.2% and 54.9% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 55.4% for placebo (delta with respect to placebo = +9.7% and -0.5%, respectively).
- In the "Normal + Fast Progressor" population, the frequency of AEs was 63.0% and 52.5% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 51.3% for placebo (delta with respect to placebo = +11.8% and +1.3%, respectively).

The frequency of suspected or not assessable AEs was moderately increased with masitinib 4.5 mg/kg/day and masitinib 3 mg/kg/day as compared with placebo.

- In the "Normal Progressor" population, the frequency of suspected or not assessable AEs was 10.6% and 8.5% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 1.4% for placebo (delta with respect to placebo = +9.3% and +7.1%, respectively).
- In the "Normal + Fast Progressor" population, the frequency of suspected or not assessable AEs was 11% and 7.5% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 1.3% for placebo (delta with respect to placebo = +9.7% and +6.3%, respectively).

Table 35 Summary of AEs

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSORS					NORMAL + FASTER PROGRESSORS					NORMAL PROGRESSORS					NORMAL + FASTER PROGRESSORS				
	P	M4.5		M3		P	M4.5		M3		P	M4.5		M3		P	M4.5		M3	
Number (%) of patients with at least one	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
AE	89 (78.1%)	92 (87.6%)	9.5	93 (84.5%)	6.5	105 (78.9%)	114 (88.4%)	9.4	111 (84.7%)	5.8	41 (55.4%)	43 (65.2%)	9.7	39 (54.9%)	-0.5	41 (51.3%)	46 (63.0%)	11.8	42 (52.5%)	1.3
Suspected/not assess.	32 (28.1%)	67 (63.8%)	35.7	50 (45.5%)	17.4	36 (27.1%)	78 (60.5%)	33.4	59 (45.0%)	18.0	1 (1.4%)	7 (10.6%)	9.3	6 (8.5%)	7.1	1 (1.3%)	8 (11.0%)	9.7	6 (7.5%)	6.3
Leading to Death[3]	8 (7.0%)	3 (2.9%)	-4.2	8 (7.3%)	0.3	12 (9.0%)	10 (7.8%)	-1.3	11 (8.4%)	-0.6	6 (8.1%)	12 (18.2%)	10.1	10 (14.1%)	6.0	6 (7.5%)	13 (17.8%)	10.3	11 (13.8%)	6.3
Suspected/not assess.	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Non-fatal SAE	19 (16.7%)	29 (27.6%)	11.0	23 (20.9%)	4.2	24 (18.0%)	40 (31.0%)	13.0	30 (22.9%)	4.9	10 (13.5%)	14 (21.2%)	7.7	10 (14.1%)	0.6	10 (12.5%)	15 (20.5%)	8.0	11 (13.8%)	1.3
Suspected/not assess.	1 (0.9%)	7 (6.7%)	5.8	4 (3.6%)	2.8	1 (0.8%)	9 (7.0%)	6.2	5 (3.8%)	3.1	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Severe AE	16 (14.0%)	26 (24.8%)	10.7	21 (19.1%)	5.1	22 (16.5%)	38 (29.5%)	12.9	29 (22.1%)	5.6	10 (13.5%)	18 (27.3%)	13.8	13 (18.3%)	4.8	10 (12.5%)	20 (27.4%)	14.9	14 (17.5%)	5.0
Suspected/not assess.	1 (0.9%)	5 (4.8%)	3.9	1 (0.9%)	0.0	1 (0.8%)	7 (5.4%)	4.7	2 (1.5%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
AE leading to study treatment permanent discontinuation (excl. deaths)	9 (7.9%)	18 (17.1%)	9.2	16 (14.5%)	6.7	12 (9.0%)	21 (16.3%)	7.3	21 (16.0%)	7.0	2 (2.7%)	6 (9.1%)	6.4	1 (1.4%)	-1.3	2 (2.5%)	6 (8.2%)	5.7	1 (1.3%)	-1.3
Suspected/not assess.	3 (2.6%)	14 (13.3%)	10.7	9 (8.2%)	5.6	3 (2.3%)	15 (11.6%)	9.4	10 (7.6%)	5.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.4%)	1.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.3%)	1.3
AE leading to study treatment temporarily interruption	2 (1.8%)	15 (14.3%)	12.5	3 (2.7%)	1.0	2 (1.5%)	16 (12.4%)	10.9	3 (2.3%)	0.8	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Suspected/not assess.	0 (0.0%)	11 (10.5%)	10.5	0 (0.0%)	0.0	0 (0.0%)	12 (9.3%)	9.3	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
AE leading to study treatment dose reduction	12 (10.5%)	35 (33.3%)	22.8	17 (15.5%)	4.9	14 (10.5%)	43 (33.3%)	22.8	23 (17.6%)	7.0	6 (8.1%)	9 (13.6%)	5.5	4 (5.6%)	-2.5	6 (7.5%)	9 (12.3%)	4.8	4 (5.0%)	-2.5
Suspected/not assess.	2 (1.8%)	25 (23.8%)	22.1	10 (9.1%)	7.3	4 (3.0%)	30 (23.3%)	20.2	13 (9.9%)	6.9	0 (0.0%)	3 (4.5%)	4.5	0 (0.0%)	0.0	0 (0.0%)	3 (4.1%)	4.1	0 (0.0%)	0.0

Serious adverse event / deaths / other significant events

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 as per MAH conclusions.

Considering that ALS is a rapidly progressing disease with fatal outcome, where each patient can suffer from very diiferent progression, the analysis of AEs leading to death during the first 48 weeks will provide a more homogeneous pool and is therefore more instructive to analyse the mortality.

During the first 48 week period, the frequency of adverse events leading to death was slightly lower with masitinib 4.5 as compared with masitinib 3.0 mg/Kg/day or placebo, regardless of the population, and the difference was not statistically significant.

- In the “Normal Progressor” population, the frequency of AEs leading to death was 2.9% and 7.3% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 7.0% for placebo (delta with respect to placebo = -4.2%% and +0.3%, respectively).
- In the “Normal + Fast Progressor” population, the frequency of SAEs was 7.8% and 8.4% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 9.0% for placebo (delta with respect to placebo = -1.3% and -0.6%, respectively).

During the protocol period, the frequency of serious adverse events (SAE) (any causality) was moderately increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo, regardless of the population.

- In the “Normal Progressor” population, the frequency of SAEs was 27.6% and 20.9% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 16.7% for placebo (delta with respect to placebo = +11.0% and +4.2%, respectively).
- In the “Normal + Fast Progressor” population, the frequency of SAEs was 31% and 22.9% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 18% for placebo (delta with respect to placebo = +13% and +4.9%, respectively).

Likewise, the frequency of suspected or not assessable SAEs was moderately increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo.

- In the “Normal Progressor” population, the frequency of suspected or not assessable SAEs was 6.7% and 3.6% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 0.9% for placebo (delta with respect to placebo = +5.8% and +2.8%, respectively).
- In the “Normal + Fast Progressor” population, the frequency of suspected or not assessable SAEs was 7.0% and 3.8% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 0.8% for placebo (delta with respect to placebo = +6.2% and +3.1%, respectively).

During the extension period, the frequency of serious adverse events (SAE) (any causality) was moderately increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo, regardless of the population.

- In the “Normal Progressor” population, the frequency of SAEs was 21.2% and 14.1% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 13.5% for placebo (delta with respect to placebo = +7.7% and +0.6%, respectively).

- In the “Normal + Fast Progressor” population, the frequency of SAEs was 20.5 % and 13.8% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 12.5% for placebo (delta with respect to placebo = +8.0% and +1.3%, respectively).

SEVERE ADVERSE EVENTS

The frequency of suspected or not assessable SAEs was similar with masitinib as compared with placebo, regardless of the dose and the population.

During the protocol period, the frequency of severe adverse events was moderately increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo, regardless of the population.

- In the “Normal Progressor” population, the frequency of severe AEs was 24.8% and 19.1% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 14.0% for placebo (delta with respect to placebo = +10.7% and +5.1%, respectively).
- In the “Normal + Fast Progressor” population, the frequency of severe AEs was 29.5% and 22.1% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 16.5% for placebo (delta with respect to placebo = +12.9% and +5.6%, respectively).

However, when considering the causality of severe AEs, the frequency of suspected or not assessable severe adverse events was only slightly increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo, regardless of the population.

- In the “Normal Progressor” population, the frequency of suspected or not assessable severe AEs was 4.8% and 0.9% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 0.9% for placebo (delta with respect to placebo = +3.9% and +0%, respectively).
- In the “Normal + Fast Progressor” population, the frequency of suspected or not assessable severe AEs was 5.4% and 1.5% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 0.8% for placebo (delta with respect to placebo = +4.7% and +0.8%, respectively).

This increase in severe AEs was spread across system organ class.

Table 36 Frequency of severe AE by SOC/PT

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
	P	M4.5		M3		P	M4.5		M3		P	M4.5		M3		P	M4.5		M3	
System Organ Class/Preferred Term	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
At least one severe AE	**16 (14.0%)**	**26 (24.8%)**	**10.7**	**21 (19.1%)**	**5.1**	**22 (16.5%)**	**38 (29.5%)**	**12.9**	**29 (22.1%)**	**5.6**	**10 (13.5%)**	**18 (27.3%)**	**13.8**	**13 (18.3%)**	**4.8**	**10 (12.5%)**	**20 (27.4%)**	**14.9**	**14 (17.5%)**	**5.0**
Blood And Lymphatic System Disorders	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**3 (2.7%)**	**2.7**	**0 (0.0%)**	**2 (1.6%)**	**1.6**	**4 (3.1%)**	**3.1**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Anaemia Vitamin B12 Deficiency	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Normochromic Normocytic Anaemia	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Microcytic Anaemia	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Neutropenia	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Lymphopenia	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	2 (1.5%)	1.5	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Iron Deficiency Anaemia	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Cardiac Disorders	**2 (1.8%)**	**2 (1.9%)**	**0.2**	**5 (4.5%)**	**2.8**	**3 (2.3%)**	**2 (1.6%)**	**-0.7**	**5 (3.8%)**	**1.6**	**0 (0.0%)**	**1 (1.5%)**	**1.5**	**2 (2.8%)**	**2.8**	**0 (0.0%)**	**1 (1.4%)**	**1.4**	**2 (2.5%)**	**2.5**
Cardio Respiratory Arrest	1 (0.9%)	1 (1.0%)	0.1	4 (3.6%)	2.8	2 (1.5%)	1 (0.8%)	-0.7	4 (3.1%)	1.5	0 (0.0%)	1 (1.5%)	1.5	2 (2.8%)	2.8	0 (0.0%)	1 (1.4%)	1.4	2 (2.5%)	2.5
Myocardial Infarction	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Cardiopulmonary Failure	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Cardiac Arrest	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Ear And Labyrinth Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Endocrine Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Eye Disorders	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Eye Irritation	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Gastrointestinal Disorders	**4 (3.5%)**	**6 (5.7%)**	**2.2**	**5 (4.5%)**	**1.0**	**4 (3.0%)**	**6 (4.7%)**	**1.6**	**6 (4.6%)**	**1.6**	**2 (2.7%)**	**6 (9.1%)**	**6.4**	**0 (0.0%)**	**-2.7**	**2 (2.5%)**	**7 (9.6%)**	**7.1**	**0 (0.0%)**	**-2.5**
Dysphagia	3 (2.6%)	5 (4.8%)	2.1	5 (4.5%)	1.9	3 (2.3%)	5 (3.9%)	1.6	6 (4.6%)	2.3	2 (2.7%)	6 (9.1%)	6.4	0 (0.0%)	-2.7	2 (2.5%)	7 (9.6%)	7.1	0 (0.0%)	-2.5
Pneumoperitoneum	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Intestinal Obstruction	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
General Disorders And Administration Site Conditions	**1 (0.9%)**	**0 (0.0%)**	**-0.9**	**0 (0.0%)**	**-0.9**	**1 (0.8%)**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Euthanasia	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Hepatobiliary Disorders	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Liver Disorder	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Immune System Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Infections And Infestations	**1 (0.9%)**	**1 (1.0%)**	**0.1**	**0 (0.0%)**	**-0.9**	**3 (2.3%)**	**1 (0.8%)**	**-1.5**	**1 (0.8%)**	**-1.5**	**4 (5.4%)**	**8 (12.1%)**	**6.7**	**4 (5.6%)**	**0.2**	**4 (5.0%)**	**8 (11.0%)**	**6.0**	**4 (5.0%)**	**0.0**
Pneumonia	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	2 (1.5%)	0 (0.0%)	-1.5	0 (0.0%)	-1.5	2 (2.7%)	4 (6.1%)	3.4	2 (2.8%)	0.1	2 (2.5%)	4 (5.5%)	3.0	2 (2.5%)	0.0
Pneumonia Viral	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (1.4%)	2 (3.0%)	1.7	0 (0.0%)	-1.4	1 (1.3%)	2 (2.7%)	1.5	0 (0.0%)	-1.3
Lower Respiratory Tract Infection	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	1 (1.4%)	1 (1.5%)	0.2	1 (1.4%)	0.1	1 (1.3%)	1 (1.4%)	0.1	1 (1.3%)	0.0
Infection	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Respiratory Tract Infection	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Bronchitis	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	1 (1.4%)	1.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.3%)	1.3

