London, 13 December 2012
EMA/CHMP/795704/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ruvise

International non-proprietary name: imatinib mesilate

Procedure No. EMEA/H/C/002551/0000

Note

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

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RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the Rapporteurs consider that the application for Ruvise (imatinib) in the treatment

"for adults as add-on therapy for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity in patients with pulmonary vascular resistance ≥ 800 dyn·s·cm-5 who remain symptomatic and are receiving maximum tolerated PAH-specific therapy, which may include any combination of an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor or prostacyclin. Treatment with Ruvise should only be initiated in patients who are not showing signs of rapid disease progression. Ruvise has been studied only in combination with two or more conventional PAH-specific therapies.

Efficacy has been shown in patients from WHO Functional Class II and III with idiopathic PAH, heritable PAH and in PAH associated with connective tissue disease."

is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The major objections pertain to the efficacy and safety of imatinib in PAH patients and include the following principal deficiencies:

1. The efficacy of imatinib has not been robustly demonstrated.
2. The safety of imatinib in patients with PAH has not been established.
3. There is an unexplained higher risk of subdural haemorrhage associated with imatinib use.

The details of these major objections are provided in the preliminary list of outstanding issues (Section VI).

Questions to be posed to additional experts

N/A

Inspection issues

N/A

New active substance status

Based on the review of the data the Rapporteur considers that the active substance Imatinib mesylate contained in the medicinal product Ruvise 100mg and 400mg, film-coated tablets is not to be qualified as a new active substance in itself as the same active substance is already approved for use in Glivec, indicated for oncological treatment.

1. EXECUTIVE SUMMARY

Problem statement

Pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterized by the presence of increased pulmonary arterial pressure (mean PAP ≥ 25 mmHg), normal pulmonary arterial wedge pressure (PAWP ≤ 15 mmHg) and normal or reduced Cardiac Output (CO) as assessed by right heart

catheterization at rest[1]. Most cases of PAH are idiopathic (i.e. not associated with known risk factors or conditions), but PAH also occurs in a heritable form and in association with other disorders, including collagen vascular diseases, congenital systemic-to-pulmonary shunts, ingestion of drugs/toxins, and other conditions. PAH is an orphan disease, which affected less than 2 in 10,000 people in the European Union (EU), equivalent to a total of fewer than 92,000 patients in Europe.

In PAH, pathological lesions affect the distal pulmonary arteries (<500 µm of diameter) in particular. They are characterized by medial hypertrophy, intimal proliferative and fibrotic changes (concentric, eccentric), adventitial thickening with moderate perivascular inflammatory infiltrates, complex lesions and thrombotic lesions. Pulmonary veins are classically unaffected.

The pathogenesis of PAH is not fully understood, but is thought to involve abnormal interactions between pulmonary vascular endothelial and smooth muscle cells, leading to an increase in pulmonary vascular resistance due to vasoconstriction, vascular endothelial and smooth muscle cell proliferation, and in situ thrombosis. Vasoconstriction and proliferative vascular lesions in the pulmonary circulation lead to high pulmonary vascular resistance, increasing the workload on the right ventricle, and limiting cardiac output, which results in severe exercise limitation. In patients who are poorly controlled, daily functional performance declines steadily and right ventricular failure is the most common cause of death.

The currently available PAH therapies act predominantly as vasodilators, although all have additional effects in experimental systems. The phosphodiesterase type 5 inhibitors (PDE5Is) such as sildenafil and tadalafil potentiate the vasodilatory, anti-platelet, and antiproliferative effects of nitric oxide on vascular smooth muscle. The endothelin receptor antagonists (ERAs) such as bosentan and ambrisentan reduce pulmonary vasoconstriction by blocking the actions of endothelin, and also reduce vascular smooth muscle cell proliferation in vitro. The prostacyclin analogues (PGI2s) such as epoprostenol, iloprost, and treprostinil are potent vasodilators that also inhibit platelet aggregation and vascular smooth muscle cell proliferation in vitro.

In the past few years, treatment of PAH has undergone an evolution. The average survival of patients with PAH is estimated to be 4 to 5 years after diagnosis. The seriousness of the disease, the inability of single drugs to prevent deterioration, and the fact that the approved drugs target different vasodilator pathways have made combination therapy a necessity for most patients. Among the 3 classes of PAH-specific drugs (PDE5Is, ERAs and PGI2s), dual therapy with any 2, and triple therapy with all 3, are common. Indeed, in the largest PAH Registry conducted to date, which includes 2,525 U.S. adults meeting traditional haemodynamic criteria, nearly half of the patients are treated with two or more PAH-specific medications (Badesch et al 2010). Nevertheless, many patients still deteriorate on combination therapy, creating a major unmet medical need in these patients.

About the product

Imatinib (imatinib mesilate or imatinib mesilate, also known as QTI571 and STI571, and formerly known as CGP 57148B) inhibits the tyrosine kinase activity of the BCR-Abl oncoprotein and also inhibits the stem cell factor (c-Kit) and the PDGF receptor (PDGF-R) kinases. Imatinib (under the trade names Glivec®, Gleevec®) is currently approved in the EU and other countries for the treatment of haematological malignancies (chronic myeloid leukaemia, CML), solid gastrointestinal tumours (gastrointestinal stromal tumours, GIST) and other oncological indications at doses of 400 – 800 mg QD, and 100 mg QD or 400 mg QD for aggressive systemic mastocytosis, hypereosinophilic syndrome and chronic eosinophilic leukaemia.

[1] Galiè et al, Guidelines for the diagnosis and treatment of pulmonary hypertension, European Heart Journal (2009) 30, 2493-2537.

In PAH, the tyrosine kinase activity of imatinib is hypothesised to reverse pulmonary vascular remodelling, thus may have a potential to reduce pulmonary vascular resistance and improve haemodynamics. In the initial application, the applicant proposed the following indication:

> Ruvise is an antiproliferative agent indicated for adults as add-on therapy for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization (WHO) Diagnostic Group 1) to improve exercise capacity and cardiopulmonary haemodynamics in patients with pulmonary vascular resistance ≥ 800 dynes.sec.cm^{-5} and who remain symptomatic despite treatment with two or more PAH-specific vasodilator therapies.
>
> Efficacy has been shown in patients from WHO Functional Class II, III and IV with idiopathic PAH, heritable PAH and in PAH associated with connective tissue disease.

The proposed posology was:

> Therapy should be initiated under the supervision of a physician experienced in the treatment of patients with PAH.
>
> Posology for PAH patients
>
> The recommended target maintenance dose of Ruvise is 400 mg/day.
>
> Treatment should be initiated at 200 mg/day, increasing to 400 mg/day after 2 weeks as tolerated.
>
> Doses exceeding 400 mg/day have not been studied in PAH patients and are not recommended.
>
> Clinical signs of efficacy may not become apparent until after 12 weeks of therapy (see section 5.1). Treatment should be continued as long as the patient continues to benefit from Ruvise.

With the day 120 responses, the applicant proposed the following modifications to the indication and the posology:

> Ruvise is indicated for adults as add-on therapy for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity in patients with pulmonary vascular resistance ≥ 800 dyn·s·cm-5 who remain symptomatic and are receiving maximum tolerated PAH-specific therapy, which may include any combination of an endothelin receptor antagonist, a phosphodiesterase type 5 inhibitor or prostacyclin. Treatment with Ruvise should only be initiated in patients who are not showing signs of rapid disease progression. Ruvise has been studied only in combination with two or more conventional PAH-specific therapies.
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exceeding 400 mg/day have not been studied in PAH patients and are not recommended. Clinical signs of efficacy may not become apparent until after 12 weeks of therapy (see section 5.1). Treatment should be continued as long as the patient continues to benefit from Ruvise. If, during treatment with Ruvise, a sustained decrease in 6-minute walk distance is observed, treatment should be discontinued.

The development programme/compliance with CHMP guidance/scientific advice

Following case reports showing benefits of imatinib in individual patients with advanced PAH, imatinib was evaluated as add-on therapy to existing PAH-specific treatments in an exploratory controlled Phase II trial and a pivotal randomized controlled Phase III trial.

CHMP have issued a Guideline on clinical investigation of medicinal products for the treatment of PAH (EMEA/CHMP/EWP/356954/2008). The Phase III study design was developed following discussions with the Spanish AEMPS (15 Apr 2009), Netherlands Medicines Evaluation Board (MEB) (14 May 2009), CHMP Scientific Advice (EMEA/H/SA/493/6/2009/III) and US and Japanese agencies. Compliance with this SA is assessed in the relevant sections.

General comments on compliance with GMP, GLP, GCP

According to the Applicant, the studies have been performed in compliance with GLP and GCP regulations. In the pivotal trial, a number of protocol violations have occurred, which are related to a computer system that did not perform as required. Computer system validation, which is a GCP requirement, has failed in this issue, which is further discussed under clinical efficacy.

Type of application and other comments on the submitted dossier

- Legal basis

Novartis Europharm Limited submitted a Marketing Authorization Application for Ruvise® (Imatinib mesilate) 100 mg and 400 mg Film Coated Tablets, in accordance with article 8(3) of Directive 2011/83/EC as amended; via the optional scope of the centralized procedure in accordance with Article 3(2) Therapeutic innovation of Regulation (EC) No.726/2004.

- Accelerated procedure

N/A

- Conditional approval

N/A

- Exceptional circumstances

N/A

- Biosimilar application

N/A

- 1 year data exclusivity

N/A

- Significance of paediatric studies

A paediatric investigation plan (PIP, EMEA-000463-PIP02-10) and an application for a deferral under Article 20 of Regulation (EC) No 1901/2006,and a waiver under Article 13 of the said regulation were submitted to the EMA on 30 April 2010 and approved on 8 April 2011 (EMA decision P/85/2011).

According to these, research in children of less than 6 month of age is waived and development in children will be completed by September 2013. However, a request to modify the paediatric investigation plan (PIP) is under evaluation and will be discussed with PDCO.

2. SCIENTIFIC OVERVIEW AND DISCUSSION

2.1. Quality aspects

Drug substance

The active substance is the mesylate salt form of imatinib, a phenylaminopyrimidine derivative and is the 4-[(4-methyl-1-piperazinyl) methyl]–N–[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]-benzamide methanesulfonic acid salt. It is a white to off-white to brownish or yellowish tinged powder and is prepared using a fully synthetic process. During the development the product has been referred to as STI571 or QTI571.

The synthesis of imatinib mesylate is completed in 4 main steps and the Ccrude imatinib mesylate is recrystallised. A detailed description of the manufacturing process has been provided and evaluated, including reaction conditions, quantities of raw materials and yields.

Evidence of the chemical structure has been provided in the form of an examination of the route of synthesis, elemental analysis, IR, UV/VIS, 1H-NMR, 13C-NMR, mass spectrometry and X-ray diffraction. matinib mesilate does not have chiral centers and it is not optically active. The solubility of imatinib mesilate in aqueous solutions depends on pH. It is soluble in polar solvents, but only slightly soluble to insoluble in low polar solvents. The free base has very low solubility in water and in aqueous solutions that are slightly alkaline. Two different crystalline forms are known.

Specification

The specification includes limits on the main impurities observed in batches produced by the defined route of synthesis.Water is checked by Karl-Fischer method. Clarity and colour of the solution are carried out according to general methods of the Ph. Eur.

Related substances are quantified by HPLC, GC, IC and MS methods. Inorganic impurities are determined by sulphated ash and heavy metals. The heavy metals are checked by IPC-OES or XRF method.

A HPLC method similar to the related substances method is used in order to determine the content calculated as imatinibAll method validation studies are in agreement with the current ICH-guideline.

A specification for particle size is also included.

Stability

Formal stability data of 6 production scale batches , of which one batch is used in pre-clinical and clinical studies, are presented. The batches were stored in double LDPE bags in a metal drum or a fibre drum.

The stability studies have been performed under ICH conditions and other experimental conditions have been reported. No apparent change of the drug substance quality was observed in these studies. A re-test period of 5 years stored below 30°C is proposed when the substance is stored in tight packing protected from light. The photostability data should be presented to support this storage condition.

Drug product

Composition

The product is presented as film-coated tablets available in two strengths, 100 mg and 400 mg. The core excipients are crospovidone, cellulose microcrystalline, hypromellose, silica colloidal anhydrous and magnesium stearate. The coating material consists of hypromellose, iron oxide yellow, iron oxide red, talc and polyethylene glycol. The tablets are packaged in PVC-Al blisters (100mg) and triplex PVC/PE/PVDC-Al blisters (400mg).

The pharmaceutical development of the proposed drug product is concise as the formulation is the same as the registered Glivec tablets. The only difference is the score-line introduced on the 400 mg tablets and a slight change in the amount of film-coating material due to the score-line and the introduction of bevelled edges. Comparative dissolution data between these formulations have demonstrated that the differences have no significant impact on the dissolution. For both strengths of tablets and for the capsules and for both divisible and non-divisible 400 mg tablets rapid dissolution was achieved. In addition, similar profiles were obtained after testing of the dissolution of a half tablet of 400mg compared to two tablets of 100mg, i.e. 200mg dose in both cases.

Manufacturing process

The manufacturing process is a standard wet granulation tableting process. The validation data presented on the nine production scale batches demonstrate the suitability of the manufacturing process at both manufacturing sites.

Excipients

All individual excipients are of pharmacopoeial grade. The coating mixture is tested in-house. Acceptable in-house specifications were provided for the coating mixture. No excipients of animal or human origin are used. Magnesium stearate is of vegetable origin.

