22 May 2014
EMA/CHMP/327108/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Masiviera

International non-proprietary name: MASITINIB

Procedure No.: EMEA/H/C/002659/0000

Note

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

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Product information

Name of the medicinal product:	Masiviera
Applicant:	AB Science 3, Avenue George V 75008 Paris FRANCE
Active substance:	Masitinib mesylate
International Nonproprietary Name/Common Name:	MASITINIB
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agents, protein kinase inhibitors (L01XE22)
Therapeutic indication:	Masiviera in combination with gemcitabine is indicated for the first-line treatment of non-resectable locally advanced or metastatic pancreatic cancer in adult patients presenting with: - specific genetic biomarker (GBM) (population 1) - pain (population 2). Adult patients eligible for Masiviera treatment should present with pain estimated as strictly higher than 20 mm / 100 mm on a visual analogue scale.
Pharmaceutical form:	Film-coated tablet
Strengths:	100 mg and 200 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package size:	30 tablets

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List of abbreviations

AE	Adverse events
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under Curve
BE	Bioequivalence
CI	Confidence Interval
Cl	Clearance
Cl/F	apparent clearance
CL/F	Total clearance
CLr	renal clearance
Cmax	Maximum concentration
CNS	Central nervous system
CR	Complete response
Ct	Cycle Threshold
CYP	Cytochrome p450
DCt	Delta Ct
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Human epidermal growth factor
EMA	European medicine agency
F	Bioavailability
FGFR3	fibroblast growth factor receptor 3
HR	Hazard ratio
KPS	Karnofsky Performance Status
M+G	Masitinib + gemcitabine
mITT	modified Intent To Treat
M-RECIST	Modified Response Evaluation Criteria In Solid Tumours
NA	Not applicable or not assessable
NOAEL	No observable adverse effect level
OS	Overall Survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PDAC	pancreatic ductal adenocarcinoma
PDGFR	Platelet-derived growth factor receptor

PFS	Progression Free Survival
P+G	Placebo + gemcitabine
P-gp	Permeability glycoprotein
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PP	Per Protocol
PR	Partial Response
QoL	Quality of Life
QLQ-C30	Quality of Life Questionnaire C30
RECIST	Response Evaluation Criteria In Solid Tumours
RNA	Ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	Serious adverse events
SD	Stable Disease
t1/2	half life
TKI	Tyrosine Kinase Inhibitor
Tmax	Time to maximum concentration
TTP	Time to progression
ULN	Upper limit of normal
VAS	Visual analogue scale
Vd	Volume of distribution
WT	Wild Type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AB Science submitted on 30 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Masiviera, 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 17 November 2011.

Masiviera was designated as an orphan medicinal product EU/3/09/684 on 28 October 2009. Masiviera was designated as an orphan medicinal product in the following indication: treatment of pancreatic cancer.

The applicant applied for the following indication:

Masiviera in combination with gemcitabine for the first-line treatment of non-resectable locally advanced or metastatic pancreatic cancer in adult patients presenting with:

- specific genetic biomarker (GBM) (population 1)

or

- pain (population 2). Adult patients eligible for Masiviera treatment should present with pain estimated as strictly higher than 20 mm / 100 mm on a visual analogue scale.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that masitinib was considered to be a new active substance.

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.

This application was submitted, in accordance with Article 82.1 of Regulation (EC) No 726/2004 as a multiple of Masican for which an opinion on the refusal of the granting of the conditional marketing authorisation was adopted by CHMP on 21 November 2013.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an 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:

The Applicant has provided a document claiming that the medicinal product falls within the scope of Article 2 of the Commission Regulation (EC) No 507/2006 and that the requirements for conditional marketing authorisation set out in Article 4 of this Regulation are fulfilled, in particular:

- The applicant considered that the benefit-risk balance for masitinib in the treatment of unresectable locally advanced or metastatic pancreatic cancer in patients presenting the 'aggressive genetic fingerprint' or in patients suffering from 'pain' was considered favourable: the pivotal AB07012 study demonstrated a benefit in overall survival of masitinib in combination with gemcitabine in these patient populations.
- The unmet medical needs will be fulfilled and the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required: Patients diagnosed with pancreatic cancer often have a poorer prognosis compared with other malignancies in part because early detection is difficult. Current therapies approved or used in clinical practice in pancreatic cancer patients are gemcitabine, erlotinib, and folfirinox.
- At the time of the registration request, two studies have been evaluated: the pivotal phase III AB07012 study and the supportive phase II AB05034 study. The applicant proposed to complete and confirm clinical results already obtained in the pivotal study with a confirmatory phase III, prospective, multicentre, double-randomized, open label, 2-parallel groups study to compare the efficacy and safety of masitinib in combination with gemcitabine against gemcitabine as a single agent, in the first-line treatment of patients with non resectable locally advanced or metastatic pancreatic cancer. This study has not been initiated to date.

New active Substance status

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

Protocol Assistance

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

Centre Spécialités Pharmaceutiques (CSP)
76 avenue du midi
FR-63800 Cournon d'Auvergne Cedex
France

Excella GmbH
Nuernberger Str. 12
90537 Feucht
GERMANY

1.3. Steps taken for the assessment of the product

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

Rapporteur: Jens Ersbøll Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 30 August 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 December 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 December 2012.
- During the PRAC meeting on 10 January 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 17 January 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 January 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 July 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 September 2013.
- During the PRAC meeting on 5 September 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 19 September 2013, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 3 December 2013.

- During the PRAC meeting on 5 December 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 18 December 2013 outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 23 January 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Masiviera.

1.4. Steps taken for the re-examination procedure

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

Rapporteur: Harald Enzmann Co-Rapporteur: Concepcion Prieto Yerro

- The applicant submitted written notice to the EMA on 24 January 2014 to request a re-examination of Masiviera CHMP opinion of 23 January 2014.
- During its meeting on 20 February 2014 the CHMP appointed Harald Enzmann as Rapporteur and Concepcion Prieto Yerro as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 27 March 2014. The re-examination procedure started on 28 March 2014.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 6 May 2014. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 30 April 2014.
- During a meeting of the Scientific Advisory Group (SAG) Oncology on 7 May 2014, experts were convened to consider the grounds for re-examination.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 16 May 2014.
- During the CHMP meeting on 22 May 2014, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22 May 2014, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for grant of conditional marketing authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Introduction

In Europe, cancer of the pancreas is the seventh most frequent cancer, accounting for some 2.8% of cancer in men and 3.2% in women. It is the fifth leading cause of cancer-related death with ~70 000 estimated deaths each year and predicted to become the fourth cause of cancer death in both

sexes in due course in the European Union. Mortality in men is ~35 000 cases per year. Mortality in women is also ~35 000 cases per year. Incidence increases with age and the majority of cases are diagnosed above the age of 65. Pancreatic cancer still has a dismal prognosis, >95% of those affected die of the disease. The high mortality rate is due to late diagnosis, early metastasis and poor response to chemo- and radiotherapy in most cases.

The only curative treatment of pancreatic cancer is radical surgery. This approach is mainly suitable for patients with early stage of disease mainly stage I and some stage II. For patients with advanced or metastatic disease, gemcitabine monotherapy has been the standard for many years. Patients receiving gemcitabine have a median survival of 6.2 months and a 1-year survival rate of 20%. A recent phase III trial comparing gemcitabine with a combination of 5-FU, irinotecan and oxaliplatin (FOLFIRINOX) has shown a response rate of 31.6%, a median survival of 11.1 months (hazard ratio 0.57, 95% confidence interval 0.45–0.73), and 1-year survival rate of 48.4% in the FOLFIRINOX arm. In this trial, patients >75 years were excluded and eligibility was restricted to PS 0 and 1.60% of patients had cancers of the body and tail of pancreas. The human epidermal growth factor (EGFR) tyrosine kinase inhibitor Tarceva (erlotinib) has been approved in combination with gemcitabine.

Masitinib (AB1010) is a protein tyrosine kinase inhibitor (TKI). In vitro, masitinib inhibits the c-Kit wild type (WT) and its mutated forms (exon 9 and 11), as well as the platelet-derived growth factor alpha (PDGFRA) receptor.

In this application, AB Science requested the approval of:

Masiviera (masitinib) in combination with gemcitabine for the first-line treatment of non-resectable locally advanced or metastatic pancreatic cancer in adult patients presenting with:

- *specific genetic biomarker (GBM) (population 1).*

or

- *pain (population 2). Adult patients eligible for Masiviera treatment should present with pain estimated as strictly higher than 20 mm / 100 mm on a visual analogue scale.*

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 mesylate) as active substance.

Other ingredients are: microcrystalline cellulose (Avicel pH101 and pH200), povidone, crospovidone, magnesium stearateand film-coating, titanium dioxide, talc, polyethylene glycol and sunset yellow lake (E110)).

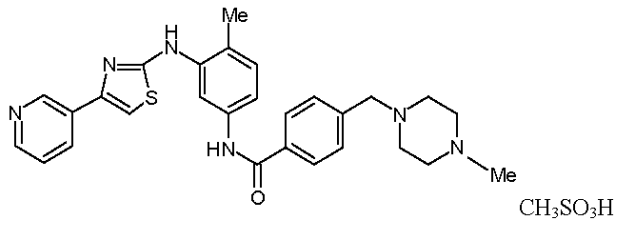
The product is available in high density polyethylene (HDPE) bottles with child resistance closures.

2.2.2. Active substance

An ASMF for masitinib mesylate was submitted by Excella GmbH for masitinib mesylate. 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.

The chemical name of masitinib mesylate 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:



The molecular structure of masitinib mesylate has been confirmed by elemental analysis, IR, H-NMR and LC-MS using a reference batch of masitinib mesylate.

Masitinib mesylate is a white to pale yellow powder, slightly hygroscopic, practically insoluble in acetone, slightly soluble in ethanol, sparingly soluble in methanol and soluble in water.

The molecular structure does not contain asymmetric carbon atoms.

Three polymorphic forms of masitinib mesylate were identified by Differential Scanning Calorimetry and X-ray spectrometry. The masitinib mesylate is consistently manufactured as polymorphic Form DRX1, anhydrous and the most stable. The polymorphic forms can be differentiated by melting point/range. Melting point is included in the active substance specification.

An ASMF for masitinib mesylate was submitted. The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture

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.

Starting materials are acceptable One of the starting materials is considered a complex molecule and should instead be considered as intermediate of the synthesis. The description of its synthesis was provided and it was identified that its manufacture has potential to significantly impact the impurity profile of the active substance. Hence, redefining of this starting material was needed. The applicant failed to address the major objection on the redefinition of the starting material.

Other minor concerns on the manufacture of active substance, control of intermediates and declared batch size were left outstanding.

Due to the above, the information on the manufacturing of the active substance could not be considered satisfactory.

Specification

The active substance specification includes tests for: appearance, identity (IR, HPLC), assay (HPLC/UPLC), impurities (HPLC/UPLC), residual solvents (GC), water content (KF), heavy metals (Ph. Eur.), particle size (laser diffraction), melting point (DSC) and residue on ignition (Ph. Eur.).

The remaining analytical methods were adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Major objections where identified pertaining to setting impurities in the active substance specification. The issues related to further information needed in regard to impurities demonstrating that these impurities are not genotoxic, and not including a formal limit for unknown single impurity in the specification.

Another major concern is also unresolved in relation to the adequacy of the proposed particle size distribution specification.

Batch analysis data (pilot scale, n=4) of the active substance were provided. The results were consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance from the proposed manufacturer stored sealed transparent PE bags inside a PE/aluminium bag, with a desiccant in between the bags, for up to 24 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, melting point, water content, assay and related substances. The analytical methods used were the same as for release and were stability indicating.

A photostability study in accordance with EU/ICH Q1B was conducted showing that the active substance is not photo labile. Forced-degradation studies demonstrated that solutions of the active substance were sensitive towards heat, UV-light, heat & acid and heat & hydrogen.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable and that there is no shift of its polymorphic form. The stability results justify the proposed retest period of 36 months (extrapolated from 24 months of data) in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

During Phase I studies 100 mg of masitinib mesylate was delivered in a manually filled size 1 capsule with no other excipients. In order to reduce the size of the pharmaceutical form and to accommodate a higher strength, tablet formulations were developed.

The active substance masitinib mesylate was initially synthesised at four different manufacturers using the same synthetic route. Ultrafine manufactured batches of masitinib mesylate for toxicological trials only and batches from one of the manufacturers were used in phase 1 and some phase 2 clinical studies. The synthesis of this manufacturer was then transferred to a second manufacturer. Finally, two manufacturers were proposed for the commercial scale manufacture of masitinib mesylate. Batches from these manufacturers were used in some phase 2 and phase 3 studies.

During evaluation the applicant removed one of the proposed manufacturers of the active substance as it would not be used in commercial batches.

The formulation development was deficient and different concerns were raised, see below.

The excipients proposed 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 particle size of the active substance and core tablet hardness of the batches used in the clinical trials and batches of both strengths manufactured as proposed for the market vary significantly. The data provided comparing the dissolution profiles between batches was not able to bridge data between the different versions of the product, nor support the specification proposed for these parameters. This is of serious concern as the bioavailability of the active substance was not proven to be consistent between batches and no extrapolation to the intended critical quality attributes for commercial manufacture was possible.

The applicant failed to submit data in support of the discriminatory nature of the dissolution method. This is of major concern as the comparability exercise between biobatches and batches manufactured according to the details included in Module 3 are not validated, moreover commercial batch release testing would not be able to detect batches with a potential jeopardized product performance.

The primary packaging is HDPE bottles closed with a polypropylene child resistance closure with an induction sealed aluminium/polyethylene liner, where the polyethylene side is in contact with the tablets. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of 8 main steps: weighing, preparation of binder solution, granulation, drying, milling, compression, tablet coating and packaging. The process is considered to be a standard manufacturing process.

Critical steps in the manufacturing process have been identified. The appropriateness of the in-process controls for the proposed manufacturing process cannot be verified due to the several issues detailed in this report.

No process validation data was provided, this is justified as the manufacturing process of masitinib follows a standard wet granulation process, moreover one evaluation batch of each strength has been manufactured and shown to be compliant with the finished product specification. A satisfactory process validation protocol was provided, as required by current guidance.

Product specification

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

The validation data provided for analytical method was not sufficient with regards the methods for related substances determination and dissolution.

The finished product specification covers appropriate parameters for this dosage form and is broadly acceptable. However, some issues remain unresolved.

Major objections remain with regards the limit still to be defined for impurity found to be threshold-dependent genotoxic. Other concerns are outstanding for the specifications of tablet hardness and total impurities.

Batch analysis results are provided for two batches of 100 mg and five batches of 200 mg tablets manufactured at the proposed commercial manufacturing site, at commercial scale, confirming the consistency of the manufacturing process.

Minor concerns on the description and control of the container closure system remain unresolved.

Stability of the product

Stability data of one batch of finished product of 100 mg and three batches of 200 mg batches of finished product (all at commercial scale) stored under long term conditions up to 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, moisture content, assay of masitinib, impurity content and dissolution.

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

In addition, photostability studies showed a slight fading of the colour of film-coating; however the proposed HDPE primary packaging offers sufficient protection from light exposure.

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

A number of quality issues were considered not resolved at the end of the procedure but would be resolved after update of module 3 (new proposed specifications) within a formal correct procedure. .. These issues relate to, *inter alia*, the unsatisfactory regulatory control of the manufacture and specification of the active substance, in itself and as intended to be used in the medicinal product; deficient data supporting the bridging of biobatches with the product intended for commercial release, control of consistence manufacture to the intended product performance, control of impurities and validation of analytical methods.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

At the time of the opinion the CHMP has identified a number of non-resolvable quality related issues, which precluded positive conclusions on the quality data provided.

The applicant failed to address the major objection on the redefinition of the starting material used in the synthesis of the active substance. Inadequate control of starting materials has potential to significantly impact the impurity profile of the active substance.

The bioavailability of the active substance was not proven to be consistent between batches and no extrapolation to the intended critical quality attributes for commercial manufacture was possible. Furthermore, the applicant failed to provide data in support of the discriminatory nature of the dissolution method. This is of major concern as the commercial batch release testing would not be able to detect batches with a potential jeopardized product performance.

In view of the above listed limitations and other minor quality related unresolved issues, the CHMP concluded that the quality of the product was not sufficiently demonstrated.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

In vivo studies were performed in mouse, rat, rabbit and dog. All the principal nonclinical safety and toxicology studies were conducted in compliance with current Good Laboratory Practice (GLP) standards as claimed by the applicant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Using recombinant truncated c-Kit, it was shown that masitinib is a competitive inhibitor of c-Kit tyrosine kinase activity with an IC_{50} of 200 nM. Masitinib competes with ATP for the ATP-binding site of c-Kit.

Masitinib (0.01 to 1 µM) induces a dose-dependent inhibition of IgE mediated release of histamine and TNF alpha from human mast cells. Hence, the maximal inhibition of histamine and TNF alpha release was 25% and 43%, respectively, following treatment with 1 µM masitinib.

Studies in transfected Ba/F3 cells as well as cell lines expressing wild-type human c-Kit showed that masitinib is a potent (IC_{50}< 0.15 µM) inhibitor of proliferation of cells expressing wild-type c-Kit. Masitinib inhibited the proliferation of the human mast cell line HMC-1 expressing endogenous c-Kit bearing a mutation in the juxtamembrane domain (V560G) with an IC_{50} of 0.05 µM. Moreover, it was reported that masitinib induced apoptosis of HMC-1 cells (V560G) with an IC_{50} of 0.1 µM. However, since the number of replicates was two and not specified for the proliferation and apoptosis assays, respectively, the validity of these findings is not fully clear.

The major masitinib metabolite AB3280 was approximately a 2-fold less potent inhibitor of human c-Kit than the parent compound.