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
	P	M4.5		M3		P	M4.5		M3		P	M4.5		M3		P	M4.5		M3	
System Organ Class/Preferred Term	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
Injury Poisoning And Procedural Complications	**0 (0.0%)**	**2 (1.9%)**	**1.9**	**2 (1.8%)**	**1.8**	**0 (0.0%)**	**3 (2.3%)**	**2.3**	**2 (1.5%)**	**1.5**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Scapula Fracture	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Rib Fracture	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Femur Fracture	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Subarachnoid Haemorrhage	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Laceration	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Fall	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Face Injury	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Investigations	**2 (1.8%)**	**5 (4.8%)**	**3.0**	**4 (3.6%)**	**1.9**	**2 (1.5%)**	**7 (5.4%)**	**3.9**	**6 (4.6%)**	**3.1**	**0 (0.0%)**	**1 (1.5%)**	**1.5**	**1 (1.4%)**	**1.4**	**0 (0.0%)**	**1 (1.4%)**	**1.4**	**1 (1.3%)**	**1.3**
Blood Phosphorus Decreased	0 (0.0%)	3 (2.9%)	2.9	0 (0.0%)	0.0	0 (0.0%)	3 (2.3%)	2.3	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Weight Decreased	0 (0.0%)	1 (1.0%)	1.0	1 (0.9%)	0.9	0 (0.0%)	1 (0.8%)	0.8	1 (0.8%)	0.8	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Gamma Glutamyltransferase Increased	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	2 (1.6%)	1.6	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Transaminases Increased	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Aspiration Bronchial	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (1.4%)	1.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.3%)	1.3
Neutrophil Count Decreased	1 (0.9%)	0 (0.0%)	-0.9	1 (0.9%)	0.0	1 (0.8%)	0 (0.0%)	-0.8	1 (0.8%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Haemoglobin Decreased	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Blood Triglycerides Increased	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Blood Potassium Increased	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Blood Glucose Increased	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Blood Calcium Decreased	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Aspartate Aminotransferase Increased	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Alanine Aminotransferase Increased	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Metabolism And Nutrition Disorders	**1 (0.9%)**	**2 (1.9%)**	**1.0**	**1 (0.9%)**	**0.0**	**2 (1.5%)**	**2 (1.6%)**	**0.0**	**2 (1.5%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (1.4%)**	**1.4**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (1.3%)**	**1.3**
Hypophosphataemia	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Hypokalaemia	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Obesity	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Hyponatraemia	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Hypertriglyceridaemia	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	1 (0.8%)	0 (0.0%)	-0.8	1 (0.8%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (1.4%)	1.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.3%)	1.3
Musculoskeletal And Connective Tissue Disorders	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0.0**	**1 (1.4%)**	**0 (0.0%)**	**-1.4**	**0 (0.0%)**	**-1.4**	**1 (1.3%)**	**0 (0.0%)**	**-1.3**	**0 (0.0%)**	**-1.3**
Muscular Weakness	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Muscle Atrophy	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (1.4%)	0 (0.0%)	-1.4	0 (0.0%)	-1.4	1 (1.3%)	0 (0.0%)	-1.3	0 (0.0%)	-1.3
Neoplasms Benign Malignant And Unspecified (Incl Cysts And Polyps)	**2 (1.8%)**	**0 (0.0%)**	**-1.8**	**0 (0.0%)**	**-1.8**	**2 (1.5%)**	**0 (0.0%)**	**-1.5**	**0 (0.0%)**	**-1.5**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Pleural Mesothelioma	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
	P	M4.5		M3		P	M4.5		M3		P	M4.5		M3		P	M4.5		M3	
System Organ Class/Preferred Term	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
Invasive Ductal Breast Carcinoma	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Nervous System Disorders	**0 (0.0%)**	**3 (2.9%)**	**2.9**	**3 (2.7%)**	**2.7**	**1 (0.8%)**	**4 (3.1%)**	**2.3**	**3 (2.3%)**	**1.5**	**1 (1.4%)**	**2 (3.0%)**	**1.7**	**0 (0.0%)**	**-1.4**	**1 (1.3%)**	**2 (2.7%)**	**1.5**	**0 (0.0%)**	**-1.3**
Amyotrophic Lateral Sclerosis	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	1 (1.4%)	1 (1.5%)	0.2	0 (0.0%)	-1.4	1 (1.3%)	1 (1.4%)	0.1	0 (0.0%)	-1.3
Occipital Neuralgia	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Hypercapnic Coma	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Dysarthria	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Brain Injury	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Myoclonic Epilepsy	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Muscle Spasticity	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Hyperreflexia	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (1.4%)	0 (0.0%)	-1.4	0 (0.0%)	-1.4	1 (1.3%)	0 (0.0%)	-1.3	0 (0.0%)	-1.3
Brain Oedema	0 (0.0%)	0 (0.0%)	0.0	2 (1.8%)	1.8	0 (0.0%)	0 (0.0%)	0.0	2 (1.5%)	1.5	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Pregnancy Puerperium And Perinatal Conditions	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Psychiatric Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (0.9%)**	**0.9**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Anxiety	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Agitation	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Renal And Urinary Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Reproductive System And Breast Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Respiratory Thoracic And Mediastinal Disorders	**6 (5.3%)**	**4 (3.8%)**	**-1.5**	**8 (7.3%)**	**2.0**	**9 (6.8%)**	**13 (10.1%)**	**3.3**	**12 (9.2%)**	**2.4**	**8 (10.8%)**	**7 (10.6%)**	**-0.2**	**6 (8.5%)**	**-2.4**	**8 (10.0%)**	**8 (11.0%)**	**1.0**	**7 (8.8%)**	**-1.3**
Respiratory Failure	2 (1.8%)	1 (1.0%)	-0.8	4 (3.6%)	1.9	4 (3.0%)	9 (7.0%)	4.0	8 (6.1%)	3.1	4 (5.4%)	3 (4.5%)	-0.9	5 (7.0%)	1.6	4 (5.0%)	3 (4.1%)	-0.9	6 (7.5%)	2.5
Dyspnoea	1 (0.9%)	2 (1.9%)	1.0	0 (0.0%)	-0.9	1 (0.8%)	3 (2.3%)	1.6	0 (0.0%)	-0.8	2 (2.7%)	1 (1.5%)	-1.2	0 (0.0%)	-2.7	2 (2.5%)	1 (1.4%)	-1.1	0 (0.0%)	-2.5
Respiratory Arrest	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	3 (4.5%)	4.5	1 (1.4%)	1.4	0 (0.0%)	3 (4.1%)	4.1	1 (1.3%)	1.3
Acute Respiratory Failure	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	1 (0.8%)	1 (0.8%)	0.0	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Respiratory Distress	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Pulmonary Embolism	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	2 (2.7%)	0 (0.0%)	-2.7	0 (0.0%)	-2.7	2 (2.5%)	0 (0.0%)	-2.5	0 (0.0%)	-2.5
Pneumonia Aspiration	1 (0.9%)	0 (0.0%)	-0.9	1 (0.9%)	0.0	1 (0.8%)	1 (0.8%)	0.0	1 (0.8%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Pulmonary Oedema	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Obstructive Airways Disorder	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Increased Bronchial Secretion	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Dyspnoea At Rest	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Skin And Subcutaneous Tissue Disorders	**0 (0.0%)**	**2 (1.9%)**	**1.9**	**1 (0.9%)**	**0.9**	**0 (0.0%)**	**2 (1.6%)**	**1.6**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Rash Maculo Papular	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Rash Generalised	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Pruritus Generalised	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
	P	*M4.5*		*M3*		*P*	*M4.5*		*M3*		*P*	*M4.5*		*M3*		*P*	*M4.5*		*M3*	
System Organ Class/Preferred Term	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
Drug Reaction With Eosinophilia And Systemic Symptoms	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Social Circumstances	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Surgical And Medical Procedures	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Vascular Disorders	**1 (0.9%)**	**0 (0.0%)**	**-0.9**	**0 (0.0%)**	**-0.9**	**1 (0.8%)**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**-0.8**	**1 (1.4%)**	**0 (0.0%)**	**-1.4**	**0 (0.0%)**	**-1.4**	**1 (1.3%)**	**1 (1.4%)**	**0.1**	**0 (0.0%)**	**-1.3**
Venous Thrombosis	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Hypotension	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Deep Vein Thrombosis	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (1.4%)	0 (0.0%)	-1.4	0 (0.0%)	-1.4	1 (1.3%)	0 (0.0%)	-1.3	0 (0.0%)	-1.3

It is not common to have not assessable causality in severe adverse events, when strong efforts should be made to impute causality.

ADVERSE EVENTS MOST INCREASED WITH MASITINIB

The AEs most increased during the protocol period for masitinib at 4.5 mg/kg/day were rash maculo-papular, nausea, respiratory failure, oedema peripheral, iron deficiency anaemia, dyspnoea and anxiety. For masitinib at 3 mg/kg/day, oedema peripheral, diarrhoea, respiratory failure, and rash maculo-papular, albeit to a lesser extent. There was no increase in iron deficiency anaemia, dyspnoea and nausea at a masitinib dose of 3 mg/kg/day. Except for respiratory failure with masitinib 3 mg/kg/day, these AEs were not increased during the extension period.

