8 May 2014
EMA/174182/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Masican

International non-proprietary name: MASITINIB

Procedure No. EMEA/H/C/002670/0000

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:	Masican
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:	Masican is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after progression with imatinib treatment.
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
AUC	Area under Curve
CI	Confidence Interval
Cl	Clearance
C_{max}	Maximum concentration
CR	Complete Response
CV	Coefficient of Variation
CYP	Cytochrome p450
DDR1	Discoidin domain receptor 1
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
F	Bioavailability
GIST	Gastrointestinal Stromal Tumour
HPLC	High Performance Liquid Chromatograph
HR	Hazard ratio
MTD	Maximum tolerated dose
OS	Overall Survival
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PFS	Progression Free Survival
P-gp	Permeability glycoprotein
PR	Partial Response
SAE	Serious adverse events
SD	Stable Disease / Standard Deviation
TKI	Tyrosine Kinase Inhibitor
t_{max}	Time to maximum concentration
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 2 July 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Masican, 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.

Masican was designated as an orphan medicinal product EU/3/04/251 on 21 December 2004. Masican was designated as an orphan medicinal product in the following indication: treatment of malignant gastro intestinal stromal tumours.

The applicant applied for the following indication: Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after progression with imatinib treatment.

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 bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/014/2012 on the granting of a product-specific 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 requests for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the

following claim(s):

The Applicant has provided a document justifying that the medicinal product falls within the scope of the conditional marketing authorisation Regulation (Article 2) and that the requirements for conditional marketing authorisation are fulfilled (Article 4), in particular:

- The applicant considered that the benefit-risk balance for masitinib in treatment of GIST was considered favourable: The pivotal AB07001 study demonstrated superiority of masitinib over sunitinib in terms of overall survival (OS).
- At the time of the registration request, three studies have been evaluated: the pivotal AB07001 phase II study, the supportive AB03002 phase I study, and the supportive AB04016 phase II study.
- 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: Despite the survival benefits brought about by imatinib and second-line treatments for imatinib-resistant patients, GIST remains a serious and life-threatening disease with a real unmet medical need for patients.
- The applicant proposed to complete and confirm clinical results already obtained in the pivotal study with a confirmatory phase III study. This confirmatory phase III study is a prospective, multicentre, randomized, open-label, active-controlled, two-parallel groups, study in patients with gastrointestinal stromal tumour after progression with imatinib up to 800 mg/day bid.

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 received Protocol Assistance from the CHMP on 12 January 2005, 30 August 2005 and 19 July 2011. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

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-63802 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: Greg Markey

- The application was received by the EMA on 2 July 2012.
- The procedure started on 18 July 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 October 2012.
- During the meeting on 15 November 2012, 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 15 November 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 May 2013.
- The final GCP Integrated Inspection Report (IIR) of the inspection carried out at two investigator sites (inspection dates 10-14 December 2012 and 7-11 January 2013) and the sponsor site in France (inspection dates 14-18 January 2013) was issued on 22 March 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 July 2013.
- During the PRAC meeting on 11 July 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 September 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 October 2013.
- During the PRAC meeting on 10 October 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 21 October 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 21 November 2013, 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 Masican.

1.4. Steps taken for the re-examination procedure

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

Rapporteur: David Lyons Co-Rapporteur: Pierre Demolis

- The applicant submitted written notice to the EMA on 29 November 2013 to request a re-examination of Masican CHMP opinion of 21 November 2013.
- During its meeting on 19 December 2013 the CHMP appointed David Lyons as Rapporteur and Pierre Demolis as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 20 January 2014 . The re-examination procedure started on 21 January 2014.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 12 February 2014. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 13 February 2014.
- During a meeting of the Scientific Advisory Group (SAG) Oncology on 5 March 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 28 February 2014.
- The Applicant submitted additional argumentation in response to the quality assessment outcome included on the Joint Assessment Report on 18 March 2014.
- During the CHMP meeting on 18 March 2014, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20 March 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 authorisation and did not recommend the granting of the marketing authorisation .
- The revised final Opinion was adopted by the CHMP with written procedure on 8 May 2014.

2. Scientific discussion

2.1. Introduction

Gastrointestinal stromal tumours (GIST) are uncommon sarcomas. KIT, and to a lesser extent Platelet-derived growth factor receptor (PDGFR), are the oncogenic driving force in the tumourigenesis of GIST. Activating KIT mutations occur in at least 80 to 85% of GIST and the majority (70%) of these KIT mutations are located in the juxtamembrane domain (exon 11). About 10% of KIT mutations in GIST are found in exon 9 and they lead to the same functional consequences as exon 11 mutations. PDGFR mutations are reported in about 3% of patients.

Treatment of GIST includes complete surgical resection, which is curative in a proportion of patients. However, recurrence is common and conventional chemotherapy is not particularly effective. The introduction of molecular targeted therapies tyrosine kinase inhibitors (TKIs) has revolutionised the treatment of patients with unresectable and/or metastatic malignant GIST (imatinib) and patients with unresectable and/or metastatic malignant GIST after the failure of imatinib treatment due to resistance or intolerance (sunitinib). There is currently no standard of care in the setting of resistance to both these medicinal products.

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 masitinib for *the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after progression with imatinib treatment*.

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 stearate and the film-coating containing notably, titanium dioxide, talc, polyethylene glycol and sunset yellow lake (E110)).

The product is available in high density polyethylene (HDPE) bottles with child resistance closures at a pack size of 30 tablets.

2.2.2. Active substance

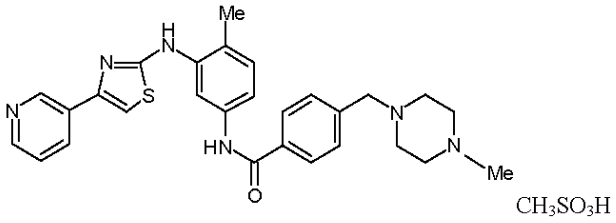
The active substance masitinib mesylate was stated to have been synthesised at four different manufacturers using the same synthetic route. Ultrafine manufactured batches of masitinib mesylate for toxicological trials only and Archemis batches were used in phase 1 and some phase

2 clinical studies. Manufacturing was then transferred from Archemis to Biocon Limited, India as Archemis ceased the production of masitinib mesylate. Two current manufacturers were initially proposed for the commercial scale manufacture of masitinib mesylate: Biocon Limited, India and Excella GmbH, Germany. The Biocon batches were used for some phase 2 and then phase 3 studies while Excella batches were used for phase 3 studies.

Full information of masitinib mesylate manufacture and control was submitted in section 3.2.S.3 to support the quality of Biocon as a manufacture of the active substance. The applicant removed this source from the marketing authorisation application after the Day 120 List of Questions adopted by CHMP.

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.

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.

Most of starting materials are acceptable. One of the starting material 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.

Unsatisfactory data was submitted to support the individual limit of not more than 0.10 % for two impurities. Similarly the limit proposed for unspecified impurities cannot be accepted as it is not in accordance to the applicable guidance considering the maximum daily dose of 1200 mg of masitinib. These two major concerns are still outstanding.

A major concern was left outstanding on 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 in the proposed container.

2.2.3. Finished medicinal product

The 100 mg and 200 mg finished product are both presented as light orange, capsule shaped, double debossed film-coated tablets. The 100 mg is debossed with 'C)' on one side and '100' on the other side. The 200 mg finished product is debossed with 'C)' on one side and '200' on the other side.

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 formulation and to accommodate a higher strength, tablet formulations were developed. The manufacture of the medicinal product was transferred from Catalent (USA) to Excella (DE) during the clinical trials.

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 (with the exception of Opadry coating agent). 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. This issue remained as unresolved.
There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

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 major and minor objections on the data submitted in support of the quality of the active substance and finished product remain unresolved despite being raised at the several stages of the procedure and the different attempts from the active substance manufacture and applicant to resolve them. 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-resolved 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 addition the applicant failed to justify limits proposed for the impurities, including potential genotoxic impurities. This deficiency was also considered critical.

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

The goal of the nonclinical studies was to support the registration of masitinib for the treatment of GIST.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Pharmacodynamic studies were conducted aimed at demonstrating masitinib's inhibitory potential against its primary targets, c-Kit and PDGFR. Both *in vitro* and *in vivo* experiments were performed. A comparison was presented between masitinib and the two other TKIs currently marketed in the treatment of non-resectable GIST, namely imatinib and sunitinib.

In vitro AB1010 was a potent and selective inhibitor of both WT and mutated c-Kit. It was an inhibitor of the catalytic activity of the c-Kit kinase, being able to block the phosphorylation of a peptide substrate as well as the phosphorylation of the receptor kinase itself. This inhibitory activity resulted in an anti-proliferative activity in cell lines expressing the c-Kit receptor. AB1010 also selectively inhibited the autophosphorylation of JM mutant c-Kit and c-Kit WT while requiring higher concentration (>10 µM) for the inhibition of catalytic domain mutant forms of Kit.

Masitinib was a selective kinase inhibitory compound. Twelve kinases are targeted by masitinib: Type III receptors tyrosine kinases (Kit and its closely related homologs CSF1R, PDGFRα and PDGFRβ; DDRs receptors, which are known to be targeted by the majority of kinase inhibitory compounds and SFKs: LYN, FYN, LCK, FRK, FGR and BLK. An in vitro study showed that AB1010 inhibition is highly selective for c-Kit in comparison to other kinases (including: EGFR, RET, TRKB, FGFR1, FGFR3, and FLT3).

The N-desmethyl derivative of AB1010, which is the main plasma metabolite found in animals and humans after oral administration of AB1010, retains the activity and selectivity profiles of the parent compound. This compound may contribute to the in vivo therapeutic activity of AB1010.

The evaluation of the anti-proliferative and pro-apoptosis effects of AB1010 on various mammalian cell lines expressing mutated and WT c-Kit revealed that AB1010 inhibited SCF induced proliferation of c-Kit WT cells and the spontaneous proliferation of cells expressing c-Kit

mutated in the JM domain, but did not affect the growth of c-Kit mutated in the catalytic domain nor control cells such as T lymphocytes and Ku812. The absence of an effect on human T lymphocyte proliferation suggests that AB1010, when used at low concentrations, does not have a pronounced non-specific cytotoxic activity resulting from the inhibition of key cellular kinases, common to many cells and essential for general mechanisms such as mitogenesis. These data indicate that AB1010 inhibits the proliferation of cells that express JM mutations on c-Kit, with an IC_{50} in the nM range. AB1010 was also shown to be a potent inhibitor of Kit WT and JM mutated Kit, which induces apoptosis.

The potent inhibitory action of AB1010 on c-Kit kinase activity, as showed in an in vitro enzymatic assay and a HMC1 α 155 cell proliferation assay, is thought to be responsible for the inhibition of both cell proliferation and colony formation. AB1010 showed a complete inhibition of tyrosine phosphorylation of c-Kit in Target Mast cells.

The investigation of anti-proliferative and pro-apoptosis activities of AB1010 on cell lines rendered resistant to imatinib revealed that these experiments suggest that imatinib-resistant cell lines (Ba/F3 mKit Δ27 imatinib-resistant cells) remain sensitive to higher concentration of AB1010 but not to imatinib, while the parental cell lines are highly sensitive to both imatinib and AB1010. AB1010 also induced apoptosis of imatinib-resistant Ba/F3 Δ27.

A comparison of in vitro efficacy of masitinib as compared with sunitinib and imatinib on c-Kit WT and c-Kit mutants associated with GIST revealed that AB1010 efficiently inhibits spontaneous proliferation of cells expressing activated mutant c-Kit found in GIST. These include c-Kit mutated in the JM domain (human c-Kit V559D) and in the extracellular domain (human c-Kit AY502-503) (IC_{50}=5 nM and 40 nM, respectively). AB1010 is slightly more potent towards c-Kit WT and mutants GIST including the T670I resistance mutants (secondary resistance) when compared to imatinib. AB1010 is less efficient than sunitinib on c-Kit WT and mutants. However, masitinib is more selective and does not inhibit kinases that are linked to toxic events such as Abl kinases.

Two in vivo studies were conducted in order to evaluate the antitumor activity of masitinib in nude mice (female Balb/cNu/Nu mice) that were subcutaneously grafted with a transgenic murine hematopoietic cell line (i.e. Ba/F3 transfected with the gene encoding Kit JM Δ27) following per os and IP administration. In the first study AB1010 given twice a day for ten consecutive days resulted in a marked inhibition of tumour growth at all doses levels. In addition, AB1010 at either the mid- or top-dose resulted in a complete resorption of the tumour at completion of the 10-day treatment. In the second study the antitumor activity of masitinib was tested following two types of administration: intraperitoneal injection (IP) and per os in a nude mice model. AB1010 at 30 mg/kg IP induced a potent inhibition of tumour growth with a significant increase in survival. AB1010 induced a marked tumour growth inhibition in a dose dependent manner. A marked tumour growth inhibition occurred at 30 and 45 mg/kg. AB1010, given per os twice a day at 100 mg/kg for five consecutive days, completely blocked tumour growth. AB1010 demonstrated a strong anti-tumour activity on Ba/F3 Δ27 tumours. AB1010 showed an anti-tumour activity regardless of the tumour volume at the beginning of the treatment and for both IP and oral route.

Secondary pharmacodynamic studies

Studies and references were submitted with respect to masitinib properties on inhibition of the

Discoidin domain receptor 1 (DDR1) receptors which appears to be involved in the homing of tumoural cells in hepatic metastasis; inhibition of mast cells since they appear to be involved in the tumour microenvironment where they release e.g. pro-angiogenic mediators; inhibition of c-Kit signalling in immature dendritic cells, which may promote dendritic cell-mediated NK cell activation; inhibition of the Lyn/FAK pathway which is implicated with cell proliferation and migration. In addition, a reference was submitted which described how imatinib and sunitinib induce secretion of anti-inflammatory cytokine IL-10 in macrophage cultures, indicating that treatment with these inhibitors might contribute to an immune suppressive microenvironment in GIST.

Safety pharmacology programme

The results from the safety pharmacology studies conducted with masitinib are presented in the table below.