Literature data indicate that high mast cell counts in the intratumoural border zone correlates with the presence of lymphatic and microvascular invasion, lymph node metastasis, and that they are an independent prognostic factor for overall survival in patients with pancreatic ductal adenocarcinoma (PDAC). Mast cells express the receptor for stem cell factor (KIT) and tumour-derived stem cell factor is believed to cause the recruitment and activation of mast cells in tumours. Once activated, mast cells release inflammatory factors which among other things are involved in remodelling of tumour stroma and angiogenesis. Being a c-KIT inhibitor, it is believed that masitinib could reduce tumour growth via inhibiting mast cell activation in the tumour microenvironment. Similarly, since mast cells release mediators which may cause pain via nociceptors activation, masitinib-induced inhibition of mast cell activity may reduce the pain in patients suffering from pancreatic cancer.

The efficacy of masitinib in animal models of pancreatic cancer was tested in mice carrying tumours derived from the human pancreatic cancer cell line Mia Paca-2. The results showed that masitinib exerted no statistically significant effect on tumour growth.

Secondary pharmacodynamic studies

The target selectivity of masitinib was evaluated via a KINOMEscan™ analysis consisting of competition binding assay data for 451 kinases at a masitinib concentration of 1 µM. These data were complemented by IC_{50} determinations for a panel of 50 different recombinant kinases via quantifying the phosphorylation of a peptide substrate. Overall, the following kinases were inhibited by masitinib (IC_{50} < 1 µM): CSF1R, PDGFRα, PDGFRβ, DDR1 and 2 receptors and several members of the Src-family kinases namely LYN, FYN, LCK, FGR, FRK and BLK. In addition, ABL1 was inhibited with an IC_{50} of 1.2 µM.

Safety pharmacology programme

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. Toxicokinetic sampling was not performed but based on allometric scaling a dose of 150 mg/kg administered to rats corresponds roughly to three-fold the recommended daily human dose (9 mg/kg/day). 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 IC_{50} value was 8.3 µM. Considering a masitinib free fraction in human blood of 2.12%, the reported clinical plasma C_{max} of 1206 ng/mL masitinib corresponds to an unbound plasma concentration of approximately 51 nM. Hence, only a minimal effect on the hERG channel is expected at clinical C_{max}. No effect was observed on electrocardiogram parameters in telemetered dogs (n=3) receiving 50 mg/kg. This dose level roughly corresponds to the recommended daily dose for patients receiving masitinib.

Pharmacodynamic drug interactions

No studies were submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Absorption

In vitro studies in Caco-2 cells, indicated that masitinib may be a substrate of P-gp mediated transport at concentrations <10 µM. At higher concentrations (≥10 µM), masitinib appeared to be an inhibitor of P-gp mediated transport which was likely to be due to saturation of P-gp-mediated efflux. It was not possible to establish an exact IC_{50}, however approximated IC_{50} values were calculated, and in the range of 63.24 to 154.22 µM. The free fraction of masitinib in plasma was well below this range, hence inhibition of systemic P-gp was considered unlikely, whereas the concentration of masitinib in the gut was much higher than the approximated IC_{50} values, and inhibition of P-gp in the gut was a risk.

The absorption of masitinib was studied after single i.v. and p.o administration of ^{14}C-masitinib to Beagle dogs and Sprague-Dawley rats. No gender differences were observed following single p.o. and i.v. dosing to rats and dogs. Mean T_{max} following p.o. dosing was 2.2 h in dogs and 4 h in rats. Elimination half-life ($T_{½}$) 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 following a single p.o. administration. Masitinib displayed 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.

Gender differences were observed in rats following repeated dosing hence higher masitinib plasma exposure levels were observed in females relative to males and T_{max} occurred earlier. Plasma exposure to the major metabolite AB3280 on the other hand was around 2-fold higher in males than in females. Moreover, AB3280 T_{max} varied 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.

Distribution

The binding to human, rat, mouse, dog and rabbit plasma proteins was high with 93.93%, 92.15%, 86.12%, 93.33% and 97.5%, respectively and not saturable within the applied masitinib concentration range (0.2-5 µM). In plasma, binding to human serum albumin was high (48.91%) while a lower binding occurred on α1-acid-glycoprotein (8.4%) and gamma-globulin (1.8%). In human blood, the free fraction was constant at 2.12% as long as the protein concentration did not vary. Preliminary data indicate that 88% of AB3280 is bound to human plasma proteins.

Following oral administration of 10 mg/kg ^{14}C-masitinib to Sprague-Dawley rats, quantifiable levels of radioactivity (which decreased with time) were found in all tissues at 24 hours except for muscle and/or brain. Radioactivity levels were above quantifiable limits in most tissues at 168 hours. The highest levels were seen in the adrenals, kidneys, spleen and intestines of both sexes and pancreas of males while lower levels were found in the pancreas of females and skin, lymph nodes, stomach, thymus and ovaries of the males and/or females.

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 formed in human hepatocytes. Moreover, MET1/AB5235, which is genotoxic in the presence of S9 fraction *in vitro* (please refer to the section on metabolites), was only detected in mouse hepatocytes. Again, no human specific metabolites were observed.

In vitro studies showed that CYP3A4/5 was the enzyme primarily responsible for the metabolism of masitinib. The data also indicated that CYP2C8 has the capacity to catalyse the formation of AB3280 from masitinib.

In *in vivo* i.v. and p.o. metabolite studies conducted in rats and dogs, no masitinib plasma metabolites were detected. Still, 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 AB2436and/or its counterpart 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.

While the genotoxic metabolite AB2436 as well as its genotoxic metabolite AB5235 were detectable in the urine of mice, only AB2436 was detected in rat urine and neither metabolite could be found in rat plasma. Similarly, these metabolites were not detected in human plasma, while AB2436 was found in human urine (AB5235 was not analyzed for in human urine). The provided *in vitro* and *in vivo* data show that the genotoxic aniline metabolites AB2436 and AB5235 are formed predominantly in mice but to a lower extent in rats and humans.

Excretion

The excretion of ^{14}C-masitinib was evaluated in rats and dogs over a 168 hour period. No gender differences in excretion pattern were observed (data not shown). Following i.v. dosing of rats, the radioactivity in the faeces and urine was eliminated fast with >81% of the total recovered dose in the faeces and urine being excreted within 24 hours following injection. Similarly, the administered radioactivity was excreted relatively rapidly following p.o. dosing with >91% of the total recovered dose in faeces being eliminated within the first 48 hours after oral gavage while >84% of the total recovered dose in urine was excreted within 24 hours.

Pharmacokinetic drug interactions

Identification of the major drug metabolising enzymes involved in the human hepatic metabolism of masitinib (SR-1-abs-02, GLP)

In order to identify which cytochrome P450 (CYP) enzymes(s) are responsible for the metabolism of masitinib, 14C-masitinib (5 µM) was incubated with liver microsomes prepared from 16 individual donors, CYP-selective chemical inhibitors and recombinant CYP450 enzymes (CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4). In addition, it had been verified that the liver microsomes expressed CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5 and 4A11 activity. Radiolabelled masitinib was metabolized to up to 4 discrete metabolite fractions of which the major metabolite was identified as AB3280 (N-desmethyl masitinib) based upon co-chromatography with non-radiolabelled AB3280 reference standard. Further analysis showed that CYP3A4/5 was the enzyme primarily responsible for the metabolism of masitinib. The data also indicated that CYP2C8 has the capacity to catalyse the formation of AB3280 from masitinib.

Evaluation of CYP450 inhibitory properties of masitinib and AB3280 (SR-2-pr6513-3vt2081, GLP)

The CYP450 inhibitory properties of masitinib and AB3280 towards CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 were investigated in human liver microsomes. CYP3A4/5 inhibition was studied using three different substrates i.e. midazolam, testosterone and nifedipine. Neither CYP1A2, 2C8, 2C19 nor 2E1 were inhibited at masitinib concentrations up to 5 µM while CYP2C9 was inhibited with IC50 values in ≥17.5 µM. Masitinib was a weak to moderate inhibitor of CYP3A4/5 and CYP2C9, as well as CYP2D6 with IC50 values of 14 µM, 20 µM and > 30 µM, respectively. This inhibition was partly reversible. Moreover, AB2380 showed no inhibitory potential towards CYP450 isotypes at concentrations up to 2 µM.

Evaluation of CYP450 induction properties of masitinib and AB3280 (SR-3-pr6537-5vt2085, GLP)

The activities of CYP1A2, 2C9, 2C19 and 3A4/5 enzymes in human hepatocytes were evaluated before and following a 3 to 4-day incubation period with masitinib or AB3280. In one of two tested

hepatocyte batches, masitinib treatment (500 and 1000 ng/mL) gave rise to a 20-60% decrease of CYP3A4/5 activity. Similarly, treatment with AB3280 (1000 ng/mL) resulted in a 20% decrease in CYP3A4/5 activity. Moreover, AB3280 treatment resulted in a 10-20% decrease in CYP2C9 activity at 500 and 1000 ng/mL.

P-gp

Masitinib was incubated with cultured Caco-2 cell monolayers grown on membrane supports (transwells) in a 24 well format to investigate its potential as a P-gp substrate and inhibitor. Masitinib was assessed as a potential substrate for P-gp transport at 1, 50 and 500 µM by determining the apparent permeability (Papp) for Apical – Basolateral (A-B) transport and for Basolateral – Apical (B-A) transport in the presence and absence of verapamil (a known P-gp transport inhibitor).

Masitinib was assessed as a potential inhibitor of P-gp transport at 1, 10 and 100 µM by determining the apparent permeability (Papp) for Apical – Basolateral (A-B) transport At lower concentrations (<10 µM), Masitinib appears to be a substrate of P-gp mediated transport. At higher concentrations (≥10 µM), AB1010 appears to be an inhibitor of P-gp mediated transport, likely to be due to saturation of P-gp-mediated efflux.

Other transporters

There are no data on the possible influence on other transporters.

2.3.4. Toxicology

Single dose toxicity

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

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 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.

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.

Renal toxicity was observed in rats and dogs. 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 nephropathy were observed with an overall No observable adverse effect level (NOAEL) of 10 mg/kg/day. In dogs, presence of protein and blood in the urine and a reduction in urinary pH were observed with a NOAEL of 10 mg/kg/day. In the mouse there was urinary bladder urothelial hyperplasia in male mice which was not fully reversible during a recovery period.

Masitinib exerted gastrointestinal toxicity in the dog in the form of vomiting, regurgitation and soft/liquid faeces. In addition, reddish or greenish coloured faeces were observed in dogs administered 150 mg/kg/day for 4 weeks. As for the majority of anti-cancer treatment, nausea, diarrhoea and vomiting are very common findings in patients treated with masitinib.

Female genital organs showed morphological changes indicative of oestrous cycle disturbance in rats from 10 mg/kg/day. At 100 mg/kg/day, the ovaries had moderate to large number of luteal and/or follicular haemocysts, no or few corpora lutea, and very few or few follicular development. Depending on ovarian stage, this was associated with endometrial cell atrophy or hypertrophy together with vaginal epithelial cell hyperplasia, hyperkeratinisation or mucification. Ovary weight was increased and on the macroscopic level, discoloured and enlarged ovaries were observed.

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

Slight to moderate hyperostosis were observed in the bones of rats administered 100 mg/kg/day for 6 months.

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.

Genotoxicity

The results from the genotoxicity studies are given in the table below.

Table 1 - Genotoxicity studies

Type of test / study ID / GLP	Test system	Concentration range / Metabolising system	Results
Gene mutations in bacteria/SR-1-24351/GLP	Salmonella strains TA1535, TA1537, TA98, TA100, TA102 E. Coli WP2 uvrA	Experiments without S9 WP2 uvrA: 156.3-2500 µg/plate TA98, TA100: 19.53-312.5 µg/plate TA1535, TA1537, TA102: 39.06-625 µg/plate Experiments with S9 WP2 uvrA: 312.5-5000 µg/plate TA1537, TA100: 19.53-312.5 µg/plate TA98, TA102, TA1535: 39.06-625 µg/plate	Negative
Gene mutations in mammalian cells/SR-2-24352/GLP	Human lymphocytes	Experiments without S9 3 h treatment/20 h harvest: 2.29-20.58 µg/mL 20 h treatment/20 h harvest: 2.5-10 µg/mL 44 h treatment/44 h harvest: 30 µg/mL Experiments with S9 3 h treatment/20 h harvest: 2.29-30 µg/mL 3 h treatment/44 h harvest: 30 µg/mL	Negative
Gene mutations in mammalian cells/SR-3-24354-mly/GLP	L5178Y $TK^{+/-}$ mouse lymphoma cells	Experiments without S9 3 hours treatment: 1.3-20 µg/mL 24 h treatment: 0.16-7.5 µg/mL Experiments with S9 3 h treatment: 2.5-40 µg/mL	Negative
Chromosomal aberrations in vivo/SR-1-24353-mas/GLP	Mouse, micronuclei in bone marrow; 5/sex/group	437.5, 875, 1750 mg/kg/day for two days p.o. (gavage) Sacrificed 24 h after treatment	Negative

Carcinogenicity

Long-term carcinogenicity studies conducted with masitinib in CD-1 mice and Sprague-Dawley rats.

Masitinib-treatment was associated with mortality in the mice. Hence, the overall survival rates ranged from 26-38% in the treated animals versus 40% in the control group. Due to high mortality rates, the study treatment period and the administered doses were reduced. Urinary bladder transitional carcinomas and papillomas were seen in 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.

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 finding was 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.

Reproduction Toxicity

An overview of the performed reproductive and developmental toxicity studies is given in the table below.

Table 2 - Reproductive and developmental toxicity studies

Study type / Study ID / GLP	Species; Number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg/day)
Male fertility/SR-1-26311-rsr/GLP but not the bioanalysis	Sprague-Dawley rat; 24 males/group	10, 30, 100 mg/kg/day p.o.	29 days prior to mating - female sacrifice	None	100
Female fertility/SR-1-26311-rsr/GLP but not the bioanalysis	Sprague-Dawley rat; 24 females/group	10, 30, 100 mg/kg/day p.o.	29 days prior to mating – day 7 *post-coitum*	↓fertility indices, ↓ corpora lutea, ↓implantation sites, ↑ pre-implantation loss	10
Female fertility/SR-2-aa19859/GLP	Sprague-Dawley rat; 25 females/group	15, 50 mg/kg/day p.o.	28 days followed by a recovery period of two weeks before mating	Acyclic oestrous cycle	15
Embryo-fœtal development/SR-1-29395-rsr/GLP but not the bioanalysis	Sprague-Dawley rat; 24 females/group	10, 30, 100 mg/kg/day	Day 6 - 17 *post-coitum*	F0: ↓ body weight gain, ↓ food consumption, macroscopic findings F1: ↓ foetal weight, skeletal variations	F0: <10 F1: 30
Embryo-fœtal development/SR-2-29398-rsl/GLP but not the bioanalysis	New Zealand White rabbit; 22 females/group	10, 30, 100 mg/kg/day	Day 6 – 18 *post-coitum*	F0: ↓ body weight F1: skeletal variations	F0: <10 F1: 100

GD, gestation day

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-foetal development were evaluated in rats and rabbits. In the rat study, a lower (-10%) mean foetal 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 foetal bone (5th and 6th sternebra) were observed in the rabbit embryo-foetal 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 foetal weight observed in rats. The NOAEL for maternal toxicity (reduced body weight/macroscopic findings) is considered < 10 mg/kg/day.

Toxicokinetic data

While control samples collected in the 4-week and 13-week repeat-dose toxicity studies conducted in rats were not analysed for the presence of masitinib, very low levels of masitinib (namely 1.51, 4.34, and 8.37 ng/mL) were detected in three control animals included in the 26 weeks repeat-dose toxicity study in rats. These levels were much lower than those quantified in the test-treated groups and were attributed to test item contamination.

A low level of masitinib (1.64 ng/mL) was detected in a single plasma sample (2 h) collected on study day 28 from a control animal included in the 4-week study in dogs. However, no masitinib was detected in plasma samples from control animals included in the 13-week and 39-week studies conducted with masitinib in dogs.

An overview of the toxicokinetic data obtained in the repeat-dose toxicity studies conducted with masitinib was provided (data not shown).

Local Tolerance

Evaluation of skin sensitization potential in mice using the local lymph node assay (LLNA):
Masitinib induced delayed contact hypersensitivity in the murine Local Lymph Node Assay.

According to the EC3 value obtained in the experiment (0.7%), masitinib should be considered as a strong sensitizer when applied on the skin.

Acute dermal irritation in rabbits: Masitinib was slightly irritant when applied topically to rabbits for up to 72 hours. Hence, mean scores over 24, 48 and 72 hours were 0.3, 1.0 and 0.7 for erythema and 0.0, 0.0 and 0.0 for oedema.

Acute eye irritation in rabbits: Masitinib was severely irritant when administered by ocular route to rabbits.

Other toxicity studies

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 aniline metabolite AB2436 gave rise to gene mutations in both bacteria and human lymphocytes in the presence of S9.

2.3.5. Ecotoxicity / environmental risk assessment

Table 3 - Summary of main study results

Substance (INN / Invented name): masitinib / Masiviera			
CAS-number (if available): 790 299-79-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	potentiometric (pH-metric) technique	3.75	Potential PBT (Y)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (e.g. prevalence, literature)	0.002 to 0.004	µg/L	< 0.01 threshold (N)

2.3.6. Discussion on non-clinical aspects

Inhibition of c-KIT and PDGFRs by masitinib has been shown. There is indirect evidence that these receptor tyrosine kinases could play a role in the progression of pancreatic cancer due to the involvement of mast cells. The drug inhibits proliferation and functions of cells bearing these receptors in vitro and in vivo. Masitinib alone does not act directly on pancreatic cancer cells, however it potentiates gemcitabine effect in vitro, an effect which is not apparent in vivo. Additional mechanisms of action such as potentiation of deoxycytidine kinase and inhibition of discoidin domain kinase receptors can be hypothesized based on experimental data.