Control of Drug Product

An identical specification has been developed for release and end of shelf-life. Tests include appearance, identification, mean mass, dissolution, uniformity of dosage units by mass variation, degradation products, assay by HPLC and microbial quality. Control methods have been validated and the specification is considered to be relevant for a product of this type. Given the moisture sensitivity a test on water content or loss on drying should be included.

Batch analysis data have been presented on twelve batches of the 100mg tablets and six batches of the 400mg tablets. The batches used for process validation have been included. The results demonstrate compliance with the release specification with consistent results.

Stability

Stability data have been presented on 4 production and 2 pilot batches of the 100mg tablets and 7 production scale and 2 pilot batches of the 400mg tablets. Up to 60 months of stability data has been presented. The tablets were tested in different packaging materials with increasing protection; PVC-Al blisters, triplex PVC/PE/PVDC-Al blisters and full aluminium blisters.

The photostability data demonstrate the unpacked drug product is not sensitive to light. Exposure parameters are in line with ICH Q1b with 1.2 million lux hours and NLT 200 watt hours per square meter. There was no change observed between exposed and unexposed sample.

The shelf-life of 36 months for the 100 mg tablets in PVC-Al blister and 24 months for the 400 mg tablets in PVC/PE/PVDC-Al blister, if stored not above 30°C, is accepted. Store in the original package in order to protect from moisture.

Discussion on chemical, pharmaceutical and biological aspects

Satisfactory documentation was provided to confirm the acceptable quality of this medicinal product and no major objections have been raised during evaluation. The drug substance was adequately characterized and the specification is acceptable in view of the route of synthesis and the various ICH guidelines. The solid drug substance is stable with respect to degradation. Concerning the finished product, the complete control strategy guarantees consistent control of the product quality.

Conclusions on the chemical, pharmaceutical and biological aspects

In general, the drug product is acceptable from a chemical-pharmaceutical point of view.

2.2. Non clinical aspects

Pharmacology

Imatinib mesilate is a small molecule protein-tyrosine kinase inhibitor that inhibits the activity of the BCR-ABL tyrosine kinase (TK), as well as several receptor TKs: platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta), Kit, the receptor for stem cell factor (SCF), the discoidin domain receptors (DDR1) and DDR2) and the colony stimulating factor receptor (CSF-1R).

Applicant has provided a literature-based discussion on the potential mechanism of action of imatinib in the treatment of patients with PAH. According to this discussion the anti-angiogenic effect induced by inhibition of PDGFR signalling by imatinib is the main mode of action for a potential beneficial effect of imatinib treatment in PAH. A specific activity of this anti-angiogenic effect for 'diseased' lung vessels is not expected, however it is likely that tissues with high angiogenic activity, such as in lungs of patients with PAH, will be most affected.

The Applicant has performed only one proof of concept study in monocrotaline treated rats. In this model both prophylactic, but more importantly also therapeutic treatment with imatinib resulted in a (partial) reversal of right ventricle pressure, right ventricle hypertrophy and muscularisation of pulmonary vessels. The observed effects indicate that the disease pathology is reduced, however the relation of these observations with clinically relevant endpoints is not clear. Yet two other studies, publications, in the same and another model of PAH (chronic hypoxia induced PAH) similar results were noted, in addition, also an effect on mortality was found in the monocrotaline model, with a reduction in mortality from 50 to 0% at day 42 following PAH induction with imatinib treatment starting at day 28. Although recent publications describe that both models do not present the neointimal and plexiogenic lesions characteristic of PAH patients, the applicant justifies adequately the suitability of monocrotaline and hypoxia induced animal models in determining therapeutic drug efficacy. In addition, in response to CHMP Day 120 List of Questions Clinical Aspects, the company describes a more recent study that demonstrate the therapeutic efficacy of imatinib in hypoxia/SUGEN5416 rat model, a more recently developed PAH animal model exhibiting obstructive, neointimal lesions

The inhibition of c-KIT and c-Abl have also been discussed as potential further mechanisms which may contribute to the beneficial effect of imatinib on PAH disease pathology. These have been included as secondary pharmacodynamic studies because they are likely to be relevant, but extensive mechanistic data is missing, and the relative contribution to PAH treatment cannot be assessed.

Inhibition of c-kit by imatinib reduces the mobilisation and thus systemic circulation of c-kit+ cells. Indeed decreased recruitment of c-KIT+ cells has been reported following imatinib treatment in a chronic hypoxia but not in a monocrotaline-induced PAH model and treatment with nilotinib or sorafenib caused greater dilatation in pulmonary arterial rings in chronic hypoxia/SUGEN5416 preclinical rat model than imatinib. The Applicant has clarified that the mechanism by which inhibition of KIT could confer efficacy in the pathology of PAH is via reduction in the infiltration and survival of pathologic cell populations into the pulmonary vasculature. In chronic hypoxia model it was confirmed that the cells infiltrating into vascular lesions were bone marrow-derived and that infiltration was inhibited by imatinib. However, inhibition of KIT in monocrotaline model does not suppose a therapeutic advantage because the model does not reproduce the increased circulation and lesion infiltration of KIT^+ bone marrow-derived precursor populations, which are the imatinib´s targets. On the other hand, the presence of c-KIT+ cells at the site of vascular remodelled tissue does not necessarily mean that they actively contribute to the remodelling. Thus, it is still not clear whether inhibition of KIT and ABL by imatinib in vivo contributes to the therapeutic advantage of imatinib treatment.

NQO2, DDR-1 and -2 and CSF-1R are also target of imatinib. Despite the potential involvement of DDR-1 and -2 and CSF-1R in PAH, their inhibition is unlikely to contribute to imatinib therapeutic effect but their inhibition could lead to other secondary and not therapeutic effects. A mouse model lacking NQO2 exhibited alterations in bone marrow and peripheral blood. Side effects of imatinib on both tissues have been described, so the clinical relevance of NQO2 inhibition by imatinib can be considered characterized. However, potential secondary effects induced by imatinib through inhibition of DDR-1, DDR-2 and CSF-1R were still not sufficiently discussed by the Applicant. (Outstanding issue)

There is some data indicating imatinib treatment can inhibit fibrosis by reversing TGFβ-signalling (through c-abl inhibition). While the role of (lung) fibrosis in disease pathology of PAH is not discussed by the Applicant it is stated that PAH is a comorbidity in approximately a quarter of idiopathic pulmonary fibrosis (IPF) patients, and more commonly with systemic sclerosis (SSc) patients. It thus appears that fibrosis may be one of the underlying causes for PAH, and as such, based on these data it may be hypothesised that treatment with imatinib may have some additional beneficial effect this patients.

Similarly, it can by hypothesised that inhibition of c-abl by imatinib may result in smooth muscle relaxation and thus reduce hypertension. However no significant effect of imatinib treatment on systemic blood pressure was observed in the monoctrotaline PAH rat model, only a transient decrease (5 minutes) was seen in the CV safety pharmacology study (Study 606205). It is therefore unlikely that the potential effect on smooth muscles will contribute significantly to the PD activity of imatinib in PAH.

The efficacy of imatinib is improved in combination with sildenafil in vitro and in a monocrotaline induced rat model. Due to imatinib is indicated as add-on therapy for PAH, pharmacodynamic studies with different standard treatment combinations would be valuable.

The safety pharmacology studies with imatinib were performed before the initial marketing authorisation. Sufficient human data on these aspects are now available for assessment of these safety aspects.

No PD drug interaction studies were performed. The currently available clinical data should be sufficient for the evaluation of potential drug-drug interactions.

Pharmacokinetics

The applicant sufficiently validated the analysis methods to determine imatinib and the metabolites CGP74588 and CGP53715 in plasma. Stability of the plasma and tissue samples was confirmed under both storage and analysis conditions.

Imatinib is a substrate of the human efflux transporter P-glycoprotein and to a minor extent BCRP, but not of MRP2. Imatinib may also be subject to uptake transport by OCT1. The affinity of imatinib for the drug transporters OATP1B1, OATP1B3, OCT2, OAT1, OAT3, and BSEP was not investigated by the applicant. However these data are already available in the public domain due to the use of imatinib in oncology indications, therefore no question is asked.

In an in situ experiment, the highest apparent absorption was observed in the ileum and duodenum, indicating that these sections are the main absorption site of imatinib after oral administration. In the jejunum, the largest segment of the intestine, about 15% of the dose was absorbed.

Absorption and oral bioavailability of imatinib was good to excellent in rats, dogs, Cynomolgus monkeys and human. C_{max} was rapidly achieved after PO administration in all species including human.

The AUC and C_{max} dose-proportionality were species and dose dependent. In mice (30-800 mg/kg), AUC and C_{max} values increased in a manner approximately proportional to the dose. In rats, AUC values increased dose proportionally in the range of 7.2 to 200 mg/kg, but the increase was less than dose proportional at the high dose of 600 mg/kg. In rabbits, there was a trend of more than dose proportional increase in the AUC values after dosing of 10 to 100 mg/kg. In dogs, AUC values increased more than dose-proportional in the dose range 3-10 mg/kg, proportional in the range 10-30 mg/kg, and less than dose-proportional at the high dose (50 mg/kg). In Cynomolgus monkey, exposure to imatinib increased dose-proportional (10-300 mg/kg).

Accumulation ratios after repeated dosing were <2 in mice, 1 to 3 in rats, 0.5 to 1.5 in dogs and Cynomolgus monkeys. This is comparable to the values of 1.3 and 1.5 found in patients receiving 400 and 600 mg imatinib, respectively.

The volume of distribution was 3.3 L/kg in rat, 6.7-10.4 L/kg in dog and 11 L/kg in Cynomolgus monkey. The human volume of distribution is 6.2 L/kg.

The elimination half-life ranged from 2.8-9.0 h in the non-clinical species and was 22 h in humans. The blood clearance was moderate in rat, moderate to high in dog, high in monkey, and low in humans.

Gender differences in exposure were observed. Exposure was slightly greater in female rats than in male rats. A different observation was made in dogs, where males exhibited a 16 to 20% greater AUC than females. This is most likely because imatinib is a substrate for CYP3A4. No gender difference was observed in Cynomolgus monkeys.

Species differences were observed for the blood/plasma distribution and plasma protein binding. The fraction associated with blood cells (Fe) was 49% in mouse, 35% in rat, 40% in dog, and 13-40% in humans (increasing with increasing imatinib concentration). The plasma protein binding of imatinib was 98% in mouse, 95% in rat, 81% in dog, 90% in Cynomolgus monkey, and 89-96% in humans (decreasing with increasing imatinib concentration). In the non-clinical species, the blood-plasma distribution and plasma protein binding was independent of the concentration. For the major human metabolite CGP74588, the plasma protein binding was similar and Fe was lower than imatinib.

Imatinib distributed to glandular tissues (adrenal, thyroid, pituitary, spinal) and organs involved in metabolism and excretion (liver, kidney). No to slight accumulation was observed after repeated dosing. Distribution to the lung was observed (target organ for the treatment of pulmonary arterial

hypertension) and was still present in lung tissue after 168 h post-dose. Imatinib binds to melanin and is slowly cleared from melanin-containing tissues, e.g. eye and skin. However, clinical experience with imatinib as Glivec indicates there is not concern about phototoxicity. Its elimination is very slow from eyes, adrenal gland, liver, kidney, bone marrow and melanin containing tissues. The organ distribution is independent of gender, route of administration (oral and intravenous) and after single or multiple dosing. Non-significant accumulation in organ and tissues of imatinib was observed after multiple dosing.

Imatinib can pass the placenta and in the toxicology study foetuses were continuously exposed to compound-related material up to 24 hours post-dose and presumably throughout gestation.

Imatinib is metabolised by CYP and conjugation enzymes and in mice also by an enzyme present in plasma. Metabolism was similar in all investigated species except for the mouse. The major human metabolite is CGP74588. Around 21% of the AUC_{0-24h} radioactivity in humans was attributed to by several metabolites all formed for less then 2%. Overall, these data indicate extensive biotransformation with one major human metabolite.

CYP3A4 is the predominant human CYP enzyme catalysing the biotransformation of imatinib. CYP1A2, CYP2C9, and CYP2D6 provide a minor contribution to the metabolism of imatinib. Sildenafil and bosentan are medications metabolized via the CYP3A4 pathway, commonly used in PAH treatment. Clinical trials corroborated these results; sildenafil and bosentan concentration were raised by imatinib. On the other hand, in vitro metabolism studies showed that CYP3A4 was the major human P450 enzyme catalysing the biotransformation of imatinib. Thus, co-administration of drugs inhibiting CYP3A4 as ketoconazole, erythromycin (IC_{50}=50 µM), cyclosporine A (IC_{50}=4.4 µM) and fluconazole (IC_{50}=118 µM) inhibited imatinib metabolism, increasing the exposition to imatinib, while drugs inducing CYP3A4 as rifampicin reduced imatinib exposition. Imatinib concentrations fell with bosentan and were unchanged by sildenafil in humans. Most likely CYP3A4 is responsible for the formation of the major human metabolite CGP74588. Metabolite CGP53715 is most likely produced mainly by CYP1A1/2, which is a major CYP enzyme present in the lung. The mutagenic metabolite formed in mice was not observed in humans, but could be formed locally in the lung.

Imatinib is mainly cleared via metabolism. However, no information on metabolites (as percentage of dose) was provided for faeces and urine. The applicant only provided information on imatinib concentrations and total radioactivity for the excreta. In humans, about 40% of the radioactivity was imatinib and the major metabolite. The remaining radioactivity was unidentified. Overall, these data indicate that imatinib is extensively metabolised before excretion.

The applicant did not provide information on specific Phase II enzymes involved in the metabolism of imatinib. However sufficient clinical data are available on drug-drug interactions due to the use of imatinib in oncology indications, therefore no question is asked.