Table 1 - Safety pharmacology studies

Organ System Evaluated (Study Report No.) GLP-status	Species / Number	Dose / Method of Administration	Results	NOAEL
Cardiovascular system (2-24367-sac) GLP	Beagle dogs/6 females/group	10, 50, 150 mg/kg p.o. (gavage) single dose	3/6 and 6/6 animals vomited within an hour after administration of 50 and 150 mg/kg, respectively. Hence, any treatment-related effect on CV parameters could not be evaluated at 150 mg/kg. No effect on heart rate, diastolic, systolic and mean arterial blood pressure or duration of PQ, QRS, QT intervals when evaluated via implantation of telemetric devices.	**50 mg/kg p.o. (n=3)**
hERG channel (4-ps05d91) GLP	4 cells/group	0.1, 1, 10, 30 µmol/L	Masitinib inhibited the hERG tail current by 8%, 14%, 54% and 73% at 0.1, 1, 10 and 30 µM in HEK cells stably expressing the hERG potassium channel. IC_{50}: 8.3 µM Positive control: E-4031 (0.1 µmol/L)	**<0.1 µM**
Respiratory System (1-24366-sar) GLP	Conscious Sprague-Dawley rats/8 females/group	15, 50, 150 mg/kg p.o. (gavage) single dose	No effect on respiratory rate, peak inspiratory and expiratory flows, tidal volume, minute volume or enhanced pause when measured using whole body plethysmography. Positive control: carbamylcholine	**150 mg/kg p.o.**
Central nervous system (3-24368-sar) GLP	Sprague-Dawley rats/ 8 females/group	15, 50, 150 mg/kg p.o. (gavage) single dose	No effect observed in a functional observation battery. Positive control: chlorpromazine (10 mg/kg)	**150 mg/kg p.o.**

Pharmacodynamic drug interactions

No non-clinical studies evaluating the potential for pharmacodynamic drug interactions have

been submitted.

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 IC50 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 sexesand 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.

A single dose study in rats showed that radio labelled masitinib crossed the blood-brain barrier to a very limited extent where it was rapidly eliminated (not detectable 48 hours following administration).

Metabolism

In vitro metabolites

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, was only detected in mouse hepatocytes. Again, no human specific metabolites were observed.

In vivo metabolites

In in vivo i.v. and p.o. metabolite studies conducted in rats and dogs, no masitinib plasma metabolites were detected. The applicant ascribes the lack of detectable masitinib metabolites, the poor sensibility of the analytical method. 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 AB2436 and/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.

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 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 2 - 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	<u>Experiments without S9</u> WP2 uvrA: 156.3-2500 µg/plate TA98, TA100: 19.53-312.5 µg/plate TA1535, TA1537, TA102: 39.06-625 µg/plate <u>Experiments with S9</u> 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	<u>Experiments without S9</u> 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 <u>Experiments with S9</u> 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	<u>Experiments without S9</u> 3 hours treatment: 1.3-20 µg/mL 24 h treatment: 0.16-7.5 µg/mL	Negative

		Experiments with S9 3 h treatment: 2.5-40 µg/mL	
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 mastinib in CD-1 mice and Sprague-Dawley rats.

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

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 3 - 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 4 - Summary of main study results

Substance (INN / Invented name): masitinib / Masican			
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 (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ refined (e.g. prevalence, literature)	0.002 to 0.004	µg/L	< 0.01 threshold (N)

The PEC surfacewater value for masitinib is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

Mutations in the KIT gene have been identified in approximately 80-85% of GIST, indicating a critical role in the pathogenesis of GIST. Some GISTs with wild-type KIT genotype present mutations in the platelet-derived growth factor-alpha (PDGFR-α) kinase. These mutations lead to gain of function and ligand independent constitutive activity of the receptor and consequently to tumour growth and cell proliferation. Using recombinant truncated c-Kit, it was shown that masitinib was a competitive inhibitor of c-Kit tyrosine kinase activity with an IC50 of 200 nM.

Studies in transfected Ba/F3 cells as well as cell lines expressing wild-type and mutant c-Kit showed that masitinib is a potent (IC50< 0.15 µM) inhibitor of proliferation of cells expressing wild-type c-Kit as well as c-Kit mutated in exon 9 (fifth extracellular domain) and exon 11 (juxtamembrane region). Moreover, the proliferation of Ba/F3 cells expressing PDGFRα and an EGF-PDGFRβ construct was inhibited with IC50 values of 0.25 nM and 10 nM, respectively. Masitinib was less active in cells expressing c-Kit mutated in the exon 17 (catalytic domain). Overall, masitinib appears to be a slightly more potent inhibitor of cells expressing wild-type as well as mutated c-Kit when compared to imatinib. It should be noted however that the majority of the results were based only on duplicate determinations.

In a study comparing the anti-proliferative effects of masitinib, imatinib and sunitinib, sunitinib was the most potent inhibitor of proliferation of Ba/F3 cells expressing human wild-type c-Kit, mutated c-Kit (exon 9 or 11) or wild-type human PDGFRα. Similarly, masitinib displayed slightly more potent anti-proliferative effects than imatinib. Neither of the tested kinase inhibitors was able to inhibit c-Kit mutated in the catalytic domain (T670I mutation).

Masitinib was a potent (IC50≤ 0.2 µM) inducer of apoptosis in cells expressing wild-type c-Kit and c-Kit with mutations in the juxtamembrane domain whereas cells expressing c-Kit mutated in the catalytic domain were not affected.

The anti-tumour activity of masitinib was evaluated in female nude mice bearing BA/F3 c-Kit Δ27 subcutaneous (s.c.) tumours. Following twice daily p.o. treatment of small size tumours, the tumour doubling time was 1 day and 2 days in the vehicle and 10 mg/kg treatment groups, respectively, while tumour stabilization was observed at doses ≥ 30 mg/kg twice daily. Similarly, the anti-tumour activity of masitinib was evaluated in mice with large tumours. Twice daily p.o. treatment with 100 mg/kg for 5 days resulted in a tumour doubling time of 5 days in the vehicle control group while tumour stabilization was obtained in the 100 mg/kg masitinib group. Similarly, tumour growth inhibition (T/C%) of 19%, 0.4%, 0.4% was observed in BA/F3 c-Kit Δ27 bearing nude mice treated with 50, 100 and 200 mg/kg masitinib twice daily for 10 days.

In the secondary pharmacology section alternative modes of action through which masitinib may impact tumour maintenance and evasiveness were discussed. However, it remains to be demonstrated that these potential secondary mechanisms of action play a role in the anti-tumour activity of masitinib.

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.

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 catalyze 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.

Based on the environmental risk assessment, masitinib is not expected to pose a risk to the environment.

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 and metabolites.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant claimed that the clinical trials were performed in accordance with GCP. Following review of the documentation, the CHMP requested a triggered GCP inspection. It was found that all subjects signed informed consents before enrolment. The main findings of the inspection carried out in December 2012 are briefly summarised below:

- The result of the first clinical trial site inspection was a total of 23 findings. There were 6 critical, 11 major and 6 minor findings. As the main focus during the inspection was the pivotal trial AB07001 all the findings relate to this trial.
- The result of the second clinical trial site inspection was a total of 15 findings. There were 4 critical, 9 major and 2 minor findings. All findings have relation to the pivotal trial AB07001 and 3 of the critical findings did also relate to the supportive trial AB04016.
- The result of the sponsor site inspection was a total of 43 findings. There were 13 critical, 25 major and 5 minor findings. One critical finding relates to trial AB04016 only, all other findings are related to trial AB07001 or both of them.
- The overall result of the three inspections was a total number of 81 findings; 23 critical, 45 major and 13 minor findings. All findings, except one, had relevance for the pivotal trial AB07001.

In terms of the recommendation for the acceptability of the clinical trial data, the following was stated:

The inspection revealed critical deficiencies, which raise concerns about the efficacy and safety data reported in the CSR of the pivotal trial AB07001 for investigator sites 01 and 03 (22 patients' records out of 43 patients in total in the trial representing 51% of the patients in this pivotal trial).

Inspectors cannot recommend that the presented data and CSR is accepted by the CHMP or used for further assessment.

The sponsor and investigators have declared in their responses that they are in the process of re-monitoring trial AB07001 in the aim "to release error-free data listings from which an updated version of the CSR will be written and communicated to the competent authorities".

Most of the unreported or misreported data are present at sites and can be collected or corrected. Visit windows can however not be changed and assessors has to evaluate if this can have any impact on the PFS.

The Applicant, in response to the inspector's findings, provided a follow-up of the post inspection corrective action plan. The Applicant has responded to the numerous GCP inspection findings with corrective measures whenever possible.

- 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	AB1010-PIHV04015	5.3.1.1	to 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
BE	AB1010-PIHV05031	5.3.1.2	to evaluate the food intake influence on pharmacokinetic profiles	Cross over	Tablet, 200mg, oral	12	healthy volunteers	Single dose	Complete, Full
PK	AB1010-PIHV03001	5.3.3.1	to 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	to 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

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
PK/Efficacy	AB03002	5.3.3.2 and 5.3.5.2	to assess safety /tolerability, PK parameters of AB1003, clinical activity of masitinib, to determine MTD	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
Efficacy	AB07001	5.3.5.1	to assess the efficacy and safety of masitinib in GIST patients resistant to imatinib	randomized, active-controlled	Tablet, 12mg/kg/day, oral	44	patients with GIST resistant to imatinib	Until progression	Complete, Full
Efficacy	AB04016	5.3.5.2	to assess the efficacy and safety of masitinib in non-pretreated, inoperable patients with locally advanced/metastatic GIST	multicenter, single group	Tablet, 7.5mg/kg/day, oral	30	non pre-treated, inoperable patients with locally advanced/metastatic GIST	16 weeks + extension phase	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 5 – 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)

- 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 interindividual 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 6 – 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

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

This stratification fails to support the weight-based posology as suggested by the Applicant. (data not shown).

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* wild type (WT) receptor and its mutated forms (exon 9 and exon 11), as well as the platelet-derived growth factor alpha (PDGFRA) receptor.

Confirmation of the activity of masitinib *in vivo* was provided by xenograft studies in nude mice; orally administered masitinib reduces tumour volumes in a dose dependent manner in nude mice that were subcutaneously grafted with a transgenic murine hematopoietic cell line (BA/F3 c-Kit d27 model).

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 2 studies in healthy volunteers and in one study of target populations. 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.

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.

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/QTs 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 studies

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 were:

- Study No AB1010 PIST 03002 - A phase I, open-label, dose escalating study of oral AB1010 in patients with solid tumours
- Study AB04016 - Phase II study of oral AB1010 in non-pretreated, inoperable patients with locally advanced/metastatic gastro-intestinal stromal tumour (GIST)

The selection of the 12 mg/kg/day dose for future studies in second line therapy for GIST is based on the efficacy and safety results in 10/19 patients with GIST in the phase I/II study AB03002 in which 4 dose levels (< 3 mg/kg/day; 7.5 mg/kg/day; 12 mg/kg/day, and 15 mg/kg/day) were investigated.

In this phase I dose-escalating study, 40 patients with advanced and/or metastatic cancer including 19 patients with GIST, were enrolled. This study aimed to determine the maximum tolerated dose (MTD) for orally administered masitinib over a 12-week period. Secondary objectives were clinical assessment of masitinib activity in cancer patients and establishment of the pharmacokinetic profile.

Among the 19 GIST patients included in this study, all were considered as imatinib-resistant: 15/19 (78.9%) were resistant to 800 mg/day as maximal prior imatinib dose received, 3/19 (15.8%) were noted by the investigator as resistant to 400 mg/day, and for one (5.3%) patient the dose of imatinib resistance was not collected.

In this study, most patients were in end-stage disease. This is reflected by a higher number of lines of treatment undergone by patients before study enrollment, and by a greater proportion of patients having a worse Eastern Cooperative Oncology Group (ECOG) performance status (i.e. an ECOG value of 1) compared with study AB07001.

No mutational analysis was performed on patients in the phase I AB03002 study and therefore the c-Kit and PDGFR mutational status is unknown.

The 19 GIST patients received masitinib doses ranging from 0.7 to 17.2 mg/kg/day:

- Three patients received low masitinib doses ranging from 0.7 to 2.1 mg/kg/day. These patients will be referred to as the “< 3 mg/kg/day” cohort.

- Two patients received masitinib doses around 7.5 mg/kg/day, the dose used in first-line treatment for GIST (doses of 6.8 and 8.5 mg/kg/day, respectively). These patients will be referred to as the "7.5 mg/kg/day" cohort.

- Ten patients received masitinib doses around 12 mg/kg/day, the dose used in second-line treatment for GIST (dose range of 10.8 to 13.0 mg/kg/day). These patients will be referred to as the "12 mg/kg/day" cohort.

- Four patients received masitinib doses around 15 mg/kg/day (dose range of 15.1 to 17.2 mg/kg/day). These four patients will be referred to as the "15 mg/kg/day" cohort.

Patients from the "< 3 mg/kg/day" cohort received doses lower than 3 mg/kg/day which are too far from the 12 mg/kg/day target dose used in treatment of GIST patients resistant to imatinib. These patients were therefore of little relevance for efficacy analysis. The dose of 15 mg/kg/day was identified as the toxicity limiting dose from which gastrointestinal adverse events including vomiting were more frequently reported.

Hence, efficacy analysis was performed on the study's overall GIST population of 19 patients, and also on the 12 patients with the appropriate dose regimen, i.e. the two patients from the "7.5 mg/kg/day" cohort, and the ten patients from the "12 mg/kg/day cohort". This latter group of patients is hereafter referred to as the "selected GIST cohort".

Evaluation of PFS in all 19 GIST patients included in the study revealed that median PFS was 1.8 months (95% CI [1.3; 3.0]) with PFS rates at 6, 12 and 18 months of treatment of 20.5%, 6.8% and 6.8%, respectively.

PFS analysis in the selected GIST cohort showed that median PFS was 2.5 months (95% CI [1.4; 6.5]) with PFS rates at 6, 12 and 18 months of treatment of 28.6%, 9.5% and 9.5%, respectively.

2.5.2. Main studies

Study AB07001

Methods

Study AB07001 is a prospective, multicentre, randomised, open-label, active-controlled, 2-parallel group, Phase II study to compare efficacy and safety of masitinib at 12 mg/kg/day to sunitinib at 50 mg/day in treatment of patients with gastro-intestinal stromal tumour resistant to imatinib.