The efficacy of masitinib in animal models of pancreatic cancer was tested in mice carrying tumours derived from the human pancreatic cancer cell line Mia Paca-2. The results showed that masitinib exerted no statistically significant effect on tumour growth. According to the Applicant, preliminary data from a study in the K-rasG12D transgenic mice model of pancreatic cancer

show that masitinib inhibits pre-cancerous lesions in the pancreas and that masitinib inhibits infiltration of mast-cells within the pancreatic tumour. However, at present, the anti-tumour efficacy of masitinib in in vivo models of pancreatic cancer has not been verified.

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. Considering a masitinib free fraction in human blood of 2.12%, the reported clinical plasma Cmax of 1206 ng/mL masitinib corresponds to an unbound plasma concentration of approximately 51.3 nM. Hence, only a minimal effect on the hERG channel is expected at clinical Cmax. No effect was observed on electrocardiogram parameters in telemetered dogs (n=3) receiving 50 mg/kg. This dose level roughly corresponds to the recommended daily dose for patients receiving masitinib.

No non-clinical studies on the potential for pharmacodynamic drug interactions were conducted. However this was considered acceptable, since masitinib will not be co-administered with drugs which have an identical pharmacological target and/or have similar or opposing pharmacodynamic effects.

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. Overall, the major metabolites detected in humans were also formed in animals and as such the species used for toxicity testing are considered valid animal models. The Applicant has not provided a quantitative comparison of the metabolite levels detected in humans and the species used for toxicity testing. Since no human specific metabolites have been detected, this was acceptable as no further metabolite qualification studies was required since masitinib is intended for the treatment of advanced cancer (ICH S9 guidance).

The plasma protein binding was high in all species: more than 90% in human plasma and more than 85% in dog, mouse and rat plasma. The free fraction of AB3280 in animal plasma was about twice as high as in human plasma. The applicant should provide an estimate of the expected contribution of AB3280 to the in vivo efficacy and an assessment as to whether it should be included in drug interaction considerations. While the genotoxic metabolite AB2436 as well as its genotoxic metabolite AB5235 was detectable in the urine of mice, only AB2436 was detected in rat urine and neither metabolite could be found in rat plasma. Similarly, these metabolites were not detected in human plasma, while AB2436 was found in human urine (AB5235 was not analysed for in human urine). The provided *in vitro* and *in vivo* data show that the genotoxic aniline metabolites AB2436 and AB5235 are formed predominantly in mice but to a lower extent in rats and humans. According to the Applicant, 0.05% of the administered masitinib dose (molar units) was detected as AB2436 in human urine. However, it is not fully clear how the value of 0.05% was derived.

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

In vitro studies showed that CYP3A4/5 was the enzyme primarily responsible for the metabolism of masitinib. The data also indicated that CYP2C8 has the capacity to catalyse the formation of AB3280 from masitinib.

The CYP450 inhibitory properties of masitinib and AB3280 towards CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4/5 were investigated in human liver microsomes. Neither CYP1A2, 2C8, 2C19 nor 2E1 were inhibited at masitinib concentrations up to 5 µM while CYP2C9 was inhibited with IC_{50} values in ≥17.5 µM. Masitinib was a weak to moderate inhibitor of CYP3A4/5 and CYP2C9, as well as CYP2D6 with IC_{50} values of 14 µM, 20 µM and > 30 µM, respectively. This inhibition was partly reversible. It is not possible to conclude if inhibition is competitive or non-competitive. The risk of inhibition of hepatic enzymes is very low, due to the limited free fraction in plasma, whereas the inhibition in the gut is a risk due to high concentrations of masitinib prior to absorption from the gut. AB2380 showed no inhibitory potential towards CYP450 isotypes at concentrations up to 2 µM.

Based on an *in vitro* study in human hepatocytes, masitinib neither increase the activity nor induce the levels of expression of CYP1A2, CYP2B6 or CYP3A4 at concentration up to 10 µM (cytotoxicity occurred at 30 µM).

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. These findings were also reported in the clinical setting. Findings also concerned the female genital tract in rats and the male genital tract in dogs. At higher dose-levels, these nonclinical findings were accompanied by bodyweight changes and mortality.

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.

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. Still, the overall toxicokinetic data indicate that while the bone marrow toxicity, renal toxicity, reproductive toxicity in male dogs and oestrous cycle disturbances in female rats occurred at or below clinically relevant exposure levels, small to moderate (3 to 10-fold) exposure margins may exist for the observed liver toxicity, ovarian toxicity, hyperostosis and myocardial toxicity.

Masitinib was non-genotoxic in a test battery comprising the following assays: Ames test, human lymphocytes, L5178Y TK+/- mouse lymphoma cells and in vivo mouse micronuclei test.

Although not required for an anti-cancer drug intended for treatment of advanced cancer, the Applicant submitted long-term carcinogenicity studies conducted with masitinib in CD-1 mice and Sprague-Dawley rats. Overall, based on the presently available data, it could not be excluded that masitinib may exert a carcinogenic effect in humans.

Masitinib did not affect the fertility of male rats. In female rats, in the general toxicity studies, masitinib was shown to disrupt ovarian function as evidenced by haemorrhagic ovarian follicular cysts seen in several studies. This disruption may be the cause of reduced fertility observed in the Segment I study. The “return to fertility” study suggested that the ovarian dysfunction was rapidly reversible. In the Segment I study, there was evidence of increased post-implantation loss in treated rats, indicating an embryotoxic action. This was not observed in the Segment II studies in rats or rabbits. In the rat segment II study, treatment with AB1010 resulted in reduced litter weight and reduced ossification. These findings may be indicative of slightly delayed development, as a consequence of maternal toxicity. There was no evidence of teratogenicity in the rat or the rabbit, over dose-levels up to those causing maternal toxicity.

Three studies were conducted to assess local tolerance. In an acute dermal irritation study masitinib mesylate was found to be a slight irritant when applied topically to rabbits. Masitinib mesylate was severely irritating when administered by the ocular route to rabbits. Masitinib mesylate showed skin sensitization potential in a murine LLNA.

The PEC surfacewater value for masitinib is below the action limit of 0.01 µg/L. However, as the log Kow is> 3, a bioaccumulation study would need to be performed.

2.3.7. Conclusion on the non-clinical aspects

Overall, the nonclinical data submitted was adequate. However, further information would be required with regards to plasma protein binding, metabolites and environmental risk assessment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Type of study	Study number	Location in eCTD	Objective(s) of the study	Study Design and Type of Control	Test product, dosage regimen, route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status, type of report
BA (food-effect)	AB1010-PIHV05031	5.3.1.1 (study-report-1)	evaluate the food intake influence on pharmacokinetic profiles	Cross over	Tablet, 200mg, oral	12	healthy volunteers	Single dose	Complete, Full
Comparative BA	AB1010-PIHV04015	5.3.1.2 (study-report-1)	compare the relative BA of AB1010 from two formulations (capsule or tablet)	Cross over	Tablet, Capsules, 100mg, oral	12	healthy volunteers	Single dose	Complete, Full
PK	AB1010-PIHV03001	5.3.3.1 (study-report-1)	determine safety / tolerability and PK parameters of AB1003	Double blind, placebo-controlled	powder for solution, ascending doses (40, 100, 200, 400 and 800 mg), oral	40	healthy volunteers	Dose escalations, single dose	Complete, Full
PK	AB1010-PIHV03003	5.3.3.1 (study-report-2)	determine safety / tolerability and PK parameters of AB1003	Double blind, placebo-controlled	Capsule, ascending doses (40, 100, 200, 400 and 800 mg), oral	32	healthy volunteers	7 days	Complete, Full
PK	AB05034	5.3.3.2 (study-report-1)	Assess efficacy and safety of the combination treatment and PK parameters of AB1003	multicenter, single group	9 mg/kg/day of masitinib (tablets, oral) + gemcitabine at 1,000 mg/m2 (IV)	22	patients with advanced pancreatic cancer	Until tumor progression or toxicity	Complete, Full
PK	AB03002	5.3.3.2 (study-report-2)	assess safety /tolerability and determine the MTD, assess PK parameters of AB1003, assess clinical activity of masitinib	open-label, dose escalating study	doses ranging from 40 to 1,000 mg/day	40 (with 19 GIST patients)	patients with advanced and/or metastatic solid tumors	12 weeks + extension phase	Complete, Full
PK/PD	AB05034	5.3.4.2 (study-report-1)	Assess efficacy and safety of the combination treatment and PK parameters of AB1003	multicenter, single group	9 mg/kg/day of masitinib (tablets, oral) + gemcitabine at 1,000 mg/m2 (IV)	22	patients with advanced pancreatic cancer	Until tumor progression or toxicity	Complete, Full
Efficacy	AB07012	5.3.5.1 (study-report-1)	compare efficacy and safety of masitinib at 9 mg/kg/day in combination with gemcitabine to placebo in combination with gemcitabine	Multicenter, randomized, double-blind, placebo-controlled, 2-parallel group	9 mg/kg/day of masitinib (tablets, oral) + gemcitabine at 1,000 mg/m2 (IV)	353	patients with advanced/metastatic pancreatic cancer	until disease progression	Complete, Full
Efficacy	AB05034	5.3.5.2 (study-report-1)	Assess efficacy and safety of the combination treatment (masitinib plus gemcitabine) and PK parameters of AB1003	multicenter, single group	9 mg/kg/day of masitinib (tablets, oral) + gemcitabine at 1,000 mg/m2 (IV)	22	patients with advanced pancreatic cancer	Until tumor progression or toxicity	Complete, Full

2.4.2. Pharmacokinetics

Absorption

Following oral administration, masitinib was relatively slowly absorbed with Tmax values between 2-5 hrs. No absolute bioavailability studies have been performed.

- Bioequivalence

Study AB1010-PIHV04015 evaluated the relative bioavailability of masitinib from two different formulations capsule used in phase I studies or tablet (the-to-be-marketed formulation) in 12 healthy male volunteers after a 100 mg masitinib base single oral administration. This was a single centre, open, two-way cross-over study, in which twelve healthy male volunteers, aged 18 to 45 years, received a single oral dose of masitinib (100 mg) on Day 1 of each of both treatment periods (tablet=treatment A and capsule=treatment B), separated by at least a one-week interval where no masitinib was taken in order to prevent any carry-over effect. The results are tabulated below.

Table 4 – Geometric mean and CV% pharmacokinetic parameters of AB1003 following single oral administration

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

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

Pharmacokinetic parameters were in the same range for healthy volunteers and patients with pancreatic cancer after repeated-dose administration. Values of tmax were between 1.6 and 2.8 hours in the AB05034 study and between 3 and 4 hours in the study AB03003.

The rate and extent of absorption was higher in patients suffering from pancreatic cancer compared to healthy volunteers. Mean half-life of AB1010 was similar: around 14h in patients with pancreatic cancer and around 18h in healthy volunteers. In terms of concentrations of the active metabolite AB3280, they were equivalent and corresponded to 1/4 of AB1010 concentrations in both patient groups.

- Influence of food

Study No. AB1010-PIVH05031 was a single centre, open, randomized, two-way cross-over study, in which 12 healthy male volunteers, aged 18 to 45 years, received a single oral administration of 200 mg AB1010 tablets during two treatment periods (fed conditions and fasted conditions as a high fat breakfast), separated by a two-week washout period. Thirteen (13) patients were initially

randomized, but one patient withdrew from the study and was therefore not considered in the pharmacokinetic analysis.

Based on AUC0-∞, the mean relative bioavailability (Fed/Fasted) was 1.23, the associated inter-individual variability, as expressed by the CV%, was quite low (16%). Cmax increased by 19%. Although the tmax for AB1003 was increased by 1 hour after a high fat breakfast, the difference was not statistically significant. There was also a slight increase in the extent of formation of AB3280 metabolite as illustrated by the increase of AUC0-t by 17%. Metabolite Cmax and tmax were not affected by concomitant food intake.

Distribution

At 100 mg and 400 mg repeated doses of masitinib, volumes of distribution of 1935 L and 1043 L respectively were determined.

The binding of ^{14}C-masitinib was determined on human blood cells, human plasma proteins and isolated human plasma proteins (HSA, AAG, GG). The ^{14}C-masitinib concentrations used, 100-3000 ng/mL, corresponds to a plasma concentration expected under therapeutically conditions. The binding to plasma proteins was 94 %. Binding to human serum albumin (HSA) was high, 91 %. A lower binding occurred on α1-acid-glycoprotein (AAG) and on gamma-globulin (GG), 74% and 46%, respectively.

Elimination

- Excretion

Steady state apparent oral clearance and renal clearance were between 0.7-1.4 L/min and 9-18 mL/min, respectively. Elimination half-life was around 16-18 hrs. No mass balance studies were performed. Urinary recovery rates were low with approximate recoveries of 1.5% of dose for masitinib and 6% for its primary metabolite, respectively.

- Metabolism

From in vitro studies of human liver microsomes, three metabolites have been identified with the N-demethylated (AB3280) form clearly dominating quantitatively. Recombinant cDNA expression studies and studies in human liver microsomes, demonstrated that CYP3A4 almost solely catalyses the formation of the primary metabolite with possible minor contributions from CYP2C8.

Dose proportionality and time dependencies

- Dose proportionality

The applicant presented data from the target population for a primary analysis of dose proportionality. The Applicant presented data for dose as well as for weight-adjusted dose.

Statistical inferences test are tabulated below:

Table 5 – Coefficient of correlation between Cmax or AUC and dose levels

	All tested subjects (N = 28)*	
	AUC ng.h/mL	C_{max} ng/mL
Dose (mg)	0.79	0.79
dose/weight (mg/kg)	0.80	0.83

**Excluding patient 6-05 and 7-03*

No adequate formal inference test has been provided. Additionally, analysis from healthy volunteer study clearly suggested a lack of dose-proportionality with exposures increasing more than expected: i.e. in study AB1010-PIHV03003, in the dose range 100 to 400 mg, mean Cmax increased in a ratio of 2.6 and 7.6 when dose increased in a ratio of 2 and 4, while the mean AUC0-τ increased in a ratio of 2.5 and 8.0 and mean Ctrough increased in a ratio of 2.4 and 7.6.

- Time dependency

Pharmacokinetics (PK) data from day 7 in the repeated-dose study in healthy volunteers were presented. The mean ratio of Cmax observed between Day 7 and Day 1 was 1.60, 1.54 and 2.09 following treatment with masitinib 100, 200 and 400 mg respectively. In addition the mean ratio of Ctrough was 2.31, 2.54 and 2.71 over this dose range. No significant difference of ratio was elicited between the levels of dose. However, it was observed that the ratio of Ctrough was statistically higher ($p<0.0001$) than the theoretical ratio calculated from the terminal t1/2. In the dose range 100 to 400 mg, mean Cmax increased in a ratio of 2.6 and 7.6 when dose increased in a ratio of 2 and 4, while the mean AUC0-τ increased in a ratio of 2.5 and 8.0 and mean Ctrough increased in a ratio of 2.4 and 7.6.

Special populations

No special population PK studies performed.

The applicant has stratified PK data from the target population with respect to gender and age.

- Gender

Gender did not appear to influence Cmax and AUC of masitinib to a clinically relevant degree (data not shown).

- Elderly

This stratification does not allow for a meaningful assessment of the influence of age due to the small sample presented (data not shown).

- Weight

No specific stratification has been made according to weight other than an evaluation of correlation coefficients between dose; weight-adjusted dose and AUC/Cmax and correlation coefficients stratified according to dose (Table 6).

Table 6 – Correlation coefficient between Cmax or AUC and dose levels

Dose (mg)		**AUC ng.h/mL**	**C_{max} ng/mL**
150-500	N = 11	0.62	0.57
500-1000	N = 12	0.68	0.5-
Dose/weight (mg/kg)		**AUC ng.h/mL**	**C_{max} ng/mL**
0.6-2	N = 7	0.72	0.72
3-6	N = 4	0.83	**0.91**
7-12	N = 10	0.44	0.52

Pharmacokinetic interaction studies

In vitro studies were discussed in the nonclinical section. No results from *in vivo* DDI studies have been provided since clinical studies are still on-going.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action has been deducted from animal models and in vitro systems. Masitinib is a tyrosine kinase inhibitor with anti-tumoural and anti-inflammatory activity. Masitinib is an inhibitor of the *KIT* wildtype (WT) receptor and its mutated forms (exon 9 and exon 11), as well as the platelet-derived growth factor alpha (PDGFRA) receptor.

Primary and Secondary pharmacology

No Primary and Secondary pharmacology studies have been submitted (see discussion on clinical pharmacology).

QTc intervals from study AB1010-PIHV03001 and study AB1010-PIHV03003 were presented. Given the in vitro data and data from other TKI's, prolongation of the QTc interval may be a clinically relevant issue. The data available from healthy volunteer studies were not entirely consistent, but there appeared to be a dose-related increase in QTc intervals that for the higher doses approach 20-30ms (data not shown).

2.4.4. Discussion on clinical pharmacology

The PK of masitinib has been investigated in two studies in healthy volunteers and in one study of target population as well as a supportive data from a study in patients suffering from solid tumours. Additionally, one BE study has been made to bridge PK data from the early formulation used to the to-be-marketed formulation. One study on food-interaction has also been conducted. There are no clinically relevant differences in PK parameters between healthy volunteers and those obtained in the target population.

The absorption profile of masitinib demonstrated a relatively slow absorption with Tmax values between 2 and 5 hours at suggested clinical doses. Bioequivalence has been adequately demonstrated for the to-be-marketed tablet formulation versus the formulation used in phase I.

Following a high fat meal, Cmax and AUC of masitinib increased by 19% and 23%, respectively. This is a moderate order of magnitude and appeared unlikely to be of clinical relevance.

The PK of masitinib has not been studied in any special populations. The Applicant has only stratified according to gender and age based on limited data and therefore few conclusions can be drawn. Gender does not appear to influence PK of masitinib to a clinically meaningful degree. The amount of data does not allow for estimation of the possible influence of age. There are no data on renal or hepatic impairment.

While the population PK analysis to some extent supports a weight-based posology, such level of evidence opposing a fixed-dose posology is very weak. Additionally, the selection of 9mg/kg as opposed to 6mg/kg is weakly substantiated and based on the fact that MTD was not reached at 9 mg/kg and speculations and extrapolations on systemic exposure in vitro IC50 values of hypothetical secondary targets.