Table 37 Adverse events most increased with masitinib

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
Class/Preferred Term	*P* (N=114)	*M4.5* (N=105)	(M4.5 - P)	*M3* (N=110)	(M3 - P)	*P* (N=133)	*M4.5* (N=129)	(M4.5 - P)	*M3* (N=131)	(M3 - P)	*P* (N=74)	*M4.5* (N=66)	(M4.5 - P)	*M3* (N=71)	(M3 - P)	*P* (N=80)	*M4.5* (N=73)	(M4.5 - P)	*M3* (N=80)	(M3 - P)
Rash Maculo Papular	1 (0.9%)	9 (8.6%)	7.7	5 (4.5%)	3.6	1 (0.8%)	11 (8.5%)	7.7	6 (4.6%)	3.8	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Nausea	6 (5.3%)	13 (12.4%)	7.1	7 (6.4%)	1.1	6 (4.5%)	15 (11.6%)	7.1	8 (6.1%)	1.6	0 (0.0%)	0 (0.0%)	0.0	1 (1.4%)	1.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.3%)	1.3
Respiratory Failure	3 (2.6%)	2 (1.9%)	-0.7	4 (3.6%)	1.0	5 (3.8%)	13 (10.1%)	6.3	9 (6.9%)	3.1	4 (5.4%)	3 (4.5%)	-0.9	6 (8.5%)	3.1	4 (5.0%)	3 (4.1%)	-0.9	7 (8.8%)	3.8
Oedema Peripheral	1 (0.9%)	8 (7.6%)	6.7	5 (4.5%)	3.6	1 (0.8%)	9 (7.0%)	6.2	7 (5.3%)	4.5	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Iron Deficiency Anaemia	2 (1.8%)	9 (8.6%)	6.8	3 (2.7%)	0.9	2 (1.5%)	9 (7.0%)	5.5	3 (2.3%)	0.8	1 (1.4%)	1 (1.5%)	0.1	1 (1.4%)	0.0	1 (1.3%)	1 (1.4%)	0.1	1 (1.3%)	0.0
Dyspnoea	2 (1.8%)	8 (7.6%)	5.8	1 (0.9%)	-0.9	3 (2.3%)	10 (7.8%)	5.5	3 (2.3%)	0.0	3 (4.1%)	1 (1.5%)	-2.6	0 (0.0%)	-4.1	3 (3.8%)	1 (1.4%)	-2.4	0 (0.0%)	-3.8
Anxiety	1 (0.9%)	7 (6.7%)	5.8	4 (3.6%)	2.7	1 (0.8%)	8 (6.2%)	5.4	5 (3.8%)	3.0	1 (1.4%)	0 (0.0%)	-1.4	1 (1.4%)	0.0	1 (1.3%)	0 (0.0%)	-1.3	1 (1.3%)	0.0
Weight Decreased	7 (6.1%)	10 (9.5%)	3.4	9 (8.2%)	2.1	9 (6.8%)	14 (10.9%)	4.1	13 (9.9%)	3.1	4 (5.4%)	3 (4.5%)	-0.9	7 (9.9%)	4.5	4 (5.0%)	3 (4.1%)	-0.9	7 (8.8%)	3.8
Dyspepsia	3 (2.6%)	6 (5.7%)	3.1	3 (2.7%)	0.1	4 (3.0%)	9 (7.0%)	4.0	3 (2.3%)	-0.7	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Diarrhoea	4 (3.5%)	10 (9.5%)	6.0	9 (8.2%)	4.7	5 (3.8%)	10 (7.8%)	4.0	11 (8.4%)	4.6	0 (0.0%)	2 (3.0%)	3.0	2 (2.8%)	2.8	0 (0.0%)	2 (2.7%)	2.7	2 (2.5%)	2.5
Fall	7 (6.1%)	10 (9.5%)	3.4	8 (7.3%)	1.2	7 (5.3%)	12 (9.3%)	4.0	9 (6.9%)	1.6	3 (4.1%)	2 (3.0%)	-1.1	0 (0.0%)	-4.1	3 (3.8%)	2 (2.7%)	-1.1	0 (0.0%)	-3.8
Abdominal Pain Upper	3 (2.6%)	8 (7.6%)	5.0	2 (1.8%)	-0.8	3 (2.3%)	8 (6.2%)	3.9	4 (3.1%)	0.8	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Blood Bilirubin Increased	1 (0.9%)	5 (4.8%)	3.9	0 (0.0%)	-0.9	1 (0.8%)	6 (4.7%)	3.9	0 (0.0%)	-0.8	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Rash	4 (3.5%)	9 (8.6%)	5.1	2 (1.8%)	-1.7	6 (4.5%)	10 (7.8%)	3.3	3 (2.3%)	-2.2	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Constipation	2 (1.8%)	4 (3.8%)	2.0	0 (0.0%)	-1.8	2 (1.5%)	6 (4.7%)	3.2	2 (1.5%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (1.4%)	1.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.3%)	1.3
Cystitis Bacterial	2 (1.8%)	4 (3.8%)	2.0	2 (1.8%)	0.0	2 (1.5%)	6 (4.7%)	3.2	3 (2.3%)	0.8	4 (5.4%)	2 (3.0%)	-2.4	0 (0.0%)	-5.4	4 (5.0%)	2 (2.7%)	-2.3	0 (0.0%)	-5.0
Urinary Tract Infection	2 (1.8%)	5 (4.8%)	3.0	4 (3.6%)	1.8	2 (1.5%)	6 (4.7%)	3.2	5 (3.8%)	2.3	0 (0.0%)	1 (1.5%)	1.5	2 (2.8%)	2.8	0 (0.0%)	1 (1.4%)	1.4	2 (2.5%)	2.5
Eyelid Oedema	0 (0.0%)	3 (2.9%)	2.9	0 (0.0%)	0.0	0 (0.0%)	4 (3.1%)	3.1	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Upper Respiratory Tract Infection	1 (0.9%)	3 (2.9%)	2.0	1 (0.9%)	0.0	1 (0.8%)	5 (3.9%)	3.1	2 (1.5%)	0.7	1 (1.4%)	0 (0.0%)	-1.4	0 (0.0%)	-1.4	1 (1.3%)	0 (0.0%)	-1.3	0 (0.0%)	-1.3
Cough	3 (2.6%)	7 (6.7%)	4.1	0 (0.0%)	-2.6	3 (2.3%)	7 (5.4%)	3.1	0 (0.0%)	-2.3	0 (0.0%)	1 (1.5%)	1.5	1 (1.4%)	1.4	0 (0.0%)	1 (1.4%)	1.4	1 (1.3%)	1.3
Rash Generalised	0 (0.0%)	4 (3.8%)	3.8	1 (0.9%)	0.9	0 (0.0%)	4 (3.1%)	3.1	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0

DEATHS

At the cut-off of 15 December 2016, there were 71 adverse events with fatal outcome reported in amyotrophic lateral sclerosis patients (ALS - study AB10015).

In ALS study (randomisation ratio 2:1), there were 54 fatal SAEs in masitinib arm and 17 fatal SAEs in placebo arm, all of them considered as not related to study medication (masitinib/placebo) by both investigator and sponsor. Seventeen (17) cases were reported with placebo arm and did not involve masitinib. Although acquired data possibly do not allow further causality conclusions, it is important to notice the asymmetry of deaths between masitinib treated patients (54 / 260 = 20.8%) and placebo patients (17/133 = 12.8%).

Events of special interest

Upon CHMP request, the MAA has performed a specific analysis of events of special concern, namely fractures / osteoporosis / hypophosphatemia, anaemia, weight loss and nausea.

Bone fractures / osteoporosis / hypophosphatemia

Frequency of bone fracture

The occurrence of bone fracture was comparable between the “Normal Progressor” and “Normal + Fast Progressor” populations. As such, analysis below is only provided for the “Normal + Fast Progressor” population, which incorporates the greater number of patients.

- Protocol period (W0-W48 period): During the protocol period, the frequency of bone fracture was moderately increased with masitinib 4.5 mg/kg/day but not with masitinib 3 mg/kg/day as compared with placebo. The frequency of bone fracture was 6.7% and 3.6% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 3.5% for placebo (delta with respect to placebo = +3.2% and +0.1%, respectively). When considering the causality, none of the cases of bone fracture were considered as suspected or not assessable bone fracture. There were two cases of severe bone fracture with masitinib 4.5 mg/kg/day, both considered as suspected or not assessable. There were four cases of serious bone fracture with masitinib 4.5 mg/kg/day, and one with placebo, none considered as suspected or not assessable.

- Extension period (>W48): During the extension period, the frequency of bone fracture was increased with masitinib 4.5 mg/kg/day as compared with placebo. The frequency of bone fracture was 7.0% and 3.8% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 3.8% for placebo (delta with respect to placebo = +3.2% and +0.0%, respectively). None of the cases were suspected or not assessable.

Frequency of osteoporosis

The occurrence of osteoporosis was comparable between the “Normal Progressor” and “Normal + Fast Progressor” populations. As such, analysis below is only provided for the “Normal + Fast Progressor” population, which incorporates the greater number of patients.

- Protocol period (W0-W48 period): During the protocol period, the frequency of osteoporosis was not increased with masitinib. The frequency of osteoporosis was 0.0% at the masitinib doses of 4.5 and 3.0 mg/kg/day, as compared with 0.0% for placebo.

- Extension period (>W48):During the extension period, there was one case of osteoporosis reported with masitinib 3 mg/kg/day. The frequency of osteoporosis was 0.0% and 1.3% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 0% for placebo (delta with respect to placebo = +0.0% and +1.3%, respectively). None of the cases were suspected or not assessable. When considering the causality, no case of osteoporosis was considered as suspected or not assessable osteoporosis.

Frequency of hypophosphataemia

The occurrence of hypophosphataemia was comparable between the “Normal Progressor” and “Normal + Fast Progressor” populations. As such, analysis below is only provided for the “Normal + Fast Progressor” population, which incorporates the greater number of patients.

- Protocol period (W0-W48 period): During the protocol period, the frequency of hypophosphataemia was comparable between the treatment arms. The frequency of hypophosphataemia was 0.8% and 0.0% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 0% for placebo. The case of hypophosphataemia reported with masitinib 4.5 mg/kg/day was severe and was considered as suspected or not assessable. There was no case of serious hypophosphataemia.

- Extension period (>W48): During the extension period, there was no case of hypophosphataemia.

Impact of bone fracture on efficacy

There were very few patients with bone fracture, which make the interpretation difficult, especially given the variability in ALSFRS-S score. In patients with bone fracture, the deterioration in ALSFRS-R score was greater than in patients without bone fracture, suggesting a negative impact of this AE on functional score. In patients with bone fracture, there was a numerical disadvantage for masitinib in terms of change in ALSFRS-R score, except in the normal + faster progressor with masitinib 4.5 mg/kg/day where there was an advantage. This situation is however difficult to interpret due to the limited number of patients with bone fracture

Anaemia

The occurrence of anemia was comparable between the “Normal Progressor” and “Normal + Fast Progressor” populations. As such, analysis below is only provided for the “Normal + Fast Progressor” population, which incorporates the greater number of patients.

- Protocol period (W0-W48 period): During the protocol period, the frequency of anemia was increased with masitinib 4.5 mg/kg/day and moderately increased with masitinib 3 mg/kg/day as compared with placebo. The frequency of anemia was 15.5% and 6.9% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 3.0% for placebo (delta with respect to placebo = +12.5% and +3.9%, respectively). Increase in anemia with masitinib as compared with placebo was primarily due to iron deficiency. When considering the causality, the frequency of anemia was increased with masitinib 4.5 mg/kg/day, but not with masitinib 3 mg/kg/day as compared with placebo. The frequency of suspected or not assessable anemia was 10.1% and 1.5% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 1.5% for placebo (delta with respect to placebo = +8.6% and +0.0%, respectively). There were two cases of severe anemia with masitinib 4.5 mg/kg/day and two cases of severe anemia with 3.0 mg/kg/day. For one patient, the hemoglobin (Hb) count did not confirm Hb results<8g/dL justifying grade severe. There were also two cases of anemia reported as SAEs, one with masitinib 4.5 mg/kg/day and one with masitinib 3.0 mg/kg/day. In both case, the causality of masitinib was considered as not related or not assessable by the investigator. Two patients (1.6%) receiving masitinib 4.5 mg/kg/day discontinued treatment due to severe anemia. The median time of occurrence of anemia ranged between 27 and 40 days in the masitinib treatment-arms, versus 37 days in the placebo arm.

- Extension period (>W48): During the extension period, there was no increase in anemia with masitinib. The frequency of anemia was 3.0% and 2.8% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 2.7% for placebo (delta with respect to placebo = +0.3% and +0.1%, respectively). None of the cases were suspected or not assessable.

Impact of anaemia on efficacy

In patients with aneamia, the deterioration in ALSFRS-R score was greater than in patients without aneamia, suggesting a negative impact of this AE on functional score.

Weight loss

The occurrence of weight loss was comparable between the “Normal Progressor” and “Normal + Fast Progressor” populations. As such, analysis below is only provided for the “Normal + Fast Progressor” population, which incorporates the greater number of patients.

- Protocol period (W0-W48 period): During the protocol period, the frequency of weight loss was moderately increased with masitinib 4.5 and 3 mg/kg/day as compared with placebo. The frequency of weight loss was 10.9% and 9.9% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 6.8% for placebo (delta with respect to placebo = +4.1% and +3.1%, respectively). When considering the causality, the frequency of suspected or not assessable weight loss similar between the treatment arms. It was 0% at the masitinib doses of 4.5 and 3.0 mg/kg/day as compared with 0.0% for placebo. There was no one case of severe weight loss with masitinib of 4.5 mg/kg/day and one with masitinib of 3 mg/kg/day, versus none with placebo. There were also two cases (1.6%) of weight loss reported as a SAE with masitinib of 4.5 mg/kg/day and 3 cases (2.3%) with masitinib of 3 mg/kg/day, versus one case (0.8%) with placebo. None of these SAEs were considered as suspected or not assessable. The cases of weight loss severe and serious reported in patients treated with masitinib (and placebo) were related to difficulty in eating due to disease progression. In almost all cases, the weight decrease was associated with a gastrostomy for nutritional support.

- Extension period (>W48): During the extension period, the frequency of weight loss was 4.1% and 8.8%% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 5.0% for placebo (delta with respect to placebo = -0.9% and +3.3%, respectively). One case with masitinib 4.5 mg/kg/day was severe. None of these cases were reported as serious AEs.

Impact of weight loss on efficacy

In patients with weight loss, the deterioration in ALSFRS-R score was greater than in patients without weight loss, suggesting a negative impact of this AE on functional score.

Nausea

The occurrence of nausea was comparable between the “Normal Progressor” and “Normal + Fast Progressor” populations. As such, analysis below is only provided for the “Normal + Fast Progressor” population, which incorporates the greater number of patients.

- Protocol period (W0-W48 period): During the protocol period, the frequency of nausea was increased with masitinib 4.5 mg/kg/day and not with masitinib 3 mg/kg/day as compared with placebo. The frequency of nausea was 11.6% and 6.1% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 4.5% for placebo (delta with respect to placebo = +7.1% and +1.6%, respectively). When considering the causality, the frequency of suspected or not assessable nausea was 8.5% and 4.6% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 2.3% for placebo (delta with respect to placebo = +6.2% and +2.3%, respectively). There was no case of severe nausea. There was also no case of nausea reported as a SAE. One patient receiving masitinib 4.5 mg/kg/day discontinued treatment due to a moderate nausea.