Study Participants

Inclusion criteria consisted of:

- Men or women, age >18 years
- Histological proven, metastatic, or locally advanced and non-operable GIST
- Measurable tumour lesions with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan according RECIST criteria
- KIT (CD117) positive tumours detected immunohistochemical and documented mutation of c-Kit at any time if available
- Patients resistant to imatinib at the dose of 400 mg/day.

- ECOG ≤ 2
- Patient with adequate organ function
- Patient with life expectancy > 6 months

Amongst exclusion criteria were:

- Patient treated for a cancer other than GIST within 5 years before enrolment, with the exception of basal cell carcinoma or cervical cancer in situ.
- Patient with active central nervous system (CNS) metastasis or with history of CNS metastasis.
- Patient presenting with defined cardiac disorders.

Treatments

Subjects were randomised 1:1 to treatment Group 1 or Group 2:

- Group 1 - Oral masitinib, to be taken twice daily during meals. Each tablet contained 100 mg or 200 mg. Patients received an initial starting daily dose of 12 mg/kg/day.
- Group 2 - 50 mg/day sunitinib once daily for 4 consecutive weeks out of every 6 weeks (Group 2). Dose escalation was not allowed during the study (any dose escalation was considered as progression).

Objectives

The objectives of this randomized, open-label, parallel-group study were to assess the efficacy and safety of masitinib in GIST patients under progression with imatinib.

Outcomes/endpoints

The primary endpoint was progression-free survival (PFS) measured from the date of randomization to the date of documented progression according to RECIST or death.

Secondary endpoints included:

- Overall Survival (OS) and Overall Time to progression (TTP)
- Objective response rate (CR + PR) and the Disease Control rate measured at weeks 8, 16, 24, 36 and after Week 36 and the best response (CR or PR or SD or PD) during the study.
- PFS analysis according to different assessment criteria for progression: 1/ according to the investigator, 2/ according to RECIST and centrally reviewed by an independent response review committee, 3/ according to CHOI centrally reviewed by an independent response review committee and 4/ according to Time to Treatment Failure, defined as the time between randomization and switch to post-study or death, whichever occurred first.
- Correlation between PFS, OS, TTP, objective response, control disease rate and the phenotype of mutations on c-Kit/PDGF
- Quality of life according to the EORTC QLQ-C30 questionnaire, the Karnofsky Performance Status, and the ECOG Performance Status at weeks 8, 16, 24, 36 and after Week 36.

PFS, OS, TTP, objective response rate and disease control rate, and best response were assessed by CT scan according to RECIST 1.1 criteria.

Sample size

Hypotheses for sample size calculation were the same for the two treatment groups, masitinib and sunitinib:
• Duration of accrual period: 24 months
• Duration of follow-up period-time from end of accrual to analysis: 6 months
• Alpha set to 0.10
• Power set to 0.8
• One-sided test
• The median survival time for the null and alternative hypotheses were respectively 3 months (largest PFS that implied that masitinib was not to be chosen for further studies) and 5 months (smallest PFS that implied that masitinib was to be chosen for further studies)
• PFS was assumed to be exponentially distributed

19 patients were necessary in each treatment group with the following hypotheses:
• H0: median PFS < 3 months
• HA: median PFS > 5 months

38 PP patients were necessary to achieve this study. The number of patients required was 44 patients (22 per group) in order to take into account major protocol deviations or early drop-outs (estimated rate around 15%).

Randomisation

Subjects were randomised in a 1:1 ratio. Treatment group was to be allocated according to a modified minimization method (random assignment) which allows for reducing the differences in size between the two treatment groups within the different strata of KIT mutation (exon 9 exon 11 other).

Blinding (masking)
Not applicable.

Statistical methods
As stated in the study protocol, from a statistical point of view this study was not designed as a comparative study between masitinib and sunitinib, so comparison of confidence intervals between groups were to be exploratory.

The Initial Hypothesis was:

- “H0: median PFS < 3 months, HA: median PFS > 5 months”. This test is conclusive if the lower bound of the 90% one-sided confidence interval is greater than 3 months (H0 hypothesis rejected) and greater than 4.12 months (HA hypothesis fulfilled).

- This hypothesis was based upon historical data from the sunitinib phase II/III study [Demetri, 2006; Seddon, 2008; Morgan, 2006].

The Hypothesis has been revised as follows:

- “H0: median PFS < 3 months, HA: median PFS > 3 months”. This test is conclusive if the lower bound of the 90% one-sided confidence interval is greater than 3 months (H0 hypothesis rejected and HA hypothesis fulfilled).

- This revised hypothesis was proposed by experts of the data review committee held in December 2011 before database lock.

The main analysis was conducted with a data cut-off fixed on January 31st 2012.

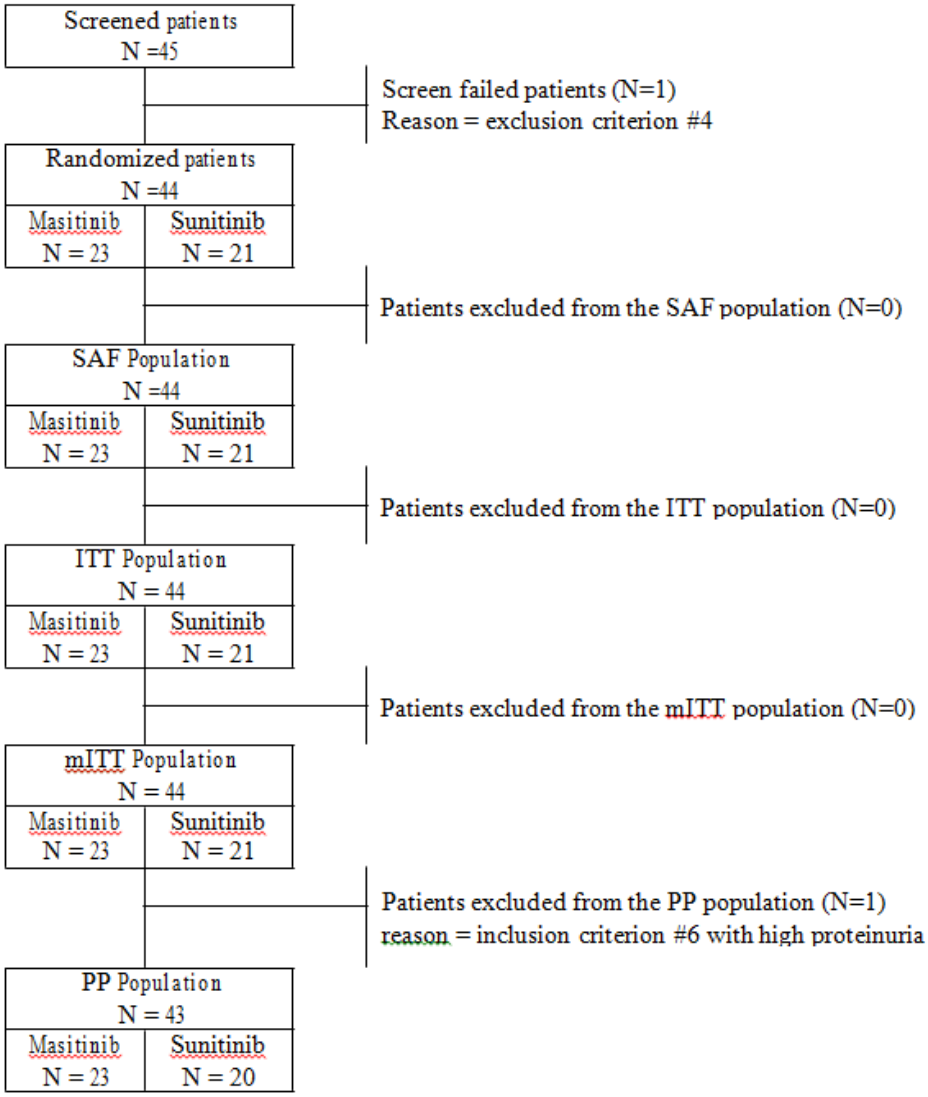
Intent to Treat (ITT) population: composed of all included patients, whether they have received the study treatment or not. The documented lack to take at least one dose of the study drug and patients with no efficacy measure after first treatment intake was discussed on a case-by-case basis.

Modified Intent-to-treat population (mITT): all ITT patients but excludes the patients that exited the study prematurely for well-documented non treatment-related cause.

Per Protocol (PP) population: The PP dataset consists of all patients of the ITT dataset without any major protocol deviations. Patients terminating the study prematurely were included in the PP dataset provided that there was no protocol deviation.

Results

Participant flow



Recruitment

This study AB07001 was carried out in 9 centres in France.

Conduct of the study

The study was initiated in February 2009 and the cut-off date was 31st January 2012.

Baseline data

Demographics and baseline characteristics are summarised in the table below.

Table 7 – Patient demographics and baseline characteristics, ITT population

	MASITINIB (N=23)	SUNITINIB (N=21)	p-value
Sex			**1.000 (F)**
Male	11 (47.8%)	11 (52.4%)	
Female	12 (52.2%)	10 (47.6%)	
Age (years)			**0.424 (W)**
Mean ± Std	62.1 ± 15.1	66.7 ± 12.3	
Median	64.0	67.0	
Range	31.0 - 82.0	41.0 - 85.0	
Age class			**0.563 (F)**
≤ 65-year old	12 (52.2%)	9 (42.9%)	
> 65-year old	11 (47.8%)	12 (57.1%)	
Baseline weight (kg)			**0.306 (W)**
Mean ± Std	64.9 ± 14.6	69.2 ± 12.6	
Median	62.0	73.0	
Range	44.0 ; 90.5	42.0 ; 88.0	
Weight ≥ 60 kg	14 (60.9%)	17 (81.0%)	**0.194 (F)**

(W) Wilcoxon test; (F) Fisher's exact test

At the time of first diagnosis, localization of primary tumours was mainly intestinal (47.8% of masitinib-treated patients and 52.4% of sunitinib-treated patients), and gastro-oesophageal (34.8% and 28.6% of masitinib- and sunitinib-treated patients, respectively). No significant difference was observed between the two treatment arms.

Tumour classification was equally distributed between patients of both groups, most of them with metastatic tumours. In particular among masitinib-treated patients, 2 (8.7%) had locally advanced tumours, and 21 (91.3%) patients had metastases. In sunitinib-treated patients, 3 (14.3%) had locally advanced tumours, and 18 (85.7%) had metastases.

Biopsies of the tumours were taken in patients prior to the beginning of the treatment and KIT and PDGFR mutational status are summarized below.

Table 8 - KIT mutation analysis

	MASITINIB (N=23)	SUNITINIB (N=21)	p-value
***KIT* positive expression**	23 (100.0%)	21 (100.0%)	
Exon Mutation			**1.000 (F)**
N	19	17	
No mutation	1 (5.3%)	-	
Exon 9	3 (15.8%)	2 (11.8%)	
Exon 11	15 (78.9%)	14 (82.4%)	
Exon 11 + Exon 17	*1 (5.3%)*	*1 (5.9%)*	
Exon 13	-	1 (5.9%)	
PDGFR expression			
Positive	3 (13.0%)	3 (14.3%)	
Negative	3 (13.0%)	5 (23.8%)	
Unknown	17 (73.9%)	13 (61.9%)	

(F) Fisher's exact test

Among previous therapies for GIST, most patients (91.3% of masitinib-treated patients and 85.7% of sunitinib-treated patients) experienced surgery resections. Tumourectomy in particular was experienced in 52.2% of masitinib-treated patients, and in 66.7% of sunitinib-treated patients.

56.5% and 42.9% of patients aimed to receive masitinib and sunitinib respectively, experienced other surgeries for their GIST.

None of the sunitinib-treated patients had radiotherapy for their GIST, while only one patient receiving masitinib experienced previous and curative radiotherapy.

All patients included in the study previously received imatinib and had to be resistant to imatinib at the dose of 400 mg. The table below describes the highest previous imatinib dose received by patients of each treatment arm before entering the study, as well as the duration of this treatment.

Table 9 – Previous treatment with imatinib

Number (%) of patients with	MASITINIB (N=23)	SUNITINIB (N=21)	p-value
Last imatinib treatment termination because of lack of efficacy	23 (100.0%)	21 (100.0%)	
Last imatinib treatment: Progression within 6 months with imatinib	3 (13.0%)	4 (19.0%)	**0.693 (F)**
Maximal previous dose of imatinib			**0.494 (F)**
400 mg/day	16 (69.6%)	17 (81.0%)	
800 mg/day after progression with 400 mg/day	7 (30.4%)	4 (19.0%)	
Cumulative duration (months)			**0.707 (W)**
Mean ± Std	41.4 ± 26.8	45.9 ± 38.1	
Median	32.7	28.2	
Min; Max	8.8; 103.3	5.4; 114.3	
Cumulative duration – N (%)			
> 24 months	17 (73.9%)	11 (52.4%)	**0.211 (F)**
> 36 months	9 (39.1%)	7 (33.3%)	**0.761 (F)**

(F) Fisher's exact test; (W) Wilcoxon test

Numbers analysed

23 subjects were randomised to masitinib and 21 subjects were randomised to sunitinib. Forty-four patients were included in the ITT and SAF population.. One patient was excluded from the PP population (43 patients).