In vitro data suggested that there be a number of clinically relevant drug-drug interactions. Further investigation would be required.

No specific studies on primary and secondary pharmacology have been performed. The pharmacogenomic substudy performed by the applicant to retrospectively stratify the population is strictly hypothesis generating (see clinical efficacy).

QTc intervals from study AB1010-PIHV03001 and study AB1010-PIHV03003 were presented. Given the in vitro data and data from other TKIs, prolongation of the QTc interval may be a clinically relevant issue. The data available from healthy volunteer studies were not entirely consistent, but there appeared to be a dose-related increase in QTc intervals that for the higher doses approach 20-30ms. In the healthy volunteer study (AB03003), observed QT increases were subsequently considered to be normal following a re-reading of the electrocardiograms (ECGs). The descriptive narratives of the patients who experienced cardiac events did not provide clear evidence of an effect of masitinib on the QT/QTc interval. However, an effect of masitinib on QTc cannot be ruled out. The clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for non-anti-arrhythmic drugs would be required to address whether masitinib has the potential to induce QTc interval prolongation.

2.4.5. Conclusions on clinical pharmacology

Overall, the PK of masitinib would require further investigation. Additional studies in special populations, on drug-drug interactions and a thorough QT/QTc study are also needed.

2.5. Clinical efficacy

2.5.1. Dose response study

Early dose finding studies were:

- Study AB1010-PIHV03001 - A phase I, double blind, placebo-controlled study to determine the safety, tolerability and PK profiles of ascending, single oral doses of AB1010 in healthy, young male subjects
- Study AB1010-PIHV03003 - A phase I, double blind, placebo-controlled study to determine the safety, tolerability and PK profiles of ascending, multiple oral doses of AB1010 in healthy, young male subjects.

Dose response studies was:

- Study No AB101003002 - A phase I, open-label, dose escalating study of oral AB1010 in patients with solid tumours

Experiments in human Mia Paca-2 cells with increasing concentrations of masitinib showed that masitinib at a concentration of 1 µM and beyond inhibited tyrosine kinase phosphorylation. Gemcitabine-resistant cell-lines pre-treated with 5 or 10 µM masitinib overnight, were significantly sensitized to gemcitabine as evidenced by a substantial reduction in IC50 of gemcitabine (>400-fold) [Humbert et al, 2010]. Therefore, a masitinib concentration between 1 and 5 µM was expected to lead to a resensitization of gemcitabine-resistant cancer cells in vivo.

In patients with solid tumours (supportive PK study) a dose range study was performed by assigning increasing doses of masitinib, starting from 40 mg/day, to subsequent cohorts of patients. Plasma concentrations were evaluated after a single masitinib dose on Day 1 and after 14 days of a repeated-dose regimen. The doses administered were not taking into account the patient's weight, but results were weight-adjusted a posteriori in order to determine the relationship between the dose in mg/kg/day and the in vivo plasma concentration (Cmax). Patients receiving between 1.5 and 3.5 mg/kg/day had a Cmax between 158 and 679 ng/mL, corresponding to a concentration between 0.3 and 1.4 µM, respectively. Patients receiving approximately 7.5 mg/kg/day had a Cmax of 802 ng/mL corresponding to a concentration of 1.6 µM. Patients receiving 9 mg/kg/day had a Cmax of 1441 ng/mL corresponding to a concentration of 2.9 µM. Patients receiving a concentration between 10.5 and 13.5 mg/kg/day had a Cmax between 1206 and 1841 ng/mL, respectively, corresponding to a plasma concentration between 2.4 to 3.7 µM, respectively. Finally, patients receiving a dose of 15 mg/kg/day presented a mean plasma concentration of 1800 ng/mL, corresponding to 3.6 µM.

2.5.2. Main study

Study AB07012

Methods

Study AB07012 was a prospective, multicentre, randomized, double-blind, placebo-controlled, 2-parallel group, phase III study to compare efficacy and safety of masitinib at 9 mg/kg/day in combination with gemcitabine, to placebo in combination with gemcitabine, in treatment of patients with advanced/metastatic pancreatic cancer.

Study Participants

Inclusion criteria consisted of:

- Histologically or cytologically confirmed adenocarcinoma of the pancreas
- Chemo-naïve patients with advanced/metastatic disease
- Documented decision justifying non eligibility for surgical resection. The documentation of the non-eligibility for surgical resection was reviewed by an independent committee.
- Measurable tumour lesions with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan according Response Evaluation Criteria In Solid Tumours (RECIST) criteria
- ECOG ≤ 1
- Patient with a BMI > 18 kg/m² and weighing at least 40 kg
- Patient with organ function as follows:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - Haemoglobin ≥ 10 g/dL
  - Platelets ≥ 100 x 10^9/L
  - AST/ALT ≤ 2.5x ULN (≤ 5 x ULN in case of liver metastases)
  - GammaGT < 3 x ULN (< 5 x ULN in case of liver metastases)
  - Bilirubin ≤ 1.5x ULN (≤ 3 x ULN in case of hepatic metastases)
  - Creatinine clearance ≥ 50 mL/min (Cockcroft and Gault formula)
  - Albuminemia ≥ 1 x LLN (32g/L)
  - Urea ≤ 2 x ULN
  - Proteinuria < 30 mg/dL on the dipstick; in case of proteinuria ≥ 30 mg/dL, 24-hour proteinuria should be < 1.5g/24 hours
- Patient with life expectancy > 12 weeks
- Men and women, age >18 years

Amongst exclusion criteria were:

- Patient treated for a cancer other than pancreatic cancer within 5 years before enrolment, with the exception of basal cell carcinoma or cervical cancer in situ
- Patient with, or with history, of central nervous system (CNS) metastasis
- Patient presenting with defined cardiac disorders.
- Any previous anti-tumour therapy (any chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy) within 6 months prior to baseline.

Treatments

Group 1: masitinib at 9 mg/kg/day plus gemcitabine 1,000mg/m^2 weekly.

Group 2: placebo plus gemcitabine 1,000mg/m^2 weekly.

The dose of gemcitabine was 1,000mg/m^2, administered by a 30 minute IV infusion once every 7 days, for up to 7 weeks, followed by a week of rest. Subsequent cycles consisted of IV infusion, once every 7 days, for 3 consecutive weeks out of every 4 weeks.

Objectives

The objective was to compare the efficacy and safety of masitinib at 9 mg/kg/day in combination with gemcitabine, to placebo in combination with gemcitabine, in treatment of patients with advanced/metastatic pancreatic cancer.

During this study, an ancillary pharmacogenomic study was performed in order to define predictive criteria of efficacy (all efficacy variables: survival and tumor assessment) from genomic data.

Outcomes/endpoints

The primary endpoint was Overall survival (OS). It was measured from the date of randomization to the date of documented death. If death was not observed, data on OS were censored at the last date the patient was known to be alive.

Secondary endpoints included:

- OS rate every 6 months
- Progression Free Survival (PFS). Progression is assessed by CT scan according to Modified RECIST (M-RECIST).
- Time to Progression (TTP). Progression is assessed by CT scan according to M-RECIST.
- Objective response rate (CR + PR) and control disease rate (CR + PR + SD) at week 24, 48 and 72.
- Best response along study. Best response was defined as the best response from baseline [complete response (CR) or partial response (PR) or stable disease (SD) or progressive disease (PD)] according to M-RECIST assessed by CT scan during the study. Two measures will be calculated: unconfirmed response and confirmed response 2 months apart. Rate of patients presenting with CR or PR as best response will be provided. Rate of patients presenting with CR or PR or SD as best response will be provided.
- The change in absolute value and % between baseline and at week 24, 48 and 72 for the following criteria: Level of serum CA 19-9, Quality of Life according to the EORTC QLQ-C30 questionnaire, Patient's visual analogue scale (VAS) of pain ranging from 0 ("No pain") to 100 ("Very severe pain"), The frequency and percentage of patients at week 24, 48 and 72 for ECOG Performance Status and Analgesic consumption.
- Pharmacogenomic assessment: Relationship between genomic data and all efficacy variables (survival and tumour assessment)
- Safety: Adverse events (AEs) and per-treatment arising changes in physical examination, neurological examination, vital signs (blood pressure, pulse rate and body temperature), cardiologic investigations (ECG), and clinical laboratory tests (biochemistry, haematology) will be graded based on NCI CTC v3.0 classification.

For the ancillary pharmacogenomics study, the sponsor collected biopsies of pancreatic tumors performed in patients included in this study and for whom kinases expression had been tested by immunohistochemistry (c-Kit, PDGF-R, FGF-R3, JAK, LYN, FYK, LCK). A DNA analysis of the regions coding for these kinases was done and the results were correlated to the protein expression. Two specific blood samples per patient were taken on a regular basis on W0, W1, W2 and W12 to conduct RNA analysis. These samples were taken according to the process described in the Manual

for pharmacogenomic study in order to identify potential variations of biomarkers and to correlate them to the efficiency or non-efficiency of the study treatment.

Sample size

In the overall population, based on survival rates phase 2 study masitinib in pancreatic cancer (AB05034) and literature on gemcitabine, 320 patients were considered necessary to detect a difference between groups with a power of 80% using a two-sided log rank test with a significance level of 0.05. Expected number of events at Month 12 was 252. Assuming a major protocol deviation rate between 8 and 10%, the total sample size was 353 patients, split equally between the two groups.

Sample size within a subgroup of patients: Within a sub-population of patients, a sample size of 220 patients (approximately 2/3 of patients) achieve 80% power to detect a difference between treatment group based on an HR of 1.5 using a two-sided alpha level 5% (ratio 1:1 inclusion= 21 months, follow-up= 12 months).

Randomisation

Patients were randomised in a 1:1 ratio. The randomisation was stratified by country and disease status (locally advanced/metastatic).

Blinding (masking)

This was a double-blind study using a matching placebo.

Statistical methods

The primary analysis foreseen in the statistical analysis plan was the re-randomization test in the mITT population.

Stratified log-rank test was to be performed on observed data, and test statistic will be provided along with p-value. Stratification factors at baseline included patients with locally advanced pancreatic cancer versus patients with metastatic pancreatic cancer (data from IVRS) and country.

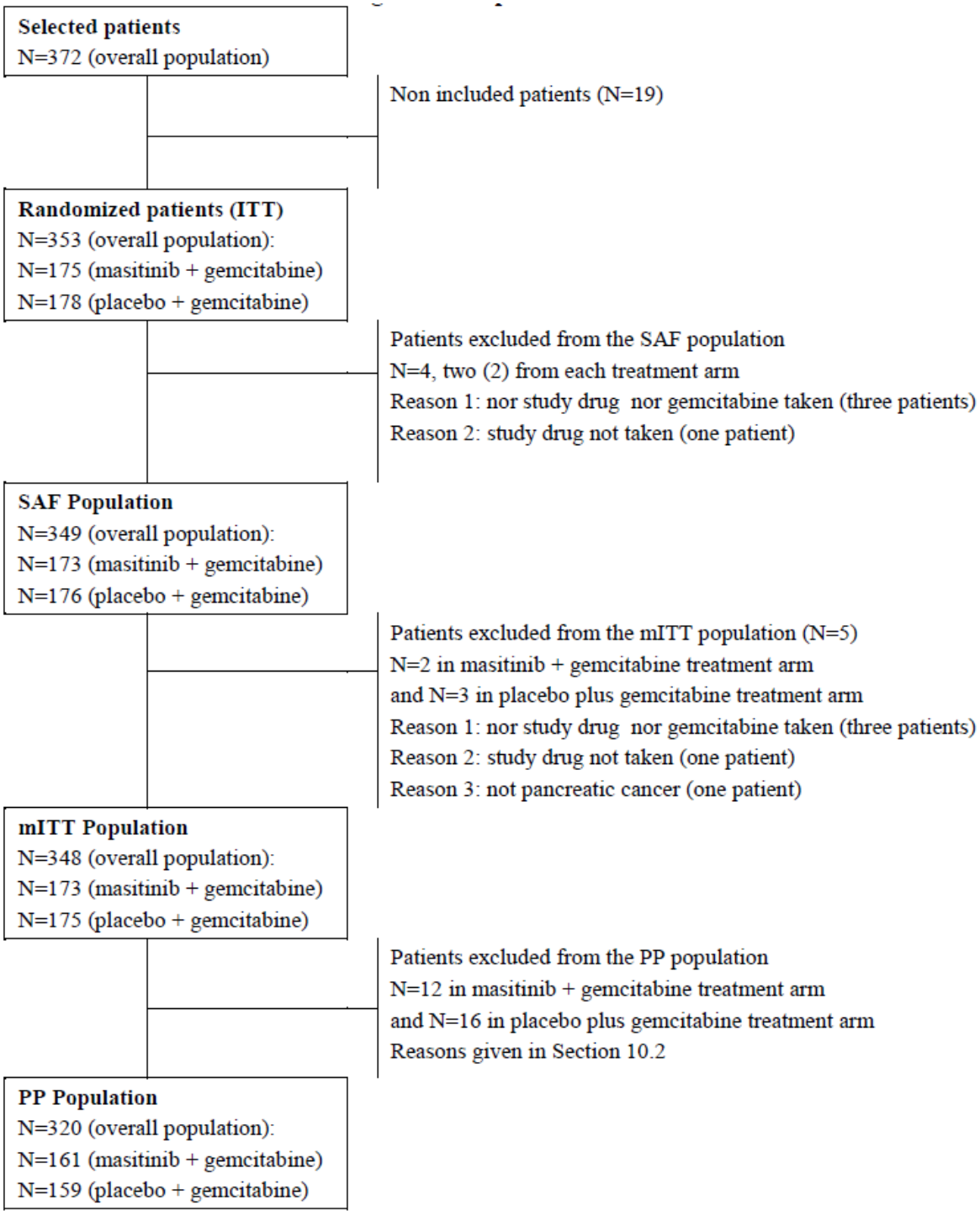
The type I (α) error was 5% (two-sided) for all comparative analyses, otherwise stated. Results were presented with a two-sided 95% CI.

As part of the pharmacogenomic assessment, the relationship between genomic data and all efficacy variables (survival and tumor assessment) was evaluated. For the ancillary DNA analysis, a sample size of 80 patients treated with masitinib was needed to achieve 80% power to detect a hazard ratio of 1.9 in the Cox model with an alpha level 5% two sided. For the RNA analysis, 100 patients in each group were needed to achieve 80% power to detect a difference of 1 for 10 genes (corresponding to a treatment effect two times higher in the masitinib arm).

Results

During the evaluation, the applicant submitted version 2.0 (dated July 2013) of the clinical study report revised further to findings of a GCP inspection conducted at the sponsor site on another clinical trial.

Participant flow



Recruitment

This study was carried out in 92 sites including 73 active sites: France (37 sites), USA (15 sites), Czech Republic (10 sites), Lebanon (5 sites), Poland (2 sites) and Romania (4 sites).

Conduct of the study

The first patient was randomized on 25 November 2008. Recruitment of patients in the study was completed on 6 July 2010. At the cut-off date of 1 March 2012, one patient was still ongoing.

Baseline data

Baseline demographics and disease characteristics and presented in the tables below.

Table 7 - Baseline demographics in the mITT-population and subpopulations: Patient characteristics

	All N = 348	Patients with pain intensity score N = 312	Pain VAS>20 N = 137	Below median pain N = 107	No pain, no morphine N = 68	Patients with genetic data N = 119	GBM N = 66	No GBM N = 53
Sex								
M + G								
N	173	155	64	57	34	60	34	26
male	86 (49.7%)	78 (50.3%)	32 (50.0%)	29 (50.9%)	17 (50.0%)	32 (53.3%)	19 (55.9%)	13 (50.0%)
female	87 (50.3%)	77 (49.7%)	32 (50.0%)	28 (49.1%)	17 (50.0%)	28 (46.7%)	15 (44.1%)	13 (50.0%)
P + G (N)								
N	175	157	73	50	34	59	32	27
male	102 (58.3%)	90 (57.3%)	41 (56.2%)	29 (58.0%)	20 (58.8%)	36 (61.0%)	21 (65.6%)	15 (55.6%)
female	73 (41.7%)	67 (42.7%)	32 (43.8%)	21 (42.0%)	14 (41.2%)	23 (39.0%)	11 (34.4%)	12 (44.4%)
p-value	0.109 (C)	0.215 (C)	0.471 (C)	0.461 (C)	0.465 (C)	0.397 (C)	0.418 (C)	0.685 (C)
Age								
M + G								
Age at screening								
Mean (SD)	62.6 (9.8)	62.8 (9.8)	63.8 (10.2)	61.6 (10.1)	62.7 (8.3)	63.9 (9.3)	65.8 (9.2)	61.4 (9.9)
Median	64.0	64.0	65.5	62.0	63.0	65.5	66.0	61.5
Range	36.0 ; 84.0	36.0 ; 84.0	36.0 ; 81.0	37.0 ; 78.0	44.0 ; 84.0	43.0 ; 84.0	43.0 ; 84.0	45.0 ; 79.0
Age at screening (class)								
≤ 65-year old	97 (56.1%)	87 (56.1%)	32 (50.0%)	34 (59.6%)	21 (61.8%)	30 (50.0%)	14 (41.2%)	16 (61.5%)
> 65-year old	76 (43.9%)	68 (43.9%)	32 (50.0%)	23 (40.4%)	13 (38.2%)	30 (50.0%)	20 (58.8%)	10 (38.5%)
P + G								
Age at screening								
Mean (SD)	61.7 (10.3)	62.3 (10.4)	64.0 (10.6)	60.0 (10.3)	62.3 (9.6)	62.4 (9.7)	61.2 (9.5)	63.9 (9.9)
Median	62.0	64.0	66.0	60.0	64.0	64.0	62.5	64.0
Range	31.0 ; 79.0	31.0 ; 79.0	31.0 ; 79.0	37.0 ; 79.0	35.0 ; 79.0	40.0 ; 79.0	43.0 ; 76.0	40.0 ; 79.0
Age at screening (class)								
≤ 65-year old	112 (64.0%)	96 (61.1%)	36 (49.3%)	37 (74.0%)	23 (67.6%)	38 (64.4%)	22 (68.8%)	16 (59.3%)
> 65-year old	63 (36.0%)	61 (38.9%)	37 (50.7%)	13 (26.0%)	11 (32.4%)	21 (35.6%)	10 (31.3%)	11 (40.7%)
p-value on 'age at screening'	0.417 (A)	0.719 (A)	0.914 (A)	0.410 (A)	0.851 (A)	0.409 (A)	0.052 (A)	0.348 (A)
p-value on 'age class'	0.131 (C)	0.368 (C)	0.936 (C)	0.117 (C)	0.612 (C)	0.112 (C)	**0.025 (C)**	0.865 (C)