- Extension period (>W48): During the extension period, there was one case of nausea with masitinib 3.0 mg/kg/day.

Of all the events of special interest, nausea is highlighted among other factors affecting masitinib safety. Bone fractures, anaemia and weight loss apparently have an impact on efficacy as measured by ALSFRS-R.

Laboratory findings

There were abnormal biochemistry values associated to masitinib in ALS during the 48 week treatment period:

- Alanine aminotransferase

Masitinib had an effect on alanine aminotransferase.

Among the “Normal + Fast Progressor” patients tested for high abnormal ALT level and with a normal level of ALT at baseline, 48.6% in the masitinib 4.5 mg/kg/day arm and 36.7% in the masitinib 3 mg/kg/day arm versus 26.1% in the placebo arm presented with a high level of grade 1 as worst grade. None in the masitinib 4.5 mg/kg/day arm or 2.0% masitinib 3 mg/kg/day arm versus none in the placebo arm presented with a high level of grade 2. 2.7% in the masitinib 4.5 mg/kg/day arm and 2.0% in the masitinib 3 mg/kg/day arm versus none in the placebo arm presented with a high level of grade 3.

- Aspartate aminotransferase

Masitinib had a slight effect on AST level.

Among the “Normal + Fast Progressor” patients tested for high abnormal AST level and with a normal level of AST at baseline, 62.5% in the masitinib 4.5 mg/kg/day arm and 35.8% in the masitinib 3 mg/kg/day arm versus 16.4% in the placebo arm presented with a high level of grade 1 as worst grade. None in the masitinib 4.5 mg/kg/day arm and 3.8% in the masitinib 3 mg/kg/day arm versus none in the placebo arm presented with a high level of grade 2. 2.1% in the masitinib 4.5 mg/kg/day arm and none in the masitinib 3 mg/kg/day arm versus 3.6% in the placebo arm presented with a high level of grade 3.

- Bilirubin

Masitinib had a slight effect on Bilirubin.

Among the “Normal + Fast Progressor” patients tested for high bilirubin level and with a normal level of bilirubin at baseline, 30.2% in the masitinib 4.5 mg/kg/day arm and 18.6% in the masitinib 3 mg/kg/day arm versus 8.9% in the placebo arm presented with a high level of grade 1 as worst grade. 3.8% in the masitinib 4.5 mg/kg/day arm and 10.2% masitinib 3 mg/kg/day arm versus 5.4 in the placebo arm presented with a high level of grade 2. 2.1% in the masitinib 4.5 mg/kg/day arm and none in the masitinib 3 mg/kg/day arm versus 1.9% in the masitinib 4.5 mg/kg/day arm presented with a high level of grade 3.

Among the “Normal + Fast Progressor” patients tested for low abnormal phosphate level and with a normal level of phosphate at baseline, 3.4% in the masitinib 4.5 mg/kg/day arm and 8.3% in the masitinib 3 mg/kg/day arm versus none in the placebo arm presented with a low level of grade 1 as worst grade. 16.9% in the masitinib 4.5 mg/kg/day arm and 3.3% in the masitinib 3 mg/kg/day arm versus 4.9% in the placebo arm presented with a low level of grade 2.

- Biochemistry parameters not impacted with masitinib

Masitinib had no effect on albumin level, alkaline phosphatase level, calcium level, cholesterol level, creatinine level, Gamma GT level, glucose level, potassium level, sodium level, and triglycerides level.

Abnormal blood cell counts

There were abnormal blood cell counts in Masitinib in ALS:

- Hemoglobin

Masitinib had a slight effect on hemoglobin count.

Among the “Normal + Fast Progressor” patients tested for high abnormal hemoglobin level and with a normal level of hemoglobin at baseline, 50.0% in the masitinib 4.5 mg/kg/day arm and 30.0% in the masitinib 3 mg/kg/day arm versus 26.6% in the placebo arm presented with a high level of grade 1 as worst grade, and 3.2% in the masitinib 4.5 mg/kg/day arm and 3.3% in the masitinib 3 mg/kg/day arm versus 3.1% in the placebo arm presented with a high level of grade 2.

Among the “Normal + Fast Progressor” patients tested for low abnormal hemoglobin level and with a normal level of hemoglobin at baseline, 54.4% in the masitinib 4.5 mg/kg/day arm and 31.0% in the masitinib 3 mg/kg/day arm versus 27.9% in the placebo arm presented with a high level of grade 1 as worst grade, and 3.5% in the masitinib 4.5 mg/kg/day arm and 3.4% in the masitinib 3 mg/kg/day arm versus 3.3% in the placebo arm presented with a low level of grade 2.

- Leucocytes

Masitinib had a slight effect on leucocytes count.

Among the “Normal + Fast Progressor” patients tested for high abnormal leucocytes level and with a normal level of leucocytes at baseline, 26.6% in the masitinib 4.5 mg/kg/day arm and 15.9% in the masitinib 3 mg/kg/day arm versus 10.8% in the placebo arm presented with a high level of grade 1 as worst grade, and none in the masitinib 4.5 mg/kg/day arm or 3.3% masitinib 3 mg/kg/day arm versus 1.5% in the placebo arm presented with a high level of grade 2.

Among the “Normal + Fast Progressor” patients tested for low abnormal leucocytes level and with a normal level of leucocytes at baseline, 27.0% in the masitinib 4.5 mg/kg/day arm and 16.4% in the masitinib 3 mg/kg/day arm versus 11.3% in the placebo arm presented with a high level of grade 1 as worst grade, and none in the masitinib 4.5 mg/kg/day arm or 3.3% masitinib 3 mg/kg/day arm versus 1.6% in the placebo arm presented with a low level of grade 2.

- Lymphocytes

Masitinib had a slight effect on lymphocytes count.

Among the “Normal + Fast Progressor” patients tested for high abnormal lymphocytes level and with a normal level of lymphocytes at baseline, 17.5% in the masitinib 4.5 mg/kg/day arm and 22.6% in the masitinib 3 mg/kg/day arm versus 7.7% in the placebo arm presented with a high level of grade 1 as worst grade, and 14.3% in the masitinib 4.5 mg/kg/day arm and 8.1% in the masitinib 3 mg/kg/day arm versus 6.2% in the placebo arm presented with a high level of grade 2.

Among the “Normal + Fast Progressor” patients tested for low abnormal lymphocytes level and with a normal level of lymphocytes at baseline, 19.0% in the masitinib 4.5 mg/kg/day arm and 23.0% in the masitinib 3 mg/kg/day arm versus 7.9% in the placebo arm presented with a high level of grade 1 as worst grade, and 15.5% in the masitinib 4.5 mg/kg/day arm and 8.2% in the masitinib 3 mg/kg/day arm versus 6.3% in the placebo arm presented with a low level of grade 2.

- Neutrophils

Masitinib had a slight effect on neutrophil count.

Among the “Normal + Fast Progressor” patients tested for low abnormal neutrophil level and with a normal level of neutrophil at baseline, 14.1% in the masitinib 4.5 mg/kg/day arm and 6.5% in the masitinib 3 mg/kg/day arm versus 3.1% in the placebo arm presented with a high level of grade 1 as worst grade, and 1.6% in the masitinib 4.5 mg/kg/day arm and 3.2% in the masitinib 3 mg/kg/day arm versus 1.6% in the placebo arm presented with a low level of grade 2.

One grade 4 neutropenia was reported in the masitinib 3 mg/kg/day arm, but the case was however doubtful. The patient continued treatment and the AE was resolved under treatment.

As for platelets, masitinib had no effect on platelets count.

Vital signs, Physical Findings and Other Observations Related to Safety

For vital signs analysis, only patients with normal values at baseline and having at least one value available post baseline were considered as patients with vital sign e.g. systolic and diastolic blood pressures "normal at baseline". Patients with normal vital signs at baseline but without any value after baseline were excluded from the analysis.

Analysis of systolic, diastolic blood pressure change and heart rate

Masitinib had no effect on systolic, diastolic blood pressure and heart rate.

There was no assessment on weight loss or weight change during the trial, and how this might correlate with patient adverse events and response.

Pregnant and breast-feeding women

There were no pregnant patients enrolled in any study across the clinical development of masitinib. However, 2 female patients became pregnant during treatment: One female patient in study AB06006 (Mastocytosis, patient 16202) discovered that she was pregnant about 1 month after the last intake of study treatment, however this patient was found to be administered the placebo. One female patient in study AB04010 (Mastocytosis, patient 1211) became pregnant in September 6, 2006 despite hormonal contraception. On September 24, 2006 an abortion was performed and study drug was maintained. It is not well established whether the pregnancy is related to the failure of the contraception methods used.

There were no reported cases of women breast-feeding in any masitinib-tested clinical trial.

Renal impaired patient

In all masitinib-tested clinical trials, patients were considered to have renal impairment if the blood creatinine level was > 120 µmol/L at baseline.

In the clinical development of masitinib, there were 2 patient exposed to masitinib treatment with renal impairment. There were no renal impaired patients enrolled in the ALS phase 2/3 study.

There were no ALS patients exposed to masitinib with renal impairment. In non-oncology studies, there were 2 patients with renal impairment exposed to masitinib. Patients were considered to have renal impairment if their baseline blood creatinine was > 120 µmol/L. Considering the small sample size, no relevant analysis of the data could be performed.

No independent study was conducted specifically in patients with renal disorders with masitinib.

Hepatic impaired patient

No study was conducted specifically in patient with hepatic disorders with masitinib. However, the safety profile of masitinib was assessed in patients with and without hepatic disorders.

Patient was considered hepatic impaired if he has a baseline blood Aspartate aminotransferase (AST)>126 IU/L, or Alanine aminotransferase (ALT)>180 IU/L or Bilirubin>25.65 µmol/L or Gamma-Glutamyl transferase (GGT>) 150 IU/L.

There were 7 “Normal + Fast Progressor” ALS patients (6 patients at a dose of 4.5 mg/kg/day and 1 patient at 3.0 mg/kg/day) and 9 non-oncology patients (6 patients at a dose of 4.5 mg/kg/day and 3 patient at 3.0 mg/kg/day) exposed to masitinib with hepatic impairment. A comparative analysis on this patient population is provided hereafter. However, this analysis should be regarded as preliminary to identify possible trends in the data but not conclusive due to the small sample size.

In ALS patients, at a dose of 4.5 mg/kg/day, a higher frequency of all AEs (100% vs 82.5%), SAEs (33.3% vs 21.1%) and AEs leading to discontinuation (33.3% vs 14.0%) were reported in patients with hepatic impairment compared to without hepatic impairment. A frequency of severe AEs was higher in patients without hepatic impairment (16.7% vs 28.1%).

Immunological events

The applicant has not performed a detailed analysis on immunological events.

Safety related to drug-drug interactions and other interactions

No cases of drug-drug interactions were reported by investigators in study AB10015. Similarly, there were no cases of drug-drug interactions in all non-oncological studies.

To identify any risk related to drug interactions, several in vitro studies were conducted with masitinib mesilate (AB1010) in order to evaluate protein binding, hepatic metabolism and potential for drug-drug interactions. The results of these studies showed that:

- AB1010 had a high binding capacity to plasma protein in humans (93.93%).

- AB1010 was metabolized in several metabolites (MET 1 to MET 3) and AB3280 as major metabolite.

- AB1010 was metabolized primarily by cytochrome P450 3A4 (CYP3A4), with a minor contribution of CYP2C8 (biotransformation ratio = 18.9% at 5 µM) and CYP2C8 was partly involved in the formation of AB3280 (AB3280 formation ratio = 7.0% at 5 µM).

- AB1010 was a weak to moderate inhibitor of the CYP3A4/5 and CYP2C9, as well as CYP2D6 with IC50 values of 14, 20 and > 30 µM, respectively. This inhibition was partly reversible.

- AB1010 did not increase the activity of CYP3A4/5, CYP2C9 and 2C19 but slightly increase CYP1A2 activity. AB1010 did not affect the mRNA of CYPs 1A2, 2B6 and 3A4/5.

- At lower concentrations (<10 µM), AB1010 appeared to be a substrate of P-gp mediated transport while at higher concentrations (≥10 µM), AB1010 appeared to be an inhibitor of P-gp mediated transport which is likely to be due to saturation of P-gp-mediated efflux.

- AB1010 was a weak inhibitor of OATP1B1 (IC50 not reached) and a slight inhibitor towards OATP1B3 (IC50 of 130 µM).

- AB1010 was found not to be an OATP1B1 or OATP1B3 substrate.

- AB1010 was a strong inhibitor of human BCRP with a calculated IC50 of 0.7 µM.