Outcomes and estimation

Primary Endpoint - PFS according to central RECIST

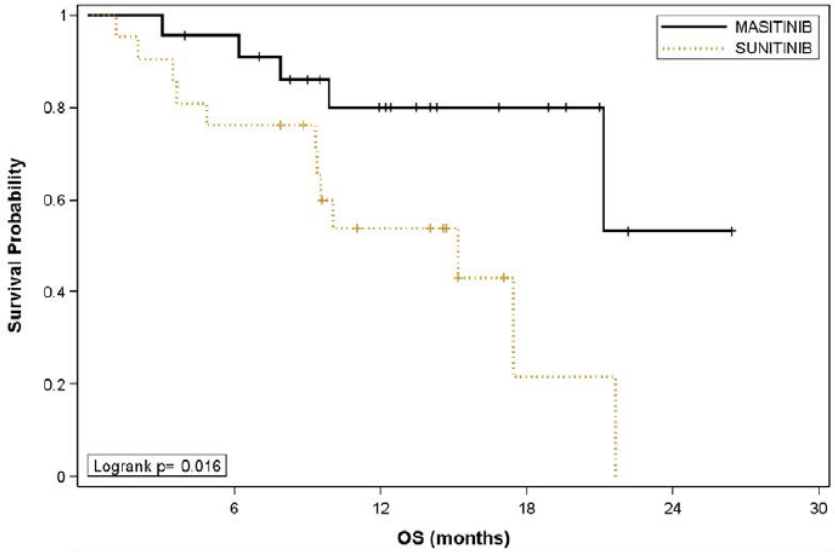
Table 10. Summary of PFS central RECIST analyses and results from statistical tests according to the ITT population - Cut-off date: 31 January 2012

	Median PFS in months [95% two-sided CI] (lower bound 90% one-sided CI)	Patients censored n (%)	First test conclusive (Yes/No) H0: median PFS < 3 M HA: median PFS > 5 M Test conclusive if CI lower bound > 4.12 M		Second test conclusive (Yes/No) H0: median PFS < 3 M HA: median PFS > 3 M Test conclusive if CI lower bound > 3 M	
Progression-Free Survival according to central RECIST						
Method of censoring - as per protocol			Two-sided 95%	One-sided 90%	Two-sided 95%	One-sided 90%
MASITINIB (N=23)	3.7 [1.9; 6.0] (3.7)	5 (22%)	No	No	No	**Yes**
SUNITINIB (N=21)	1.9 [1.8; 4.4] (1.9)	3 (14%)	No	No	No	No
Method of censoring –analysis #1			Two-sided 95%	One-sided 90%	Two-sided 95%	One-sided 90%
MASITINIB (N=23)	3.7 [2.0;6.0] (3.7)	2 (8.7%)	No	No	No	**Yes**
SUNITINIB (N=21)	1.9 [1.8;4.4] (1.9)	3 (14%)	No	No	No	No
Method of censoring –analysis #2			Two-sided 95%	One-sided 90%	Two-sided 95%	One-sided 90%
MASITINIB (N=23)	3.7 [2.0; 8.8] (3.7)	5 (22%)	No	No	No	**Yes**
SUNITINIB (N=21)	1.9 [1.8; 4.4] (1.9)	3 (14%)	No	No	No	No

Secondary Endpoints and Outcomes

- Overall Survival (OS) - 31 January 2012

At the time of cut-off date, median follow-up for OS was 14 months in the masitinib arm and 15 months in the sunitinib. OS was increased in the masitinib arm, with a median OS estimated to be higher than 21.2 months (95% CI [21.2; NA]) as compared with a median OS of 15.2 months in sunitinib arm (95% CI [9.4; 21.7]). The estimated HR was 0.29 [0.10; 0.85] (p-value=0.016) (Figure 1).



Number of patients at risk at	Month 6	Month 12	Month 18	Month 24	Month 30
MASITINIB	21	12	6	1	0
SUNITINIB	16	8	1	0	0

Figure 1 - Kaplan-Meier OS analysis - Overall population – Study AB07001

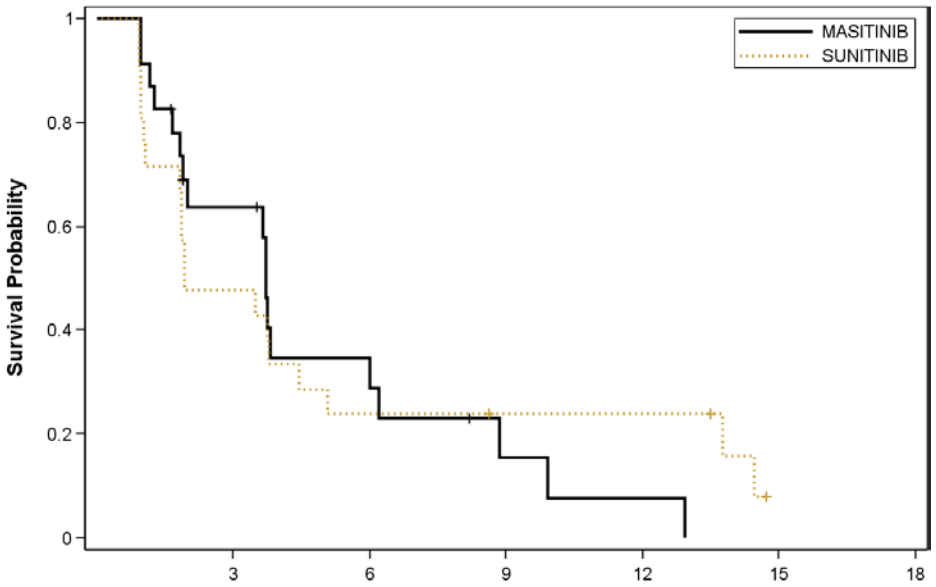
- Progression Free Survival (PFS) - 31 January 2012

Results of the primary analysis based upon the primary endpoint PFS according to RECIST criteria centrally reviewed, are presented in the table and figure below.

Table 11 - PFS according to RECIST

PFS according to centralized RECIST	N	Median PFS (months) [95% CI] (lower bound 90% one-sided CI)	PFS rates over time (% [95% CI]) Month 6	Month 12
Overall population				
Method of censoring – as per protocol				
MASITINIB	23	3.7 [1.9; 6.0] (3.7)	34.7 [14.7; 55.6]	7.7 [0.6; 28.2]
SUNITINIB	21	1.9 [1.8; 4.4] (1.9)	23.8 [8.7; 43.1]	23.8 [8.7; 43.1]
*log-rank p-value**		*0.833*		
*Hazard ratio for progression [95% CI]**		*1.07 [0.54 ; 2.13]*		
***KIT* Exon 11 mutation**				
Method of censoring – as per protocol				
MASITINIB	15	2.0 [1.7; 6.0] (1.8)	29.1 [7.5; 55.5]	9.7 [0.6; 34.7]
SUNITINIB	14	1.9 [1.1; 4.4] (1.8)	21.4 [5.2; 44.8]	21.4 [5.2; 44.8]
log-rank p-value		*0.751*		
Hazard ratio for progression [95% CI]		*1.14 [0.50; 2.61]*		
***KIT* Exon 9 mutation**				
Method of censoring – as per protocol				
MASITINIB	3	3.8 [1.2; NA] (1.3)	33.3 [0.9; 77.4]	NR
SUNITINIB	2	3.0 [1.0; 5.1] (1.0)	0.0	0.0
log-rank p-value		*0.586*		
Hazard ratio for progression [95% CI]		*0.58 [0.08; 4.26]*		
Imatinib 400 mg				
Method of censoring – as per protocol				
MASITINIB	16	3.7 [3.6; 6.2] (3.7)	40.6 [15.3; 64.9]	12.2 [0.9; 39.0]
SUNITINIB	17	3.5 [1.8; 5.1] (1.9)	23.5 [7.3; 44.9]	23.5 [7.3; 44.9]
*log-rank p-value**		*0.953*		
*Hazard ratio for progression [95% CI]**		*1.02 [0.46; 2.26]*		
Imatinib 800 mg				
Method of censoring – as per protocol				
MASITINIB	7	1.7 [1.1; 9.9] (1.2)	21.4 [1.2; 58.6]	0.0
SUNITINIB	4	1.4 [1.0; NA] (1.0)	25.0 [0.9; 66.5]	25.0 [0.9; 66.5]
*log-rank p-value**		*0.625*		
*Hazard ratio for progression [95% CI]**		0.68 [0.15; 3.18]		

NR: not reached; NA: not assessable



Number of patients at risk at	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18
MASITINIB	12	6	2	1	0	0
SUNITINIB	10	5	4	4	0	0

Figure 2 - Kaplan-Meier PFS analysis according to RECIST – Overall population

- Tumour response assessment and best response during the study

Tumour assessment was performed on CT scan evaluations according to RECIST criteria and investigator's decision. Responses during the study were performed without and with confirmation RECIST criteria. Results are presented in the table below.

Table 10 – Response during the study – Assessment according to RECIST

Number (%) of patients with	MASITINIB (N=23)	SUNITINIB (N=21)	p-value
Without confirmation criteria			
Best response during the study			**0.813 (MH)**
Complete response (CR)	-	-	
Partial response (PR)	1 (4.3%)	2 (9.5%)	
Stable disease (SD)	18 (78.3%)	15 (71.4%)	
Progressive disease (PD)	4 (17.4%)	4 (19.0%)	
Disease control rate (CR +PR+SD) [95% CI]	**19 (82.6% [62.9;93.0])**	**17 (81.0% [60.0; 92.3])**	**1.000 (F)**
Objective Response Rate (CR+PR) [95% CI]	**1 (4.3% [0.8; 21.0])**	**2 (9.5% [2.7; 28.9])**	**0.599 (F)**
With confirmation criteria			
Disease control rate (CR +PR+SD) [95% CI]	**17 (73.9% [53.5; 87.5])**	**14 (66.7% [45.4; 82.8])**	**0.744 (F)**
Objective Response Rate (CR+PR) [95% CI]	**1 (4.3% [0.8; 21.0])**	**1 (4.8% [0.8; 22.7])**	**1.000 (F)**
Clinical benefit [95% CI] (confirmed PR 4 weeks or CR 4 weeks or SD 16 weeks)	**6 (26.1% [12.5; 46.5])**	**6 (28.6% [13.8; 50.0])**	**1.000 (F)**

(F) Fisher's exact test; (MH) Mantel-Haenszel Chi-square test

- Quality of Life

QoL response was defined as improvement (> 10 points), stable or worsening (< 10 points), based on Global health status scale of EORTC QLQ-C30 questionnaire. Assessment of quality of life response was available for 15 (75.0%) subjects in the masitinib arm and 13 (65.0%) subjects in the sunitinib arm.

Table 11 – QoL response during the study

	MASITINIB (N=23)	SUNITINIB (N=21)	p-value
Assessment available at baseline	**20 (87.0%)**	**20 (95.2%)**	
Assessment post baseline available	15 (75.0%)	13 (65.0%)	
QoL response			**0.378 (MH)**
N	15	13	
Improvement	2 (13.3%)	3 (23.1%)	
Stable	9 (60.0%)	2 (15.4%)	
Worsening	4 (26.7%)	8 (61.5%)	
QoL response			**0.063 (F)**
N	15	13	
Improvement or stable	11 (73.3%)	5 (38.5%)	
Worsening	4 (26.7%)	8 (61.5%)	

(MH) Mantel-Haenszel Chi-square test; (F) Fisher's exact test

Ancillary analyses

Not applicable

Summary of main study

The following tables summarise the efficacy results from the main study 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 12 – Summary of Efficacy for trial AB07001

Title: A prospective, multicenter, randomized, open-label, active-controlled, 2-parallel group, Phase II study to compare efficacy and safety of masitinib at 12 mg/kg/day to sunitinib at 50 mg/day in treatment of patients with gastro-intestinal stromal tumor resistant to imatinib			
Study identifier	Study AB07001 EUDRACT number: 2007-005889-12		
Design	Prospective, multicenter, randomized, open-label, active-controlled, 2-parallel group, Phase II study		
Hypothesis	Exploratory		
Treatments groups	Group 1		22 patients were to receive masitinib at 12 mg/kg/day, until disease progression
	Group 2		22 patients were to receive sunitinib at 50 mg/day for 4 consecutive weeks out of every 6 weeks until disease progression
Endpoints and definitions	Primary endpoint	PFS	Progression Free Survival according to RECIST criteria centrally reviewed

	Secondary endpoint	OS	Overall survival
Database lock	31 January 2012		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Progression Free Survival according to RECIST criteria based on central review. Lower bound of the 90% one-sided confidence interval greater than 3 months.		
PFS (median, months)	3.7 months in the masitinib treatment-arm with a lower bound of the 90% unilateral confidence interval being 3.7 (greater than the tested lower bound of 3 months).		
Descriptive statistics and estimate variability	Treatment group	Masitinib	Sunitinib
	Number of subject	23	21
	PFS (median, months)	3.7	3.8
	95% CI	2.6-6.2	1.9-4.4
	OS (median, months)	21.2	15.2
	95% CI	21.2-NA	9.4-21.7
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Masitinib vs Sunitinib
		HR	0.98
		95% CI	0.49-1.98
		P-value	0.964
	Secondary endpoint OS	Comparison groups	Masitinib vs Sunitinib
		HR	0.29
		95% CI	0.10-0.85
		P-value	0.016

CI: confidence interval; HR: hazard ratio; NA: not assessable

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

Not applicable.

Clinical studies in special populations

No studies in patients with hepatic or renal impairment have been submitted.

Supportive studies

Study AB03002

In this phase I dose-escalating study, 40 patients with advanced and/or metastatic cancer including 19 patients with GIST, were enrolled. This study aimed to determine the MTD for orally

administered masitinib over a 12-week period. Secondary objectives were clinical assessment of masitinib activity in cancer patients and establishment of the pharmacokinetic profile.

Primary endpoint: The dose determined to be used for future phase II studies was 12 mg/kg/day.

Secondary endpoints: Evaluation of PFS in the subgroup of patients included in the study with GIST revealed that median PFS was 1.8 months (95% CI [1.3; 3.0]) with PFS rates at 6, 12 and 18 months of treatment of 20.5%, 6.8% and 6.8%, respectively.

The "selected GIST patients" consisted of the GIST patients included in the phase I study that were treated with masitinib with dose ranging from 7.5 mg/kg/day to 12 mg/kg/day (excluding the patients that were treated with lower or higher doses of masitinib).

PFS analysis in the selected GIST cohort showed that median PFS was 2.5 months (95% CI [1.4; 6.5]) with PFS rates at 6, 12 and 18 months of treatment of 28.6%, 9.5% and 9.5%, respectively.

The 19 GIST patients were followed for overall survival for a median of 72.9 months, and showed a median OS of 12.4 months (95% CI [7.3; 26.8]) with OS rates at 1, 2, 3, 4, and 5 years of 52.6%, 36.8%, 15.8%, 10.5%, and 5.3%, respectively.