In all investigated species, imatinib was eliminated predominantly by metabolism. The predominant route of elimination in mouse, rat, dog, monkey, and human was faecal. The minor excretion route was via urine. Radioactivity was excreted fast in mouse, rat, dog, and monkey (69% to 94 % of the PO dose within 24h), but slow in human (16% within 48 h). In bile duct-cannulated rats and dogs following a single oral dose, 32% and 68% of the dose, respectively, was found in the bile. In rats, imatinib represented only 4% of the total radioactivity in the bile, indicating rapid metabolism and rapid transport of imatinib and its metabolites into bile.

Upon IV administration to bile-duct cannulated rats, only minor enterohepatic circulation was observed (3.42% of the dose), indicating that the effect of enterohepatic recirculation on imatinib elimination and pharmacokinetics is limited.

Imatinib-related radioactivity is rapidly passed into the milk of lactating rats and is also enriched. Therefore, human nursing neonates would be exposed to imatinib and/or its metabolites following administration of imatinib to the nursing mother.

No drug-drug interactions on the level of blood-to-plasma distribution or plasma protein binding displacement are expected with imatinib.

Imatinib is an inhibitor of CYP2D6 and CYP3A4/5-mediated metabolism at clinically relevant concentrations, but not an inhibitor of the other CYP enzymes and the phase II enzymes UGT, GST and SULT. The major human metabolite CGP74588 showed a weaker potential for inhibition of CYP2D6 and CYP3A4/5 compared to the parent compound and is therefore not expected to contribute significantly to the CYP inhibition potential of imatinib.

Imatinib and its major metabolite CGP74588 do not induce PXR-, CAR-, and AhR-regulated metabolic enzymes via at clinically relevant concentrations. Therefore, imatinib and CGP74588 are not expected to affect pharmacokinetics of co-medications by induction.

Based on the biotransformation data, co-administered drugs inhibiting CYP3A4 may increase exposure to imatinib, while drugs inducing CYP3A4 may decrease imatinib levels. This is already stated in the SPC by the applicant.

In vitro experiments in membrane vesicles indicate that imatinib may be an inhibitor of the efflux transporter protein MXR (BCRP) with an IC_{50} value of about 1 µM. MXR is expressed in the gastrointestinal tract and in the placenta; thus it may affect the bioavailability of drugs and/or their transport across the maternal-fetal barrier. Additionally, different in vitro studies suggested imatinib to be a substrate of the human efflux transporters MDR1 (P-gp) and BCRP (MXR). However, an effect of efflux transporter inhibitors on imatinib systemic exposure is not expected, since the nearly complete bioavailability of imatinib indicates absence of relevant first pass elimination by efflux transport. The brain penetration of imatinib increased when it was co-administered with MDR1/BCRP inhibitors as PSC833 (valspodar), LY335979, zosuquidar, and elacridar.

The N-oxide metabolites CGP71422 and CGP72383 are largely converted in the intestinal lumen into imatinib by N-oxide reduction, followed by uptake of imatinib.

Toxicology

The non-clinical safety profile of imatinib was assessed in mice, rats, dogs, monkeys and rabbits. Single dose studies in mouse and rat indicate that imatinib has low potential for acute toxicity.

Repeated dose oral toxicity studies were performed in mouse, rat, dog and monkey. Most of the studies were conducted at doses leading to exposures similar to or lower than those observed in the human therapeutic range.

Mild to moderate haematological changes were noted in mice, rats, dogs and monkeys, accompanied by bone marrow changes in rats and dogs. This, as well as effects on lymphoid tissues might however be attributable to pharmacological effects of the compound. Target organs of toxicity were the liver in dogs and to a minor degree in rats, the kidney in rats and monkeys, the GI tract dog and monkey and to a lesser extent in rat. Most of the effects were reversible or showed a tendency towards reversibility.

Alterations in the female and male genital organs were noted in rat, dog and monkey. The reversibility of the effects is not clear.

Effects on the lung (influx of foamy macrophages) were seen primarily in the rat repeated dose toxicity studies. Additional changes were observed in the 2 year rat carcinogenicity study but these might

represent secondary changes due to the cardiac alterations and congestive heart failure. The clinical relevance of the accumulation or influx of macrophages in the lung is not clear, however as inflammation can play a role in PAH pathology a potential adverse effect, exacerbation of disease cannot be excluded if macrophage influx also occurs in humans treated with imatinib.

Effects on the rodent cardiovascular system were observed in the 2-year rat carcinogenicity study. Additional preclinical toxicity and mechanistical studies were performed addressing potential cardiotoxicity in response to a publication indicating that imatinib might be cardiotoxic. The weight of evidence of the animal experience indicate a limited potential for cardiac effects of imatinib treatment, and it appears that this is reflected in the clinical experience as congestive heart failure appears an infrequent event in imatinib treated patients.

Vascular changes were sometimes noted in some of the studies (e.g. dog study Study 966024) which were considered to be of questionable toxicological significance due to their low incidence and/or background observation in untreated animals (e.g. study 966105 vasculitis/perivasculitis and arteritis/periarterits in various organs (uterus, lung)).

Data in animal models of cardiovascular disease are less clear and contradictory effects have been reported. Data in animal models of cardiovascular disease indicate that that PDGFR inhibition by imatinib has an anti-proliferative and/or anti-angiogenic effect and/or may reduce neo-intima formation. This may be beneficial for PAH patients when this effects occurs in the lung, however it may be unwanted effects when it occurs in the heart as it restricts the vessel remodelling and compensatory response needed to cope the high pulmonary arterial pressure. The end balance between the advantageous effects in the lungs and unwanted effects in the heart appeared positive in some models but not in others. It is therefore difficult to determine whether the anti-proliferative/anti-angiogenic effects of imatinib treatment will be beneficial or disadvantageous for PAH patients. Yet it seems that also in animals of cardiovascular disease the balance is positive. Whether this is indeed the case in humans with PAH should be determined in the clinic. No further non-clinical data on potential cardiotoxic effects are deemed necessary.

In vitro and in vivo genotoxicity testing showed that imatinib is not considered to be genotoxic under the conditions of therapeutic use.

In the 2-year rat carcinogenicity study, administration of imatinib resulted in a statistically significant reduction in the longevity of males at 72 mg/kg/day and females at ≥ 36 mg/kg/day. Histopathological examination was performed on animals that died revealed cardiomyopathy (both sexes), chronic progressive nephropathy (females) and preputial gland papilloma as principal causes of death or reasons for sacrifice. Target organs for neoplastic changes were kidneys, urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach. The NOEL for tumorigenic findings is 18 mg/kg/day. However trend towards an increase in the incidence of hyperplasia were already detected in the lowest dose group for the kidney, bladder, parathyroid glands and preputial glands.

The applicant has performed several mechanistical studies to investigate potential modes of action by which imatinib may induce proliferative changes that lead to the observed hyperplasia/neoplasia.

Gene expression profiling indicated transcriptional responses associated with tissue injury and inflammation, and tissue repair, up regulation of genes involved in cell proliferation and down regulation of genes involved in apoptosis and differentiation and up regulation of genes involved in immunity. It was suggested that the gene expression profiling analysis indicated that two components, toxicity and pharmacology (compensatory response to loss of function of c-kit+ immune cells). It was noted that in liver and kidney cortex the toxicity signature is predominant while in the bladder,

preputial gland and to a lesser extend jejunum and kidney medulla, the pharmacological effect is more pronounced.

Most explanations on the neoplastic findings were hypothetical or only partially supported by data. Based on the available data the assessor concludes that the non-clinical data indicate that there is a cause for a carcinogenic concern with kidneys (renal tubule and renal pelvis), urinary bladder, urethra, preputial and clitoral gland, small intestine, parathyroid glands, adrenal glands and non-glandular stomach as target organs for neoplastic findings. The relevance of these findings for the clinical situation are unknown.

Since the life-expectancy for PAH patients is relatively low, even with treatment, the risk of carcinogenicity caused to imatinib treatment is likely limited. It is agreed that further non-clinical data are not needed, given the availability of clinical data albeit in a patient population with also a limited life-expectancy.

In the rat fertility study no effect on fertility index (male and female) was noted, however decreased testes and epididymis weight and reduced sperm motility were observed. It is known that the fertility of male rats is less sensitive to changes in sperm motility than man. Furthermore a longer duration of treatment might be necessary to observe an effect, as evidenced by the atrophic changes in the 2-year rat study. Imatinib was embryotoxic in rats and rabbits and teratogenic in rats.

Ecotoxicity / environmental risk assessment

The environmental risk assessment is still not completed. As imatinib can be prescribed for the treatment of more than one indication, the PECsurface water should be calculated as the sum all of each indication PECs and its PEC/PNEC ratios should be revised. In addition, the Phase IIB assessment could not be completed as the sediment toxicity study was not reliable, and the dossier was incomplete with respect to the PBT assessment.

Discussion on non-clinical aspects

The Company has answered adequately the question on mode of action of imatinib. The secondary effects of DDR-1, DDR-2 anfCSF-1R inhibition should be further discussed prior to marketing authorisation.

The safety concerns have been sufficiently addressed by the Applicant. However the ERA cannot yet be completed.

Conclusion on non-clinical aspects

From a non-clinical point of view, Ruvise could be recommended for approval, provided the applicant gives satisfactory responses to the last few outstanding issues, see below.

2.3. Clinical aspects

Tabular overview of clinical studies

Pharmacokinetics

Imatinib is very or freely soluble in water and aqueous solutions at low pH levels. The solution tends to become supersaturated. The solubility in an aqueous buffer solution drops to ‘insoluble’ as the pH increases from pH 5.5 to 8.0.

Imatinib is soluble in polar solvents such as methanol and ethanol but only slightly soluble or insoluble in low polar solvents.

Imatinib mesilate does not contain a chiral centre.

ADME

The absorption and distribution of imatinib after intravenous and oral administration is moderate fast with t_{max} after oral administration as solution of 1 – 4 h. The absolute oral bioavailability is high (98%) indicating a small first pass effect. The mean apparent half-life for imatinib and its major metabolite is about 18 h and 40-50 h, respectively.

Bioequivalence for imatinib after administration of 400 mg as capsules (4x100 mg), tablets (4x100 mg) and tablets (1x400 mg) was established. The 90% confidence intervals for the rate and extent of absorption are well within the acceptance range for bioequivalence.

Food (high fat meal) did influence the bioavailability slightly but not in a clinical significant way.

Imatinib is extensively bound to plasma proteins, albumin and alpha-1-glycoprotein.

The total protein binding is about 98% at the clinically relevant concentrations. In this study it is confirmed that the exposure in plasma of the main metabolite is less than 20% of the parent compound. The volume of distribution is about 6 l/kg.

The results of a mass-balance study confirm that the extent of absorption of imatinib after oral administration is high. The main excretion route is probably by the liver trough the bile, as the absolute bioavailability is high and therefore the contribution to non-absorbed imatinib in the faeces is small. Excretion by the kidney is only 13% of the dose and considered of no clinical relevance. A total recovery of more than 80% of the dose in excreta is acceptable.

Imatinib is metabolised in the liver, mainly by the CYP3A4 and CYP3A5 isoenzyme system with potential minor contribution by CYP1A2, CYP2C9, and CYP2D6. The main circulating metabolite in humans is the N-demethylated piperazine derivative (CGP74588. The plasma AUC for this metabolite was found to be only approximately 16% of the AUC for imatinib

At single and multiple doses, imatinib has shown a dose-proportionality for the dose range of 25-1000 mg in patients diagnosed with CML. However, most of pharmacokinetics studies have included a very limited number of subjects. Also the exposure to the main metabolite is nearly dose proportional.

The inter- and intra-individual variability in the pharmacokinetic variables of imatinib are acceptable considering that the main route of metabolism is by CYP 3A4 which shows also a high inter subject variability in expression.

After multiple dose administration of imatinib for 29 days, no unexpected accumulation occurs in the pharmacokinetic variables. The AUC_{0-inf} after single doses as comparable with the AUC_{0-24h} after multiple doses, indicating no time dependency in the pharmacokinetics of imatinib.

Special populations

The two-fold increased exposure in real impaired patients compared with healthy subjects is probably due to the increase concentration of alpha-1 glycoprotein and not due to the renal function. Studies with CML patients with mild and moderate renal failure that were receiving higher doses did not show clinically meaningful toxicity or drug-related AE. For PAH, lower exposures are expected, even in renal failure, because the recommended dose is lower. Dose reductions based on renal function would not be necessary. Also, the SPC the SPC states that patients with mild or moderate renal failure must be watched with caution because dose reductions might be necessary in case of intolerance, and that there is no data in patients with severe renal failure or dialysis.

Regarding hepatic failure, no information is available on the impact of hepatic failure in the PK of imatinib in PAH patients, but sufficient data in CML patients is provided. These data show that the variation in the AUC between normal liver function and severe liver disease (Child-Pugh C) is less than 15%, which is unlikely to be of clinical significance. Since the PK of imatinib is comparable between CML and PAH patients, no dose adjustments should be required based on hepatic function.

Gender, race and weight do not affect the pharmacokinetics of imatinib in a clinical significant way.

The influence of age on the PK of imatinib is not clinically significant in CML patients. Whether this can be extrapolated to PAH patients is not clear.

Dosing in children from 2 to 19 years of age at 260 and 340 mg/m^2 achieved the same exposure, respectively, as doses of 400 mg and 600 mg in adult patients. The comparison of AUC_{0-24} on Day 8 and Day 1 at 340 mg/m^2 dose level revealed a 1.7-fold drug accumulation after repeated once daily dosing. At this time, there is no pharmacokinetic data available for paediatric PAH patients. Imatinib for the use in PAH patients is not indicated for paediatric patients.