- AB1010 was an inhibitor of OCT2 (IC50 of 16.9 µM ± 2.1 µM) and a slight inhibitor of OAT1 and OAT2 (IC50 >100 µM for both).

In a clinical study conducted in healthy volunteers (Study AB14004), there was a significant increase in exposure to masitinib in healthy subjects when it was co-administered with itraconazole, a CYP3A4 inhibitor and P-gp inhibitor (the mean Cmax and AUCt of masitinib rose by 26% and 41.6%, respectively). The exposure to the main active metabolite of masitinib (AB3280) was significant increased but less than the exposure to masitinib (the mean Cmax and AUCt of masitinib rose by 11% and 34.8%, respectively).

In summary,

- The plasma concentration of masitinib could thus be increased in a concomitant intake of CYP3A4 or P-gp inhibitor. So caution should be taken when administering masitinib with an inhibitor of CYP3A4 or P-gp.

- The plasma concentration of masitinib could be reduced in a concomitant intake of CYP3A4 inducer. The dose intended for the registration is 4.5 mg/kg/day which can cover the necessary mechanisms of action of the drug candidate. Even if the plasma concentration of masitinib is reduced, a dose at 3 mg/kg/day remains active against mast cells (inhibition of c-Kit with this dosage).

Discontinuation due to AES

Adverse events leading to permanent discontinuation.

The table below presents the frequency of the AEs leading to permanent discontinuation during the protocol period and during the extension phase of the study.

Table 38 Frequency of AE leading to permanent discontinuation by SOC / PT

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
	P	*M4.5*		*M3*		*P*	*M4.5*		*M3*		*P*	*M4.5*		*M3*		*P*	*M4.5*		*M3*	
System Organ Class/Preferred Term	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
At least one non fatal AE leading to study drug permanent discontinuation	**9 (7.9%)**	**18 (17.1%)**	**9.2**	**16 (14.5%)**	**6.7**	**12 (9.0%)**	**21 (16.3%)**	**7.3**	**21 (16.0%)**	**7.0**	**2 (2.7%)**	**6 (9.1%)**	**6.4**	**1 (1.4%)**	**-1.3**	**2 (2.5%)**	**6 (8.2%)**	**5.7**	**1 (1.3%)**	**-1.3**
Blood And Lymphatic System Disorders	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**2 (1.6%)**	**1.6**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Anaemia Vitamin B12 Deficiency	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Normochromic Normocytic Anaemia	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Microcytic Anaemia	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Cardiac Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (0.9%)**	**0.9**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Cardio Respiratory Arrest	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
	P	M4.5		M3		P	M4.5		M3		P	M4.5		M3		P	M4.5		M3	
System Organ Class/Preferred Term	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
Ear And Labyrinth Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Eye Disorders	**0 (0.0%)**	**2 (1.9%)**	**1.9**	**1 (0.9%)**	**0.9**	**0 (0.0%)**	**2 (1.6%)**	**1.6**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Periorbital Oedema	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Eye Irritation	0 (0.0%)	1 (1.0%)	1.0	1 (0.9%)	0.9	0 (0.0%)	1 (0.8%)	0.8	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Gastrointestinal Disorders	**4 (3.5%)**	**4 (3.8%)**	**0.3**	**7 (6.4%)**	**2.9**	**6 (4.5%)**	**4 (3.1%)**	**-1.4**	**9 (6.9%)**	**2.4**	**1 (1.4%)**	**2 (3.0%)**	**1.7**	**0 (0.0%)**	**-1.4**	**1 (1.3%)**	**2 (2.7%)**	**1.5**	**0 (0.0%)**	**-1.3**
Dysphagia	4 (3.5%)	3 (2.9%)	-0.7	4 (3.6%)	0.1	6 (4.5%)	3 (2.3%)	-2.2	5 (3.8%)	-0.7	1 (1.4%)	2 (3.0%)	1.7	0 (0.0%)	-1.4	1 (1.3%)	2 (2.7%)	1.5	0 (0.0%)	-1.3
Nausea	0 (0.0%)	1 (1.0%)	1.0	1 (0.9%)	0.9	0 (0.0%)	1 (0.8%)	0.8	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Pancreatitis	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Constipation	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Abdominal Pain Upper	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
General Disorders And Administration Site Conditions	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**1 (0.8%)**	**0.8**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Oedema Peripheral	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Hepatobiliary Disorders	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**2 (1.8%)**	**1.8**	**0 (0.0%)**	**1 (0.8%)**	**0.8**	**2 (1.5%)**	**1.5**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Liver Disorder	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Jaundice	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Cholecystitis	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Immune System Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Infections And Infestations	**0 (0.0%)**	**2 (1.9%)**	**1.9**	**0 (0.0%)**	**0.0**	**1 (0.8%)**	**3 (2.3%)**	**1.6**	**0 (0.0%)**	**-0.8**	**1 (1.4%)**	**5 (7.6%)**	**6.2**	**0 (0.0%)**	**-1.4**	**1 (1.3%)**	**5 (6.8%)**	**5.6**	**0 (0.0%)**	**-1.3**
Pneumonia Viral	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	2 (3.0%)	3.0	0 (0.0%)	0.0	0 (0.0%)	2 (2.7%)	2.7	0 (0.0%)	0.0
Pneumonia	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (1.4%)	2 (3.0%)	1.7	0 (0.0%)	-1.4	1 (1.3%)	2 (2.7%)	1.5	0 (0.0%)	-1.3
Urinary Tract Infection	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Oropharyngeal Candidiasis	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Oral Candidiasis	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Infection	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Upper Respiratory Tract Infection	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Respiratory Tract Infection	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Injury Poisoning And Procedural Complications	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Investigations	**1 (0.9%)**	**2 (1.9%)**	**1.0**	**3 (2.7%)**	**1.9**	**1 (0.8%)**	**2 (1.6%)**	**0.8**	**5 (3.8%)**	**3.1**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Transaminases Increased	0 (0.0%)	2 (1.9%)	1.9	0 (0.0%)	0.0	0 (0.0%)	2 (1.6%)	1.6	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Weight Decreased	0 (0.0%)	0 (0.0%)	0.0	3 (2.7%)	2.7	0 (0.0%)	0 (0.0%)	0.0	4 (3.1%)	3.1	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Platelet Count Decreased	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Haematocrit Increased	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Metabolism And Nutrition Disorders	**1 (0.9%)**	**0 (0.0%)**	**-0.9**	**0 (0.0%)**	**-0.9**	**1 (0.8%)**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Dehydration	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Musculoskeletal And Connective	**2 (1.8%)**	**1 (1.0%)**	**-0.8**	**0 (0.0%)**	**-1.8**	**2 (1.5%)**	**1 (0.8%)**	**-0.7**	**0 (0.0%)**	**-1.5**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (1.4%)**	**1.4**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (1.3%)**	**1.3**

	W0 TO W48										EXTENSION PERIOD									
	NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR					NORMAL PROGRESSOR					NORMAL + FAST PROGRESSOR				
	P	M4.5		M3		P	M4.5		M3		P	M4.5		M3		P	M4.5		M3	
System Organ Class/Preferred Term	*(N=114)*	*(N=105)*	*(M4.5 - P)*	*(N=110)*	*(M3 - P)*	*(N=133)*	*(N=129)*	*(M4.5 - P)*	*(N=131)*	*(M3 - P)*	*(N=74)*	*(N=66)*	*(M4.5 - P)*	*(N=71)*	*(M3 - P)*	*(N=80)*	*(N=73)*	*(M4.5 - P)*	*(N=80)*	*(M3 - P)*
Muscular Weakness	2 (1.8%)	1 (1.0%)	-0.8	0 (0.0%)	-1.8	2 (1.5%)	1 (0.8%)	-0.7	0 (0.0%)	-1.5	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Muscle Atrophy	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	1 (1.4%)	1.4	0 (0.0%)	0 (0.0%)	0.0	1 (1.3%)	1.3
Neoplasms Benign Malignant And Unspecified (Incl Cysts And Polyps)	**1 (0.9%)**	**1 (1.0%)**	**0.1**	**0 (0.0%)**	**-0.9**	**1 (0.8%)**	**1 (0.8%)**	**0.0**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Transitional Cell Carcinoma	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Invasive Ductal Breast Carcinoma	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Nervous System Disorders	**0 (0.0%)**	**1 (1.0%)**	**1.0**	**2 (1.8%)**	**1.8**	**0 (0.0%)**	**1 (0.8%)**	**0.8**	**2 (1.5%)**	**1.5**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Amyotrophic Lateral Sclerosis	0 (0.0%)	1 (1.0%)	1.0	1 (0.9%)	0.9	0 (0.0%)	1 (0.8%)	0.8	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Myoclonic Epilepsy	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Brain Oedema	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Psychiatric Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**1 (0.9%)**	**0.9**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**2 (1.5%)**	**1.5**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Anxiety	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	2 (1.5%)	1.5	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Renal And Urinary Disorders	**1 (0.9%)**	**0 (0.0%)**	**-0.9**	**0 (0.0%)**	**-0.9**	**1 (0.8%)**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Haematuria	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Reproductive System And Breast Disorders	**1 (0.9%)**	**0 (0.0%)**	**-0.9**	**0 (0.0%)**	**-0.9**	**1 (0.8%)**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**-0.8**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Amenorrhoea	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Respiratory Thoracic And Mediastinal Disorders	**1 (0.9%)**	**0 (0.0%)**	**-0.9**	**3 (2.7%)**	**1.9**	**2 (1.5%)**	**1 (0.8%)**	**-0.7**	**4 (3.1%)**	**1.5**	**1 (1.4%)**	**1 (1.5%)**	**0.2**	**0 (0.0%)**	**-1.4**	**1 (1.3%)**	**1 (1.4%)**	**0.1**	**0 (0.0%)**	**-1.3**
Respiratory Distress	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	1 (1.5%)	1.5	0 (0.0%)	0.0	0 (0.0%)	1 (1.4%)	1.4	0 (0.0%)	0.0
Respiratory Failure	0 (0.0%)	0 (0.0%)	0.0	2 (1.8%)	1.8	1 (0.8%)	1 (0.8%)	0.0	3 (2.3%)	1.5	1 (1.4%)	0 (0.0%)	-1.4	0 (0.0%)	-1.4	1 (1.3%)	0 (0.0%)	-1.3	0 (0.0%)	-1.3
Increased Bronchial Secretion	1 (0.9%)	0 (0.0%)	-0.9	0 (0.0%)	-0.9	1 (0.8%)	0 (0.0%)	-0.8	0 (0.0%)	-0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Dyspnoea	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Skin And Subcutaneous Tissue Disorders	**0 (0.0%)**	**6 (5.7%)**	**5.7**	**3 (2.7%)**	**2.7**	**0 (0.0%)**	**6 (4.7%)**	**4.7**	**3 (2.3%)**	**2.3**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Urticaria	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Skin Toxicity	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Rash Pruritic	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Rash Maculo Papular	0 (0.0%)	1 (1.0%)	1.0	2 (1.8%)	1.8	0 (0.0%)	1 (0.8%)	0.8	2 (1.5%)	1.5	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Rash Generalised	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Rash	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Pruritus Generalised	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Drug Eruption	0 (0.0%)	1 (1.0%)	1.0	0 (0.0%)	0.0	0 (0.0%)	1 (0.8%)	0.8	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Drug Reaction With Eosinophilia And Systemic Symptoms	0 (0.0%)	0 (0.0%)	0.0	1 (0.9%)	0.9	0 (0.0%)	0 (0.0%)	0.0	1 (0.8%)	0.8	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0	0 (0.0%)	0 (0.0%)	0.0	0 (0.0%)	0.0
Surgical And Medical Procedures	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**
Vascular Disorders	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0 (0.0%)**	**0.0**	**0 (0.0%)**	**0.0**

During the protocol period, the frequency of AEs leading to permanent treatment discontinuation was slightly increased at a masitinib dose of 4.5 mg/kg/day and at a masitinib dose of 3 mg/kg/day, regardless of the population.

- In the “Normal Progressor” population, the frequency of AEs leading to permanent discontinuation was 17.1% at a masitinib dose of 4.5 mg/kg/day as compared with 7.9% for placebo (corresponding to a delta of +9.2% with respect to placebo), and the frequency of AEs leading to permanent discontinuation was 14.5% at a masitinib dose of 3 mg/kg/day (corresponding to a delta of +6.7% with respect to placebo).
- In the “Normal + Fast Progressor” population, the frequency of AEs leading to permanent discontinuation was 16.3% at a masitinib dose of 4.5 mg/kg/day as compared with 9.0% for placebo (corresponding to a delta of +7.3% with respect to placebo), and the frequency of AEs leading to permanent discontinuation was 16% at a masitinib dose of 3 mg/kg/day (corresponding to a delta of +7% with respect to placebo).