OS analysis in the selected GIST cohort revealed that median OS was 23.4 months (95% CI [12.4; 34.4]) with OS rates at 1, 2, 3, 4, and 5 years of 75.0%, 50.0%, 25.0%, 16.7%, and 8.3%, respectively.

Study AB04016

The supportive study AB04016 was a phase II study in 30 non-pretreated, inoperable patients with locally advanced/metastatic GIST and with an ECOG PS of 0-2. Masitinib was administered at 7.5 mg/kg/day.

Major efficacy endpoints were objective response rate, PFS, OS, and metabolic response rate.

Best response analysis showed that four patients (13.3%) had a complete response (CR), 13 patients (43.3%) had a partial response (PR), 12 patients (40.0%) had stable disease (SD), and one patient (3.3%) had progressive disease (PD).

Metabolic response was assessed by FDG-PET: At 2 months 3 patients (21.4%) had a complete metabolic response (CMR) and 9 patients (64.3%) had a partial metabolic response. Two patients (14.3%) had stable metabolic response. The overall metabolic response rate was 85.7% (95% CI [57.2; 98.2]) at 2 months.

The median PFS was 41.3 months (95% CI [17.5; 53.8]) and PFS rates were 77.3%, 61.0%, 57.0%, and 32.0%, after 1, 2, 3, and 4 years of treatment, respectively.

With a median follow-up of 65 months in patients with GIST and receiving masitinib as first-line treatment, the median OS in study AB04016 was not reached (estimated as higher than 53 months), with survival rates of 96.7%, 90.0%, 86.5%, 76.2%, 61.5%, and 55.9% at 1, 2, 3, 4, 5 and 6 years, respectively.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This application for marketing authorisation is supported by the phase II study AB07001, the supportive phase I study AB03002 and the supportive phase II study AB04016. Study AB07001 was planned only as an exploratory trial to determine whether it was worthwhile investigating masitinib further. The study was not planned to provide statistical comparisons between masitinib and sunitinib. The overall design of the study is acceptable for an exploratory trial. However, a GCP inspection of the sponsor site and of two clinical trial sites of pivotal trial AB07001 revealed numerous critical and major findings related to the conduct of the study and collection of efficacy and safety data, including poor adherence to scheduling of visits to assess PFS. The Applicant has responded to the numerous GCP inspection findings with corrective measures whenever possible.

Efficacy data and additional analyses

The primary endpoint of study AB07001 was PFS. This is an acceptable primary endpoint and the concept of utilising PFS in the patient setting was agreed during CHMP scientific advice. The median PFS according to RECIST did not differ between treatment arms (3.7 vs. 1.9 months for masitinib vs. sunitinib, hazard ratio = 1.07; 95% C.I.: 0.54 ; 2.13; log-rank p-value = 0.833).

The fact that the majority of patients had progressed on a dose of imatinib of 400 mg prior to inclusion in the study is not fully in accordance with current clinical guidance, and the patient population may therefore not be representative of future patients in terms of prior exposure to imatinib. The slight imbalance in the number of dose-escalated patients between the masitinib and sunitinib groups is not considered important for the interpretation of the efficacy results.

The efficacy claim is mainly based on an exploratory analysis of the secondary endpoint overall survival (OS) of trial AB07001. In this analysis (database cut-off January 2012), the median overall OS for masitinib arm was estimated to be at least 21.2 months (95% C.I.: 21.2; not estimable) as compared with 15.2 months in the sunitinib group (hazard ratio = 0.27; 95% C.I.: 0.09; 0.85; log-rank p-value=0.016). In an updated analysis (database cut-off December 2012), the median OS was 29.8 vs 17.4 months for masitinib versus sunitinib, respectively (hazard ratio = 0.40, 95% CI = [0.16; 0.96]; p-value = 0.033).

Firm evidence in support of efficacy claims generally requires that the results of the confirmatory trials demonstrate that the investigational product under test has clinical benefits. Exploratory trials generally cannot be the basis of the formal proof of efficacy. In addition, where the evidence of efficacy is based on a single pivotal study, the study has to be exceptionally compelling and special attention has to be paid, among other aspects, to data quality, the degree of statistical significance and internal consistency with all important endpoints showing similar findings. Concerning masitinib in the claimed indication, evidence from confirmatory trials is lacking. Despite the OS differences observed in the exploratory trial, due to the exploratory nature of the trial and analyses presented, the choice of hypothesis may be data dependent. Consequently, the OS results reported in the exploratory study should be viewed only as hypothesis generating and would need to be confirmed in a phase III study. Furthermore, the degree of statistical significance of the exploratory OS analyses presented cannot be considered

as statistically compelling in the context of a single pivotal trial and convincing supportive evidence from other clinically relevant endpoints is lacking.

Further data have been submitted but the EPAR AR has not been updated (data not shown).

2.5.4. Conclusions on the clinical efficacy

The evidence provided is insufficient to establish the efficacy of masitinib. The efficacy of masitinib in GIST has not been demonstrated based on the data presented.

2.6. Clinical safety

Patient exposure

The safety population included 1122 patients/healthy volunteers from 35 studies. These include 4 studies in GIST patients with masitinib used as monotherapy. In the additional studies masitinib has been given as single agent in non-oncology indications in much lower doses than the proposed dose or in oncology indications in combination with chemotherapy, in lower doses as well.

Overall, 423 patients were exposed for at least 3 months to masitinib, 253 patients were exposed for at least 6 months, 140 patients were exposed for at least 1 year, 77 patients for at least 2 years, and 42 patients for at least 3 years. A total of 519 patients have been treated with masitinib as single agent; however 407 of these patients were treated for non-oncology indications.

In the assessment the focus has therefore mainly been on the safety profile of masitinib used as monotherapy in GIST patients, thus including 112 patients.

In contrast to the Efficacy Part that had two supportive studies (AB03002 and AB04016), the Applicant has besides these two studies also included the ongoing phase III study AB04030 in 1st GIST as supportive study in the Safety part. As this study is ongoing no Clinical Study Report (CSR) is available yet.

The cut-off date for the safety analysis of the pivotal trial AB7001 was 31 January 2012. At the time the pivotal study only included 44 patients, (23 were treated with masitinib, 21 with sunitinib). The supportive GIST studies included 19, 30 and 40 patients, respectively.

In the pivotal study patients received a masitinib dose of 12 mg/kg/day. The supportive study AB03002 was a dose escalating trial investigating masitinib doses of 0.7 to 17.2 mg/kg/day. The dose of 15 mg/kg/day was considered dose limiting due to gastrointestinal toxicities. In this study ten patients were treated with masitinib doses of 10.8 to 13.0 mg/kg/day and two patients were treated with doses of 6.8 and 8.5 mg/kg/day, respectively. The Applicant has pooled these patients in a so called “selected GIST cohort” as they all received doses “approximating” the proposed 12 mg/kg/day dose. In the supportive studies AB04016 and AB04030 patients were all treated with a 7.5 mg/kg/day dose.

The median exposure was 4.7 months in the pivotal study and ranged from 1.8-31.5 months in the supportive studies. The longest exposure occurred in study AB04016 (median exposure 31.5 months) which resulted in an increased number of reported adverse events.

Long-term data (at least 12 months) were only available for 37 patients treated for GIST of whom only a few received the proposed dose of 12 mg/kg/day. The majority received less.

Adverse events

Adverse events (AE) reported in at least 5% of patients according to treatment arm are displayed in Table 13. The reporting of common AEs was overall very similar in other GIST studies.

Table 13 – Adverse events reported in at least 5% of patients from study AB07001, according to treatment arm

System Organ Class/Preferred Term	MASITINIB (N=23)	SUNITINIB (N=21)
At least one AE	**22 (95.7%)**	**21 (100%)**
Blood And Lymphatic System Disorders	**13 (56.5%)**	**14 (66.7%)**
Anaemia	**10 (43.5%)**	**6 (28.6%)**
Leukopenia	2 (8.7%)	4 (19.0%)
Lymphopenia	3 (13.0%)	3 (14.3%)
Neutropenia	2 (8.7%)	**5 (23.8%)**
Thrombocytopenia	-	**6 (28.6%)**
Cardiac Disorders	**2 (8.7%)**	**1 (4.8%)**
Tachycardia	2 (8.7%)	
Eye Disorders	**9 (39.1%)**	**5 (23.8%)**
Eyelid Oedema	6 (26.1%)	2 (9.5%)
Gastrointestinal Disorders	**19 (82.6%)**	**16 (76.2%)**
Abdominal Pain	1 (4.3%)	**5 (23.8%)**
Abdominal Pain Upper	3 (13.0%)	2 (9.5%)
Cheilitis	2 (8.7%)	2 (9.5%)
Diarrhoea	**11 (47.8%)**	**11 (52.4%)**
Dyspepsia	1 (4.3%)	2 (9.5%)
Gastroesophageal Reflux Disease	3 (13.0%)	3 (14.3%)
Nausea	**14 (60.9%)**	**5 (23.8%)**
Stomatitis	2 (8.7%)	2 (9.5%)
Vomiting	**9 (39.1%)**	2 (9.5%)
General Disorders And Administration Site Conditions	**16 (69.6%)**	**18 (85.7%)**
Asthenia	**8 (34.8%)**	**13 (61.9%)**
Fatigue	3 (13.0%)	3 (14.3%)
Mucosal Inflammation	1 (4.3%)	**6 (28.6%)**
Oedema	3 (13.0%)	-
Oedema Peripheral	**6 (26.1%)**	4 (19.0%)
Pyrexia	-	2 (9.5%)
Systemic Inflammatory Response Syndrome	-	1 (4.8%)

System Organ Class/Preferred Term	MASITINIB (N=23)	SUNITINIB (N=21)
Hepatobiliary Disorders	**-**	**2 (9.5%)**
Hepatic Pain	-	1 (4.8%)
Jaundice	-	1 (4.8%)
Infections And Infestations	**6 (26.1%)**	**3 (14.3%)**
Bronchitis	2 (8.7%)	-
Urinary Tract Infection	1 (4.3%)	2 (9.5%)
Investigations	**6 (26.1%)**	**4 (19.0%)**
Blood Bilirubin Increased	2 (8.7%)	-
Weight Decreased	2 (8.7%)	3 (14.3%)
Metabolism And Nutrition Disorders	**7 (30.4%)**	**5 (23.8%)**
Anorexia	**5 (21.7%)**	4 (19.0%)
Musculoskeletal And Connective Tissue Disorders	**4 (17.4%)**	**8 (38.1%)**
Back Pain	1 (4.3%)	2 (9.5%)
Muscle Spasms	2 (8.7%)	-
Myalgia	-	2 (9.5%)
Pain In Extremity	2 (8.7%)	2 (9.5%)
Nervous System Disorders	**3 (13.0%)**	**13 (61.9%)**
Dysgeusia	1 (4.3%)	**6 (28.6%)**
Headache	1 (4.3%)	4 (19.0%)
Psychiatric Disorders	**3 (13.0%)**	**3 (14.3%)**
Moaning	2 (8.7%)	-
Renal And Urinary Disorders	**1 (4.3%)**	**3 (14.3%)**
Respiratory And Thoracic And Mediastinal Disorders	**5 (21.7%)**	**3 (14.3%)**
Dyspnoea	3 (13.0%)	2 (9.5%)
Skin And Subcutaneous Tissue Disorders	**14 (60.9%)**	**14 (66.7%)**
Dry Skin	3 (13.0%)	2 (9.5%)
Erythema	2 (8.7%)	2 (9.5%)
Palmar Plantar Erythrodysesthesia Syndrome	1 (4.3%)	**6 (28.6%)**
Rash	**7 (30.4%)**	2 (9.5%)
Vascular Disorders	**1 (4.3%)**	**8 (38.1%)**
Hypertension	-	**6 (28.6%)**
Phlebitis	-	2 (9.5%)

Table 14 presents all severe adverse events (i.e. adverse events of grade ≥3) reported in study AB07001.

Table 14 – Study AB07001 – Severe adverse events

Number (%) of patients with at least one	Masitinib 12 mg/kg/d (N=23)				Sunitinib 50 mg/kg/d (N=21)			
	All*	Grade 3	Grade 4	Grade 5	All*	Grade 3	Grade 4	Grade 5
At least one severe AE	**6 (26.1%)**	**6 (26.1%)**	**1 (4.3%)**	-	**16 (76.2%)**	**16 (76.2%)**	-	**3 (14.3%)**
Blood And Lymphatic System Disorders	**3 (13.0%)**	**2 (8.7%)**	**1 (4.3%)**	-	**5 (23.8%)**	**5 (23.8%)**	-	-
Anaemia	3 (13.0%)	2 (8.7%)	1 (4.3%)	-	1 (4.8%)	1 (4.8%)	-	-
Lymphopenia	-	-	-	-	2 (9.5%)	2 (9.5%)	-	-
Thrombocytopenia	-	-	-	-	2 (9.5%)	2 (9.5%)	-	-
Thrombotic Microangiopathy	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Cardiac Disorders	**-**	**-**	**-**	**-**	**1 (4.8%)**	**1 (4.8%)**	**-**	**-**
Congestive Cardiomyopathy	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Ear And Labyrinth Disorders	**-**	**-**	**-**	**-**	**1 (4.8%)**	**1 (4.8%)**	**-**	**-**
Vertigo	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Gastrointestinal Disorders	**1 (4.3%)**	**1 (4.3%)**	**-**	**-**	**2 (9.5%)**	**2 (9.5%)**	**-**	**-**
Abdominal Pain	1 (4.3%)	1 (4.3%)	-	-	2 (9.5%)	2 (9.5%)	-	-
General Disorders And Administration Site Conditions	**3 (13.0%)**	**3 (13.0%)**	**-**	**-**	**6 (28.6%)**	**6 (28.6%)**	**-**	**1 (4.8%)**
Asthenia	1 (4.3%)	1 (4.3%)	-	-	4 (19.0%)	4 (19.0%)	-	-
General Physical Health Deterioration	-	-	-	-	1 (4.8%)	-	-	1 (4.8%)
Fatigue	1 (4.3%)	1 (4.3%)	-	-	1 (4.8%)	1 (4.8%)	-	-
Oedema Peripheral	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Mucosal Inflammation	1 (4.3%)	1 (4.3%)	-	-	-	-	-	-
Infections And Infestations	**-**	**-**	**-**	**-**	**1 (4.8%)**	**1 (4.8%)**	**-**	**-**
Urinary Tract Infection	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Lung Infection	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Injury, Poisoning And Procedural Complications	**1 (4.3%)**	**1 (4.3%)**	**-**	**-**	**-**	**-**	**-**	**-**
Wrist Fracture	1 (4.3%)	1 (4.3%)	-	-	-	-	-	-
Investigations	**1 (4.3%)**	**1 (4.3%)**	**-**	**-**	**-**	**-**	**-**	**-**
Blood Bilirubin Increased	1 (4.3%)	1 (4.3%)	-	-	-	-	-	-
Metabolism And Nutrition Disorders	**-**	**-**	**-**	**-**	**1 (4.8%)**	**1 (4.8%)**	**-**	**-**
Cachexia	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Nervous System Disorders	**-**	**-**	**-**	**-**	**3 (14.3%)**	**2 (9.5%)**	**-**	**1 (4.8%)**
Syncope	-	-	-	-	1 (4.8%)	-	-	1 (4.8%)
Dysgeusia	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Headache	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Psychiatric Disorders	**-**	**-**	**-**	**-**	**1 (4.8%)**	**1 (4.8%)**	**-**	**-**
Disorientation	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-