Pharmacokinetics in the target population

The POP-PK analysis showed that haemoglobin levels correlated with both clearance and volume of distribution, which indicates distribution in the red blood cells. Polycythaemia can occur in PAH patients due to chronic hypoxia, which may affect distribution and clearance. The data provided acknowledges that variations in haemoglobin and haematocrit translate to variations on imatinib concentrations over time and Vd. However, these variations do not have a clinically significant impact on total exposure and concentrations attained, therefore dose adjustments based on plasmatic concentrations of variations in haemoglobin and haematocrit are not required.

Interactions

In Vitro

In vitro inhibition studies demonstrated that imatinib inhibited CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 in human liver microsomes with Ki values of 27, 60, 7.5 and 7.9 µmol/L, respectively, Based on maximal plasma concentrations of imatinib in oncology patients of 2 to 4 µmol/L, inhibition of CYP2D6 and/or CYP3A4/5-mediated metabolism of co-administered drugs is possible.

In Vivo

Effect of other products on the pharmacokinetics of imatinib

Following rifampin co-administration, the mean imatinib C_{max}, $AUC_{(0-24)}$ and $AUC_{(0-inf)}$ decreased by 54%, 68% and 74%, respectively. The increase in Cl/F was nearly 4-fold to 385.0% after rifampin pre-treatment. Pre-treatment with rifampin significantly decrease the plasma concentrations of imatinib in healthy volunteers by more than 50%. Concomitant use of imatinib and rifampin or other potent inducer of CYP3A4 may therefore result in sub therapeutic plasma levels of imatinib.

There was a significant increase in exposure to imatinib in healthy volunteers when co-administered with ketoconazole. Although the increase in imatinib exposure was well tolerated in healthy subjects caution should be taken when administering imatinib with inhibitors of the CYP3A family. The decrease in the exposure to the metabolite is in accordance with the increased exposure to the parent compound after inhibition of CYP 3A4.

Effect of imatinib on the pharmacokinetics of other products

Co-administration of imatinib (400 mg) at steady state with 40 mg simvastatin increases the exposure (C_{max} and AUCs) to simvastatin significantly by 2-3 fold with exception of t_{max}. Therefore, caution

should be taken when administering imatinib with CYP3A4 substrates with a narrow therapeutic window. The increase of the simvastatin exposure indicates that imatinib is a moderate inhibitor of CYP 3A4, and that consequently caution should be taken when CYP 3A4 substrates are administered concomitantly with imatinib.

Co-administration of imatinib resulted in a moderate increase in metoprolol plasma exposure, approximately 21% for both C_{max} and AUC values. Although the increase appeared to be greater in EM patients, the elevated level in these patients was still lower than those in IM patients at the control condition (without imatinib). Thus, CYP2D6 status does not appear to be a risk factor for drug-drug interactions between metoprolol and imatinib. The formation rate of hydroxymetoprolol appeared to be decreased in the presence of imatinib, however, the overall AUC exposure of this metabolite was increased, and suggesting that elimination of this metabolite was probably decreased as well in the presence of imatinib. According to the results of this study, imatinib can be considered as a weak CYP2D6 inhibitor as the increase in metoprolol exposure when administered concomitantly with imatinib is increased only slightly even in extensive metabolizers.

Imatinib has no clinically relevant effects on the plasma exposure of acetaminophen (≤1000 mg) in CML patients. There was no evidence that acetaminophen affected the pharmacokinetics of imatinib. No dose adjustment for acetaminophen or imatinib will be necessary if the two drugs are co-administered.

Sildenafil concentrations were raised by imatinib (64%), and lowered by bosentan (44%), and the net effect of both interactions was no change in sildenafil concentration. Bosentan concentrations were raised by imatinib (51%) and by sildenafil (53%), and the net effect of both interactions was an increase in bosentan concentrations (132%). Imatinib concentrations fell with bosentan (-33%) and were unchanged by sildenafil. The net effect of both interactions was a fall in imatinib concentrations (-35%).

Although a significant increase in concentrations of bosentan was observed when it was co-administered with imatinib, this did not result in safety problems in the clinical study. This is line with the shallow slope of the bosentan dose response curve; however the liver toxicity of bosentan is known to be dose dependent and should be taken into account.

Sildenafil concentrations were raised by imatinib but when sildenafil was co administered with a combination of bosentan and imitanib no change in sildenafil concentration was observed. The effect of sildenafil on the transporters OATP1B1/OATP1B3 does explain the selective rise in bosentan concentration. Bosentan is a substrate of these transporters, which inhibition leads to lower hepatic uptake and therefore higher exposure. This explains the reason for which imatinib concentrations are unaltered by sildenafil, as this drug is not a substrate of the abovementioned transporters. Therefore, from a PK perspective dose adjustments of imatinib when co-administered with sildenafil would not be necessary. In the clinical study the increased concentration of sildenafil apparently did not result in an increase of safety problems related to the use of sildenafil.

Pharmacodynamics

No separate pharmacodynamic or PK/PD studies have been performed in support of this application. According to the applicant the Phase III study [QTI571A2301, referred to as A2301 in the rest of the document] included sufficient PK/PD measures to characterize imatinib in the PAH patient population. Moreover, this was not considered necessary by the applicant due to the available previous experience with imatinib in other indications. This view is not fully supported, as the indication and the target population are quite different from the oncology indication for which imatinib was originally developed.

Discussion on clinical pharmacology

Mechanism of action: The mechanism of action of imatinib in the oncology and haematology indications is based on inhibition of the Bcr-Abl tyrosine kinase (TK), as well as several receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors alpha and beta (PDGFR-alpha and PDGFR-beta). Imatinib can also inhibit cellular events mediated by activation of these receptor kinases. In vitro, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumours (GIST) cells, which express an activating kit mutation. Constitutive activation of the PDGF receptor or the Abl protein tyrosine kinases as a consequence of fusion to diverse partner proteins or constitutive production of PDGF have been implicated in the pathogenesis of haematologic and malignancies and solid tumours (Figure PD1). Imatinib is currently marketed under the trade name Glivec/Gleevec for chronic myeloid leukaemia (CML), GIST and related indications.

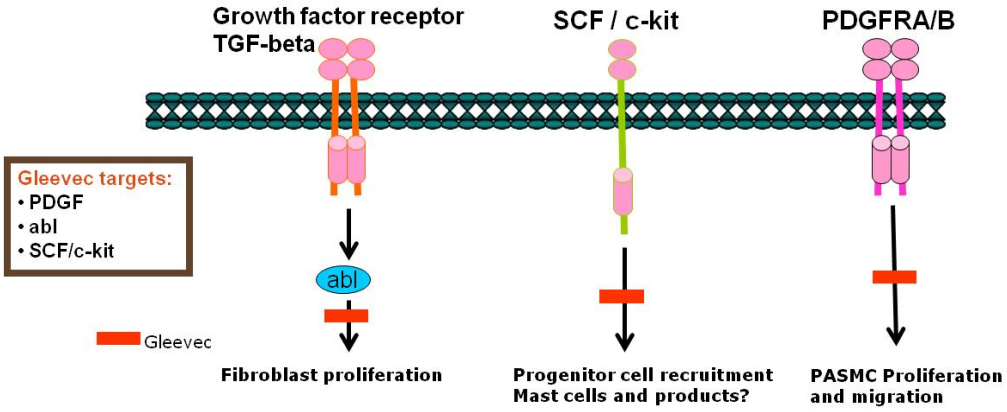


Figure PD1 Mechanism of action of imatinib

The hypothesis that imatinib may benefit PAH was first supported by case studies in patients with PAH which demonstrated clinical benefit with imatinib as add-on therapy for PAH (Ghofrani, Seeger and Grimminger 2005; Patterson et al 2006). This prompted the company to conduct a phase II exploratory study in PAH [CSTI571E2203, referred to as E2203 in the rest of the document].

In PAH, inhibition of platelet-derived growth factor (PDGF) and the stem cell factor (c-Kit) may be most relevant. This hypothesis is supported by in vitro experiments and rodent studies. In rodent animal models, these factors appear to play a role in the pulmonary vascular remodelling that occurs in PAH. (please refer to pre-clinical section). In the Day 120 responses, the company supplied data about the hypoxia/Sugen animal model which better mimics human disease and shows effects of imatinib on a histological level.

The concentration used in the rat study (Abe et al., 2011), corresponding to the upper range of human steady state concentrations at a 400 mg dose, had a clear vasodilatory effect which could be one of the contributory mechanisms of action of imatinib in PAH (refer to results of systemic vascular resistance in both controlled studies, see below). In the Day 120 responses, the Applicant commented that in rats an oral dose of 50 mg/kg would be anti-proliferative and an intravenous dose of 50 mg/kg would be vasodilatory. This difference in pharmacodynamic effect depending on the route of administration is not well supported.

The mechanism of action and the pharmacodynamic effects of different doses in PAH are uncertain. These uncertainties concern dose selection, the expected benefit and possible adverse events. The possible clinical implications of the manipulation of the pathways as shown in Figure PD1 in the PAH

setting are not investigated. The specificity of the tyrosine kinase inhibitory profile plays an important role, as recently shown in the case of dasatinib, where cases of dasatinib-induced PH were observed (Montani et al., 2012). Although both agents share the same mechanism of action in CML, dasatinib displays a less specific target profile than imatinib. Dasatinib is a potent inhibitor of additional important families of receptors of tyrosine kinases, including the Src and the Eph receptors/ephrin tyrosine kinases. c-Src tyrosine kinase is abundantly expressed in vascular tissue, and activation of Src appears to play a critical role for smooth muscle cell proliferation and vasoconstriction. Although such cases of severe pre-capillary PH were only reported with dasatinib in the French registry, this AE is also mentioned in the SmPC of Glivec.

Primary Pharmacology

Study E2203 is a phase II trial and is considered the proof of concept study. This was a randomized, placebo-controlled, 24 weeks study to investigate the safety and efficacy of imatinib in patients with PVR>300 dyn·s·cm^{-5} in spite of using one or more PAH specific medications (PGI2s, ERAs or PDE5Is).

The selected dose for imatinib 400 mg is also currently proposed in the SmPC. The dose was selected based on tolerability and an expectation of effectiveness, but not supported by a dose-ranging trial. In haematology and oncology, administered doses range from 400-800 mg QD. The primary endpoint (6MWT) is in line with those specified for PD studies in the relevant guideline (EMEA/CHMP/EWP/356954/2008). In addition, long term haemodynamic parameters were investigated. However, no parameter that could support the proposed mechanism of action (i.e. anti-proliferative effect) has been investigated.

The duration of the study (24 weeks) is considered sufficient to show an effect on the 6MWT. Patient's flow is shown in Figure PD2.

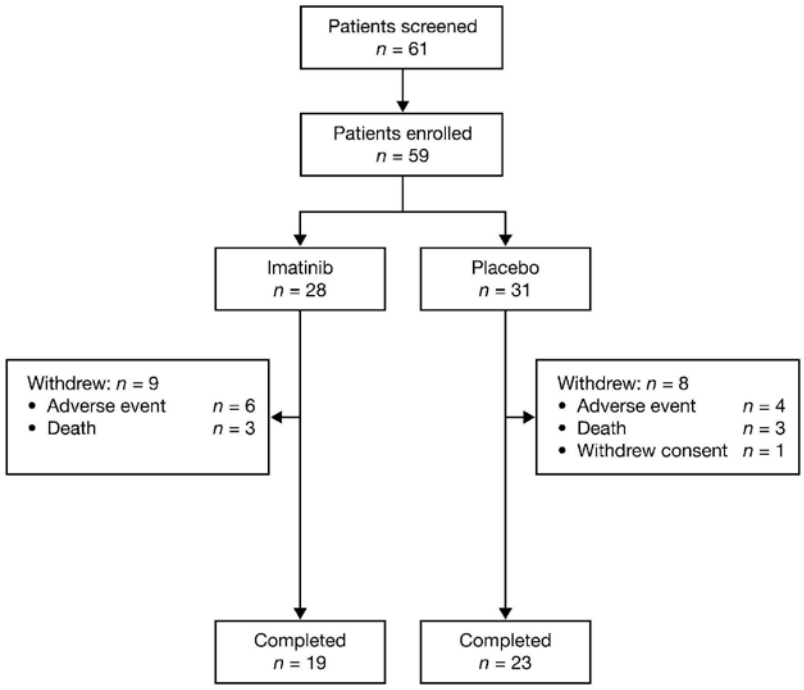


Figure PD2 Participant flow in E2203

Table PD1 summarises the baseline data of the whole cohort in study E2203 and the data of the subgroup that was eventually identified by the applicant to benefit the most from the treatment, that is, patients with PVR≥800 dyn·s·cm^{-5} in spite of using two or more PAH specific medications. These eventually became the target population.

Table PD1 Main baseline features and disposition in Study E2203 and the selected subgroup.