The most frequent AEs leading to permanent discontinuation with masitinib as compared with placebo were Skin and Subcutaneous Tissue Disorders, followed by gastrointestinal disorders, investigations and Blood and Lymphatic System disorders (anemia)..

During the extension period, the frequency of AEs leading to permanent treatment discontinuation was slightly increased with masitinib 4.5 mg/kg/day compared to placebo, and was decreased for the masitinib 3 mg/kg/day treatment-arm when compared with the placebo arm, regardless of the population.

- In the “Normal Progressor” population, the frequency of AEs leading to permanent discontinuation was 9.1% at a masitinib dose of 4.5 mg/kg/day as compared with 2.7% for placebo (corresponding to a delta of +6.4% with respect to placebo), and the frequency of AEs leading to permanent discontinuation was 1.4% at a masitinib dose of 3 mg/kg/day (corresponding to a delta of -1.3% with respect to placebo).
- In the “Normal + Fast Progressor” population, the frequency of AEs leading to permanent discontinuation was 8.2 % at a masitinib dose of 4.5 mg/kg/day as compared with 2.5% for placebo (corresponding to a delta of +5.7% with respect to placebo), and the frequency of AEs was 1.3% at a masitinib dose of 3 mg/kg/day (corresponding to a delta of -1.3% with respect to placebo).

The most frequent AEs leading to permanent discontinuation with masitinib 4.5 mg/kg/day as compared with placebo were infections and infestations and gastrointestinal disorders.

Adverse events leading to dose reduction

Protocol period (W0-W48 period):

During the protocol period, the frequency of AEs leading to dose reduction was increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo. The frequency of AEs leading to dose reduction was 12.4% and 2.3% at the masitinib doses of 4.5 and 3.0 mg/kg/day, respectively, as compared with 1.5% for placebo (delta with respect to placebo = +12.4 % and +0.8%, respectively).

The most frequent AEs leading to dose reduction with masitinib at a dose of 4.5 mg/kg/day as compared with placebo were gastrointestinal disorders, Skin and Subcutaneous Tissue Disorders, followed by Eye Disorders (oedema) and Blood,Lymphatic System Disorders (Iron Deficiency Anaemia and Anaemia Macrocytic) and investigations (weight decreased).

Extension period (>W48):

During the extension period, only 1 case of AEs leading to dose reduction was reported at a masitinib dose of 4.5 mg/kg/day.

2.6.1. Discussion on clinical safety

Safety databases and patient exposure

To support the MAA in the above claimed population, AB Science conducted one pivotal phase 2/3 study in patients with ALS (AB10015). Of all, in normal progressors 105 patients received masitinib at a dose of 4.5 mg/kg/day, 110 patients received masitinib at a dose of 3 mg/kg/day, and 114 patients received placebo. The mean treatment duration was 9.5 months (ranging from 0.3 to 11.7 months) in the masitinib 4.5 mg/kg/day arm, 9.1 months (ranging from 0.7 to 12.8 months) in the masitinib 3 mg/kg/day arm, and 9.8 months (ranging from 0.2 to 14.5 months) in the placebo arm. In Normal + Faster Progressors 129 patients received masitinib at a dose of 4.5 mg/kg/day, 131 patients received masitinib at a dose of 3 mg/kg/day, and 133 patients received placebo. The mean treatment duration was 9.1 months (ranging from 0.3 to 11.7 months) in the masitinib 4.5 mg/kg/day arm, 9.0 months (ranging from 0.7 to 12.8 months) in the masitinib 3 mg/kg/day arm, and 9.6 months (ranging from 0.2 to 14.5 months) in the placebo arm.

Adverse events

Very common adverse events:

The main very common AEs that were observed to be increased in the masitinib 4.5 mg/kg/day arm with respect to the placebo arm during the protocol period were the following; difference between treatment-arms expressed as ± delta (masitinib minus placebo):

- Nausea (+7.1%)

- Dysphagia (-0.4%)

Common adverse events:

The main common AEs that were observed to be increased in the masitinib 4.5 mg/kg/day arm with respect to the placebo arm during the protocol period were the following; difference between treatment-arms expressed as ± delta (masitinib minus placebo):

During the protocol period, common AEs having greatest positive difference of frequency between masitinib and placebo treatment-arms, regardless of the population and regardless of the dose, were: rash maculo-papular (+7.7%),, oedema peripheral (+6.3%), anxiety (+6.2%), weight decreased (+5.4%) and diarrhea (+4.1%)

AEs of special interest

The following events were among the most severe AEs occurring during the clinical development of masitinib: severe neutropenia, Rash, Steven-Johnson Syndrome (SJS) and Drug-Rash with Eosinophilia and Systemic symptoms (DRESS). Other AE of special interest are diarrhoea, oedemas, nausea, vomiting, hepatotoxicity, renal toxicity, cardiotoxicity. Risk of carcinogenicity has not been considered in the analysis as this is less relevant for the ALS patient population.

The AEs most increased during the protocol period for masitinib at 4.5 mg/kg/day were rash maculo-papular, nausea, respiratory failure, oedema peripheral, iron deficiency anaemia, dyspnoea and anxiety. For masitinib at 3 mg/kg/day, oedema peripheral, diarrhoea, respiratory failure, and rash maculo-papular.

Deaths and serious adverse events

Deaths:

In ALS study (randomisation ratio 2:1), there were 54 fatal SAEs in masitinib arm and 17 fatal SAEs in placebo arm, all of them considered as not related to study medication (masitinib/placebo) by both investigator and sponsor. Seventeen (17) cases were reported with placebo arm and did not involve masitinib. Although acquired data possibly do not allow further causality conclusions, it is important to notice the asymmetry of deaths between masitinib treated patients (54 / 260 = 20.8%) and placebo patients (17/133 = 12.8%).

SAE

During the protocol period, the frequency of SAE (any causality) was moderately increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo: -“Normal Progressor” 27.6% vs 16.7% for placebo and in the “Normal + Fast Progressor” 31% vs. 18% for placebo .

Discontinuation of treatment due to SAEs

During the protocol period, the frequency of AEs leading to permanent treatment discontinuation was slightly increased at a masitinib dose of 4.5 mg/kg/day and at a masitinib dose of 3 mg/kg/day, regardless of the population: “Normal Progressor” population 17.1% vs 7.9% for placebo ; “Normal + Fast Progressor” 16.3% vs. 9.0%.

Laboratory findings and vital signs

In ALS masitinib had an ALT, AST and bilirubin effect, increasing these values up to grade 3 severity. Masitinib had no effect on albumin level, alkaline phosphatase level, calcium level, cholesterol level, creatinine level, Gamma GT level, glucose level, potassium level, sodium level, and triglycerides level. Masitinib had an effect on hemoglobin count with decrease being more frequent than an increase in haemoglobin. Masitinib had a slight effect on leucocytes count with decrease being more frequent than an increase in white blood cells. The same holds for lymphocyte count.

There was no change in blood pressure or heart rate.

The MAA has provided a detailed analysis of the different types of neoplasm which have been identified - in preclinical studies and previous clinical masitinib trials - as possibly related to masitinib. In spite of bladder cancer still being a possible risk to masitinib and is still considered a possible related risk, there is no strong evidence that masitinib may induce neoplasms with clinical relevance in ALS patients.

Upon CHMP request, the MAA has performed a specific analysis of events of special concern, namely fractures / osteoporosis / hypophosphatemia, anaemia, weight loss and nausea. Of all these nausea is highlighted among other factors affecting masitinib safety. Bone fractures, anaemia and weight loss apparently have an impact on efficacy as measured by ALSFRS-R.

The method of assessment of the impact of an adverse event which requires time to produce an effect (anemia, weight loss) did not focus on patients who had the adverse event persistently throughout a significant period in the study, but on assessment episode. Including all patients who experienced one anemia episode or one decrease in haemoglobin will dilute the effect, as many persons with a slight effect on red blood cells may also be in the placebo arm and many which will not have a systemic impact will counteract the impact of those where the effect was more prolonged. The narratives which were presented also raise a significant concern on the reliability of the acquisition and registration of AEs. To this aspect, the inspection which was carried out also raised the same concerns on AEs, and other additional safety concerns on the study population:

Subject safety at risk:

- Very high number of protocol deviations related to inclusion/exclusion (I/E) criteria, safety tests (ECGs and laboratory analysis) and investigational product (IP) intake (overdose) identified for at least 20 subjects reviewed during the inspection at Dr. Delia Chaverri's site (this site randomized 106 subjects) and at least 12 subjects reviewed during the inspection at Dr. Conrado Estol's site (this site randomized 53 subjects).
- The appropriate conditions of the storage of the IP administered to the subjects could not be ensured according to the documentation reviewed. No monitoring of IMP conditions from site to the subjects).
- Deficiencies on the subject safety oversight. Delays on adverse events (AE) and serious adverse events (SAE) notification to the Sponsor and the consequently delay of the Sponsor safety assessment.

Reliability of the data analysis:

Safety: Safety data has been updated after the submission for obtaining marketing authorization and was not provided to the Agency or to inspectors. The Applicant has also shown difficulties dealing with CROs monitoring the trial. This has had a relevant impact in the conduct of the trial, with relevant issues remain on the robustness of the collected data. It is not the impact of the individual concerns that have been identified and corrected, but the impact of the problems that may not have been identified and that were not corrected that are also of concern.

2.6.2. Conclusions on the clinical safety

Based on the assessment of the submitted data, there were a high number of very common and common AEs reported in patients treated with masitinib and placebo. Many of these AEs are also coinciding with symptoms of the disease itself, and insufficient efforts have been made to discriminate both when possible.

Some of the known class effects of TKIs are also identified in patients treated with masitinib, such as skin toxicities, anaemia and hepatotoxicity.

In light of the intended chronic use of masitinib in this population with a reduced life expectancy, severe skin toxicities, are considered important safety concerns. Also relevant are anaemia and weight loss which impacts in overall strength and wellbeing, and the risk of bone fractures, which impact on decrease mobility and muscle exercise leading to increased wasting. Nausea also had a significant impact since it may contribute to faulty nutrition and increased mealtime duration, along with dysphagia.

Since the inclusion / exclusion criteria were prepared for a phase 2 study, patients with gastrostomy and tracheostomy were excluded. Patients with other comorbidities were also excluded, thus making this population very distant from real world ALS population, further increasing unknown risks.

The overall safety evaluation is, thus severely hampered by a number of limitations, i.e. the missing or poorly acquired data of the pivotal study AB10015 (e.g. with regard to details on dose reductions and concomitant treatments and impact thereof), several issues on the control of study medication and most important, the lack of reliability on the registering and monitoring of clinical data.

2.7. Risk Management Plan

Safety Specification

The applicant included the following safety concerns in the RMP version 3.0 (dated 13 February 2018):

Summary of safety concerns	
Important identified risks	Potentially life-threatening risk: • Severe neutropenia Risks frequently observed in ALS patients: • Anemia • Liver toxicity • Renal toxicity (proteinuria and creatinine increase) Risk frequently observed in non-oncology indications: • Severe skin toxicity
Important potential risks	Risks observed in preclinical studies but not confirmed in clinical studies: • Cardiac toxicity • Reproductive toxicity including embryotoxicity and teratogenicity • Carcinogenicity (bladder, uterine and thyroid cancers) Other risks: • SJS and DRESS • Drug-drug interactions (DDIs)
Missing information	• Use in pregnant or lactating women • Use in patients with transaminases > 3 x ULN and bilirubin > 1.5x ULN • Use in patients with creatinine clearance < 60 mL/min • Use in patients with proteinuria >30 mg/mL • Effect on fertility • Long-term efficacy and safety • Risk of fall and injury • Misuse of masitinib in patients with gastrostomy

Pharmacovigilance Plan

Ongoing and planned studies in the PhV development plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Category 3 *In vivo* pharmacokinetic drug interaction study with rifampicin	To evaluate pharmacokinetic drug interactions between rifampicin, a strong inducer of CYP 3A4, and masitinib	Important potential risk Drug-drug interactions with strong inducers of CYP3A4	Planned for post-authorization phase	Q1 2019
Category 3 Confirmatory phase 3 study in ALS	The objective is to compare the efficacy and safety of two treatment regimens of masitinib (starting dose of 3 mg/kg/day, and starting dose of 4.5 mg/kg/day) in combination with riluzole (50 mg bid) versus corresponding placebo in combination with riluzole (50 mg bid) in the treatment of patients diagnosed with ALS.	Confirm and support the data driven from the pivotal study AB10015	Planned Q1 2017	Planned Q1 2020

Risk minimisation measures for masitinib mesilate

Summary table of additional Risk Minimisation Measures

Safety Concern	Routine Risk minimization measures	Additional risk minimisation measures
Severe neutropenia	SPC sections: • Section 4.2 Posology and method of administration • Section 4.3	• Educational material for healthcare professionals • Patient card

	Contraindications • Section 4.4 Special warnings and precautions of use • Section 4.8 Undesirable effects • Section 5.3 Preclinical safety data • Package Leaflet sections: • Section 2 What you need to know before you use Alsitek • Section 4 Possible side effects Other routine risk minimization measures: • Not applicable	
Severe skin toxicitiy	SPC sections: • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions of use • Section 4.8 Undesirable effects Package Leaflet sections: • Section 2 What you need to know before you use Alsitek • Section 4 Possible side effects Other routine risk minimization measures: • Not applicable	• Educational material for healthcare professionals • Patient card
Stevens Johnson Syndrome (SJS) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	SPC sections: • Section 4.2 Posology and method of administration • Section 4.4 Special warnings and precautions of use • Section 4.8 Undesirable effects	• Educational material for healthcare professionals • Patient card

	Package Leaflet sections: • Section 2 What you need to know before you use Alsitek • Section 4 Possible side effects Other routine risk minimization measures: • Not applicable	

Conclusion

The CHMP and PRAC, having considered the data submitted in the application were 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

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.