Number (%) of patients with at least one	Masitinib 12 mg/kg/d (N=23)				Sunitinib 50 mg/kg/d (N=21)			
	All*	Grade 3	Grade 4	Grade 5	All*	Grade 3	Grade 4	Grade 5
Respiratory, Thoracic And Mediastinal Disorders	**2 (8.7%)**	**2 (8.7%)**	**-**	**-**	**2 (9.5%)**	**1 (4.8%)**	**-**	**1 (4.8%)**
Dyspnoea	2 (8.7%)	2 (8.7%)	-	-	1 (4.8%)	1 (4.8%)	-	-
Respiratory Distress	-	-	-	-	1 (4.8%)	-	-	1 (4.8%)
Skin And Subcutaneous Tissue Disorders	**1 (4.3%)**	**1 (4.3%)**	**-**	**-**	**-**	**-**	**-**	**-**
Pruritus	1 (4.3%)	1 (4.3%)	-	-	-	-	-	-
Vascular Disorders	**-**	**-**	**-**	**-**	**4 (19.0%)**	**4 (19.0%)**	**-**	**-**
Hypertension	-	-	-	-	3 (14.3%)	3 (14.3%)	-	-
Phlebitis	-	-	-	-	1 (4.8%)	1 (4.8%)	-	-
Rash events – All #	**1 (4.3%)**	**1 (4.3%)**	**-**	**-**	**-**	**-**	**-**	**-**
Oedema events – All ##	**-**	**-**	**-**	**-**	**1 (4.8%)**	**1 (4.8%)**	**-**	**-**

** All = from grade 3 to grade 5*
#"Rash events - All" includes the following MedDRA preferred terms: excoriation; acne; giant urticaria; blister; dermatitis; dermatitis acneiform; dermatitis allergic; dermatitis psoriasiform; dry skin; eczema; erythema; erythema diffuse; erythema multiforme; erythema nodosum; generalized erythema; guttate psoriasis; dry hair; idiopathic urticaria; mucocutanous rash; palmar erythema; hand and foot syndrome; pruritus; pruritus allergic; rash; rash erythematous; rash generalised; rash macula-papular; rash pruritic; skin bleeding; skin burning sensation; skin desquamation; skin exfoliation; skin fissure; skin inflammation; skin irritation; skin lesion; skin reaction; skin toxicity; toxic skin eruption; urticaria; urticaria generalised; urticaria localized; urticaria papular; urticaria pigmentosa.
"Oedema events - All" includes the following MedDRA preferred terms: eye oedema, eyelid oedema, orbital oedema, periorbital oedema, gingival oedema, oedema mouth, tongue oedema, face oedema, generalised oedema, localized oedema, oedema, oedema peripheral, allergic oedema, breast oedema, oedema genital, scrotal oedema, testicular swelling, lymphedema.

Serious adverse event / deaths / other significant events

Deaths

All deaths but those clearly related to the disease per protocol definitions and except deaths that were not related to the investigational product, are discussed in this section.

None of the masitinib-treated patients died during study AB07001. Among sunitinib-treated patients, three deaths were reported, none of which were considered related to the study treatment.

None of the deaths occurring in study AB04016 were related to masitinib treatment.

One death suspected to be related to masitinib was reported in study AB04030: acute pulmonary oedema.

Serious Adverse Events (SAEs)

Non-fatal serious adverse events reported in study AB07001 are displayed in the table below.

Table 15 – Study AB07001 – Description of non-fatal serious adverse events

Number (%) of patients with at least one	Masitinib 12 mg/kg/d (N=23)	Sunitinib 50 mg/ d (N=21)
At least one non-fatal SAE	**3 (13.0%)**	**7 (33.3%)**
At least one suspected non-fatal SAE	-	4 (19.0%)
Blood And Lymphatic System Disorders	**1 (4.3%)**	**2 (9.5%)**
Anaemia	1 (4.3%)	1 (4.8%)
Thrombotic Microangiopathy	-	1 (4.8%)
Cardiac Disorders	-	**1 (4.8%)**
Congestive Cardiomyopathy	-	1 (4.8%)
Gastrointestinal Disorders	**1 (4.3%)**	**2 (9.5%)**
Abdominal Pain	1 (4.3%)	1 (4.8%)
Vomiting	-	1 (4.8%)
General Disorders And Administration Site Conditions	-	**1 (4.8%)**
Asthenia	-	1 (4.8%)
Infections And Infestations	-	**1 (4.8%)**
Lung Infection	-	1 (4.8%)
Urinary Tract Infection	-	1 (4.8%)
Investigations	**1 (4.3%)**	
Blood Creatinine Increased	1 (4.3%)	
Metabolism And Nutrition Disorders	-	**1 (4.8%)**
Cachexia	-	1 (4.8%)
Psychiatric Disorders	-	**1 (4.8%)**
Disorientation	-	1 (4.8%)
Renal And Urinary Disorders	-	**1 (4.8%)**
Renal Failure	-	1 (4.8%)
Vascular Disorders	**-**	**1 (4.8%)**
Phlebitis	-	1 (4.8%)

None of SAEs in the masitinib arm were considered treatment-related by the investigators. In the sunitinib arm none of the observed SAEs was reported more than once. Some patients experienced more than one SAE. The reported SAEs were considered treatment-related in four patients.

A limited number of suspected treatment-related SAEs were reported in the small dose-escalating study AB03002. More SAEs were reported in the ongoing phase III study AB04030 in 1st line that has only enrolled 40 patients in the masitinib arm. So far 8 of these patients have reported SAEs. The most common were anaemia (3 patients), diarrhoea (2 patients) and dyspnoea (2 patients). Only 2 reports of SAEs (anaemia, psoriasis) derived from study AB04016.

Events of Special Interest

During the assessment, the applicant was requested to provide a thorough discussion of masitinib Adverse Events of Special Interest (AESI) in relation to other TKIs, which is summarised below:

- Adverse events more frequently observed with masitinib than with most registered TKIs, but not necessarily sunitinib were: nausea and vomiting, skin rash and oedema.

- Adverse events observed with masitinib at a similar frequency than with most registered TKIs were: diarrhoea, musculoskeletal complaints and renal toxicity

- Adverse events less frequently observed with masitinib than with most registered TKIs were: fatigue, hepatotoxic events, stomatitis, haemorrhage, anaemia, neutropenia, severe skin toxicity, thrombocytopenia and pancytopenia, hypothyroidism and cardiotoxicity.

Signals of potential concern have been identified in relation to cardiotoxicity, QT prolongation and skin toxicities.

Laboratory findings

In general, it has been difficult to get an overview of laboratory values. Patients with a normal *biochemistry* value at baseline in the pivotal study receiving masitinib did not shift to a grade 3 or 4 value except for one patient (of the 21 patients) with normal albumin at baseline decreasing to a grade 3 albumin level and two patients (out of 15 patients) with normal phosphorus at baseline decreasing to grade 3 level. However, shifts from normal at baseline to grade 1 and 2 were common in the pivotal study concerning phosphorus decreased, bilirubin increased, alkaline phosphatase increased, gamma-GT increased, AST increased, ALT increased, glucose increased and calcium increased. Overall, the same pattern was observed for sunitinib except that the alkaline phosphatase seems to increase in three times more patients receiving masitinib compared to sunitinib.

In patients receiving sunitinib a higher proportion of patients had albumin decreased and potassium increased in patients having normal albumin or potassium, respectively, at baseline.

The shifts in biochemistry in the pivotal study are roughly in accordance with the shifts in biochemistry in the supportive studies taking the small number of patients into account.

Concerning *haematological changes* in the pivotal study decreased values of especially haemoglobin but also other haematological values were observed in the masitinib treated patients. However, it was mainly to grade 1 and to a lesser extend grade 2. Only two patients were observed with grade 3 decreases (one haemoglobin and one lymphocytes). No grade 4 decreases were observed.

Safety in special populations

No data have been submitted in patients with impaired renal or hepatic function.

In the pivotal study no major differences were observed concerning the safety profile according to age (<=65 vs. >65 years old). However, no conclusion can be drawn in view of the small number of subjects.

Discontinuation due to adverse events

In the pivotal study only one patient in the masitinib arm discontinued treatment due to an AE (dyspnoea) compared with three patients in the sunitinib arm. Only two of the causal events were considered treatment-related (anaemia, asthenia and disorientation.)

Limited information comes from the supportive GIST studies: No patients discontinued study drug due to AEs in study AB04016. Three patients discontinued treatment in the dose escalating study AB03002, two of these patients belonged to the "selected GIST cohort" (events leading to discontinuation: nausea, salivary hypersecretion, vomiting, anorexia). Four patients discontinued masitinib due to AEs in the ongoing phase III trial ABO4030 (events leading to discontinuation: diarrhoea, liver transaminase elevations, dyspnoea and hypertension).

In the pivotal study 6 patients (26.1%) in the masitinib arm experienced AEs leading to dose reductions compared to 9 patients (42.9%) in the sunitinib arm. In the masitinib arm only three of these patients had events that were considered treatment-related (elevated transaminase level, oedema, pruritus).

In the supportive GIST studies few patients required dose-reductions due to treatment-related events. Two patients in study AB04030 required dose reductions due to development of rash. Of note, there were only two reports of dose reductions due to diarrhoea or gastrointestinal disturbances in the masitinib arm although these events were commonly associated with masitinib.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety population included 1122 patients/healthy volunteers from 35 studies. However, the total GIST safety population (n=) included patients from the pivotal phase II study (AB07001) and from 3 supportive studies (dose escalating phase I study AB03002, single-arm phase II study AB04016 in 1st line and the ongoing phase III study AB04030 in 1st line). Only 23 patients from the pivotal study received masitinib as 2nd line treatment at the proposed dose of 12 mg/kg/day. In addition, ten patients in the dose-escalating study received masitinib doses in the range of 10.8 to 13.0 mg/kg/day. In the additional studies masitinib has been given as single agent in non-oncology indications in much lower doses than the proposed or in oncology indications in combination with chemotherapy, in lower doses as well.

Almost all patients in the pivotal study AB07001 reported at least one AE (22/23 or 95.7% in the masitinib arm and 21/21 or100% in the sunitinib arm).

The most common AEs associated with masitinib (> 25%) were nausea (14 patients: 60.9%), diarrhoea (11 patients: 47.8%), anaemia (10 patients: 43.5%), vomiting (9 patients: 39.1%), asthenia (8 patients: 34.8%), rash (30.4%), peripheral/eyelid oedema (6 patients: 26.1%). The reporting of common AEs was similar in other GIST studies.

These events are all representing well known safety characteristics of TKIs. However, subtle differences exist due to differences in kinase selectivity which result in slightly different safety profiles among these agents. For instance, it seems that nausea, vomiting, rash and peripheral

oedema are more commonly associated with masitinib whereas patients treated with sunitinib have a higher risk of developing asthenia, thrombocytopenia, PPES and hypertension.

After the update of the safety database following the GCP inspection, twelve (47.8%) of the masitinib-treated patients reported at least one severe adverse event. The most common severe events in the masitinib arm were Anaemia (3 patients) and Dyspnoea (2 patients). Only one event of Anaemia was of grade 4, the rest of the severe events were grade 3. The safety database update revealed that 11 (47.8%) patients in the masitinib group experienced a non-haematological Grade 3 or 4 AE.

More patients reported severe events in study AB04016 (phase II, 1st line), mainly rash, gastrointestinal disorders and anaemia/neutropenia, which can be explained by the longer exposure. Furthermore, more severe events were also reported in the ongoing phase III study AB04030 (1st line), particularly liver transaminase elevations and blood and lymphatic system disorders despite a lower dose being used.

At least one nonfatal SAE was reported in 7 patients (33.3%) in the sunitinib arm compared with 3 patients (13.0%) in the masitinib arm. The 3 reports of SAEs in the masitinib arm include one case of anaemia, one case of increased blood creatinine and one case of abdominal pain. None of these events were considered treatment-related by the investigators. The reported frequencies should be interpreted with caution due to the limited total number of patients enrolled in the pivotal study.

A limited number of suspected treatment-related SAEs were reported in the small dose-escalating study AB03002. More SAEs were reported in the ongoing phase III study AB04030 in 1st line that has only enrolled 40 patients in the masitinib arm. So far 8 of these patients have reported SAEs. The most common were anaemia (3 patients), diarrhoea (2 patients) and dyspnoea (2 patients). Only 2 reports of SAEs (anaemia, psoriasis) derived from study AB04016. However, supportive data is also available from a limited number of patients, the majority of which were treated at a lower dose and therefore does not allow drawing conclusion.

In the pivotal trial there were no reported deaths in the masitinib arm. There were three deaths in the sunitinib arm but none were considered treatment- related. In the supportive studies only one fatality was considered treatment-related. It concerned a 77-year old patient who died of acute pulmonary oedema 5 months after starting masitinib treatment. An update of reported SAEs and deaths in ongoing studies in GIST was requested, and no new safety signal has been identified.