	E2203 PVR>300 dyn·s·cm^{-5} ≥1 PAH-specific medication		Subgroup PVR≥800 dyn·s·cm^{-5} ≥2 PAH-specific medications	
Baseline features	Imatinib N = 28	Placebo N = 31	Imatinib N = 13	Placebo N = 18
Demographic characteristics				
females, n (%)	18 (64.3)	22 (71.0)	8 (61.5)	14 (77.8)
age, mean ± SD	44.4±15.3	44.2±15.7	40.1± 14.2	43.1± 15.6
Disease features				
6MWD at baseline, mean ± SD	392.4±89.0	368.8±118.4	382.2±90.9	356.6±115.5
WHO functional class				
class II, n (%)	11 (40.7)	7 (23.3)	5 (38.5)	2 (11.1)
class III, n (%)	14 (51.9)	22 (73.3)	6 (46.2)	15 (83.3)
class IV, n (%)	2 (7.4)	1 (3.3)	2 (15.4)	1 (5.6)
Disposition				
completed, n (%)	19 (67.9)	23 (74.2)	6 (46.2)	13 (72.2)
discontinued, n (%)	9 (32.1)	8 (25.8)	7 (53.8)	5 (27.8)
Adverse event(s)	6 (21.4)	4 (12.9)	6 (46.2)	2 (11.1)
Death	3 (10.7)	3 (9.7)	1 (7.7)	2 (11.1)
Withdrawn consent	-	1 (3.2)	-	-

Regarding disease features, the placebo group of the main cohort appears to have been in a slightly worse condition than the imatinib group concerning both 6MWT and WHO functional class. In the placebo group, WHO Functional class III was overrepresented and WHO Functional class II was underrepresented, compared to the imatinib group. An apparent discrepancy in the contribution of patients to WHO FC groups compared to what was presented in the publication of this trial (Ghofrani et al, 2010), was caused by an error in the publication. The applicant has confirmed that the data in the MAA are correct.

The subgroup matching the proposed indication consisted of 53% of the subjects of E2203 (46% of the imatinib subjects and 58% of the placebo subjects). The rate of discontinuation was generally comparable in the treatment groups, but with most patients withdrawing because of AEs in the imatinib group with high PVR (46.2%). However the numbers are too few precluding any robust conclusions.

The **primary efficacy variable** (6MWD) showed a trend towards a beneficial treatment effect, but did not reach statistical significance (Table PD2). In the subgroup with PVR≥800 dyn·s·cm^{-5} the effect was larger, which offers some support for the selection of this subgroup for further investigation.

Table PD2 6MWD (primary efficacy variable) (Study E2203 and subgroup with PVR≥800 dyn·s·cm-5 and ≥2 PAH-specific medications); Last observation carried forward

	E2203 PVR>300 dyn·s·cm^{-5} ≥1 PAH-specific medications		Subgroup PVR≥800 dyn·s·cm^{-5} ≥2 PAH-specific medications	
6MWD (m)	Imatinib N = 28	Placebo N = 31	Imatinib N = 13	Placebo N = 18
	(n=21)	(n=21)		
baseline value	392.4	368.8	382.2	356.6
last treatment value	418.7	398.9	451.5	382.7
treatment effect (95% CI)	**21.7 (–13.0, 56.5) (p=0.213)**		**65.2 (1.4, 128.9) (p=0.046)**	

least squares mean analysis of covariance

The **haemodynamic variables** showed a beneficial treatment effect that reached statistical significance for the main cohort in pulmonary vascular resistance (PVR) and cardiac output (CO), but

not in mean pulmonary artery pressure (PAP). Only trends in improvement were observed in the subgroup with PVR≥800 dyn·s·cm^{-5} and ≥2 PAH-specific medications (Table PD3). Although the numbers are small, this casts doubts over the definition of the population for the pivotal study A2301. The ability of PVR to distinguish patients who may or may not benefit from this drug is questioned as response differs per endpoint (better response in the 6MWT, but minimal response based on haemodynamic parameters).

Table PD3 Haemodynamic variables (Study E2203 and subgroup)

	Study E2203 PVR>300 dyn·s·cm^{-5} ≥1 PAH-specific medications		**Subgroup PVR≥800 dyn·s·cm^{-5} ≥2 PAH-specific medications**	
Haemodynamic variable	Imatinib N = 20	Placebo N = 22	Imatinib N = 13	Placebo N = 18
PVR (dyn·s·cm^{-5})	(n=19)	(n=21)		
baseline	1124	1118	1328	1303
last treatment value	730	1017	870	1158
treatment effect (95% CI)	-230 (-383, -78) (p=0.0044)		-205 (p=0.109)	
CO (L/min)				
baseline value	4.20	4.09	3.88	3.81
last treatment value	4.90	4.35	4.41	4.07
treatment effect (95% CI)	+0.68 (0.10, 1.26) (p=0.023)		+0.3 (p=0.400)	
mean PAP (mm Hg)				
baseline value	61.7	59.2	68.0	61.0
last treatment value	52.5	55.5	55.7	57.1
treatment effect (95% CI)	**-2.54 (-7.4, 2.3) (p=0.295)**		**-3.0 (p=0.477)**	

arithmetic mean (unpaired) and difference in LSM

These beneficial changes on the pulmonary haemodynamics in the main cohort were accompanied by a significant decrease in SVR [treatment effect -300 (95% CI: -510, -91; p=0.0066)]. This points to a possible vasodilatory mechanism of action, different to what is promoted by the applicant. The applicant attributes this vasodilatation to the improved CO. Currently, this theory cannot be further verified, because no measurements of the sympathetic tone are available. The changes in fluid balance caused by imatinib further complicate the picture (see later).

Secondary Pharmacology

N/A

Conclusions on clinical pharmacology

No specific PD studies or PK/PD studies are submitted, which is a major limitation for the understanding of the mechanism of action and the dose selection in PAH. Imatinib inhibits several tyrosine kinases; the clinical implications of this in the cardiology setting are not investigated, which is an important deficiency. Extrapolation from the known mechanism of action of imatinib in the oncology indication is theoretically acceptable but was not further investigated in PAH. There is limited evidence for an anti-proliferative mode of action in rat models of PAH. Acute haemodynamic measurements in humans are lacking, precluding a conclusion on the contribution of a possible direct vasodilatory effect. (OC).

The proof of concept study E2203 was triggered by some case reports showing a benefit of imatinib in PAH patients. Results showed that imatinib 400 mg was associated with some improvement in the 6MWT and haemodynamics in patients with PVR>300 dyn·s·cm^{-5}. In a post-hoc analysis to identify patients with best possible benefit, the subgroup with PVR>1000 dyn·s·cm^{-5} and administered at least 2 background medications for PAH, showed better results for the 6MWT, but worse results regarding haemodynamics, questioning the use of PVR in identifying patients. This group was later chosen as the

target group for the pivotal study. Due to recruitment problems, this cut-off value was reduced to PVR>800 dyn·s·cm^{-5} during the study. No further parameters were investigated precluding any explanation on the mode of action, but as systemic vascular pressure and resistance were also reduced, a vasodilatory MoA cannot be excluded. The applicant deleted the reference to the "anti-proliferative" MoA from the indication. This approach is acceptable, though it would have been more supportive to the application to show this new MoA clinically.

Clinical efficacy

A single pivotal study was conducted to demonstrate the efficacy of imatinib in patients with PAH and PVR ≥ 800 dyn·s·cm^{-5} and using two or more PAH specific therapies. Patient selection for this study was done based on a subgroup analysis of the phase II study (E2203) (see before). Participants in both trials could enter in long-term open-label extension studies (Table E1).

Table E1 Overview of clinical studies in PAH

Study	Objective, population	No. of patients	Study duration	Dosage	Efficacy endpoint
Exploratory, proof of concept study (phase II) Presented with Pharmacodynamics					
Study **E2203**	Efficacy and safety in PAH patients (≥ 1 PAH drug, PVR>300 dyn·s·cm^{-5})	59	24 weeks	imatinib 200/400 mg QD placebo QD	1^{o} - 6MWD post hoc - 6MWD and pulmonary haemodynamics multiple subsets
Pivotal placebo-controlled study in the target population (phase III)					
Study **A2301**	Efficacy/safety/PK in target PAH patients (≥ 2 PAH drugs, PVR≥800 dyn·s·cm^{-5})	202	24 weeks	imatinib 200/400 mg QD placebo QD	1^{o} - 6MWD Main 2^{o} - pulmonary haemodynamics , TTCW,
Interim analyses - of on-going long term open-label studies					
Study **E2203Ext**	Efficacy/safety in PAH patients (≥ 1 PAH drug, PVR>300 dyn·s·cm^{-5})	22	i.a. data ≤3 years (5 years planned)	imatinib 200-400 mg QD	6MWD
Study **A2301E1**	Efficacy/safety in PAH patients (≥ 2 PAH drugs, PVR≥800 dyn·s·cm^{-5})	144	i.a. data ≤1 year (3 years planned)	imatinib 200/400 mg QD	6MWD

i.a. = interim analysis

Summary of main efficacy results

Table E2 summarises the efficacy results from the main study (A2301), 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 E2 Summary of Efficacy for E2301

Title: A 24-week randomized placebo-controlled, double-blind multi-centre clinical trial evaluating the efficacy and safety of oral imatinib as an add-on therapy in the treatment of severe pulmonary arterial hypertension: Imatinib in Pulmonary arterial hypertension, a Randomized, Efficacy Study (IMPRES)					
Study identifier	CQTI571A2301				
Design	This was a multinational, multicentre, double blind, parallel group study using a placebo control and imatinib (imatinib). Treatment was started at 200 mg once daily for two weeks and increased to 400 mg once daily if well tolerated. If 400 mg dose was not well tolerated, a down titration to 200 mg once daily was permitted.				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks not applicable On-going (data for 72 weeks)			
Hypothesis	Superiority of imatinib over placebo				
Treatments groups	Imatinib	Imatinib (200-)400 mg, 24-weeks, n = 103			
	Placebo	Placebo, 24 weeks, n=99			
Endpoints and definitions	Primary endpoint	6MWD	Distance walked during a standardized 6-minute walk test.		
	Secondary endpoint	TTCW	Time to Clinical Worsening includes all cause mortality, overnight hospitalization for worsening of PAH, a worsening of WHO functional class by at least one level, and a 15% decrease in the 6MWD as compared to baseline confirmed by two 6MWTs		
	Secondary endpoint	PVR, CO	Pulmonary Vascular Resistance, Cardiac output		
Database lock	18 July 2011				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Full analysis set (all randomized patients), Intention to treat 24 weeks				
Descriptive statistics and estimate variability	Treatment group			Imatinib	Placebo
	Number of subjects			N = 103	N = 98
	6MWD (m) (LS Mean)			(n=92) 383	(n=93) 351
	Standard Error			9.8	9.8
	TTCW (patients with event)			37	32
	PVR [dyn s cm^{-5}] (LS Mean) baseline 24 weeks difference			(n=74) 1206 807 -366	(n=80) 1164 1140 12
	Standard Error			68	69
Effect estimate per comparison	Primary endpoint	6MWD		Imatinib/placebo	
		ANCOVA treatment difference		32	
		SE		10	
		P-value		0.002	
	Secondary endpoint	TTCW		Imatinib/placebo	
		Hazard ratio		1,16	
		95% CI		0.71-1.90	
		P-value		0.563	
	Secondary endpoint	PVR		Imatinib/placebo	
		Treatment effect		-379	
		SE		62	
		P-value		<.001	

Clinical studies in special populations

N/A

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

N/A

Supportive study

Participants in both placebo controlled trials E2203 and A2301 could enter in long-term open-label extension studies (main results are presented later).

Discussion on clinical efficacy

- **Dose-finding studies:**

No dose response studies were conducted to support the PAH indication. The selected dose of 400 mg QD is on the lower range of that used in the CML indication (400-600 mg QD), and was chosen for the PAH studies to minimise the risk of AEs like vomiting, diarrhoea, oedema and anaemia. This approach is considered acceptable as it would be expected to improve tolerability. However, it cannot be excluded that higher doses would have been associated with better efficacy results.

Dose selection in the pivotal study (A2301) was addressed in a CHMP Scientific Advice (EMEA/H/SA/493/6/2009/III). The posology scheme of initiating treatment with 200 mg QD then up-titrating to 400 mg QD was considered acceptable, provided that by end of the study enough patients would be on the proposed dose of 400 mg to allow for robust conclusions. In the day 120 responses the applicant adapted the SmPC, allowing only temporary down titration to 200 mg QD to improve tolerability. The use of this lower dose is further addressed below.

- **Design and conduct of clinical studies**

Study A2301 is the pivotal phase III trial [Imatinib in Pulmonary arterial hypertension, a Randomized, Efficacy Study (IMPRES)]. It is designed to evaluate the efficacy and safety of oral imatinib as an add-on therapy on top of two or more PAH-specific medications in severe PAH defined by high PVR. The study design is generally in line with studies previously submitted for PAH medications. The main difference is the longer study duration of 24 weeks instead of the usual 12 weeks studies. This is supported especially in view of the proposed anti-proliferative mechanism of action of imatinib. The study investigates the combined administration of PAH medications, which is the envisaged development for PAH therapy. None of the currently registered PAH specialised medications is approved for add-on use, although off-label use is acknowledged.

Submission of a single pivotal study to support the PAH indication was generally supported in the scientific advice (EMEA/H/SA.493/6/2009/III), provided the results would robustly indicate both statistical and clinical significance of the effect. In accordance with guideline CPMP/EWP/2330/99, providing minimum requirements for MA in case only one pivotal trial is submitted, a significance level substantially lower than 5% for the primary efficacy evaluation should have been pre-specified. This requirement was not met as will be seen later.

The applicant defines the target population by a PVR≥ 800 dyn·s·cm^{-5}, in spite of treatment with combination PAH therapy. Initially, this subgroup was PVR>1000 dyn·s·cm^{-5}, based on the subgroup which had best results in the 6MWT in study E2203. However due to slow recruitment, this limit was reduced to PVR≥ 800 dyn·s·cm^{-5} through a protocol amendment. This resulted in sacrificing a larger treatment effect as is shown later in Figure E5 (see below).