Periodic Safety Update Reports submission requirements

Not applicable.

2.9. New Active Substance

The applicant compared the structure of masitinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers masitinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union. However, in light of the negative recommendation, the new active substance status is not applicable at this stage.

2.10. Product information

In light of the negative recommendation, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.10.1. 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 does not yet meet 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.*

2.10.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscular paralysis reflecting degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord [Wijesekera, 2009]. Incidence (average around 1/50,000 per year) and prevalence (average around 1/20,000) are relatively uniform in Western countries, although foci of higher frequency have been reported in the Western Pacific. The mean age of onset for sporadic ALS is about 60 years. Overall, there is a slight male preponderance (male to female ratio of around 1.5:1).

Approximately two thirds of patients with typical ALS have a spinal form of the disease (limb onset) and present with symptoms related to focal muscle weakness and wasting, in which onset of symptoms may start either distally or proximally in the upper and lower limbs. Gradually, spasticity may develop in the weakened atrophic limbs, affecting manual dexterity and gait. Patients with bulbar onset ALS usually present with dysarthria and dysphagia for solids or liquids. Limb symptoms can develop almost simultaneously with bulbar symptoms and in the vast majority of cases will occur within 1-2 years. Paralysis is progressive and leads to death due to respiratory failure within 2-3 years for bulbar onset cases and 3-5 years for limb onset ALS cases. Therefore, although the disease is heterogeneous, most patients die less than 3 years from symptom-onset [Gordon, 2013]. Approximately 60 % of patients have a predictable decline in function while the remainder die suddenly, sometimes from other causes.

Median survival for ALS is 2 to 4 years from onset; only 5–10% of patients survive beyond 10 years.

3.1.2. Available therapies and unmet medical need

Main treatment options

At the time of this application, riluzole remains the only approved disease-modifying medicinal product in EU, and confers a survival advantage of 2–3 months (as reflected in the published EPAR). There is no available treatment to stop or reverse the progressive course of ALS. There has been no advance in efficacy of available therapeutic agents over the last 20 years since the introduction of riluzole, and even in its product information it is stated that: "[…] riluzole does not demonstrate a positive effect on functional symptoms of the disease whilst the magnitude of the effect on survival is modest. There are therefore remaining uncertainties on the product in the management of amyotrophic lateral sclerosis" [EMA website, 2016].

Many symptomatic treatments, which do not slow disease progression but affect quality of life, appear helpful to individuals in clinic (Table 43 lists the various symptomatic treatments commonly used for management of ALS [Jenkins 2014]). However, evidence of benefit from those drugs is generally weak and further randomized clinical trials are required to provide a more robust evidence base. This opinion is reflected in a Cochrane systematic review of treatments for spasticity in ALS by Ashworth and colleagues (published in 2006 with update in 2011) [Ashworth 2006].

Table 39 Summary of symptomatic treatments commonly used in patients with ALS [adapted from Jenkins 2014]

Drug	Population indicated / Common usage
Baclofen (Lioresal)	Indicated for the relief of spasticity of voluntary muscle resulting from such disorders, for example, multiple sclerosis. In patients 0 to <18 years it is indicated for the symptomatic treatment of spasticity of cerebral origin, including ALS.
Hyoscine	Hypersalivation
Carbocisteine	Difficulty expectorating secretions
Amitriptyline	Neuropathic pain
Gabapentin	Neuropathic pain
Citalopram	Depression and emotional lability
Venlafaxine	Depression
Nortriptyline	Depression

As such it is clear that there is an unmet medical need for the treatment of ALS, either for delay in disability progression, or to affect the loss of function and extend survival.

3.1.3. Main clinical studies

The development program of masitinib in amyotrophic lateral sclerosis (ALS) was based on the following single, pivotal phase 2/3 study:

- A Phase 2/3 study AB10015: A prospective, multicentre, randomized, 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.

The applicant initially submitted the results from an interim analysis, and later in the procedure these were supplemented by the results of the final analysis of the study. Further analyses of the data, not provided at interim and final results' submissions, were requested by CHMP to clarify specific issues on efficacy and safety.

Four amendments were implemented during the running of the study, while the primary analysis hypothesis on the expected treatment effect (Δ3.3 points on ALSFRS-R) never changed. The most relevant protocol amendment was No. 3 when the distinction between patient populations of "Normal Progressor" and "Fast Progressor" was made. Hence, for study AB10015 two distinct ALS patient populations have been defined by the Applicant. The population of "Normal Progressors" was defined as ALS patients whose progression of ALSFRS-R score before randomization is less than 1.1 points per month. The population of "Fast Progressors" was defined as ALS patients whose progression of ALSFRS-R score before randomization is more than or equal to 1.1 points per month.

After amendment 4, patients were randomly allocated to one of the three following groups: Group 1: masitinib at 4.5 mg/kg/day + riluzole; Group 2: masitinib at 3 mg/kg/day + riluzole; Group 3: placebo of masitinib + riluzole. Patients received treatment for 48 week, with a possible extension.

The design of study AB10015 compared masitinib plus riluzole in association with standard of care symptomatic treatments against placebo plus riluzole in association with standard of care symptomatic treatments. The study protocol states that: "All medications taken by the patients at the onset of study and all medication given in addition to the Investigational Medicinal Product during the study are regarded as concomitant medications", and "All concomitant medications and/or therapies should be documented in the patient file and reported in the electronic Case Report Form". Hence, there was no restriction placed on the investigator's choice of standard of care symptomatic treatments (for example, physical therapy, surgical interventions, and alternative therapies).

The patient population included mild to moderate ALS patients, with few co-morbidities and co-medications, and as such excluded patients on gastrostomy.

3.2. Favourable effects

The data yielded several results that could be considered meaningful in this population:

At the time of the interim analysis of study AB10015, in "normal + fast progressors" at the dose of 4.5 mg/Kg/day, a difference of means of 4.2859 in absolute change from baseline to week 48 in ALSFRS-R score was registered [(1-alpha) confidence interval] of [0.1376;8.4343], Re-randomization P-value 0.0213]. In theory, this difference could be considered clinically meaningful, as it represents a level of deterioration that usually takes place in the space of several months in the ALS patients' lives.

Another potential benefit was registered in the investigation of the quality of life using the ALSAQ-40. There, an absolute change from baseline to week 48 in Quality of Life (ALSAQ-40) score yielded a difference of means of -12.5695 [(1-alpha) confidence interval] [-19.5392;-5.5998], with a P-value 0.0005. There was also a reported effect on FVC, with an absolute change from baseline to week 48 in FVC score a difference of means of 11.9284, [(1-alpha) confidence interval] [1.4633;22.3934], P-value 0.0144

At the time of the assessment of the final results, the primary analysis was performed first in the "Normal Progressor" population, testing patients randomized at an initial masitinib dose of 4.5 mg/kg/day (Group 1) versus placebo patients (Group 3). This analysis yielded a statistically significant difference in the ALSFRS-R score between masitinib and placebo (Difference of least-square means=3.39; p=0.0158), with an improvement of 27%, which could be considered relevant as it is in line with the 25% threshold defined for a clinically meaningful benefit in this situation[Castrillo-Viguera, 2010].

In the same "Normal progressor" population, in the secondary efficacy evaluation, median progression free survival (PFS) was increased by 4 months with masitinib (4.5 mg/kg/day) as compared with placebo treatment-arms, and this improvement was significant (p- value=0.0159), corresponding to a 25% increase. Additionally, a statistically significant difference was observed between masitinib (P=0.0078) and placebo treatment- arms in the Quality of life assessment (improvement between 42% and 46%), in the change from baseline in FVC, and in the CAFS score (difference = 8.91, p- value=0.2626) (see Section 2.5.2. for details).

3.3. Uncertainties and limitations about favourable effects

A high number of uncertainties were identified during the assessment of this application. The CHMP expressed serious concerns about the conduct of the trial, the applied methodology and the robustness of the data used to support the claim for a positive B/R ratio of Masitinib in ALS. Additionally, there were uncertainties related to the reported effects according to the final analysis of the presented results.

Despite the claims of the applicant that the development programme was performed according to the GCP principles, the CHMP conveyed significant concerns about the conduct of the single pivotal trial, used as a basis for this application. During the procedure a triggered GCP inspection was requested, in two centres which enrolled >40% of the total study population, and in light of the nature and relevance of the findings, and the observed systematic deficiencies, as a result of this inspection it was concluded that the data obtained at the inspected sites are not trustworthy enough to support the submitted marketing authorisation application for masitinib, and seriously affect the credibility of the data in the whole application.

Independently from the issues identified in the conduct of the clinical development, there were severe methodological issues acknowledged, which considerably undermined the robustness of the data and added to the uncertainties. Study AB10015 does not meet the criteria concerning data quality and absence of indications of potential bias. There were a number of amendments, transforming the initial phase 2 trial into a phase 3 pivotal trial, which lacked a proper documented and justified rationale. Examples include revising the statistical hypothesis testing strategy between study arms, the primary analysis population and the strategy for the imputation of missing data. Initially data from the two active treatment arms were to be pooled in the primary comparison with the placebo arm. This was subsequently changed to a primary comparison of the higher dose versus placebo. There is no pharmacological rationale to support this revised strategy. Furthermore, the protocol amendment dichotomising the included patients into 'normal' and 'fast' progressors is justified neither in clinical terms nor in relation to the pharmacology of masitinib. In the absence of these amendments the single pivotal study fails to show statistically significant results on its primary endpoint: for the "normal + fast progressor" population the absolute change from baseline to week 48 in ALSFRS-R between masitinib 4.5 mg/kg/day and placebo is 2.09 [-0.55;4.73], not reaching statistical significance (P = 0.1202). Moreover, an excess of patients withdrew from treatment because of lack of efficacy and adverse events on both treatment arms compared to placebo. The handling of missing data arising from patient withdrawals is likely to give rise to important bias in the estimated treatment effect that favours masitinib.

From the results presented at the time of the final analysis, the following other inconsistencies emerged:

- There was no benefit on survival with masitinib 4.5 mg/kg/day as compared with placebo even in the Applicant-defined "Normal progressor" population.
- In terms of survival, in the same population ("normal + fast progressor") masitinib failed to show an effect at the time of the final analysis.
- The 3mg/kg/day arm data demonstrated that there was a smaller trend of effect even in the "normal progressors" group, than the one observed for the 4.5 mg dose. Like in the case of the 4.5 mg dose, most endpoints did not reach statistical significance. In the "normal + fast progressor" population masitinib 3 mg/kg/day had an absolute change from baseline to week 48 in ALSFRS-R of 1.80 [-0.91;4.51], with a P-value of 0.1918.

Although two study populations were described (normal and fast progressors) the paradigm to discriminate them was not robust, and the evidence provided does not fully explain it. Furthermore the cut-off point was based on retrospective data, and would be subjective to the point that clinicians could disregard the condition of a fast progressor if retrospective data was not available. Therefore, only the total enrolled population should be considered when assessing efficacy.