Discontinuations of treatment due to an AE was only observed in one patient in the masitinib arm in the pivotal study (dyspnoea) compared with 3 patients in the sunitinib arm. However, 6 patients (26.1%) experienced AEs leading to dose reductions in the masitinib arm compared to 9 patients (42.9%) in the sunitinib arm.

Haematological shifts from normal at baseline to worst grade under treatment in masitinib treated patients in the pivotal study were observed. Decreased values of especially haemoglobin, lymphocytes and leucocytes were observed, however, it was mainly to grade 1 and grade 2. No severe neutropenia was reported in any of the GIST studies; however, severe neutropenia was reported in other indications including a severe serious adverse event of neutropenia in a healthy

volunteer. Shifts in biochemistry in the pivotal study were mainly grade 1-2 and concerned especially hepatic parameters.

Cardiotoxicity is considered a potential safety concern in view of findings in preclinical studies (impact on hERG, fibrosis and myocardial degeneration) after masitinib treatment and cardiac AEs, SAEs, one sudden death and one case “death” included in the safety database.

Furthermore, a very small study in healthy volunteers showed prolonged QT after masitinib doses of 200 and 800 mg (see clinical pharmacology section). Newer tyrosine kinase inhibitors used in the treatment of various cancers have been noted to cause significant QT prolongation. Sunitinib, nilotinib, and dasatinib have been associated with varied amounts of QT prolongation at 10 msec, 5 to 15 msec, and 3.3 msec, respectively. In the ongoing blinded phase 3 study, AB07012, (masitinib in combination with chemotherapy) one sudden death had been observed. Arrhythmia NOS have been described two times (in the same patient) in study AB 06006 as non-fatal SAE. Two AE cases of tachycardia (8.7%) have been observed in the pivotal study; however, the type of tachycardia has not been described. In addition, in “other GIST studies” 3 cases (15.8%) of tachycardia were observed in AB03002. Syncope’s have not been observed in the pivotal study but were observed in more of the other masitinib studies. Furthermore, in an uncontrolled study with masitinib in combination with chemotherapy, one patient had QT-prolongation. No cases of Torsade de Pointes have been observed, however, such cases are seldom captured in clinical trials. As discussed in the clinical pharmacology section, an effect of masitinib on QTc cannot be ruled out and a thorough QT/QTc study according to the guideline (CHMP/ICH/2/04 E14, The clinical evaluation of QT/QTs 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.

Skin toxicity was also of concern in view of 18 SAEs observed in the entire database including several cases of toxicodermia and one case of Baboon syndrome. The cases generally occurred within some weeks after treatment start, were mainly grade 3 and resolved with sequelae. AEs of skin and subcutaneous tissue disorders were observed in 56.5% in the pivotal study and this was overall in line with the observations in the supportive studies. Additionally, a case of Steven-Johnson syndrome was diagnosed clinically by a dermatologist. No biopsy was taken from the patient to confirm the diagnosis histopathologically. The effect of masitinib on the kidney function is considered uncertain. The elimination route of masitinib has been shown to be almost entirely extra-renal. However, pre-clinical studies showed prevalence of blood and protein in the urine in dogs and rats and histopathological findings of tubular cell degeneration/necrosis in rats. Proteinuria was observed overall in 7.3% of the patients in the supportive GIST studies, however, no cases were observed in the pivotal study. In addition several different AEs, non-fatal SAEs and deaths due to the kidney function have been described in the entire safety database. No formal renal study was included with this submission. Therefore, the effect on masitinib on the kidney function should be further characterised.

Similarly, the potential influence of masitinib on liver function has not been thoroughly discussed. In preclinical studies liver toxicity was observed (increase of hepatic enzyme activity, decreased plasma concentrations of protein and albumin and microscopic changes such as bile canalicular plugs and vacuolated Kupffer cells). The metabolism of masitinib is mainly hepatic. GIST patients may have hepatic metastases which can lead to hepatic impairment. No patients in the pivotal study experienced hepatobiliary disorders; however, 16.7% of the patients in the selected cohort

of the supportive GIST study AB03002 (or 21% of all patients in the same study) experienced hyperbilirubinemia. Increase in transaminases, gamma GT, bilirubin and LDH were common in the pivotal study. In the entire safety database cases of cytolytic hepatitis were observed. According to the applicant no fatal liver disorder was considered as related to masitinib. . Therefore, starting dose adjustment in patients with mild to moderate liver impairment, dose reductions or treatment interruptions for hepatic adverse reaction would be considered warranted.

Further data have been submitted but the EPAR AR has not been updated (data not shown).

2.6.2. Conclusions on the clinical safety

Although masitinib has been investigated in a number of indications in various doses, the safety database only included a very limited number of GIST patients (n=112), of which only very few (23 patients in the pivotal phase II trial and 10 patients [dose range of 10.8 to 13.0 mg/kg/day] in the dose escalating study) have actually been treated with the proposed dose of 12 mg/kg/day. Consequently, the safety database is considered insufficient to allow an adequate assessment of the risks associated with masitinib in the proposed indication and posology.

Common AEs associated with masitinib are characteristic of the well-known safety profile of other TKIs, however, signals of potential concern have been identified in relation to cardiotoxicity, QTc prolongation and renal toxicity that would require further investigations.

Therefore, the safety of masitinib is not considered to have been adequately studied.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance system 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 (Masican) for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after progression with imatinib treatment 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**

The applicant identified the following safety concerns in the RMP:

Table 16 – Summary of the Safety Concerns

Summary of 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 Long-term efficacy and safety of masitinib at 12 mg/kg/day Use in patients with ECOG score > 2 Embryo toxicity

The PRAC considers that the updated summary of safety concerns submitted by the Applicant is acceptable though “creatinine increased” should be corrected to “creatinine increase” or “creatinine increases”.

- **Pharmacovigilance plans**

Table 17 – 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	Cardiac toxicity	Proposed	Not finalised

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

*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 Masican.

- **Risk minimisation measures**

Table 18 – 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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
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
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 that the summary table in Part V.1 was lacking information on missing information and requires updating in this regard. Specifically, the Applicant should consider whether risk minimisation measures for embryotoxicity are warranted.

Finally, the PRAC noted that the Applicant had erroneously considered the proposed risk minimisation measures for severe neutropenia, liver toxicity, proteinuria and creatinine increased as additional risk minimisation measures and these should be properly classified in an updated RMP.

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 is treatment of unresectable and/or metastatic malignant GIST in adults after progression with imatinib treatment.

The efficacy claim is mainly based on an exploratory analysis of the secondary endpoint overall survival (OS) of trial AB07001. In this analysis (database cut-off January 2012), the median overall OS for masitinib arm was estimated to be at least 21.2 months (95% C.I.: 21.2; not estimable) as compared with 15.2 months in the sunitinib group (hazard ratio = 0.27; 95% C.I.: 0.09; 0.85; log-rank p-value=0.016). In an updated analysis (database cut-off December 2012), the median OS was 29.8 vs 17.4 months for masitinib versus sunitinib, respectively (hazard ratio = 0.40, 95% CI = [0.16; 0.96]; p-value = 0.033). The median PFS was 3.7 vs. 1.9 months for masitinib vs. sunitinib, respectively (hazard ratio = 1.07; 95% C.I.: 0.54 ; 2.13; log-rank p-value = 0.833). One (4.3%) patient in the masitinib arm and two (9.5%) patients in the sunitinib arm achieved a partial response according to Response Evaluation Criteria In Solid Tumors (RECIST).

The beneficial effects of Masican in the proposed indication have not been established (see Uncertainty in the knowledge of the beneficial effects).

Uncertainty in the knowledge about the beneficial effects.

The pharmacokinetics of masitinib would require further investigation, particularly with regards to proposed posology. Additional studies in special populations and a thorough QT/QTc study are also needed.

In the setting of a marketing authorisation application supported by a single pivotal study, special attention has to be paid to data quality. A Good Clinical Practice (GCP) inspection of the sponsor site and of two clinical trial sites of pivotal trial AB07001 revealed numerous critical and major findings related to the conduct of the study and collection of efficacy and safety data, including poor adherence to scheduling of visits to assess progression-free survival (PFS). The Applicant has responded to the numerous GCP inspection findings with corrective measures whenever possible.

In study AB07001 the statistical hypotheses were defined to test if median PFS was sufficiently long to imply that masitinib will be chosen for further studies or if PFS was too short for masitinib to be chosen for further studies. From a statistical point of view, this study was not designed as comparative between masitinib and sunitinib, and any comparison between groups was exploratory.

Firm evidence in support of efficacy claims generally requires that the results of the confirmatory trials demonstrate that the investigational product under test has clinical benefits. Exploratory trials generally cannot be the basis of the formal proof of efficacy. In addition, where the evidence of efficacy is based on a single pivotal study, the study has to be exceptionally compelling and special attention has to be paid, among other aspects, to data quality, to the degree of statistical significance and internal consistency with all important endpoints showing

similar findings. Concerning masitinib in the claimed indication, evidence from confirmatory trials is lacking. Despite the OS differences observed in the exploratory trial, due to the exploratory nature of the trial and analyses presented, the choice of hypothesis may be data dependent. Consequently, the OS results reported in the study should be viewed only as hypothesis generating and would need to be confirmed in a phase III study. Furthermore, the degree of statistical significance of the exploratory OS analyses presented cannot be considered as statistically compelling in the context of a single pivotal trial and convincing supportive evidence from other clinically relevant endpoints is lacking. Thus, the evidence provided is insufficient to establish the efficacy of masitinib.

From a quality perspective, the lack of sufficient information on the manufacture and controls of the drug substance as a result of unsuitable starting material means that only when adequate information on the drug substance manufacturing process and controls is provided could the grant of the market authorisation be considered.

Risks

Unfavourable effects

The safety database is considered insufficient to allow an adequate assessment of the risks associated with masitinib in the proposed indication and posology (see Uncertainty in the knowledge about the unfavourable effect).

The most common AEs associated with masitinib (> 25%) in the pivotal were nausea (14 patients: 60.9%), diarrhoea (11 patients: 47.8%), anaemia (10 patients: 43.5%), vomiting (9 patients: 39.1%), asthenia (8 patients: 34.8%), rash (30.4%), peripheral/eyelid oedema (6 patients: 26.1%). These events are all representing well known safety characteristics of TKIs.

Haematological changes from normal at baseline to worst grade under treatment in masitinib treated patients in the pivotal study were observed. Decreased values of especially haemoglobin, lymphocytes and leucocytes were observed, however, it was mainly to grade 1 and grade 2. No severe neutropenia was reported in any of the GIST studies; however, severe neutropenia was reported in other indications including a severe serious adverse event of neutropenia in a healthy volunteer.

Changes in biochemistry in the pivotal study were mainly grade 1-2 and concerned especially hepatic parameters.

Uncertainty in the knowledge about the unfavourable effects

Although masitinib has been investigated in a number of indications in various doses, the safety database only included a very limited number of GIST patients of which only very few (23 patients in the pivotal phase II trial and 10 patients [dose range of 10.8 to 13.0 mg/kg/day] in the dose escalating study) have actually been treated with the proposed dose of 12 mg/kg/day.

The sample size of the pivotal (and supportive studies) in GIST is too small to allow an adequate assessment of the risks associated with masitinib. When comparing the reported severe events in the pivotal trial with the observed severe events in the supportive GIST studies, it is noted that more patients reported severe events in study AB04016 (1st line), mainly rash, gastrointestinal disorders and anaemia/neutropenia, which can be explained by the longer exposure. Notably,

more severe events were also reported in the ongoing phase III study ABO4030 (1st line), particularly liver transaminase elevations and blood and lymphatic system disorders despite a lower dose being used. It raises a concern that the reporting of laboratory abnormalities is more complete in the ongoing phase III trial.

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. Two cases of tachycardia (8.7%) have been observed in the pivotal study. Finaly, 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.

Benefit-risk balance

Importance of favourable and unfavourable effects

Efficacy results reported in the study should be viewed only as hypothesis generating and would need to be confirmed in a phase III study. Furthermore, the degree of statistical significance of the exploratory OS analyses presented cannot be considered as statistically compelling in the context of a single pivotal trial and convincing supportive evidence from other clinically relevant endpoints is lacking. Thus, the evidence provided is insufficient to establish the efficacy of masitinib. The safety profile of masitinib does not cause immediate concerns. However, the number of GIST patients treated at the proposed posology is too limited to allow an adequate assessment of the risk associated with masitinib.

From a quality perspective, the lack of sufficient information on the manufacture and controls of the drug substance as a result of unsuitable starting material means that only when adequate information on the drug substance manufacturing process and controls is provided could the grant of the market authorisation be considered.

Discussion on the benefit-risk balance

The efficacy of masitinib in GIST has not been sufficiently demonstrated. The safety database is considered insufficient to allow an adequate assessment of the risks associated with masitinib in the proposed indication and posology. Furthermore, the quality of the product is insufficiently controlled with regards patient exposure to impurities.

The overall benefit-risk of Masican (masitinib) in the proposed GIST indication is considered negative.

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. In addition, the timely completion of further studies required for the confirmation of a positive benefit risk balance cannot be expected in light of the observed recruitment so far in the ongoing confirmatory study. The benefit to public health of the immediate availability on the market of masitinib has not been justified and does not outweigh the risk inherent in the fact that additional data are still required.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Masican in the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after progression with imatinib treatment, 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 GIST has not been sufficiently demonstrated;
- The safety database is considered insufficient to allow an adequate assessment of the risks associated with masitinib in the proposed indication and posology;
- 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 21 November 2013

Following the CHMP conclusion that Masican was not approvable due to the lack of an established efficacy, insufficient safety database and due to the insufficiently controlled quality of the product, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation.