Defining patients based on PVR deviates from the usual definition of severity of PAH, based on WHO functional class. None of the currently approved PAH medications is registered to target PAH patients defined by PVR severity. This concern was also raised in EMA Scientific Advice

(EMEA/H/SA.493/6/2009/III). Substantial intra-subject variability and problems regarding the reproducibility of PVR read-outs were other issues raised against the use of PVR as measurement for severity. According to the applicant, no clear correlation between PVR and the functional class could be observed and the only characteristic parameter in the responding patients in the pilot study was the high PVR. In their advice, the CHMP considered a classification according to PVR could only be acceptable if further supporting evidence would reveal that PVR is the sole identifying characteristic. No such further evidence was revealed, which constitutes a problem in identifying the target population.

Exclusion criteria were quite extensive (42). They were meant to precisely define PAH in the intended patient population and to exclude pulmonary hypertension due to other causes as well as patients with certain risk factors and/or co-morbidities. However, they were not considered of relevance to be explicitly contraindicated SmPC.

The 6 minute walk test (6MWT) is an acceptable ***primary endpoint*** to support the improvement in exercise capacity as claimed in the indication. There are recognized advantages for using 6MWT, but due to the lack of correlation of this endpoint to clinical outcome, in particular survival, its use is more encouraged as part of an endpoint investigating clinical outcomes (time to clinical worsening TTCW), according to the relevant guideline (EMEA/CHMP/EWP/356954/2008). In the SA, the 6MWD was considered acceptable as a primary endpoint, provided that a minimally clinically relevant difference in 6MWD would be predefined. A difference of 50 meters or greater in 6MWD distance was considered as such and was used in the power calculation. Also, it was considered that the expected gain in exercise capacity would have to be weighed against the safety profile of imatinib in the overall benefit/risk assessment.

The main **secondary variables** were pulmonary haemodynamic parameters and time to clinical worsening (TTCW), which is supported. The definition proposed by the applicant for the TTCW i.e. all cause mortality; hospitalization for 24 hours or more for worsening of PAH; worsening of WHO functional class by one level; or a 15% decline in 6MWD measured on two consecutive occasions is also acceptable.

The ***sample size calculation*** was based on acceptable assumptions. The power calculation for TTCW is based on the PACES trial (Simonneau et al., 2009) assuming an event free survival rate at 24 weeks of 94% for imatinib and 82% for placebo. The power calculation for TTCW did not allow for a significant discontinuation rate. Therefore, the power of A2301 to detect a clinically relevant difference in TTCW remains unclear.

Randomisation and Blinding. The applicant designed a system for dispensing study drugs based on an Interactive Voice Response System IVRS which required all patients to take each day two tablets from two different bottles. The method for dispensing drugs was suitable for blinding the dose for treating physician, investigator and patient. As the IVRS was not designed consistent with the protocol, trial participants were overdosed and neither patients nor investigators could notice this. As a result of these deviations, 28 patients (13 imatinib and 15 placebo) were excluded from the per protocol analyses. This drug dispensing system was needlessly complicated and error-prone. The computer validation of the IVRS system has failed. This is a violation of the “Note for guidance on good clinical practice” (CPMP/ICH/135/95) / ICH E6 section 5.5.3a. The consequences of the 13 imatinib overdosed subjects for the interpretation of the trial are probably limited, but the overdose may have caused additional adverse events in the Imatinib group.

The ***statistical analysis*** was done using a mixed model repeated measurements approach (MMRM). This was discussed and agreed upon in the SA. The experience with the interpretation and critical assessment of findings from MMRM in the confirmatory (and not the exploratory) setting was

considered limited in the regulatory context. Missing data were further accounted for by means of sensitivity analyses. The SA also referenced guideline CPMP/EWP/2330/99, providing minimum requirements for MA in case only one pivotal trial are submitted. One important requirement is to specify a significance level substantially lower than 5% for the primary efficacy evaluation. This guideline was not followed. To correct for multiplicity by the two interim analyses, alpha levels were minimally reduced to 0.0498. A hierarchical sequence was pre-specified, by which TTCW would only be tested if the primary endpoint (6MWD) would achieve statistical significance, both at full alpha. This is acceptable. There were no clinically significant differences in responses to imatinib between the patients included in the interim analysis and those not included in the interim analysis, providing reassurance as to possible bias in the final study results.

- **Efficacy data and additional analyses**

Participant's flow is shown in Figure E1.

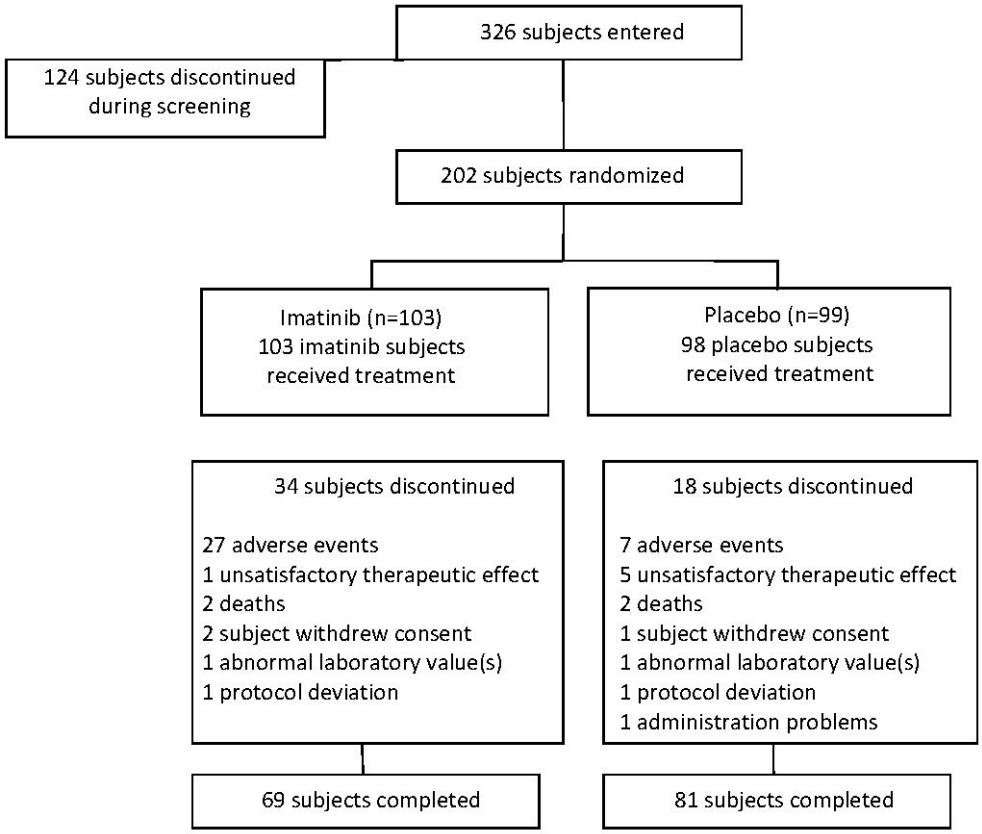


Figure E1 Participants flow in study A2301

The overall dropout rates in the A2301 study were 33.0% in the imatinib group and 18.4% in the placebo group, giving an excess dropout rate of 14.6% in the imatinib group. This is mainly due to adverse events, there was a higher dropout in the placebo group (n=5 vs. n=1 in the imatinib group) due to unsatisfactory therapeutic effect. The majority of patients who discontinued due to AEs in the imatinib group did so during the first 8 weeks of treatment, when most imatinib-related AEs occurred (this is further discussed under safety). As the purpose of the 200mg starting dose is to improve tolerability, the IVRS issue (see above) may have worsened this.

There was no difference between treatment groups in the proportion of patients who discontinued due to death (two patients in each group). The proportion of patients who discontinued due to unsatisfactory therapeutic effect was higher in the placebo group.

Forty eight patients of 202 randomized (24%) were excluded from the per protocol analysis because of major protocol deviations. Twenty-eight of these were caused by the IVRS issue. Others concerned missed in- and exclusion criteria that relate mostly to safety precautions that were not observed (like thrombocytopenia or anaemia) or baseline assessments that were not completed prior to dosing.

The demographics and types of PAH randomised in the trial represent the known disease distribution (Table E3).

- **Table E3 Main baseline features of patients (Study A2301)**

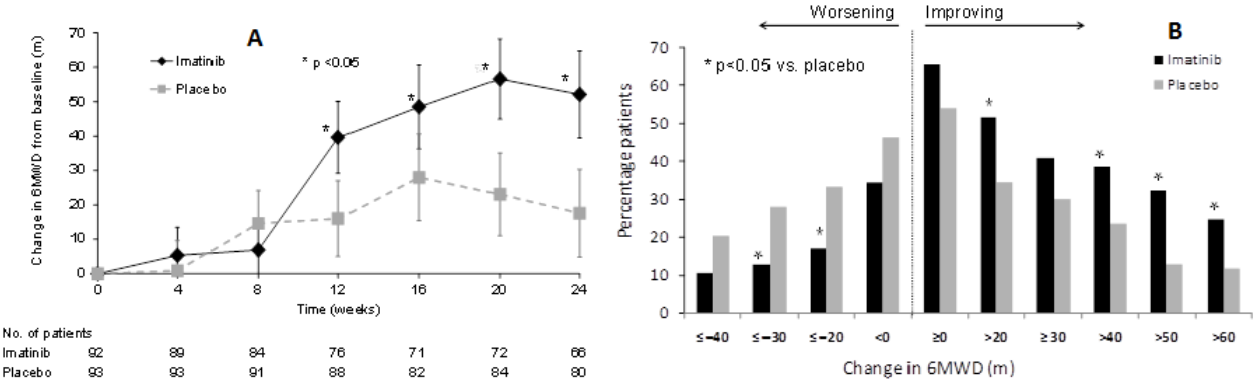
Baseline features	Imatinib N = 103	Placebo N = 98
Demographic characteristics		
females, n%	83 (80.6%)	79 (80.6%)
age, mean ± SD	50.0 ± 15.3	46.5 ± 13.6
Caucasian/Asian/Blacks, %	74.8%, 18.4%, 3.9%	73.5%, 20.4%, 5.1%
Type of PAH		
idiopathic or heritable PAH, n %	77 (74.6%)	74 (75.5%)
acquired PAH, n %	26 (25.2%)	23 (23.5%)
Disease features		
PVR at baseline, mean ± SD	1202 ± 414	1181 ± 360
6MWD at baseline, mean ± SD	336.7 ± 85.4	350.6 ± 75.3
WHO functional class		
class I, n (%)	1 (1.0)	0
class II, n (%)	23 (22.3)	28 (28.6)
class III, n (%)	71 (68.9)	65 (66.3)
class IV, n (%)	8 (7.8)	5 (5.1)
WHO functional class and PVR		
class II, *mean PVR* ± SD	1311±655	1143±297
class III, *mean PVR* ± SD	1172±319	1173±356
class IV, *mean PVR* ± SD	1207±210	1180±264
WHO functional class and 6MWD		
class II, *mean 6MWD* ± SD	397±53	390±47
class III, *mean 6MWD* ± SD	328±84	351±69
class IV, *mean 6MWD* ± SD	295±89	209±41
PAH-specific therapies		
ERA + PDE5I, n %	32 (31.1%)	27 (27.6%)
ERA + PGI2, n %	15 (14.6%)	10 (10.2%)
PDE5I + PGI2, n %	14 (13.6%)	20 (20.4%)
ERA, PDE5I + PGI2, n %	42 (40.8%)	41 (41.8%)

Baseline disease characteristics were well matched across groups. PVR was indeed high reaching a mean >1000 dyn·s·cm^{-5}. Patients were mostly of WHO FC III, with fewer patients in WHO II, which may limit the interpretation of the data in this subgroup. WHO FC I and IV were barely represented. Higher PVR does not coincide with higher WHO functional class (although all kinds of bias are thinkable); this supports the applicant's position that WHO functional class cannot replace PVR in defining the subgroup deriving most benefit from imatinib. On the other hand, WHO classification did match the 6MWT categories. The mean duration of PAH in the imatinib and placebo arm was 5.3 years each, but the median durations of PAH were 3.7 years versus 5.1 years respectively. The applicant explored the possible influence of such differences in disease duration on the different outcomes. Patients with a longer duration of PAH treated with imatinib tended to have a higher risk for TTCW versus placebo than patients with a shorter PAH duration, and less improvement in 6MWT and PVR, although the interaction values were not statistically significant (p = 0.09, 0.23 and 0.46 respectively).

Regarding baseline PAH medications: 41.4% of patients were receiving 3 PAH-specific therapies; 70.7% of patients were receiving PGI2, 29.4% were treated with PGI2 via intravenous administration, 15.9% received subcutaneous injections of PGI2, 16.4% used inhaled PGI2 and 9.0% used oral administration. These data indicate that imatinib was indeed administered in a very ill population, and on top of acceptable PAH drug combinations.

Main results. The **6MWT** was improved in the imatinib group (n=92) compared to the placebo group (n=93) at Week 24; the LS mean difference between imatinib and placebo was 31.8 meters (95% CI: 11.8-51.8; p = 0.002). In this analysis, patients with baseline and at least one post-baseline assessment are used. Note that actually observed data for Week 24 were only n=66 (imatinib) and n=80 (placebo). Because of the high dropout rate a number of sensitivity analyses were performed (See below).