(A) Analysis of variance; (C) Chi-square test; M+G: masitinib plus gemcitabine; P+G: placebo plus gemcitabine

Table 8 – Time since diagnosis and localisation of primary tumour in the overall population and subpopulations

	All N = 348	Patients with pain intensity score N = 312	Pain VAS>20 N = 137	Below median pain N = 107	No pain, no morphine N = 68	Patients with genetic data N = 119	GBM N = 66	No GBM N = 53
Time since diagnosis (months)								
M + G								
N	173	155	64	57	34	60	34	26
Mean (SD)	1.5 (3.6)	1.4 (2.2)	1.4 (2.3)	1.1 (1.5)	1.7 (2.7)	2.0 (5.5)	1.5 (2.4)	2.7 (7.8)
Median	0.8	0.8	0.9	0.7	1.0	0.7	0.7	0.9
Range	0.1 ; 40.9	0.1 ; 15.5	0.1 ; 15.5	0.2 ; 10.6	0.2 ; 13.4	0.3 ; 40.9	0.3 ; 11.6	0.3 ; 40.9
P + G								
N	174	157	73	50	34	58	32	27
Mean (SD)	1.8 (3.6)	1.7 (2.9)	1.6 (2.7)	1.9 (3.1)	1.5 (3.0)	1.2 (1.0)	1.1 (1.1)	1.3 (1.0)
Median	0.8	0.9	0.8	1.0	0.8	0.8	0.8	0.9
Range	0.0 ; 31.3	0.0 ; 17.6	0.0 ; 16.2	0.1 ; 15.2	0.1 ; 17.6	0.1 ; 4.5	0.1 ; 4.5	0.1 ; 3.7
p-value 'time since diagnosis'	0.553 (A)	0.264 (A)	0.559 (A)	0.110 (A)	0.748 (A)	0.258 (A)	0.385 (A)	0.359 (A)
Tumor localization								
M + G								
Head	93 (53.8%)	82 (52.9%)	30 (46.9%)	31 (54.4%)	21 (61.8%)	26 (43.3%)	17 (50.0%)	9 (34.6%)
Body	50 (28.9%)	46 (29.7%)	23 (35.9%)	19 (33.3%)	4 (11.8%)	21 (35.0%)	8 (23.5%)	13 (50.0%)
Tail	54 (31.2%)	48 (31.0%)	19 (29.7%)	17 (29.8%)	12 (35.3%)	21 (35.0%)	12 (35.3%)	9 (34.6%)
P + G								
Head	94 (53.7%)	84 (53.5%)	33 (45.2%)	28 (56.0%)	23 (67.6%)	34 (57.6%)	17 (53.1%)	17 (63.0%)
Body	59 (33.7%)	53 (33.8%)	29 (39.7%)	13 (26.0%)	11 (32.4%)	17 (28.8%)	12 (37.5%)	5 (18.5%)
Tail	49 (28.0%)	43 (27.4%)	23 (31.5%)	17 (34.0%)	3 (8.8%)	16 (27.1%)	10 (31.3%)	6 (22.2%)
p-value localization 'head'	0.994 (C)	0.915 (C)	0.845 (C)	0.867 (C)	0.612 (C)	0.119 (C)	0.800 (C)	**0.039 (C)**
p-value localization 'body	0.333 (C)	0.439 (C)	0.648 (C)	0.408 (C)	**0.041 (C)**	0.469 (C)	0.217 (C)	**0.016 (F)**
p-value localization 'tail	0.511 (C)	0.487 (C)	0.818 (C)	0.643 (C)	**0.008 (C)**	0.353 (C)	0.728 (C)	0.317 (C)

(A) Analysis of variance; (C) Chi-square test; (F) Fisher's exact test

Table 9 describes the tumor classification and the presence of metastases in patients at baseline in the overall population and in each subpopulation.

Table 9 – Presence of metastases at baseline in the overall population and subpopulations

Presence of metastases	All N = 348	Patients with pain intensity score N = 312	Pain VAS>20 N = 137	Below median pain N = 107	No pain, no morphine N = 68	Patients with genetic data N = 119	GBM N = 66	No GBM N = 53
M + G								
N	173	155	64	57	34	60	34	26
Clinical classification (DRC)								
Locally advanced	22 (12.7%)	19 (12.3%)	5 (7.8%)	7 (12.3%)	7 (20.6%)	6 (10.0%)	3 (8.8%)	3 (11.5%)
Metastatic	151 (87.3%)	136 (87.7%)	59 (92.2%)	50 (87.7%)	27 (79.4%)	54 (90.0%)	31 (91.2%)	23 (88.5%)
Liver localization of metastases	114 (65.9%)	103 (66.5%)	49 (76.6%)	37 (64.9%)	17 (50.0%)	46 (76.7%)	29 (85.3%)	17 (65.4%)
P + G								
N	175	157	73	50	34	59	32	27
Clinical classification (DRC)								
Locally advanced	24 (13.7%)	23 (14.6%)	12 (16.4%)	4 (8.0%)	7 (20.6%)	14 (23.7%)	7 (21.9%)	7 (25.9%)
Metastatic	151 (86.3%)	134 (85.4%)	61 (83.6%)	46 (92.0%)	27 (79.4%)	45 (76.3%)	25 (78.1%)	20 (74.1%)
Liver localization of metastases	122 (69.7%)	110 (70.1%)	48 (65.8%)	42 (84.0%)	20 (58.8%)	35 (59.3%)	22 (68.8%)	13 (48.1%)
p-value 'clinical classification'	0.784 (C)	0.536 (C)	0.127 (C)	0.467 (C)	1.000 (C)	**0.045 (C)**	0.180 (C)	0.293 (F)
p-value localization 'liver metastasis'	0.446 (C)	0.493 (C)	0.165 (C)	**0.025 (C)**	0.465 (C)	**0.042 (C)**	0.109 (C)	0.206 (C)

(C) Chi-square test; (F) Fisher's exact test; DRC: data review committee.

Numbers analysed

The *Intent-To-Treat (ITT) population* was defined as all randomized patients whether they have received the study treatment or not, i.e. 353 patients.

The *Modified Intent-To-Treat (mITT) population* included all ITT patients except for patients withdrawn prematurely from the study for a well-documented non treatment-related cause. The mITT population included 348 patients.

The *Per-Protocol (PP) Population* consisted of all patients of the mITT data set without any major protocol deviation. The PP population included 320 patients.

The *Safety population* included all enrolled patients in the study, who had received at least one dose of any of the study drug (masitinib or placebo). The safety population included 349 patients.

In addition, analyses in subgroups defined by the presence/severity of pain and by the genomic profile derived from the ancillary pharmacogenomics study were conducted to support the claimed indication of masitinib.

Outcomes and estimation

Overall survival

Table 10 and Figure 1 below summarise the median overall survival in the overall population and the survival rates at 6, 12, 18, and 24 months in the ITT and the mITT population.

Table 10 – Univariate analysis of OS in the overall population

Treatment arm	p-value re-randomization	p-value*	Hazard ratio [95%CI]	Median OS [95% CI] (months)	OS rates (%) [95% CI] M6	M12	M18	M24
ITT population								
M + G (N=175)	0.612	0.609	1.02 [0.82; 1.27]	7.7 [6.0;10.7]	58.8 [50.3;69.5]	31.0 [22.8;43.8]	16.3 [10.4;27.8]	7.6 [4.0; 16.5]
P + G (N=178)				7.8 [6.1;10.8]	59.5 [51.0;69.9]	31.7 [23.8;44.4]	16.9 [10.9;28.4]	8.0 [4.3;17.1]
mITT population								
M + G (N=173)	0.710	0.706	1.01 [0.81; 1.26]	7.8 [6.0;10.7]	59.2 [50.6; 69.9]	31.4 [23.1; 44.3]	16.4 [10.5; 28.0]	7.5 [4.0; 16.4]
P + G (N=175)				7.8 [6.1;10.7]	59.4 [50.9; 70.0]	31.6 [23.4; 44.4]	16.6 [10.7 ; 28.1]	7.6 [4.0 ; 16.6]

*stratified log-rank on clinical classification (IVRS) and country; M+G: Masitinib plus gemcitabine; P+G: Placebo plus gemcitabine

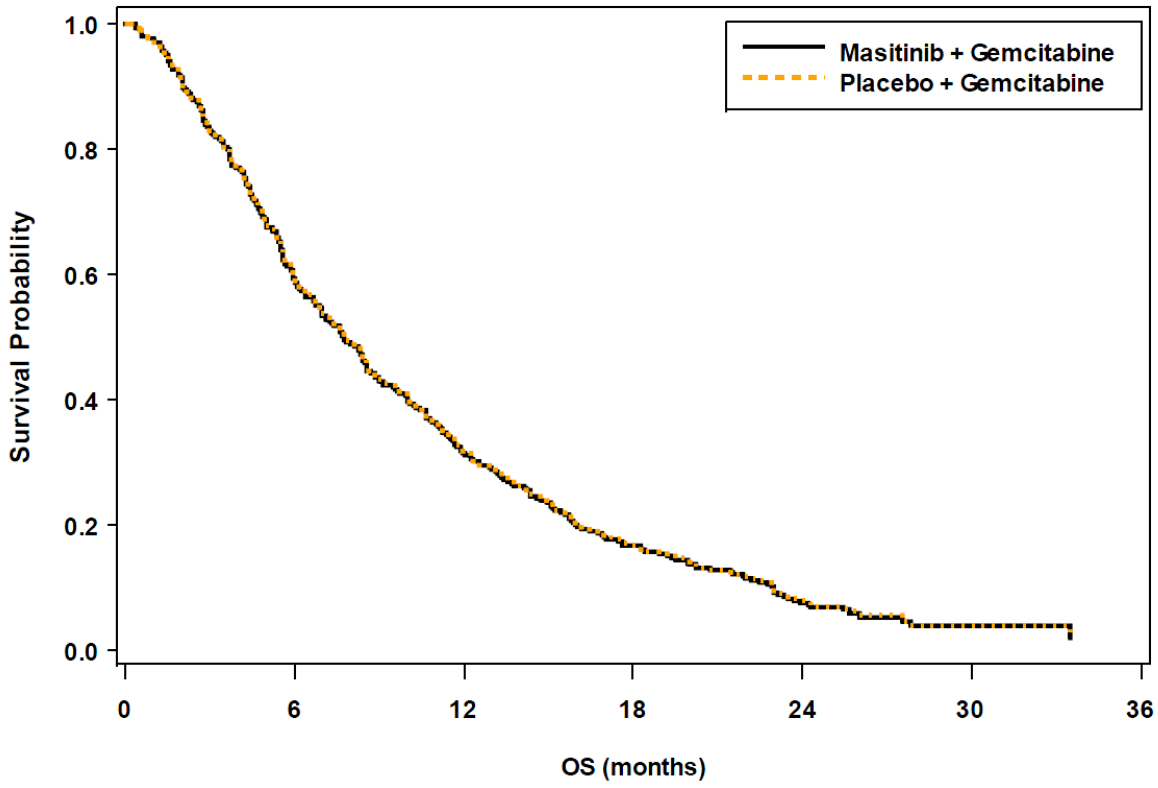


Figure 1 – OS analysis in overall population (univariate model with stratification on "locally advanced / metastatic" and "country")

OS was investigated in patients according to each baseline characteristic through a univariate analysis in patients having received the placebo plus gemcitabine treatment, in order to determine variables that may impact overall survival independently from the treatment.

Progression-free survival

The table below shows the univariate (stratified on the variables "locally advanced/metastatic" and "country") and multivariate analyses of progression-free survival for the two treatment arms.

Table 11 – PFS results in the overall population

Treatment arm	N	p-value*	Hazard ratio [95%CI]	Median PFS [95% CI] (months)	PFS rates [95% CI] (%) M6	M12	M18
Univariate analysis (stratification on the two variables 'locally advanced/metastatic' and 'country')							
M + G	173	0.058	1.26 [0.97; 1.64]	2.8 [1.9; 3.9]	19.9 [11.9;35.4]	6.5 [2.6;18.6]	2.0 [0.5;11.1]
P + G	175			3.6 [2.4; 5.5]	31.1 [21.7;46.0]	11.5 [5.7;25.1]	4.2 [1.3;16.8]
Multivariate analysis							
M + G	173	0.115	1.23 [0.93; 1.63]	2.4 [1.9; 3.7]	19.1 [11.5;32.4]	5.6 [2.2;14.8]	1.7 [0.4; 8.2]
P + G	175			3.5 [2.1; 5.0]	25.5 [17.1;38.9]	9.2 [4.3;20.2]	3.4 [1.0;12.7]

M+G: masitinib plus gemcitabine; P+G: placebo plus gemcitabine; * log-rank

Best Response, Objective Response Rate and Disease Control Rate

274 patients were evaluable for tumour response according to M-RECIST as they had at least one post-baseline tumour assessment. Table 12 presents the results of the objective response and disease control analysis in the overall population (mITT).

Table 12 – Best response, objective response and disease control (M-RECIST) in the overall population

	M + G (N=173)	P + G (N=175)	p-value
Patients evaluable for tumor response (M-RECIST)	120 (69.4%)	154 (88.0%)	
Best confirmed response over study			0.105 (F)
CR	0 (0.0%)	1 (0.6%)	
PR	13 (10.8%)	17 (11.0%)	
SD	56 (46.7%)	90 (58.4%)	
PD	51 (42.5%)	46 (29.9%)	
Objective response - CR + PR (M-RECIST), confirmed	13 (10.8%)	18 (11.7%)	0.825 (C)
Best confirmed response over study, confirmed or not			0.031 (F)
CR	1 (0.8%)	2 (1.3%)	
PR	25 (20.8%)	25 (16.2%)	
SD	43 (35.8%)	81 (52.6%)	
PD	51 (42.5%)	46 (29.9%)	
Objective response - CR + PR (M-RECIST), confirmed or not	26 (21.7%)	27 (17.5%)	0.390 (C)
Disease control - CR + PR + SD (M-RECIST)	69 (57.5%)	108 (70.1%)	0.030 (C)

(F) Fisher's exact test; (C) Chi-square test

Ancillary analyses

Specific genetic biomarker (GBM) population

The objective of the ancillary pharmacogenomics study was to evaluate modification and amplification of kinases and other genes that could be predictive of sensibility and or resistance to TKIs and so to define criteria of efficacy or no efficacy from genomic data. On the basis of this data, the applicant identified specific genetic biomarker (GBM), involving 10 genes, characterizing the genetic subpopulation. Only 119 mITT patients out of 353 enrolled in study AB07012 had genetic data available.

Table 13 – OS results in the 'GBM' subpopulation of study AB07012 (multivariate model)

Treatment arm	N	p-value*	Hazard ratio [95%CI]	Median OS [95% CI] (months)	OS rates [95% CI] (%) M6	M12	M18	M24
Univariate analysis								
M+G	34	0.0000019	0.22 [0.12; 0.40]	11.7 [8.6;17.1]	78.8 [66.7;93.2]	48.6 [32.8;74.8]	15.8 [7.1;45.4]	10.6 [4.1; 39.0]
P+G	32			5.3 [3.9; 8.6]	36.7 [21.7; 67.4]	7.5 [2.6; 35.8]	0.7 [0.1; 19.1]	0.3 [0.0; 16.3]
Multivariate analysis								
M+G	34	0.00000056	0.17 [0.09; 0.33]	12.9 [8.7;17.1]	78.7 [67.5; 93.5]	52.5 [38.0;76.8]	18.3 [9.1;44.8]	12.6 [5.7;36.9]
P+G	32			4.7 [3.7; 8.3]	31.8 [19.0; 61.8]	7.4 [3.1; 30.7]	0.8 [0.1; 20.6]	0.3 [0.0; 17.8]

M+G: masitinib plus gemcitabine; P+G: placebo plus gemcitabine; *log-rank

"Pain" subpopulation

The second subpopulation identified by the applicant on a post-hoc analysis comparing OS in a "pain" population defined as VAS > 20 mm versus a "no pain" population (VAS ≤5 mm and not taking opioid analgesics at baseline).

The results for the "pain population" (VAS > 20 mm) are shown in the table below.