3.4. Unfavourable effects

Very common adverse events:

The main very common AEs that were observed to be increased in the masitinib 4.5 mg/kg/day arm with respect to the placebo arm during the protocol period were the following;

- Nausea

- Dysphagia

Common adverse events:

The main common AEs that were observed to be increased in the masitinib 4.5 mg/kg/day arm with respect to the placebo arm during the protocol period were the following:

- rash maculo-papular
- oedema peripheral
- anxiety
- weight decreased
- diarrhoea

AEs of special interest

The following events were among the most severe AEs occurring during the clinical development of masitinib: severe neutropenia, Rash, Steven-Johnson Syndrome (SJS) and Drug-Rash with Eosinophilia and Systemic symptoms (DRESS). Other AE of special interest are diarrhoea, oedemas, nausea, vomiting, hepatotoxicity, renal toxicity, cardiotoxicity. Risk of carcinogenicity has not been considered in the analysis as this is less relevant for the ALS patient population. The AEs most increased during the protocol period for masitinib at 4.5 mg/kg/day were rash maculo-papular, nausea, respiratory failure, oedema peripheral, iron deficiency anaemia, dyspnoea and anxiety. For masitinib at 3 mg/kg/day, oedema peripheral, diarrhoea, respiratory failure, and rash maculo-papular.

Deaths:

In ALS study (randomisation ratio 2:1), there were 54 fatal SAEs in masitinib arm and 17 fatal SAEs in placebo arm, all of them considered as not related to study medication (masitinib/placebo) by both investigator and sponsor. Seventeen (17) cases were reported with placebo arm and did not involve masitinib. Although acquired data possibly do not allow further causality conclusions, it is important to notice the asymmetry of deaths between masitinib treated patients (54 / 260 = 20.8%) and placebo patients (17/133 = 12.8%).

SAE

During the protocol period, the frequency of SAE (any causality) was moderately increased with masitinib 4.5 mg/kg/day and was similar with masitinib 3 mg/kg/day as compared with placebo: -“Normal Progressor” 27.6% vs 16.7% for placebo and in the “Normal + Fast Progressor” 31% vs. 18% for placebo .

Discontinuation of treatment due to SAEs

During the protocol period, the frequency of AEs leading to permanent treatment discontinuation was slightly increased at a masitinib dose of 4.5 mg/kg/day and at a masitinib dose of 3 mg/kg/day, regardless of the population: “Normal Progressor” population 17.1% vs 7.9% for placebo ; “Normal + Fast Progressor” 16.3% vs. 9.0%.

Laboratory findings and vital signs

In ALS masitinib had an ALT, AST and bilirubin effect, increasing these values up to grade 3 severity. Masitinib had no effect on albumin level, alkaline phosphatase level, calcium level, cholesterol level, creatinine level, Gamma GT level, glucose level, potassium level, sodium level, and triglycerides level. Masitinib had an effect on hemoglobin count with decrease being more frequent than an increase in haemoglobin. Masitinib had a slight effect on leucocytes count with decrease being more frequent than an increase in white blood cells. The same holds for lymphocyte count.

Upon CHMP request, the MAA has performed a specific analysis of events of special concern, namely fractures / osteoporosis / hypophosphatemia, anaemia, weight loss and nausea. Of all these nausea is highlighted among other factors affecting masitinib safety. Bone fractures, anaemia and weight loss apparently have an impact on efficacy as measured by ALSFRS-R.

3.5. Uncertainties and limitations about unfavourable effects

There are many aspects which increase the uncertainty of data regarding safety.

Reliability of the data analysis: data has been updated after the submission for obtaining marketing authorization and was not provided to the Agency or to inspectors. The Applicant has also shown difficulties dealing with CROs monitoring the trial. This has had a relevant impact in the conduct of the trial, with relevant issues remain on the robustness of the collected data. It is not the impact of the individual concerns that have been identified and corrected, but the impact of the problems that may not have been identified and that were not corrected that are also of concern.

Subject safety at risk: a) a very high number of protocol deviations related to inclusion/exclusion (I/E) criteria, safety tests (ECGs and laboratory analysis) and investigational product (IP) intake (overdose) identified for at least 20 subjects reviewed during the inspection at Dr. Delia Chaverri's site (this site randomized 106 subjects) and at least 12 subjects reviewed during the inspection at Dr. Conrado Estol's site (this site randomized 53 subjects); b) the appropriate conditions of the storage of the IP administered to the subjects could not be ensured according to the documentation reviewed. No monitoring of IMP conditions from site to the subjects); c) deficiencies on the subject safety oversight. Delays on adverse events (AE) and serious adverse events (SAE) notification to the Sponsor and the consequently delay of the Sponsor safety assessment.

Further, the method of assessment of the impact of an adverse event which requires time to produce an effect (anemia, weight loss) did not focus on patients who had the adverse event persistently throughout a significant period in the study, but on assessment episode. Including all patients who experienced one anemia episode or one decrease in haemoglobin will dilute the effect, as many persons with a slight effect on red blood cells may also be in the placebo arm and many which will not have a systemic impact will counteract the impact of those where the effect was more prolonged.

Exclusion of gastrostomised patients precludes extrapolation both for efficacy and safety data (such as if a coagulation prolongation occurs, the risk of gastrostomy bleeding would be significant) in the general ALS population.

3.6. Effects Table

Table 40 Effects Table for masitinib in ALS.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
FAVOURABLE EFFECTS						
			Masitinib 4.5 mg/kg/day + riluzole	**Placebo + riluzole**		
Change in ALSFRS-R	Absolute change from baseline to week 48 in Amyotrophic Lateral Sclerosis functional rating scale-Revised	points	-9.24 Difference with PBO = 3.39 [0.65;6.13] P-value = 0.0157	-12.63	This result was for "Normal progressors" sub-population. ALS population was divided into normal and fast progressors, and this dichotomisation has not been sufficiently justified, and was not accepted.	Final analysis from study AB10015
PFS	Change in median progression free survival		Increase by 4 months compared to PBO P-value=0.0159		This result was for "Normal progressors" sub-population.	Final analysis from study AB10015
QoL	Quality of life as measured by the ALSAQ-40	LS Mean	19.42 Difference of means = -7.76 [-13.45;-2.06] P = 0.0078	27.18	This result was for "Normal progressors" sub-population.	Final analysis from study AB10015
FVC	Absolute change from baseline to week 48 in Forced Vital Capacity	LS Mean	Difference of means = 7.55 [0.75;14.32] P= 0.0296		This result was for "Normal progressors" sub-population.	Final analysis from study AB10015
UNFAVOURABLE EFFECTS						
Anaemia	Any anaemia	Anaemia as definedl	15.5%	3.0%	Persistent anaemia has	Final analysis

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	episode during trial				not been studied	from study AB10015
Nausea	patients with at least one episode	% of population in the arm	11.6%	4.5%	Nausea is a known AE which significantly impacts nutrition in ALS	Final analysis from study AB10015
Weight loss	weight loss reported by investigators	% of population in the arm	10.9%	6.8%	AE which significantly impacts wellbeing in ALS	Final analysis from study AB10015
Bone fractures	identifies bone fractures	Episode of fracture	6.7%	3.5%	AE which significantly impacts wasting in ALS	Final analysis from study AB10015
Rash	patients with at least one episode	% of population in the arm	7.8	4.5%	AE known to masitinib safety profile	Final analysis from study AB10015
Dysphagia		% of population in the arm	12.4%	12.8%	AE very frequent as a ALS symptom	Final analysis from study AB10015

3.7. Benefit-risk assessment and discussion

3.7.1. Importance and balance of favourable and unfavourable effects

The evaluation of the importance of the observed beneficial and unfavourable effects was significantly influenced by the trial conduct and methodological issues, described in previous sections. The latter lead to the conclusion that the credibility of the observed beneficial effects was seriously questioned, while for the unfavourable effects there were not enough well-controlled safety data were provided to potentially allow for the complete assessment of the safety profile of masitinib.

The development programme did not manage to create a clear chain of evidence supporting the use of masitinib in ALS. The transition from a pre-clinical proof-of-principle, into a justified dose- selection strategy and proof-of-concept development, and finally into confirmatory data generation from a properly designed clinical programme is lacking. Maintaining a solid, data driven and scientifically justified chain of supportive evidence is of paramount importance in the context of a single pivotal trial application, even in cases like in ALS, where it is recognized that the unmet medical need is severe. As this was not achieved, the importance of the observed beneficial effects is questionable.

Adding to the above deficiency is the fact that said benefits were only observed in a selected sub-population of patients making it difficult to predict the expected effect of masitinib in ALS patients, in real life conditions. What is more, the effects become substantially smaller and lose their statistical significance when the whole trial population is taken into account, and this is true not only for the effects described by the primary endpoint, but also for the ones observed for another important outcome – progression free survival.

Additionally, the whole chosen strategy to sub-divide the trial population into the proposed sub-groups was not accepted as it was not sufficiently justified by scientific arguments. The doubts remain, that this strategy may have, at least in part, been driven by data emerging during the trial.

Against the deficiencies, regarding the data describing the beneficial effects, the CHMP had to position the uncertainties about the unfavourable effects, created by the issues in the trial conduct (see GCP section), and the lack of sufficient amount and duration of the collected safety data. In that context, the described safety profile of masitinib may seriously underestimate the real one to be expected, if the drug is to be used in clinical practice.

3.7.2. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product were not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and seriously debilitating disease.

ALS is a progressive, incurable and fatal neurodegenerative disease. ALS is a serious neurological disease that causes muscle weakness, disability and eventually death. Median survival for ALS is 2 to 4 years from onset; only 5–10% of patients survive beyond 10 years [Chio, 2013]. The disease is heterogeneous, but most patients die less than 3 years from symptom-onset [Gordon, 2013]. The cause of death in ALS is normally of a respiratory nature. Approximately 60 % of patients have a predictable decline in function while the remainders die suddenly, sometimes from other causes.

The Applicant proposed apply for conditional Marketing authorisation (CMA), basing the claim for positive B/R balance on the results from the interim analysis. As described above, these were not considered comprehensive and compelling. As a specific obligation of the CMA the Applicant initially proposed the final results from the pivotal study to be presented, and claimed that should CHMP be requesting a second study as a specific obligation, the granting of a conditional marketing authorisation would not affect the ability to complete this second study in a timely manner. The CHMP disagreed with the proposed strategy, despite agreeing with the claim for an unmet medical need in ALS. For the Committee, the available data, from both interim and final analyses, were not sufficient to establish a positive B/R for Alsitek in ALS, thus failing to fulfil condition a of Article 4(1) of Commission Regulation (EC) No 507/2006, and not allowing a CMA to be granted.

3.8. Conclusions

The overall B/R ratio of Alsitek is considered negative in the proposed indication.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Alsitek in combination with riluzole is indicated for the treatment of adult patients with amyotrophic lateral sclerosis (ALS) (probable or definitive), the CHMP considers by consensus that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated.

The CHMP considers that:

Whereas,

While CPMP/EWP/2330/99 indicates that a single pivotal study can be an acceptable basis for licensing where certain prerequisites are met, data from the single pivotal trial of Alsitek are not adequate to establish efficacy. Study AB10015 does not meet the criteria concerning data quality and absence of indications of potential bias. Multiple crucial protocol amendments have been implemented during the course of the study and for the CHMP the reasoning and drivers for some of those remain unclear. Examples include revising the statistical hypothesis testing strategy between study arms, the primary analysis population and the strategy for the imputation of missing data. Specifically:

- Initially data from the two active treatment arms were to be pooled in the primary comparison with the placebo arm. This was subsequently changed to a primary comparison of the higher dose versus placebo. There is no pharmacological rationale to support this revised strategy. Furthermore, the protocol amendment dichotomising the included patients into ‘normal’ and ‘fast’ progressors is justified neither in clinical terms nor in relation to the pharmacology of masitinib. In the absence of these amendments the single pivotal study fails to show statistically significant results on its primary endpoint: for the "normal + fast progressor" population the absolute change from baseline to week 48 in ALSFRS-R between masitinib 4.5 mg/kg/day and placebo is 2.09 [-0.55;4.73], not reaching statistical significance (P = 0.1202).
- Concerns related to this aspect of trial conduct are compounded by the systematic deficiencies observed at the requested GCP inspection, in which it was concluded that the data obtained at the inspected sites are not trustworthy enough to support the submitted marketing authorization application for masitinib. The possibility that amendments of the analytic strategy were driven by emerging trial data cannot be excluded.
- Moreover, an excess of patients withdrew from treatment because of lack of efficacy and adverse events on both treatment arms compared to placebo. The handling of missing data arising from patient withdrawals is likely to give rise to important bias in the estimated treatment effect that favours masitinib.

Thus, a reliable estimate of efficacy has not been presented. Therefore, a positive benefit/risk balance cannot be established.

The CHMP is of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated. Therefore, the CHMP has recommended the refusal of the granting of the conditional marketing authorisation for Alsitek.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, and risk management plan cannot be agreed at this stage.