This difference (31.8) is less than the predefined clinically relevant distance of 50 m. In patients who remain in the trial, the difference becomes apparent from Week 12 onwards (Figure E2A). The difficulty in demonstrating a significant effect on the 6MWT in add-on therapy trials is acknowledged; this is probably due to a ceiling effect. In the TRIUMPH trial (inhaled treprostinil on top of either bosentan or sildenafil), the between-treatment median difference in change from baseline in peak 6MWD was 20 m at week 12 (McLaughlin et al., 2010). Also in the PHIRST trial, the gain in the 6MWT in patients administered tadalafil on top of bosentan, was much lower than that achieved in patients administered tadalafil alone (placebo-adjusted median increase of 17 metres vs. 39 m respectively)(Galie et al., 2009). Considering imatinib is administered on top of two or more PAH therapies, the 31.8 m treatment difference is considered relevant. Although the difference in 6MWT did not reach the pre-specified 50 m, it is observed that for this group, there were significantly more responders in the imatinib group (30/93; 32.3%) compared to the placebo group (12/93; 12.9%)(Figure E2B).



- **Figure E2 A. LSM changes in 6MWD over 24 weeks – ANCOVA of observed data (Study A2301) B. Changes in 6MWD at 24 weeks (Study A2301)**

A series of sensitivity analyses was performed. Two of these were pre-planned.

- In the "LOCF", missing results for Week 24 could be carried forward from Week 4 onwards.
- In the "multiple imputations", missing data were imputed without taking account of study treatment. This approach used both imatinib and placebo data to impute missing values.

Other sensitivity analyses of 6MWD were performed post-hoc. These included

- ANCOVA using baseline observation carried forward (BOCF)
- ANCOVA excluding patients with the 5 most common AEs (nausea, peripheral oedema, diarrhoea, vomiting, periorbital oedema)

- multiple imputation approaches assuming missing at random (MAR)
- multiple imputation approaches assuming missing not at random (MNAR) [SCE Appendix 1-Table E3a to Table E3c]. These were performed within the pattern-mixture model framework.

These results show that the treatment effect on 6MWD remains concordant and statistically significant.

The applicant was also requested to present

- Scenario's based on clearly unfavourable assumptions, e.g. imputing 0 m if no 6MWD was available ('worst case scenario')
- Sensitivity analysis for the per protocol dataset

In the worst case scenario the estimate of the change in 6MWD was adverse (-40.23 m; 95% CI: -87.24, 6.78). However, this scenario is considered too conservative as patients were not deteriorating before drop-out. In the other scenarios, the main outcome measure remains positive, albeit sometimes without statistical significance.

In the sensitivity analysis of the 'full analysis set' using BOCF, the LS mean difference between imatinib and placebo was 20.0 meters (95% CI: 4.81-35.22; p = 0.0102). In the sensitivity analysis of the 'per protocol' data, the results for 6MWT were non-significant (LOCF: 19.2m (-2.4; +40.8) BOCF: 16.4m (-0.3; +33.2).

In another sensitivity analysis, responder analysis was carried out assuming all drop-outs were non-responders. The between group differences were smaller but still statistically significant for >50 m (imatinib (26/103) 25.2% vs. placebo (11/98) 11.2%, p=0.011).

Subgroup Analysis. Efficacy (6MWT) in several important subgroups was explored. No robust conclusions can be drawn considering the limited numbers of patients in each subgroup (Figure E3).

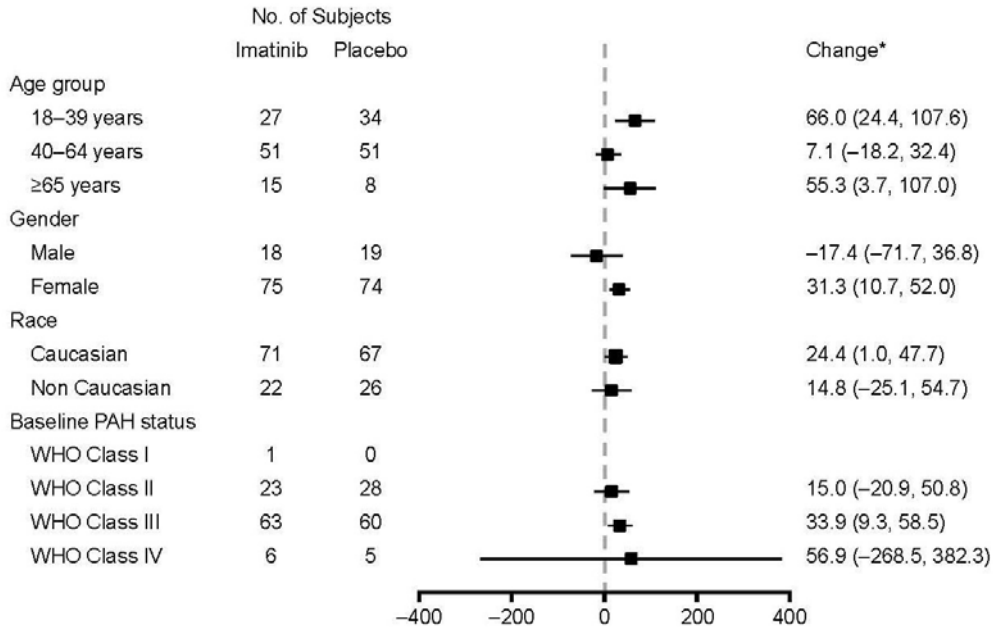


Figure E3 ANCOVA of between-treatment difference for change from baseline in 6MWD by demographics and WHO FC.

WHO FC IV patients have good responses on PVR but there was no effect on 6MWD (Difference: -2.4 m versus placebo) and the rate of patients with clinical worsening was much higher than in the overall

population (imatinib 60% vs. placebo 33%). In their response, the applicant deleted reference to this population in the in the proposed indication.

Patients with PVR at baseline >1000 dyn•s•cm-5 had a good response to treatment in terms of 6MWD (Diff. vs. placebo: 31.7 metres) with significant decrease in PVR and no different rates of clinical worsening with placebo (38% in both treatment groups).

With respect to IPAH and PAH associated to connective disease, no relevant differences in response are evident depending on the PAH aetiology. (Figure E-4)

Although recognising the low number of **men** included in the phase II and III studies (58 subjects), the significant increase in rates of clinical worsening in this subpopulation [imatinib 60% (18 of 30) vs. placebo 25% (7 of 28)] and the lack of effect in 6MWD and PVR suggest a different effect in men and in women.

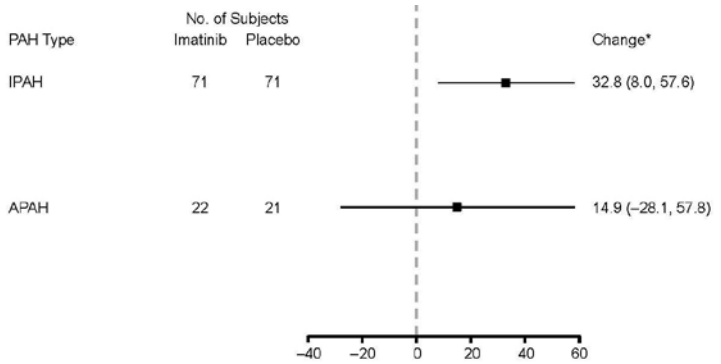


Figure E4 ANCOVA of between-treatment difference for change from baseline in 6MWD by diagnosis

Improvement is also less evident in WHO II patients (LS mean treatment difference=15 (-20.85- 50.85; p=0.401) than in WHO III patients (LS mean treatment difference=33.92 (9.35- 58.5; p=0.0074). This questions the efficacy in this subgroup, also in light of the limited representation in the study.

The response was also better in the subgroup with PVR > 1000 dyn·s·cm^{-5} than in the subgroup with PVR < 1000 dyn·s·cm^{-5} (Figure E5).

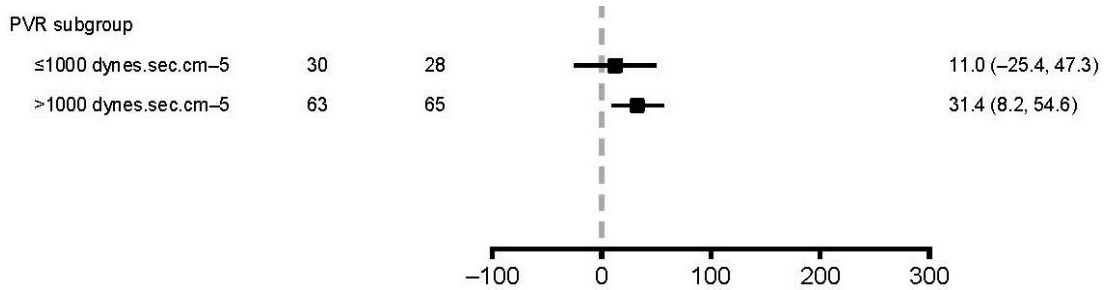


Figure E5 ANCOVA of between-treatment difference for change from baseline in 6MWD by PVR subgroup.

Responses in subgroups based on background PAH medication were concordant with each other, although only significant in the group of triple combination (Figure E6).

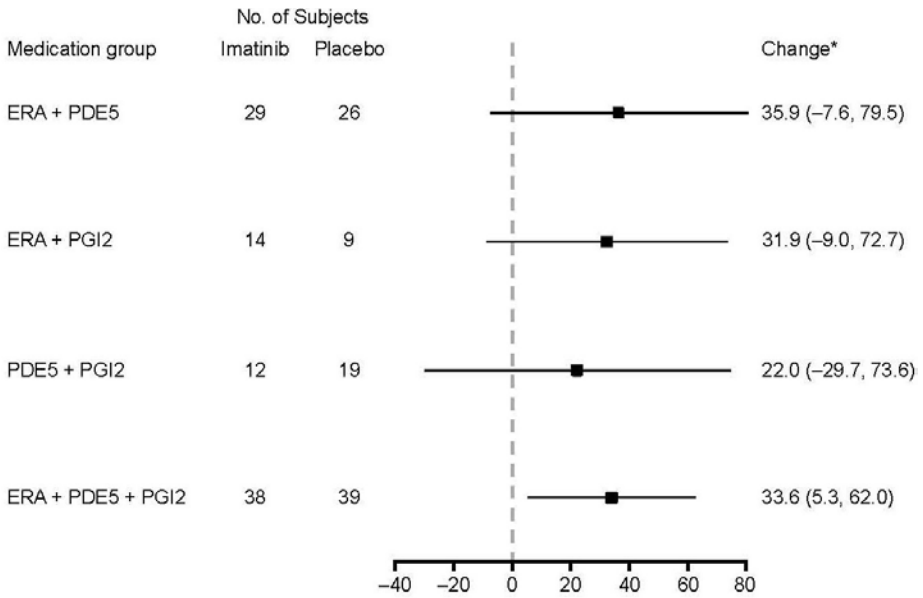


Figure E6 ANCOVA of between-treatment difference for change from baseline in 6MWD by background PAH medication

In summary, efficacy in certain subgroups (WHO FC II, PVR at baseline < 1.000 dyn.s.cm^{-5}.and APAH) needs to be further verified. The applicant is requested to present subgroup analyses (BOCF) for 6MWT, PVR and TTCW with figures, relative risks, 95% CIs and interaction p-values. The applicant is also requested to show figures of change in 6MWD and change in PVR against both baseline PVR and 6MWD, and change in 6MWD from week 24 to 48 against changes in 6MWD and PVR from week 0-24, as continuous variables, distinguishing (core) group (**OC**).

In addition the applicant should discuss why the overall efficacy of imatinib seems worse in WHO FC IV patients with respect to 6MWD and TTCW, while it is better in patients with PVR at baseline >1000 dyn·s·cm^{-5}, which are supposed to be more represented among patients with worse functional class (**OC**).

Further analysis of the results (primary and secondary endpoints: TTCW and PVR) according to the geographic location and by centre showed no meaningful differences. There were some variations by region, with the results in Europe tending to be better in study 2301 than in study 2203. However, due to the limited number of patients in the region sub-groups in both studies, the confidence intervals around the treatment estimates are wide and there is limited power to detect significant differences.

Secondary endpoints included ***time to clinical worsening*** TTCW. There is a developing trend to measure TTCW in PAH clinical trials as it provides a broader view of the clinical development of the disease compared to the 6MWT. There is some inconsistency in the definitions used across the trials; the one currently used in the pivotal trial deviates a little from that stated in the EMA guideline (EMEA/CHMP/EWP/356954/2008) as it does not include signs and symptoms of right sided heart failure. However, this is not considered a serious problem as these would eventually be presented under PAH related hospitalisations if considered severe enough.

Imatinib failed to show improvement in the TTCW compared to placebo. In the Full Analysis Set (FAS), the number of events in the imatinib group was 37 (35.9%) and 32 (32.7 %) in the placebo group (HR: 1.16; 95% CI 0.705-1.902; p=0.563).

The Kaplan Meier curve visualizes that most events in the imatinib group occur during the first 8 weeks, coinciding with the adverse events that are caused by the initiation of imatinib (Figure E7).

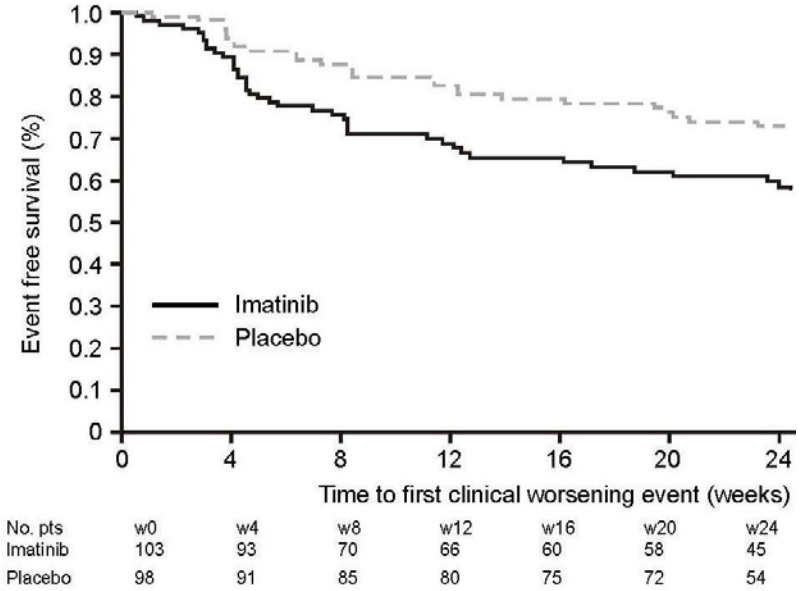


Figure E7 Kaplan Meier curves of event free survival in Full Analysis set of A2301.