A summary of the applicant's grounds for re-examination is presented below.
Clinical Ground No. 1 (exploratory nature of the study with no planned statistical comparisons between masitinib and sunitinib): The applicant considered that the study was rather a confirmatory study in view of ICH E9 guideline on Statistical Principles for Clinical Trial (dated 05 February 1998): The statistical hypothesis done on the primary analysis of study AB07001 was pre-specified and did not change according to the PFS data obtained, these PFS data not being available at the time of the choice of the statistical hypothesis but 1 year later once the CT-scans were centrally and blindly reviewed. The statistical tests performed on this primary analysis were conclusive. Statistical tests on the secondary analysis of OS (based on p-values and hazard ratios for death with their 95% confidence intervals) were pre-specified, never changed during the course of the study, and were also conclusive. Even if the sequence of secondary analyses on PFS and OS had not been pre-specified, there is still a statistically significant difference in terms

of OS between masitinib and sunitinib treatment-arms when using a conservative approach such as the Bonferroni method. The observed median OS of 29 months in the masitinib treatment-arm of study AB07001 confirms previous results obtained from a phase 1 study of masitinib in advanced GIST patients, i.e. a comparative median OS of 29.8 months, when also factoring in published survival data of sunitinib in third-line. Finally, the applicant considered that the guideline on conditional approval (EMEA/509951/2006) states that a confirmatory study is needed, meaning that the presented phase II study might legitimately have an exploratory aspect.

Clinical Ground No. 2 (results of overall survival not supported by other endpoints): The applicant considered that although PFS may provide valuable insights in certain clinical trials, OS remains, however, the gold standard for assessing efficacy in oncology, in particular for GIST. The statistical validation of surrogate endpoints such as PFS requires a high correlation between the treatment effects on PFS and OS for each indication and each treatment. In reality, a wide variety of oncological treatments fail to show a correlation between PFS, or other surrogate endpoints, and OS.

Clinical Ground No. 3 (the mechanism of action of masitinib may explain an effect on OS without any action on PFS): The applicant considered that evidence have demonstrated that the efficacy results observed for the masitinib treatment-arm of study AB07001, i.e. OS improvement with no impact on PFS, are consistent with, and corroborated by, the mechanisms of action (MoA) of both masitinib and sunitinib. This ability was not limited to patients with GIST since it was also observed in pancreatic cancer patients, in the Tel-Jak2 mice model of leukemia and in dogs with mast cell tumors. Taken together this demonstrates the findings of study AB07001 are not a chance finding.

Clinical Ground No. 4 (results of study AB07001 cannot be considered as compelling in the context of a single pivotal trial): The applicant's position was as follows: The CHMP guideline, CPMP/EWP/2330/99 on points to consider on validity and interpretation of one pivotal study, applies for full approval but does not fit the context of conditional approval.

Clinical Ground No. 5 (safety database is insufficient to allow an adequate assessment of the risks associated with masitinib in the proposed indication and posology): The safety of masitinib in GIST is sufficient since it is based on 174 masitinib-treated patients suffering from GIST (cut-off date 31 August 2013). This safety population consists of imatinib-resistant GIST patients receiving masitinib at 12 mg/kg/day and imatinib-naïve GIST patients receiving masitinib at around 7.5 mg/kg/day, the pharmacokinetics of masitinib in these patients being not different.

In addition, the overall safety profile of masitinib at the cut-off date of 31 August 2013 is based upon 1554 masitinib-treated patients including healthy volunteers, patients from oncology studies and patients from non-oncology studies.

The safety was significantly improved with masitinib compared to sunitinib-treated patients, which is a major benefit to the patients. Quality of life was also better with masitinib than with sunitinib.

Clinical Ground No. 6 (CHMP has not taken into consideration the risk calculation comparing accelerated approval versus failure to accelerate approval): the applicant considered that the risk calculations comparing masitinib's accelerated approval and failure to accelerate masitinib's

approval should be taken into consideration to aid the EMA's decision. According to the applicant, the risk of masitinib being inferior in efficacy to sunitinib was <.0001 and that there is a 90% risk that about 1000 patients/year will be harmed by withholding masitinib treatment.

Clinical Ground No. 7 (timely completion of further studies required for the confirmation of a positive benefit-risk balance cannot be expected in light of the observed recruitment so far in the ongoing confirmatory study): the applicant considered they would be able to provide comprehensive clinical data in a timely fashion upon completion of the ongoing phase III study by end of 2016.

Quality Ground No. 1 (The starting material proposed by the applicant is considered a complex molecule and should instead be considered as intermediate of the synthesis): The applicant proposed not to handle the material 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 relevant impurities are well controlled and present at acceptable levels in the final product. The analytical development would focus on the control of these impurities.

Quality Ground No. 2 (Unsatisfactory data was submitted to support the individual limit of not more than 0.10 % for impurities of concern. Similarly the limit proposed for unspecified impurities of 0.1 % cannot be accepted as it is not in accordance to the applicable guidance considering the maximum daily dose of 1200 mg of masitinib): The applicant agreed to set the specification limits for the concerned impurities. In addition, the applicant proposed to lower the limit of total impurities to be closer to the current level, mainly observed in pilot batches.

Quality Ground No. 3 (Adequacy of the proposed particle size distribution specification): Dissolution studies are ongoing to confirm the discriminatory nature of the present dissolution test method, and if necessary a new dissolution test will be developed. In the meantime, the applicant proposed to revise specification for particle size distribution . When final dissolution test conditions are defined, the applicant proposes to revise, if necessary, the particle size limits on the basis of the particle size distribution of the batches of active substance used for tablet batches of GIST clinical trials and demonstrated to have sufficient bioavailability (at least 85 % dissolved after 15 min).

Quality Ground No. 4 (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.

Quality Ground No. 5 (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 see quality ground No. 3. Concerning tablet hardness: Tthe applicant proposed to tighten the hardness specifications of the core tablets..

Quality Ground No. 6 (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 that additional dissolution studies are ongoing for demonstration of the discriminatory nature of dissolution test, confirming that the 5 minutes test point will be investigated.

Quality Ground No. 7 (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 applicant stated that additional dissolution studies are ongoing for demonstration of the discriminatory nature of dissolution test.

Quality Ground No. 8 (The validation data provided for analytical method was not sufficient with regards the methods for related substances determination and dissolution): The applicant stated that development of the improved impurity assay method is ongoing.

Quality Ground No. 9 (The limit still to be defined for impurity A, found to be threshold-dependent genotoxic): The applicant proposes to tighten the limit of impurity A.

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:

1. Does the SAG consider the difference observed between masitinib and sunitinib in the pivotal trial as a convincing and robust evidence for a clinical benefit? Please consider inclusion criteria (dose of imatinib at progression), trial conduct in respect of statistical methodology, primary and secondary hypotheses and hierarchy/contribution of all clinical efficacy endpoints.

   The SAG considers that there is no convincing and robust evidence in terms of clinical benefit.

   The pivotal study was a small exploratory randomized phase II trial. The efficacy is claimed on the basis of an observed difference in the secondary endpoint overall survival. The statistical significance of this observation is difficult to determine since the trial protocol did not aim to formally compare treatment groups and did not pre-specify adjustment for multiple efficacy analyses.

   In order to rule out a chance finding, it is important to find supportive evidence to corroborate the claimed effect on overall survival. Supporting evidence from other efficacy endpoints or other clinical trials is lacking. No difference was observed in terms of progression-free survival or response rate or any other clinically relevant endpoint.

   The discordance between overall survival and progression-free survival also raises the question about possible bias in the overall survival comparison due to possible imbalance in post-progression treatments. In theory the discordance may be explained by an

immunological mechanism of action. However, this claim is based on in vitro data that are considered hypothesis generating and there is no clinical evidence to support this theory.

In conclusion, due to the statistical design and the lack of supportive evidence, the clinical benefit cannot be considered established. The claimed effect on overall survival can only be considered hypothesis generating (provided that important biases in terms of post-progression treatments can be ruled out).

This effect should be verified in a well-conducted confirmatory trial before any conclusions can be drawn. Validation of the immunological theory as part of translational research is recommended. Investigation of patient selection based on validated biomarkers using rigorous statistical methodology, is also recommended.

Based on the data presented, there are concerns about the feasibility of the ongoing phase III trial due to reported low recruitment (5 patients/month).

2. Does the SAG consider the safety profile of masitinib as sufficiently characterized in the claimed indication at the proposed dosage?

   Due to the limited number of patients with imatinib-resistant GIST in the safety database treated at the proposed dosage, the power to detect potentially rare and serious toxicity is low. Therefore, the toxicity profile cannot be considered as sufficiently characterised.

   Notwithstanding this uncertainty, the toxicity observed in the pivotal study did not raise major concerns and compared favourably to sunitinib (e.g., lack of hand-foot syndrome). Arguably though, sunitinib dose is modulated in current clinical practice to manage toxicity compared to the fixed-dose approach previously used in the registration trials and clinical practice shortly after registration.

   However, in the absence of established efficacy, the observed toxicity and uncertainty cannot be considered acceptable.

3. The SAG should comment on the CHMP grounds for negative opinion (below) in view of the Applicant's grounds for re-examination submitted.

   The efficacy of masitinib in GIST has not been sufficiently demonstrated;

   The safety database is considered insufficient to allow an adequate assessment of the risks associated with masitinib in the proposed indication and posology;

   The SAG broadly agreed with the CHMP grounds for negative opinion. The applicant's grounds for re-examination did not resolve the issues mentioned in the grounds for negative opinion (see answers to questions No. 1 and 2).

   In view of the unmet need, if efficacy had been established, the uncertainty in the toxicity profile could probably be managed through adequate risk-management measures. However, in the absence of established efficacy, the toxicity cannot be considered acceptable.

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 maintained the view that from a statistical point of view any comparison between groups in the pivotal trial was exploratory, as stated in the study protocol; that pre-specification of secondary analyses or post-hoc handling of multiplicity using the Bonferroni method for selected tests, without careful pre-specification of handling of multiplicity, cannot be considered adequate to control the Type I error, based on general statistical principles. Furthermore, OS results of a phase I trial or historical comparisons are difficult to interpret and cannot be considered as confirmatory due to possible bias, including selection bias. Thus, based on exploratory findings of a difference in OS without supportive 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.

Concerning Clinical Ground No. 2, if the main evidence of efficacy is from exploratory studies, it is important to consider the degree of statistical significance and internal consistency to corroborate the findings. In view of the lack of an effect on PFS and the lack of other corroborating evidence, it is not possible to conclude with confidence that masitinib is associated with improvement in OS. The fact that PFS and other clinical endpoints are not valid surrogates for OS for a number of treatments and indication does not provide useful corroborating evidence to address the existing uncertainty about the benefits associated with masitinib in the proposed indication.

Concerning Clinical Ground No. 3, the hypothesised immunological rationale for the mechanism of action lacks verification with clinical evidence. Thus, the hypothesised immunological rationale does not provide robust corroborating evidence to address the existing uncertainty about the benefits associated with masitinib in the proposed indication.

Concerning Clinical Ground No. 4, the CHMP agreed that submission of results from a single pivotal trial was not in itself blocking approval or even unusual in similar oncology settings. However, due to the methodological deficiencies and lack of supportive evidence (see assessment of Clinical Grounds No. 1 and 2), there was insufficient evidence to conclude that masitinib is associated with a clinical benefit 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.

Concerning Clinical Ground No. 5, the CHMP concluded that the toxicity profile cannot be considered as sufficiently characterised. However, the CHMP acknowledged that the toxicity observed in the pivotal study did not establish grounds of a major concern. This is in line with the advice provided by the Scientific Advisory Group. The uncertainty in the toxicity profile could be managed through adequate risk-management measures however efficacy of the medicinal product has not been established.

Concerning Clinical Ground No. 6, the CHMP considered that resampling methods are not useful to address the methodological deficiencies and lack of supportive evidence (see assessment of

Clinical Grounds No. 1 and 2) and that therefore it is not possible to conclude that masitinib is associated with a benefit in the proposed indication. Due to this uncertainty, it is not possible to conclude that immediate availability of the medicinal product concerned outweighs the risks of lower efficacy compared to available treatment options. Furthermore, the resampling methodology used does not allow to conclude that the probability of masitinib being inferior in efficacy to sunitinib being <.0001 based on general statistical principles. Similarly, it cannot be concluded that there is a 90% probability that about 1000 patients/year will be harmed, since this assumes that a benefit has been established for masitinib, which is not the case due to the aforementioned methodological deficiencies and lack of supportive evidence (see assessment of Clinical Grounds No. 1 and 2).

Concerning Clinical Ground No. 7, the CHMP noted that the applicant considered they would be able to provide comprehensive clinical data in a timely fashion upon completion of the ongoing phase III study by end of 2016. However, this does not address the current uncertainty about the benefits associated with masitinib in the proposed indication and therefore at this stage a positive benefit-risk balance of the medicinal product as defined in Article 1(28a) of Directive 2001/83/EC has not been established.

Concerning Quality Ground No. 1, the CHMP considered that the proposed starting material 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 (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 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. 3, 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. Therefore, the active substance specification relating to particle size distribution as proposed by the applicant is still not acceptable due to the uncertainties on the deficient understanding of the manufacturing process - the particle size distribution should include D(0.1), D(0.5) and D(0.9) values and be tightened according to the range of particle size observed for the biobatches, where similar bioavailability has been demonstrated.

Concerning Quality Ground No. 4, 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. 5, 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. 6, the CHMP noted that a post-authorisation commitment relating to this point cannot be accepted and it is not ensured that the proposed testing time points would be sufficient. Additionally, it has to be considered that the dissolution profiles were established only with 0.01 N HCl as solvent (dissolution results at higher pH values were not provided but the dissolution of the drug substance is lowered at higher pH values) and that the discriminatory nature of the dissolution method was not demonstrated (see ground No. 7). The concern on the lack of control and reproducibility of the manufacturing process was not addressed (see ground No. 3).

Concerning Quality Ground No. 7, 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.

Concerning Quality Ground No. 8, 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. 7.

Concerning Quality Ground No. 9, see quality grounds No. 2 and No. 5.

Overall, based on the assessment of the detailed grounds for re-examination submitted by the applicant, the CHMP concluded that the benefit-risk balance of Masican cannot be considered positive.

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 GIST 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.

Concerning clinical safety, aside from the existing uncertainties about the impact of patient exposure to potential impurities resulting from unregulated changes to the quality of the active substance, the CHMP concluded that although toxicity profile cannot be considered sufficiently characterised, the toxicity observed in the pivotal study was not of major concern.

The uncertainty in the toxicity profile could be managed through adequate risk-management measures, however efficacy of the medicinal product has not been established.

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.