Table 14 –OS results in the 'pain' population (AB07012)

Treatment arm	N	p-value[1]	Hazard ratio [95%CI]	Median OS [95% CI] (months)	OS rates [95% CI] (%) M6	M12	M18	M24
Univariate analysis (stratification on the two variables 'locally advanced/metastatic' and 'country')								
M+G	64	0.109	0.76 [0.52 ; 1.09]	7.3 [5.3; 12.3]	55.2 [43.0; 73.3]	28.9 [18.1; 50.6]	14.9 [7.5; 35.4]	≤4.6* [1.5; 20.1]
P+G	73			5.6 [4.5; 10.5]	46.1 [33.6; 66.0]	20.1 [11.1; 40.7]	8.8 [3.7; 25.8]	≤2.1* [0.5; 14.0]
Multivariate analysis								
M+G	64	0.012	0.62 [0.43; 0.89]	8.0 [5.8; 11.5]	57.6 [47.9; 71.2]	31.8 [21.9;47.3]	17.9 [10.2;32.4]	≤6.3* [2.5; 17.1]
P+G	73			5.4 [4.5; 8.0]	43.7 [33.5;58.4]	17.8 [10.5;31.3]	7.9 [3.7;18.0]	≤2.0* [0.6; 8.3]

M+G: masitinib plus gemcitabine; P+G: placebo plus gemcitabine; * the nearest rate value was taken, i.e. the rate at M23.7 (time point not reached in stratified univariate and multivariate analyses). [1] log-rank test

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15 – Summary of efficacy for trial AB07012

Title: Prospective, multicentre, randomized, double-blind, placebo-controlled, 2-parallel group, Phase III study masitinib plus gemcitabine vs. placebo plus gemcitabine in patients with locally advanced and metastatic pancreatic cancer.			
Study identifier	**AB07012**		
Design	Prospective, multicentre, randomized, double-blind, placebo-controlled, 2-parallel group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Until progressive disease or toxicity with a possibility of palliative treatment in case of clinical benefit not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Masitinib + gemcitabine (M+G)		Masitinib at 9 mg/kg/day plus gemcitabine at 1,000 mg/m^2 weekly (175 patients randomised)
	Placebo + gemcitabine (P+G)		Placebo plus gemcitabine at 1,000 mg/m^2 weekly (178 patients randomised)
Endpoints and definitions	Primary endpoint	OS	Overall survival: Time from the date of randomisation to the date of documented death.
Database lock	1 March 2012		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT): 353 patients Modified intent to treat (mITT): 348 patients		
Descriptive statistics and estimate variability	Treatment group	Masitinib + Gemcitabine (ITT/mITT)	Placebo + Gemcitabine (ITT/mITT)
	Number of subject	175/173	178/175
	OS (months) 95% CI	7.7/7.8 [6.0;10.7]/[6.0;10.7]	7.8/7.8 [6.1;10.8]/[6.1;10.7]
	Hazard ratio	1.02 (0.82-1.27)/1.01 (0.81-1.26)	
	P-value (log rank)	0.609/0.706	

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

Not applicable.

Clinical studies in special populations

No studies in special populations have been submitted.

Supportive study

Supportive phase II study AB05034 was a multicentre, single group phase II study to evaluate efficacy and safety of masitinib at 9 mg/kg/day in combination with gemcitabine in the treatment of patients with advanced/metastatic pancreatic cancer.

Twenty-two patients with a KPS ≥ 70 (~ECOG score ≤ 2) were assigned to receive masitinib at 9 mg/kg/day plus gemcitabine at 1000 mg/m2 weekly. Major efficacy endpoints of this study were time to progression (TTP), progression-free survival (PFS) and overall survival (OS).

The median TTP was 6.4 months (95% CI: 2.7 - 11.7) and the median PFS was 4.4 months. The median OS was 7.1 months (95% CI: 4.8 - 17.0). The applicant also presented analysis of subgroups in this phase II study, with few patients included (n=22 total in the study). The results add little information on the efficacy of the combination.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application was supported by phase III study AB07012 designed to evaluate the efficacy of masitinib plus gemcitabine vs. placebo plus gemcitabine in patients with locally advanced and metastatic pancreatic cancer. The primary endpoint was overall survival. To support the indication of masitinib in subpopulations of patients with presenting with specific genetic biomarkers ("aggressive genetic fingerprint") and patients presenting with pain estimated as strictly higher than 20 mm / 100 mm on a visual analogue scale pain, the applicant conducted several post-hoc analyses which are considered exploratory.

The applicant failed to demonstrate a sound biological rationale correlating the selected variables (genes of the genomic signature; pain) and masitinib as well as their relationship with the mechanism of action of masitinib.

Efficacy data and additional analyses

A weight-based posology was proposed by the applicant further to analysis of correlations between weight-adjusted dose and exposure in a very small dataset from a different study population (see pharmacokinetics). This was not considered by CHMP as an adequate justification of posology recommendations.

Study AB07012 failed to show a difference in the primary endpoint overall survival between the treatments groups. Furthermore, no benefits in terms of PFS, or improved quality of life (QoL) were observed.

Overall, the efficacy of masitinib in patients with locally advanced/metastatic pancreatic cancer was not demonstrated in the overall population of the pivotal trial.

In line with CHMP Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99), a specific claim of a beneficial effect in a particular subgroup required pre-specification of the corresponding null hypothesis and an appropriate confirmatory analysis strategy.

The findings of the post-hoc exploratory analyses, suggesting a potential role of the drug in subpopulations selected on the basis of "genomic signature" and on the basis of "pain" at baseline are hampered by major shortcomings and may only be considered as hypothesis generating and results must be convincingly validated.

2.5.4. Conclusions on the clinical efficacy

The evidence provided is considered insufficient to establish the efficacy of masitinib in pancreatic cancer. The results obtained in subpopulations with "pain" and "specific genetic biomarkers" derived from post-hoc exploratory analyses and thus should only be considered as hypothesis generating. Therefore, confirmation is needed before an approval can be considered.

2.6. Clinical safety

Patient exposure

The safety population included 173 patients in the masitinib plus gemcitabine treatment arms and 176 patients in the placebo plus gemcitabine treatment arm that received at least one intake of the study drug (i.e. masitinib or placebo). Few patients in the proposed indication have been exposed to masitinib >12 months (n=10). In the entire safety database 152 patients have been exposed to masitinib > 12 months and 82 patients out of the 152 patients have been exposed for > 24 months.

Adverse events

Table 16 provides an overview of adverse events in studies with masitinib and chemotherapy.

Table 16 – Studies with masitinib and chemotherapy - Overview of adverse events

Number (%) of patients with at least one	Pancreatic cancer	
	AB07012	AB05034
	Masitinib+ Gemcitabine (N=173)	Masitinib+ Gemcitabine (N=22)
AE	173 (100%)	22 (100%)
SAE (non fatal)	107 (61.8%)	17 (77.3%)
Death	27 (15.6%)	4 (18.2%)
AE leading to permanent discontinuation	73 (42.2%)	14 (63.6%)
Severe AE	158 (91.3%)	22 (100%)
AE leading to dose reduction	28 (16.2%)	1 (4.5%)

Table 17 provides an overview of AEs reported in study AB07012 with masitinib administered in combination with gemcitabine, according to the overall population, the population 'pain' (VAS > 20 at baseline), and the population harbouring the 'aggressive genetic fingerprint' at baseline.

Table 17 – Study AB07012 - Overview of adverse events

Number of patients (%) with at least one…	Overall population (N=349)	
	M + G	P + G
	173	176
AE	173 (100.0%)	173 (98.3%)
Deaths	27 (15.6%)	36 (20.5%)
Deaths related to toxicity	14 (8.1%)	19 (10.8%)
Deaths related to disease progression	13 (7.5%)	17 (9.7%)
SAE (non fatal)	107 (61.8%)	94 (53.4%)
Hematological AE (grade 3+4):	109 (63.0%)	73 (41.5%)
Grade 3	96 (55.5%)	71 (40.3%)
Grade 4	49 (28.3%)	12 (6.8%)
Non-hematological AE (grade 3+4):	132 (76.3%)	124 (70.5%)
Grade 3	125 (72.3%)	113 (64.2%)
Grade 4	37 (21.4%)	45 (25.6%)

M+G: Masitinib plus Gemcitabine; P+G: Placebo plus Gemcitabine

In the pivotal study, the most common AEs in the masitinib plus gemcitabine group (occurring in >40%) were: anaemia (60.7%), neutropenia (50.3%), nausea (57.8%), vomiting (50.3%), oedema (all preferred terms, 44.6%), thrombocytopenia (48.0%), asthenia (48.6%), rash (all preferred terms, 41.1%) and pyrexia (40.5%). The most frequent AEs in the placebo plus gemcitabine group (occurring in >40%) were: anaemia (47.7%), nausea (46.6%) and asthenia (46.0%).

The following AEs were reported more frequently in the masitinib plus gemcitabine group than in the placebo plus gemcitabine group: anaemia, lymphopenia, neutropenia, thrombocytopenia, eyelid oedema, nausea, vomiting, pyrexia, dehydration hypokalaemia and thrombosis. The following AEs were reported more frequently in the placebo plus gemcitabine group compared to the masitinib plus gemcitabine group: Back pain, constipation and pulmonary embolism. The frequencies of cardiac disorders and infections + infestations were lower in the masitinib plus gemcitabine group compared to the placebo plus gemcitabine group.

Overall, both AEs grade 3 and grade 4 were observed with a higher frequency in the masitinib plus gemcitabine arm compared to the placebo plus gemcitabine arm in the pivotal study (85.5% vs. 71.6% and 38.2% vs. 28.4%). The difference between the treatment arms was especially due to “blood and lymphatic system disorders” (neutropenia, anemia, thrombocytopenia, leucopenia, lymphopenia) and “skin and subcutaneous tissue disorders” (rash, grade 3 only). Although the frequencies of grade 3 and 4 “gastrointestinal disorders” were almost equal more vomiting and

diarrhea were observed in the masitinib plus gemcitabine arm, however, more abdominal pain was observed in the placebo plus gemcitabine group.

In the supportive study AB05034, the percentages of the different AEs were generally higher, however, the study population was small (n=22). The incidence of cardiac disorders was lower in the pivotal study compared to the supportive study AB05034, 5.8% vs. 18.2%.

Serious adverse event / deaths / other significant events

Serious adverse events:

Non-fatal serious AEs reported in more than one patient for study AB07012 are displayed in Table 18. In the masitinib-containing arm the most common (> 4%) non-fatal SAEs were pyrexia (8.7%), neutropenia (8.1%), jaundice (6.4%), vomiting (5.8%), anaemia (5.2%), General Physical Health Deterioration (5.2%), dehydration (4.6%).

Table 18 – Study AB07012 - Most frequent (>5%) non-fatal serious adverse events in the overall population

System Organ Class/Preferred Term	Overall population M + G (N=173)	Overall population P + G (N=176)
At least one SAE	107 (61.8%)	93 (53.1%)
Blood And Lymphatic System Disorders	31 (17.9%)	10 (5.7%)
Neutropenia	14 (8.1%)	3 (1.7%)
Anemia	9 (5.2%)	7 (4.0%)
Cardiac Disorders	1 (0.6%)	6 (3.4%)
Gastrointestinal Disorders	30 (17.3%)	27 (15.4%)
Abdominal Pain	4 (2.3%)	11 (6.3%)
Vomiting	10 (5.8%)	1 (0.6%)
Subileus	5 (2.9%)	4 (2.3%)
Diarrhea	6 (3.5%)	0 (0.0%)
General Disorders And Administration Site Conditions	34 (19.7%)	22 (12.6%)
Pyrexia	15 (8.7%)	6 (3.4%)
General Physical Health Deterioration	9 (5.2%)	2 (1.1%)
Hepatobiliary Disorders	22 (12.7%)	16 (9.1%)
Jaundice	11 (6.4%)	8 (4.5%)
Cholangitis	6 (3.5%)	4 (2.3%)
Infections And Infestations	14 (8.1%)	18 (10.2%)
Sepsis	2 (1.2%)	3 (1.7%)
Infection	2 (1.2%)	2 (1.1%)
Pneumonia	3 (1.7%)	1 (0.6%)
Urinary Tract Infection	0 (0.0%)	3 (1.7%)
Cellulitis		
Investigations	11 (6.4%)	7 (4.0%)
Metabolism And Nutrition Disorders	12 (6.9%)	5 (3.4%)
Dehydration	8 (4.6%)	1 (0.6%)
Nervous System Disorders	4 (2.3%)	4 (2.3%)
Psychiatric Disorders	4 (2.3%)	5 (2.9%)
Renal And Urinary Disorders	6 (3.5%)	3 (1.7%)
Respiratory And Thoracic And Mediastinal Disorders	7 (4.0%)	21 (12.0%)
Pulmonary Embolism	3 (1.7%)	8 (4.5%)
Dyspnea	1 (0.6%)	8 (4.5%)
Skin And Subcutaneous Tissue Disorders	7 (4.0%)	0 (0.0%)
Rash	6 (3.5%)	0 (0.0%)
Vascular Disorders	3 (1.7%)	6 (3.4%)
Hemorrhage	2 (1.2%)	2 (1.1%)
Deep Vein Thrombosis	1 (0.6%)	2 (1.1%)

Deaths

Fatal AEs reported in more than one patient for study AB07012 are displayed in Table 19. The most frequent fatal AEs observed in more than two subjects in the masitinib plus gemcitabine group were: general physical health deterioration (n=7) and hepatic failure (n=3). The most frequent fatal AEs observed in more than two subjects in the placebo plus gemcitabine group were: general physical health deterioration (n=12) and disease progression (n=4).

Table 19 – Study AB07012– Any Adverse events leading to death during the study in the overall population

	Overall population	
System Organ Class/Preferred Term	**M + G (N=173)**	**P + G (N=176)**
At least one AE leading to death	27 (15.6%)	36 (20.5%)
Blood And Lymphatic System Disorders	1 (0.6%)	1 (0.6%)
Anemia	1 (0.6%)	1 (0.6%)
Cardiac Disorders	2 (1.2%)	1 (0.6%)
Cardiac Arrest	-	1 (0.6%)
Cardio-Respiratory Arrest	1 (0.6%)	-
Myocardial Infarction	1 (0.6%)	-
Gastrointestinal Disorders	-	2 (1.1%)
Constipation	-	1 (0.6%)
Ileus	-	1 (0.6%)
Peptic Ulcer	-	1 (0.6%)
General Disorders And Administration Site Conditions	12 (6.9%)	18 (10.3%)
General Physical Health Deterioration	7 (4.0%)	12 (6.9%)
Disease Progression	2 (1.2%)	4 (2.3%)
Death	2 (1.2%)	1 (0.6%)
Asthenia	1 (0.6%)	1 (0.6%)
Pain	-	1 (0.6%)
Sudden Death	1 (0.6%)	-
Hepatobiliary Disorders	5 (2.9%)	4 (2.3%)
Hepatic Failure	3 (1.7%)	-
Jaundice	1 (0.6%)	2 (1.1%)
Cholangitis	1 (0.6%)	-
Hepatic Cirrhosis	-	1 (0.6%)
Hyperbilirubinemia	-	1 (0.6%)
Infections And Infestations	5 (2.9%)	3 (1.7%)
Sepsis	2 (1.2%)	2 (1.1%)

Bacteremia	1 (0.6%)	-
Bronchitis	-	1 (0.6%)
Incision Site Infection	1 (0.6%)	-
Perirectal Abscess	1 (0.6%)	-
Pneumonia	1 (0.6%)	-
Investigations	1 (0.6%)	3 (1.7%)
Blood Albumin Decreased	0 (0.0%)	1 (0.6%)
Blood Alkaline Phosphatase Increased	0 (0.0%)	1 (0.6%)
Blood Bilirubin Increased	1 (0.6%)	1 (0.6%)
Gamma Glutamyltransferase Increased	1 (0.6%)	1 (0.6%)
Metabolism And Nutrition Disorders	1 (0.6%)	2 (1.1%)
Diabetes Mellitus	0 (0.0%)	1 (0.6%)
Hyperglycemia	-	1 (0.6%)
Hyperkalemia	-	1 (0.6%)
Hypoalbuminemia	1 (0.6%)	-
Neoplasms Benign And Malignant And Unspecified (Incl Cysts And Polyps)	1 (0.6%)	-
Tumor Invasion	1 (0.6%)	-
Nervous System Disorders	1 (0.6%)	3 (1.7%)
Hepatic Encephalopathy	-	2 (1.1%)
Brain Edema	1 (0.6%)	-
Cerebrovascular Accident	-	1 (0.6%)
Psychiatric Disorders	-	1 (0.6%)
Completed Suicide	-	1 (0.6%)
Renal And Urinary Disorders	-	3 (1.7%)
Renal Failure Acute	-	2 (1.1%)
Renal Failure	-	1 (0.6%)
Respiratory And Thoracic And Mediastinal Disorders	1 (0.6%)	4 (2.3%)
Pulmonary Embolism	1 (0.6%)	1 (0.6%)
Acute Respiratory Failure	-	1 (0.6%)
Dyspnea	-	1 (0.6%)
Hyperventilation	-	1 (0.6%)
Respiratory Distress	-	1 (0.6%)
Vascular Disorders	1 (0.6%)	-
Shock	1 (0.6%)	-

M+G: Masitinib plus Gemcitabine; P+G: Placebo plus Gemcitabine

In the supportive study only 1/22 patients died due to an AE (4.5%). Deaths due to disease progression and deaths not considered related to treatment were excluded.

Events of interest

Neutropenia was one of the most common AE (87 patients 50.3%) observed in patients treated with masitinib in the overall population as well as in the two subpopulations ('pain' subpopulation and 'aggressive genetic fingerprint') with grade 4 neutropenia significantly increased compared to controls (19.7% versus 2.8%). This AE is of clinical relevance due to the already haematological toxicity linked to gemcitabine. The occurrence of neutropenia was mainly observed in the first 2 months and in the vast majority of cases resolved without sequelae. Although the high frequency of grade 4 neutropenia in the masitinib treated arm, febrile neutropenia events, which is the most common clinical complication linked to neutropenia together with infections, were limited or not prevalent in the masitinib treated arm.

Cardiac disorders were observed in 10 patients of whom two experienced tachycardia whereas no additional information was available for the others. Three death events were reported in the masitinib treated patients (1 cardiac-respiratory arrest, 1 myocardial infarction and 1 sudden death).

Laboratory findings

Shifts in *biochemistry values*, from normal biochemistry value at baseline, were frequently observed, however, in the majority of cases to grade 1 or 2.

The following shifts from normal at baseline to grade 3-4 were observed more frequently in the masitinib plus gemcitabine group compared to placebo plus gemcitabine group: Sodium decreased (9.3% vs. 4.2%), potassium decreased (10.1% vs. 3.2%), calcium decreased (4.3% vs. 1.6%), albumin decreased (5.5% vs. 3.3%), bilirubin increased (9.6% vs. 4.3%) and alkaline phosphatase increased (6.1% vs. 2.6%).

The following shifts from normal at baseline to grade 3-4 were observed more frequently in the placebo plus gemcitabine group compared to masitinib plus gemcitabine group: Glucose increased (4.3% vs. 0%), potassium increased (1.6% vs. 0%) and AST increased (4.5% vs. 1.9%).

A shift from a normal *haematologic value* at baseline to a decrease in haemoglobin, platelets, leucocytes or neutrophils was observed more frequently in the masitinib plus gemcitabine arm compared to the placebo plus gemcitabine arm. The shifts were mainly grade 1-2, however, more than half of the shifts concerning the neutrophils were grade 3-4.

Grade 3-4 shifts were more common in the masitinib plus gemcitabine arm compared to the placebo plus gemcitabine arm concerning haemoglobin (6.8% vs. 3.4%), platelets (2.7% vs. 1.6%), leucocytes (7.1% vs. 3.2%), neutrophils (15.1% vs. 7.4%) and lymphocytes (11.2% vs. 4.8%).

Safety in special populations

No data or discussion of the safety in special populations has been presented.

The safety of masitinib in patients with hepatic impairment has not been studied, although the liver is a common metastatic site of pancreatic cancers, and masitinib is mainly metabolized by the liver. An increase in transaminase levels was reported in roughly 50% of patients. An increased level of total bilirubin (31.7% masitinib arm versus 18.3% gemcitabine arm) mainly grade 1 was also noted, although this is a common laboratory finding in pancreatic cancer patients. Moreover,

hepatobiliary disorders (5 patients) were listed among fatal AEs. No starting dose adjustment was recommended in patients with mild to moderate hepatic impairment.

Data in patients with severe renal impairment are lacking. In the pivotal study, renal disorders were observed in 17.9% of masitinib treated patients and mainly consisted of proteinuria (6.4%), haematuria (4.6%, renal failure (4%).

Safety related to drug-drug interactions and other interactions

There is no study available on drug interactions.

Discontinuation due to adverse events

AEs leading to discontinuation, interruption or dose reduction in the pivotal study AB07012 are summarised in the table below. In the supportive study AB05034, 63.6% of the patients discontinued due to an AE.

Table 20 – Study AB07012– Adverse events leading to masitinib / placebo discontinuation, interruption or dose reduction

Number of patients (%) with at least one…	M + G	P + G
N	**173**	**176**
All AEs…		
leading to discontinuation	73 (42.2%)	48 (27.3%)
leading to interruption	129 (74.6%)	90 (51.1%)
leading to dose reduction	28 (16.2%)	16 (9.1%)
Discontinuations due to non-severe AEs (grade 1, 2, or hematological grade 3)	23/73 (31.5%)	16/48 (33.3%)

M+G: Masitinib plus Gemcitabine; P+G: Placebo plus Gemcitabine

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The combination of masitinib and gemcitabine in the proposed doses and indication was supported by 195 patients, 173 patients from the pivotal study (AB07012) and 22 from the supportive phase II study (AB05034). Additional information from the entire safety database, which includes patients who received masitinib either in combination with chemotherapy/other anticancer agents or as single agent masitinib for both oncology indications and non-oncology indications is considered of limited values because of the underlying disease related toxicities and those related to gemcitabine co-administration.

The median study duration was shorter in the masitinib + gemcitabine arm (M+G arm) compared with the placebo plus gemcitabine arm (P+G arm) (61 days vs. 114 days).

The exposure time to study drug was shorter in the M+G arm compared to the P+G arm (median 1.7 months vs. 3.7 months) and so was the study drug dose (34.1% vs. 17.1% received <80% of

the planned dose). The same was true for gemcitabine exposure as well as the gemcitabine dose intensity.

The exposure data indicates that the masitinib plus gemcitabine regimen is poorly tolerated and in this relation one could question the dose finding. The toxicity of the study regimen is also supported by the higher discontinuation due to adverse events and due to “patients request/unwillingness to continue” in the M+G arm compared to the P+G arm (29.7% vs. 17.1% and 11.6% vs. 7.4%).

The most common AEs in the M+G group (occurring in >40%) were: anaemia, neutropenia, nausea, vomiting, oedema, thrombocytopenia, asthenia, rash and pyrexia. The most frequent AEs in the P+G group (occurring in >40%) were: anaemia, nausea and asthenia.

Overall, both AEs grade 3 and grade 4 were observed with a higher frequency in the M+G arm compared to the P+G arm (85.5% vs. 71.6% and 38.2% vs. 28.4%). The difference between the treatment arms was especially due to neutropenia, anaemia, thrombocytopenia, leucopenia, lymphopenia, rash, vomiting and diarrhoea in the M+G arm, however, more abdominal pain was observed in the P+G group. In the supportive study (AB05034) severe AEs were experienced in all 22 patients compared to 91.3% of the patients in the M+G arm of the pivotal study.

A high number of patients discontinued study drug permanently due to AEs in the masitinib plus gemcitabine group, n=73(42.2%), compared to the placebo plus gemcitabine group, n=48 (27.3%). A similar pattern was observed due to study drug interruptions (74.6% vs. 51.1%) and dose reductions (16.2% vs. 9.1%). In the supportive study, 63.6% of the patients discontinued due to an AE.

In the pivotal study AEs leading to death were numerically more frequent in the P+G arm (20.5%) compared to the M+G treatment arm (15.6%).

The most frequent fatal AEs observed in more than two subjects in the M+G group were: General physical health deterioration (n=7) and hepatic failure (n=3). The most frequent fatal AEs observed in more than two subjects in the P+G group were: General physical health deterioration (n=12) and disease progression (n=4). The 3 deaths due to hepatic failure are of concern. More deaths due to infections were observed in the M+G group (5 patients vs. 3 patients). However, febrile neutropenia, sepsis and overall infection were not more frequent in the M+G arm although more patients were observed with more neutropenia and more severe in this arm.

In the pivotal study, more patients in the M+G arm (61.8%) experienced non-fatal SAEs compared to the P+G arm (53.1%), but the observed difference between treatment arms is less than expected. In the M+G arm the most common (> 4%) non-fatal SAEs were neutropenia (8.1%), pyrexia (8.7%), jaundice (6.4%), vomiting (5.8%), anaemia (5.2%), General Physical Health Deterioration (5.2%), dehydration (4.6%). This pattern is not unexpected for a TKI although haematological toxicity is higher in masitinib treated patients than in those treated with a TKI for the same indication (i.e. erlotinib). Neutropenia was reported as non-fatal SAE in only 1.7% of patients in the P+G arm. However, events of febrile neutropenia or sepsis occurred with similar frequencies between treatment arms (1.7%/0.6% and 1.2%/1.7%, respectively). In the P+G arm the most common non-fatal SAEs were abdominal pain (6.3%), jaundice (4.5%), dyspnoea (4.5%) and pulmonary embolism (4.5%).

A cross comparison among available treatments for the sought indication with regard to haematotoxicity showed that M+G treatment remains the treatment with the highest

haematological toxicity among those available for the locally advanced/metastatic pancreatic cancer.

No studies have been conducted in patients with renal and hepatic impairment. In view of nonclinical findings and reported renal and hepatic disorders, the effect of masitinib on the kidney function and on the liver remains uncertain, particularly in view of the sought indication with the liver as the most common site of metastasis and local infiltration.

In the pivotal study hepatobiliary disorders were reported in the 24.9% of masitinib treated patients and 5 patients experienced deaths due to hepatic disorders. No starting dose adjustment is recommended in patients with mild to moderate hepatic impairment. To support this conclusion the Applicant defined hepatic impairment by using cholestasis and hepatic cytolysis biomarkers. These are not considered to adequately reflect the hepatic metabolic function. Thus, the provided evidence in support of no need of dose adjustment in hepatic impaired patients is considered inadequate and of poor strength and information on Child Pugh score in patients from study AB07012 (with or without hepatic cytolysis or/ and hepatic cholestasis) is lacking.

Cardiac disorders were observed in 10 patients of whom two experienced tachycardia whereas no additional information was available for the others. Three death events were reported in the masitinib treated patients (1 cardiac-respiratory arrest, 1 myocardial infarction and 1 sudden death). No further investigation of the cardiotoxic potential of masitinib has conducted although other drugs acting as tyrosine kinase inhibitors (such as imatinib) were reported to have a cardiotoxic potential. A lack of information on the potential cardiotoxicity of masitinib is noted. Although it is known that tyrosine kinase inhibitors could cause a significant QT prolongation, a specific QT study was not reported. A specific QT study is required.

2.6.2. Conclusions on the clinical safety

The lack of a complete characterisation of the safety profile of masitinib together with the existing evidence of a significant haematological toxicity amplified for the combination of masitinib plus gemcitabine are major unfavourable effects that greatly impact on the benefit risk balance of masitinib.

2.7. Pharmacovigilance

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance and risk minimisation activities at this time.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 3.0 the PRAC considered by consensus that the risk management system for masitinib (Masiviera) for the treatment of pancreatic cancer could be acceptable provided minor revisions were made to the RMP.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Important identified risks	▪ Severe neutropenia ▪ Severe skin toxicity ▪ Oedema and fluid retention ▪ Liver toxicity ▪ Proteinuria ▪ Creatinine increased ▪ Interstitial lung disease
Important potential risks	▪ Disseminated intravascular coagulation ▪ Cardiac toxicity ▪ Hypertension ▪ Hypotension ▪ Hypothyroidism ▪ Reproductive toxicity ▪ Carcinogenicity ▪ Off label use
Missing information	▪ Efficacy and safety in children ≤18 years ▪ Use in pregnant or lactating women ▪ Use in patients with grade ≥ 3 liver enzymes increased ▪ Use in patients with grade ≥ 2 blood creatinine increased ▪ Potential of drug interaction with masitinib ▪ Effect of masitinib on the fertility ▪ Use in patients with ECOG score > 2 ▪ Embryotoxicity

- **Pharmacovigilance plans**

Table 21 - Ongoing and planned studies in the PhV development plan

Activity/Study title (category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
QT/QTc study	To assess the effects of single oral doses of masitinib on QTc Interval compared to placebo using moxifloxacin as positive control.	Cardiac toxicity	Proposed	Not finalised
Specific drug drug interactions studies testing the pharmacokinetics of masitinib with CYP3A4	To evaluate pharmacokinetic interaction between itraconazole, an	Drug drug interactions masitinib with inhibitor of	Planned	Not finalised

Activity/Study title (category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
inhibitor	inhibitor of CYP3A4, and masitinib	CYP3A4		
Specific drug drug interactions studies testing the pharmacokinetics of masitinib with CYP3A4 inducer	To evaluate pharmacokinetic interaction between dexa-methasone, an inducer of CYP3A4, and masitinib	Drug drug interactions masitinib with inducer of CYP3A4	Ongoing	End of 2013
Systematic hormonal work up in non-menopausal female patients enrolled in the nononcology clinical trials	Explore a potential relationship between masitinib and hormonal unbalance in female patients	Reproductive toxicity	Ongoing	Unknown
Follow-up of confirmatory phase 3 study	To confirm the benefit risk balance of masitinib in the pain and genetic fingerprint populations	Confirm the benefit risk balance in the pain and the genetic populations	Ready for submissio n	End of 2015

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC noted various inconsistencies and ambiguities in the PhV plan for Masiviera.

- **Risk minimisation measures**

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Severe neutropenia	Posology adaptation, labeling of neutropenia	Complete blood counts performed regularly
Severe skin toxicity	Labeling of rash, pruritus, dry skin, erythema, alopecia, palmar plantar erythrodysthesia, onychoclasis, nail toxicity, pigmentation disorders, psoriasis	None
Oedema and fluid retention	Labeling of eyelid oedema, oedema peripheral, face oedema and oedema.	None
Liver toxicity	Posology adaptation, labeling of transaminases increased, gamma GT increased, bilirubine increase, LDH increase and hyperbilitubinaemia	Liver tests performed regularly

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Proteinuria	Posology adaptation, labeling of proteinuria	Renal tests performed regularly
Creatinine increased	Posology adaptation, labeling of creatinine increased	Renal tests performed regularly
Interstitial lung disease	Labeling of interstitial lung disease	None
Cardiac toxicity	Labeling of tachycardy	None
Hypertension	Labeling of hypertension	None
Hypotension	None, pharmacovigilance routine activities are considered as sufficient	None
Hypothyroidism	None, pharmacovigilance routine activities are considered as sufficient	None
Reproductive toxicity	Contraception is mandatory during and 4 months after the treatment	None
Carcinogenicity	Preclinical safety findings are mentioned in the SmPC	None
Off label use	The indication is clearly specified in the SmPC	None

The PRAC noted inconsistencies in the RMP and tables, notably in Parts III.5.1, Parts IV.3-4 and Parts V.1 and V.3 were not completed as required. Regarding Part V, missing information was not addressed.

The CHMP endorsed this advice without changes.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.9. 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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The proposed indication of masitinib was for the first-line treatment in combination with gemcitabine of non-resectable locally advanced or metastatic pancreatic cancer in adult patients

presenting with specific genetic biomarkers and patients presenting with pain estimated as strictly higher than 20 mm / 100 mm on a visual analogue scale.

The efficacy claim was based on post-hoc exploratory analyses of study AB07012.

The beneficial effects of masitinib in the proposed indication have not been demonstrated (see Uncertainty in the knowledge about the beneficial effects).

Uncertainty in the knowledge about the beneficial effects

In the pivotal study AB07012, the clinical benefit of adding masitinib to gemcitabine for the treatment of patients with locally advanced or metastatic pancreatic cancer has not been demonstrated as the study failed to show a difference in its primary endpoint, overall survival between the treatment groups: median overall survival was 7.7 and 7.8 months in the masitinib arm and in the placebo arm, respectively (p-value = 0.609). The hazard ratio was 1.02 (95% CI [0.82; 1.27]). No benefits were observed in terms of any other clinical benefit endpoint, such as in terms of PFS gain, or improved QoL.

The efficacy claim was based on post-hoc exploratory analyses of not pre-specified subgroups of study AB07012. However, the findings of these subgroup analyses on the basis of “genomic signature” and on the basis of “pain” at baseline, might only be considered as hypothesis generating and would need confirmation.

Furthermore, the applicant failed to demonstrate a sound biological rationale correlating the selected variables (genes of the genomic signature and pain) and masitinib as well as their relationship with the mechanism of action of masitinib.

From a quality perspective, the insufficient information on the manufacturing process and controls of the active substance and finished product raise uncertainties with regards a potential exposure of the patient to impurities of toxicological concern and on an inconsistent performance of the product *in vivo*.

Risks

Unfavourable effects

When compared to gemcitabine, the combination resulted in more neutropenia, anaemia, thrombocytopenia, leucopenia, lymphopenia, rash, oedema, nausea, vomiting and diarrhoea.

Uncertainty in the knowledge about the unfavourable effects

In the pivotal study cardiac disorders were observed in 10 patients. Three deaths were reported in the masitinib treated patients (1 cardiac-respiratory arrest, 1 myocardial infarction and one sudden death). Newer TKIs used in the treatment of various cancers have been noted to cause significant QT prolongation. Limited QTc data from two studies in healthy volunteers has been provided. An increase in QT of 15-20 ms from baseline was observed in one study but not in the other study. Finally, preclinical studies have shown signals concerning cardiotoxicity.

No studies have been conducted in patients with renal and hepatic impairment. In view of nonclinical findings and reported renal and hepatic disorders, the effect of masitinib on the kidney function and on the liver remains uncertain, particularly in view of the sought indication with the liver as the most common site of metastasis and local infiltration.

In the pivotal study hepatobiliary disorders were reported in the 24.9% of masitinib treated patients and 5 patients experienced deaths due to hepatic disorders. No starting dose adjustment is recommended in patients with mild to moderate hepatic impairment. To support this conclusion the Applicant defined hepatic impairment by using cholestasis and hepatic cytolysis biomarkers. These are not considered to adequately reflect the hepatic metabolic function. Thus, the provided evidence in support of no need of dose adjustment in hepatic impaired patients is considered inadequate and of poor strength and information on Child Pugh score in patients from study AB07012 (with or without hepatic cytolysis or/ and hepatic cholestasis) is lacking.

Benefit-risk balance

In the absence of established efficacy and in view of the significant toxicity, the benefit-risk balance is considered negative.

Importance of favourable and unfavourable effects

Efficacy results reported in the subgroup analyses of study AB07012 should be viewed only as hypothesis generating and would need to be confirmed prospectively. The toxicity associated with the combination, in particular haematological toxicity, is considered significant.

From a quality perspective, the insufficient information on the manufacturing process and controls of the active substance and finished product raise uncertainties with regards a potential exposure of the patient to impurities of toxicological concern and on an inconsistent performance of the product *in vivo*.

Discussion on the benefit-risk balance

Despite the acknowledged unmet medical need for the treatment of non-resectable locally advanced or metastatic pancreatic cancer, the CHMP considered that in the absence of a positive benefit-risk balance, the requirements for a conditional approval laid down in Article 4 of Commission Regulation (EC) No 507/2006, cannot be fulfilled. In addition, it is likely that the applicant will not be in a position to provide the comprehensive clinical data for the confirmation of a positive benefit-risk balance in a timely manner considering that the confirmatory study has not been initiated to date.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Masiviera in the first-line treatment, in combination with gemcitabine, of unresectable locally advanced or metastatic

pancreatic cancer in adult patients presenting with specific genetic biomarkers and patients presenting with pain, the CHMP considers by consensus that the quality, safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the conditional Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The efficacy of masitinib, in combination with gemcitabine, for the first-line treatment of unresectable locally advanced or metastatic pancreatic cancer in adult patients presenting with specific genetic biomarkers and patients presenting with pain has not been demonstrated;

In the absence of proven efficacy, the significant toxicity profile of masitinib constitutes a concern;

- The quality of the product is insufficiently controlled with regards patient exposure to impurities and the reproducibility between biobatches and commercial batches cannot be guaranteed.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

5. Re-examination of the CHMP opinion of 23 January 2014

Following the CHMP conclusion that Masiviera was not approvable based on the efficacy and quality grounds outlined above, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

Clinical Ground No. 1 (the efficacy of masitinib has not been demonstrated): The applicant modified the applied indication. The applicant considered that the advanced pancreatic cancer patients with over-expression of ACOX-1 in blood (''1-gene GBM'' subgroup) or patients with pain > 20 mm / 100 mm on a visual analogue scale (''pain'' subgroup) subpopulations both have a strong internal and external biological evidence supporting their plausibility, and are considered as the two most internally and externally biologically validated subgroups. Several publications reported by the applicant to support that there is a strong biological plausibility for the use of masitinib in the new claimed indication. The plausibility of the pain subgroup was based on a pancreatic adenocarcinoma mice model where masitinib was claimed to reduce the number of intra-tumoral mast cells, reduce pancreatic lesions, pancreatic vascularization and innervation. Regarding the 1-gene GBM subgroup, ACOX1 over-expression may flag patients with M2-polarized macrophage infiltration and poor expected survival. In study AB07012, the 1-gene GBM (ACOX1) was found to be the gene with the most important impact on OS among patients receiving placebo plus gemcitabine.

Finally, the applicant considered that a conditional approval of masitinib in the claimed subpopulations is supported by a strong biological rationale and would provide a significant clinical benefit in a non-negligible proportion of pancreatic cancer patients with a high unmet medical need.

According to the applicant current guidelines do not preclude a conditional marketing authorization of masitinib.

Clinical Ground No. 2 (the significant toxicity profile of masitinib, in the absence of proven efficacy): The applicant considered that the risk associated with the toxicity of masitinib is manageable and doesn't negatively impact the benefit/risk balance. Masitinib safety profile in the claimed subgroups was similar to that reported in the overall study population. The tolerability of masitinib did not worsen over time and a tendency of better treatment tolerance was observed over time. In addition, the masitinib safety database is sufficient to demonstrate the safety of masitinib in pancreatic cancer. Finally, the combination of masitinib + gemcitabine has no detrimental effect on the quality of life of patients with pancreatic cancer as compared with single-agent gemcitabine treatment.

Quality Ground No. 1 (piperazinyl methylbenzoic acid chloride is considered a complex molecule and should instead be considered as intermediate of the synthesis): The applicant proposed not to handle piperazinyl methylbenzoic acid chloride as an intermediate of the manufacturing process of the active substance, i.e. redefining the starting material to an earlier stage of manufacture of the active substance, but to perform at a future date additional analytical development in order to demonstrate that the impurities of piperazinyl methylbenzoic acid or its chloride derivative are well controlled and present at acceptable levels in the final product. The analytical development would focus on the control of the following impurities methylpiperazinyl methylbenzoic acid, piperazinyl methylbenzoic acid, bromomethyl benzoic acid, p-toluic acid, methylpiperazine, piperazine and succinimide.

Quality Ground No. 2 (analytical method for determination of palladium and vanadium was not described nor was validation data provided): The applicant confirmed that the analytical method for determination of palladium and vanadium and its validation had been previously included in the dossier. Of note that this was not a major objection.

Quality Ground No. 3 (Unsatisfactory data was submitted to support the limit of impurities MAS aminothiazole and demethylated masitinib, and absence of a limit for unspecified impurities): The applicant agreed to set the specification limits for impurities MAS aminothiazole and demethylated masitinib at the threshold limit for qualification of 0.083 %. In addition, the applicant proposed to lower the limit of total impurities to 0.5 % to be closer to the current level, mainly observed in pilot batches.

Quality Ground No. 4 (A major concern was left outstanding on the adequacy of the proposed particle size distribution specification): The applicant proposed to add a specification for D(0.1) 5 to 25 µm, D(0.5) 30 to 100 µm, and D(0.9) not more than 230 µm. The applicant further justified that the particle size of the active substance is independent from the dissolution behaviour of the finished product.

Quality Ground No. 5 (The compatibility studies of the active substance were not sufficient to support the compatibility of this new active substance with the excipients in the formulation): The applicant agreed that the compatibility investigation that was performed during formulation development is partial. Nevertheless, according to development methodology, such compatibility studies are made during the early stage of development to prevent risk of formulation failure related to degradation phenomena over time during stability studies. The applicant referred to the

long term stability data submitted to support the compatibility of the active substance with the excipients. Of note that this was not a major objection.

Quality Ground No. 6 (The particle size of the active substance and core tablet hardness of the batches used in the clinical trials and batches of both strengths manufactured as proposed for the market vary significantly): With regard to particle size, please refer to the discussion above on quality ground #4 above. Concerning tablet hardness: For the 200 mg core tablets the applicant proposed to tighten the hardness specifications to 105-150 N, representing a 45 N range. For the 100 mg core tablets the applicant proposed to tighten the hardness specifications to 75-105 N, representing a 30 N range.

Quality Ground No. 7 (The data provided comparing the dissolution profiles between batches was not able to bridge data between the different versions of the product, nor support the specification proposed for these parameters. This is of serious concern as the bioavailability of the active substance was not proven to be consistent between batches and no extrapolation to the intended critical quality attributes for commercial manufacture was possible): The applicant stated as dissolution is complete for all batches after 20 minutes, no calculation of f2 value can be done; moreover any differences observed between batches are not relevant given the use in the clinical trial of the batches where differences were observed.

Quality Ground No. 8 (The applicant failed to submit data in support of the discriminatory nature of the dissolution method): The applicant stated that the dissolution data provided on the concerns over particle size distribution and batch bridging data between biobatches and commercial batches support the discriminatory nature of the dissolution method. The applicant confirmed to revise the testing point schedule of the dissolution method in order to incorporate a 15 min test point. In addition, the applicant is currently reviewing data to tighten the in process specification for disintegration time to NMT 15 min. The applicant stated that additional dissolution trials will be undertaken to reinforce demonstration of discriminating conditions of the dissolution method. Results of these studies would be provided by Q3-2014.

Quality Ground No. 9 (The validation data provided for analytical method was not sufficient with regards the methods for related substances determination and dissolution): The applicant stated that the validation report of the revised method for assay and related substances, as well as complementary data of validation of the dissolution method, would be submitted to by Q2-2014.

Quality Ground No. 10 (Major objections remain with regards the limit still to be defined for impurity MAS aminothiazole, found to be threshold-dependent genotoxic): The applicant proposes to tighten the limit of MAS aminothiazole in the active substance and finished product to not more than 0.083 %. Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

Report from the SAG

The questions addressed to the SAG by the CHMP were as follows:

Does the SAG consider that the efficacy of masitinib has been convincingly demonstrated?

The applicant's claim of efficacy focussed on two subgroups, namely advanced pancreatic cancer patients with over-expression of ACOX-1 in blood or patients with pain > 20 mm / 100 mm on a

visual analogue scale. The populations selected did not reflect the pre-specified primary efficacy analysis of the study. Thus, although post-hoc analyses do not per se prevent establishing efficacy, it is important to look at methodological aspects, in particular, multiple testing and potential bias, and also to assess if there is sufficient epidemiological, pathophysiological, biological and statistical evidence to corroborate the findings, particularly in the context of a trial that failed its primary analysis.

From a methodological point of view, the claims are based on subgroup analyses without adequate pre-specification on handling of multiple testing issues. Identification of the current subgroups (concerning ACOX-1, selection was done from an initial selection of 10 biomarkers out of 27000 potential biomarkers explored) is based on exploratory analyses of the pivotal trial and the results lack validation on independent data sets or other robust validation strategy. The population recruited in the trial was heterogeneous and imbalance in prognostic factors cannot be excluded. Both locally advanced and metastatic patients have been included in the trial without stratification. Imbalances in subsequent therapies may also have played a role in the results observed.

Many of the analyses presented were based on predicted survival curves from Cox- models. This type of curves can be quite misleading since they appear to reflect the outcome of a much larger population than the claimed subgroup. Usual Kaplan-Meier have been lacking for many analyses. No information was available to assess whether the Cox-model assumptions were valid. However, the reliability of estimated parameter (hazard ratio) from such models was questioned, as they were based on small subgroups of patients (e.g. in ACOX-1 overexpression: 20 patients in each treatment arm). In the absence of a robust validation strategy and adequate control of the Type I error, the results cannot be considered convincing from a methodological point of view.

From a pathophysiological/biological point of view, some hypotheses about a possible mechanism of action involving ACOX1 have been put forward by the applicant (masitinib was claimed to reduce the number of intra-tumoral mast cells, reducing pancreatic lesions, pancreatic vascularization and innervation in a pancreatic cancer mouse model; ACOX1 over-expression may flag patients with M2-polarized macrophage infiltration and poor expected survival). However, these hypotheses are largely based on assumptions and conjectures.

The prognostic or predictive importance of the “specific” genetic biomarker selected (it is difficult to understand what the qualifier “specific” refers to) has only been studied in the current trial and there is no extensive experience about ACOX1 in pancreatic cancer or other solid tumours. The association between the chosen biomarkers and important prognostic factors (stage of the disease, ECOG PS, CA19.9) or clinical endpoints such as reduction in pain, is not well understood. Although this may be a novel finding, independent validation would add to the plausibility of the choice. Thus, the proposed biomarker may at best be considered hypothesis generating for further non-clinical studies, e.g., to show the association between tumorigenesis and ACOX-1 expression in pancreatic cancer.

Concerning the pain subgroup, the same methodological and pathophysiological/biological issues apply. Again, arguments were presented by the applicant to support the plausibility of this subgroup based on a pancreatic adenocarcinoma mice model where masitinib was claimed to reduce the number of intra-tumoral mast cells, reducing pancreatic lesions, pancreatic vascularization and innervation. Regrettably, clinical validation of this mechanism is not available. Furthermore, pain and analgesic consumption have not been followed-up longitudinally and this limits the understanding about the association between masitinib and an effect on patients with

pain.

Given that there was no difference in OS in the primary treatment comparison, identification of a subgroup with a supposed large effect on OS implies that a detrimental effect is likely in the complementary subgroup of patients (e.g., patients with no pain). This is difficult to explain from a mechanistic point of view.

In conclusion, the selection of the biomarkers used to claim efficacy of masitinib questionable since there is no clear the epidemiological, pathophysiological, biological or statistical evidence to support their use for patient selection.

Thus, efficacy of masitinib has not been convincingly demonstrated based on the data presented.

2. Does the SAG consider the adverse effects clinically relevant? Could the SAG comment on their severity and their impact on patients?

The toxicity associated with masitinib was higher compared to gemcitabine (indeed, the IDMC of the AB07012 study recommended to stop recruitment due to futility and due to an over-toxicity in the combination treatment arm leading to early discontinuation within the first months). The SAG agreed that duration of treatment in the masitinib arm was unusually short and that the proportion of patients dying due to toxicity (in both arms) was unusually high. The high rate of treatment discontinuation was unexplained and of concern (particularly in the context of combination treatment), as this could be due to toxicity or a negative effect on quality of life. This observation also raised questions about the rationale for the chosen dose given the claimed mechanism of action, and dose reduction strategies followed in the trial.

However, the toxicity profile described (assuming that safety data have been collected adequately) for masitinib in advanced pancreatic cancer was not felt to be the major issue, despite the aforementioned concerns and in view of the toxicity associated to current standard treatments for pancreatic cancer. In the absence of established efficacy, the toxicity associated with masitinib was considered unacceptable.

3. The SAG should comment on the grounds for negative opinion in view of the grounds for re-examination submitted.

The SAG broadly agreed with the CHMP grounds for negative opinion. The main issue identified is the lack of established efficacy and therefore the benefit-risk balance cannot be concluded positive. Although the applicant has presented a number of claims and arguments, these cannot be corroborated due to the methodological deficiencies, lack of validation, unclear understanding about the mechanism of action and unexplained findings.

Concerning the wording of the CHMP grounds for negative opinion, reference to “biomarkers” (and not “specific genetic biomarker”) would better reflect the claimed indication (see answers to Question No. 1). The toxicity profile of masitinib is referred to as “significant”; this could be replaced by “observed” (see answer to question No. 2).

Overall conclusion on grounds for re-examination

The CHMP assessed the detailed grounds for re-examination and argumentation presented by the applicant in writing and in the oral explanation and considered the views of the re-examination Scientific Advisory Group.

Concerning Clinical Ground No. 1, the CHMP considered that the new proposed indication is based on efficacy claims that suffer of the same methodological deficiencies as described for the previously proposed indication, i.e., those deficiencies related to exploratory analyses in the context of a trial that failed to meet its primary efficacy endpoint. Although post-hoc analyses do not per se prevent establishing efficacy, it is important to look at methodological aspects, in particular, multiple testing and potential bias, and also to assess if there is sufficient epidemiological, pathophysiological, biological and statistical evidence to corroborate the findings, particularly in the context of a trial that failed its primary analysis.

As described in detail also in the SAG advice, the selection of the markers used to claim efficacy of masitinib questionable since there is no clear the epidemiological, pathophysiological, biological or statistical evidence to support their use for patient selection.

The claimed "strong internal and external biological evidence supporting their plausibility" is based on theoretical arguments and non-clinical models that lack validation or replication in relevant non-clinical or clinical studies. The suggestions that masitinib reduced mast cell count in a mouse pancreatitis model and that masitinib reduced innervations, vascularization and pain in pancreatic adenocarcinoma mice model lack clinical validation; it is unclear how mast cell response modulation observed in melanoma models may translate to pancreatic cancer, particularly as study AB07012 failed to show a clinical benefit with respect to OS and PFS in the prospectively defined target population. The fact that mobilization of inflammatory monocytes to the tumor environment and pain has been associated with poor prognosis in pancreatic cancer patients does not help to address the aforementioned methodological deficiencies in establishing the efficacy of masitinib in the claimed indication.

In conclusion, based on exploratory findings without convincing supportive non-clinical and clinical data, it is not possible to conclude that masitinib is associated with a benefit in terms of efficacy in the proposed indication and therefore a positive benefit-risk balance of the medicinal product as defined in Article 1(28a) of Directive 2001/83/EC has not been established. The CHMP also considered that the requirements for a conditional approval laid down in Article 4 of Commission Regulation (EC) No 507/2006, namely the benefit risk balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive, has not been fulfilled.

Concerning Clinical Ground No. 2, the CHMP maintained the view that the toxicity associated with masitinib was higher compared to gemcitabine alone. The CHMP also noted the high rate of treatment discontinuation, which could be due to toxicity or a negative effect on quality of life. Overall, the toxicity profile described for masitinib in advanced pancreatic cancer was not felt to be the major issue, in view of the high unmet medical need and the toxicity associated to current standard treatments for pancreatic cancer. However, this does not help to address the absence of established efficacy (see assessment of Clinical Grounds No. 1).

Concerning Quality Ground No. 1, the CHMP considered that piperazinyl methylbenzoic acid chloride is a complex molecule with several possible routes of synthesis ways and manufacturers, and it is used in the last real synthesis step of the active substance (step 4, synthesis of masitinib base crude). The absence of regulatory oversight to a change in the synthesis of masitinib could lead to an unsatisfactory and uncontrolled quality of the finished product, with a potential detrimental effect to the benefit risk of Masican. In addition, the proposal from the applicant not to redefine the starting material would not provide the necessary assurance of GMP compliance of all critical manufacturing steps of the active substance.

Concerning Quality Ground No. 2, the CHMP confirms that the method has been described and validated for specificity, linearity, detection limit, quantitation limit, accuracy, repeatability, intermediate precision and robustness in the validation report CQK00-694-09 presented in the ASMF 91072/05/11/01. To note that this was not a major objection.

Concerning Quality Ground No. 3, the CHMP noted that the applicant addressed the issue by tightening the limits of specified, unspecified and total impurities. This could be acceptable in principle, subject to the update of the relevant sections of Module 3 of the marketing authorisation dossier.

Concerning Quality Ground No. 4, the CHMP agreed with the applicant that the influence of the active substance particle size is minimal or at least not of major importance within the particle size specified if tested with the proposed dissolution medium (0.01 N HCl), that has so far not shown to be discriminative. The real concern lies on the lack of understanding of which conditions of the manufacturing process justify the different dissolution results observed, leading to a need to tighten to the necessary extent the available controls on the manufacturing process. Still, the revised active substance specification relating to particle size distribution as proposed by the applicant may be accepted, subject to the update of the dossier, since the limits correlate to the particle size distribution of the clinical batches.

Concerning Quality Ground No. 5, the CHMP agreed with the rational provided by the applicant and the issue can be considered as resolved. To note that this was not a major objection.

Concerning Quality Ground No. 6, with regard to particle size, see quality ground No. 3 above. The tightened in process specification for hardness could be acceptable in principle, subject to the update of the relevant sections of Module 3 of the marketing authorisation dossier.

Concerning Quality Ground No. 7, the CHMP stresses that the presented dissolution data/dissolution profiles, and consequently the argumentation based on this dissolution data, cannot get accepted to be valid because the discriminatory nature of the dissolution method was not demonstrated.

Concerning Quality Ground No. 8, the CHMP considered that confirmation of biobatch vs. commercial batch comparability, and assurance of an adequate control of the manufacturing process and quality of commercial batches need to be assured before a positive recommendation can be made on quality grounds. The suitability of the dissolution method for the comparability exercise was not demonstrated. A confirmation or post-authorisation measure relating to this critical point cannot get accepted.

Concerning Quality Ground No. 9, the CHMP concluded that the development of an improved complex analytical method relating to the impurity testing (including additional validation studies, batch results and stability results) should not be handled as a post authorisation measure; see quality ground No. 1. Regarding the dissolution method, see quality ground No. 8.

Concerning Quality Ground No. 10, see quality grounds No. 3.

Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that the quality and efficacy of the above mentioned medicinal product are not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the conditional Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The efficacy of masitinib in pancreatic cancer has not been sufficiently demonstrated;
- In the absence of established efficacy, a positive benefit-risk balance has not been established;
- The quality of the product is insufficiently controlled with regards patient exposure to impurities and the reproducibility between biobatches and commercial batches cannot be guaranteed.

The CHMP considered that the requirements for a conditional approval laid down in Article 4 of Commission Regulation (EC) No 507/2006, namely the benefit risk balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive, has not been fulfilled.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.