The applicant argues this is a treatment effect and not indicative of worsening PAH. The common imatinib AEs that are most likely to affect TTCW events include peripheral oedema, nausea, vomiting and/or diarrhoea (which can result in intravascular volume depletion), as PAH patients are particularly sensitive to acute shifts in circulating fluid volume (Table E4).

Table E4 Phase III study (A2301): Time course of initial TTCW events, discontinuations, selected AEs (by first occurrence) and SAEs

	Events by Time of Occurrence				Total
	≤8 wks	>8-16 wks	>16-24 wks	>24 wks	n
TTCW events#					
Imatinib	24	6	5	2	37
Placebo	12	7	6	7	32
Discontinuations due to AEs – imatinib	20	6	2	0	28
Discontinuations due to AEs – placebo	7	2	0	0	9
SAEs – imatinib (excluding death)	30	10	4	0	44
SAEs – placebo (excluding death)	13	7	5	2	27
Selected AEs - imatinib **					
peripheral oedema	31	7	7	0	45
diarrhoea	31	2	3	0	36
vomiting	26	3	1	1	31
Selected AEs - placebo					
peripheral oedema	11	3	5	1	20
diarrhoea	13	4	2	0	19
vomiting	4	2	3	1	10

#Table displays all TTCW events by first occurrence.
**The first occurrence of three selected AEs likely to have an influence on TTCW is displayed.
All deaths are included in the TTCW events but not in the SAE events.

Nevertheless, in these 8 weeks all components of TTCW favour placebo. Hospitalisations for worsening of PAH were more observed in the imatinib group (16.5%) compared to 13.3% in the placebo group (Table E5). This seriously underscores the importance of the encountered AEs, which not only impact the tolerability of the medication, but also lead to hospitalisations. In a further analysis, the applicant has shown that the total number of hospitalisations was balanced between the treatment arms, further supporting that the reported hospitalisations relate to the management of the AE profile of imatinib. In addition, it is shown that the duration of hospitalisation was shorter in imatinib users, suggesting that these adverse treatment effects are somewhat more easily manageable than true worsening of PAH as seems to occur in placebo patients.

Table E5 Components of Clinical Worsening

Number of events	**Imatinib**		**Placebo**	
(Components of TTCW)	**N = 103**		**N = 98**	
All deaths	3	(2.9)	3	(3.1)
Hospitalization for worsening of PAH	**17**	**(16.5)**	13	(13.3)
Worsening of WHO Functional Class	**15**	**(14.6)**	11	(11.2)
15% reduction of 6MWD on two consecutive occasions	12	(11.7)	17	(17.3)
Both FC reduction and 6MWD-reduction	2	(1.9)	3	(3.1)

The lack of an improvement in TTCW is a serious issue, questioning the clinical relevance and more importantly questioning the safety of the treatment. This was communicated to the applicant during the pre-submission meeting. At least a trend of improvement would have been expected; on the contrary there is a trend that patients on placebo are doing better. Previous experience with measuring TTCW as in the PACES study (Simonneau et al., 2008) indicates that it was still possible to prevent clinical worsening within a 16 weeks study, when sildenafil was added on top of epoprostenol. There are some differences in the components of TTCW used between the studies, but for the common components death (n=7; 5.3% in the placebo vs. 0 in sildenafil) and hospitalisations due to PAH (8.4% on placebo vs. 6% on sildenafil) there was a clear benefit for adding sildenafil.

Results of the worsening in WHO (worse in the imatinib group, Table E5) are difficult to interpret, but seem also related to adverse treatment effects of imatinib that occur mainly in the first eight weeks of use.

Pulmonary haemodynamics were also investigated as a secondary endpoint (Table E6). In the ANCOVA analysis significant reduction in pulmonary vascular resistance PVR was observed in the imatinib group compared to the placebo group. The treatment difference was -379 dyn·s·cm^{-5} (95% CI: -502, -255; p<0.001) (Imatinib n=74 placebo n=80, subjects with a second RHC and successful measurement of PVR). Based on a baseline value for PVR in this population of 1192 dyn·s·cm^{-5}, this corresponds to a decrease of 32%.

Table E6 ANCOVA of change from baseline in cardiopulmonary haemodynamic parameters from right heart catheterization at end of study (Full analysis set).

		- Treatment -			- Treatment difference -			
Treatment	n	LS Mean	SE	Comparison	LS Mean	SE	95 % CI	p-value
Right atrial pressure (mmHg)								
Imatinib	73	-1.02	0.851	Imatinib - Placebo	-1.71	0.777	(-3.24, -0.17)	0.030
Placebo	81	0.68	0.855					
Mean pulmonary arterial pressure (mmHg)								
Imatinib	75	-3.54	1.585	Imatinib - Placebo	-5.18	1.437	(-8.02, -2.34)	<0.001
Placebo	82	1.63	1.586					
Mean pulmonary capillary wedge pressure (mmHg)								
Imatinib	74	0.92	0.693	Imatinib - Placebo	0.97	0.646	(-0.31, 2.25)	0.135
Placebo	80	-0.05	0.701					
Cardiac output (L/min)								
Imatinib	75	1.17	0.182	Imatinib - Placebo	0.88	0.157	(0.57, 1.19)	<0.001
Placebo	81	0.29	0.186					
Systemic vascular resistance (dynes.sec.cm^{-5})								
Imatinib	71	-467.84	78.577	Imatinib - Placebo	-379.75	74.052	(-526.21, -233.29)	<0.001
Placebo	76	-88.10	77.183					
Pulmonary vascular resistance (dynes.sec.cm^{-5})								
Imatinib	74	-366.47	67.673	Imatinib - Placebo	-378.60	62.355	(-501.88, -255.32)	<0.001
Placebo	80	12.12	68.963					
Pulmonary vascular resistance index (dynes.sec.cm^{-5}.m^{2})								
Imatinib	74	-622.16	102.031	Imatinib - Placebo	-608.64	93.824	(-794.14, -423.14)	<0.001
Placebo	80	-13.52	103.823					

A sensitivity analysis using a BOCF approach to impute missing data also showed a significant between-treatment difference for PVR at Week 24 (-266 dyn·s·cm^{-5} (95% CI: -367, -164; p<0.0001; N=103/98, all randomised).

So far in PAH studies submitted for regulatory approvals, the role of pulmonary haemodynamics is not well established. They are discerned as valid parameters to investigate the mechanism of action and in dose finding studies. However, they are not recognized as valid primary endpoints, mainly because of lack of direct robust correlation to survival. Only recently, their role has been accepted in paediatric PAH trials. One of the most studied parameters is PVR, which is thought to possibly predict survival. Right ventricular function may also be of prognostic importance and does not always correlate with PVR. Medicinal products significantly improving PVR and / or RV function may accordingly be useful. In the REVEAL registry, high PVR is shown to be predictive of mortality (Benza, 2010). In Sitbon's analysis (Sitbon et al., 2002), a PVR response of at least 30% was associated with better survival in WHO FC III-IV. In study A2301, a PVR response of at least 30% was achieved by 42/74 (56.8%) for imatinib and 16/80 (20.0%) for placebo [in those patients who completed the trial with a second RHC (Hazard Imatinib / Placebo 5.22; 95% CI: (2.54, 10.72); p < 0.0001)].

The applicant tried to clinically identify these responders, but the submitted analysis did not identify any specific characteristics which can determine the response to imatinib. A subgroup of sicker patients appears to respond better, but on the other hand there is also a subgroup of sick patients who can respond very unfavourably to imatinib: a higher incidence of deaths is reported in placebo patients who switched to imatinib in the extension study. The distinction between these 2 subgroups is not clear, which is critical for the benefit risk assessment of imatinib (LOI).

The changes in systemic vascular resistance SVR and PVR are of the same magnitude. The applicant argues that this is due to reduced sympathetic tone as a consequence of improved cardiac output. This theory cannot be currently verified due to lack of direct clinical data.

The subgroup analyses for PVR are largely concordant with the main analysis. (Figure E8-Figure E13)

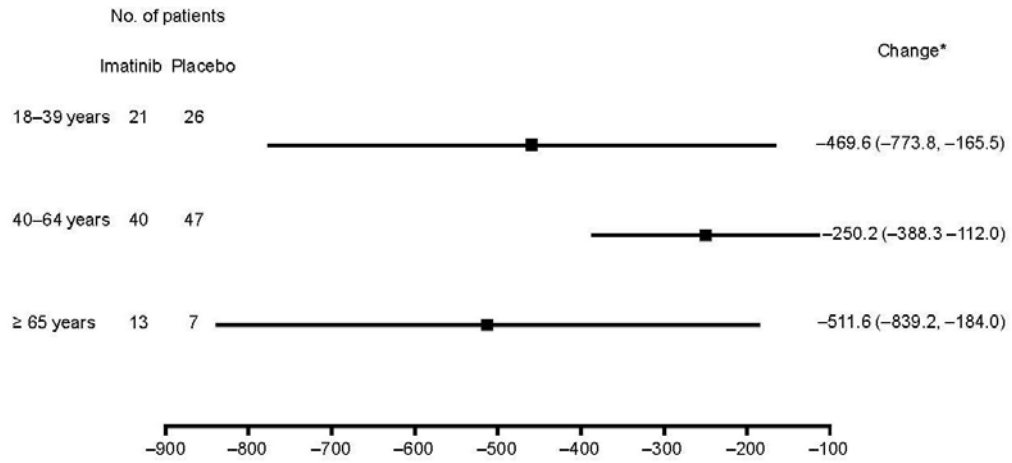


Figure E8 Between treatment differences in changes from baseline in PVR by age

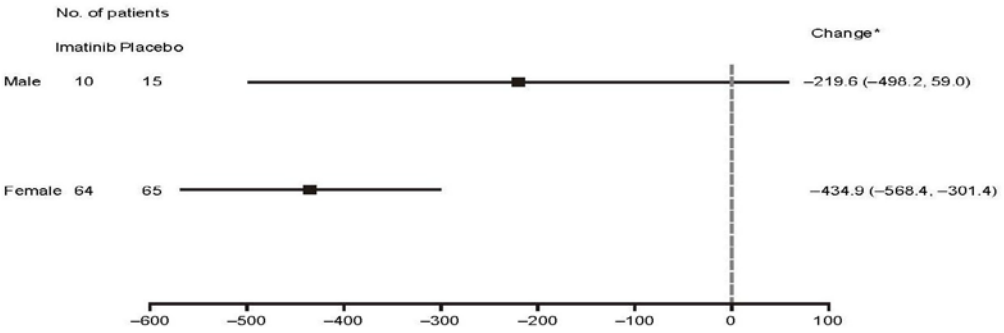


Figure E9 Between treatment differences in changes from baseline in PVR by gender

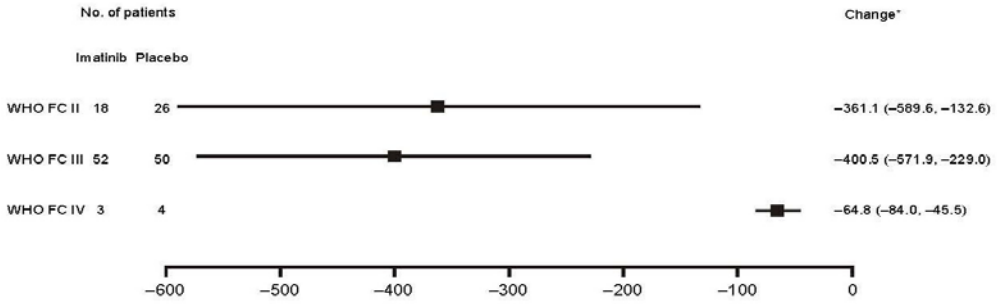


Figure E10 Between treatment differences in changes from baseline in PVR by WHO functional class

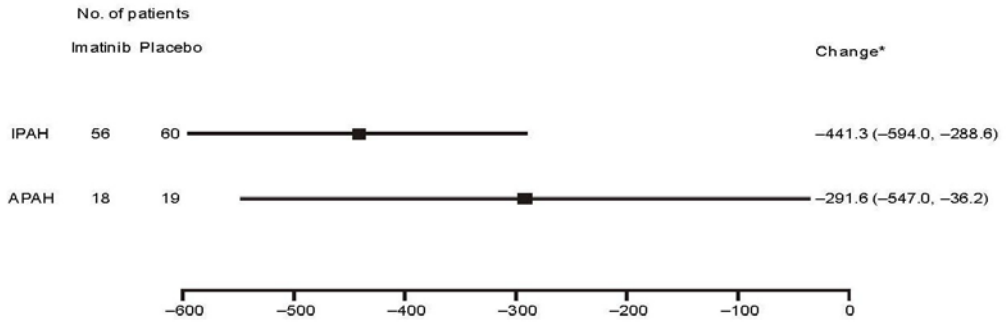


Figure E11 Between treatment differences in changes from baseline in PVR by type of PAH

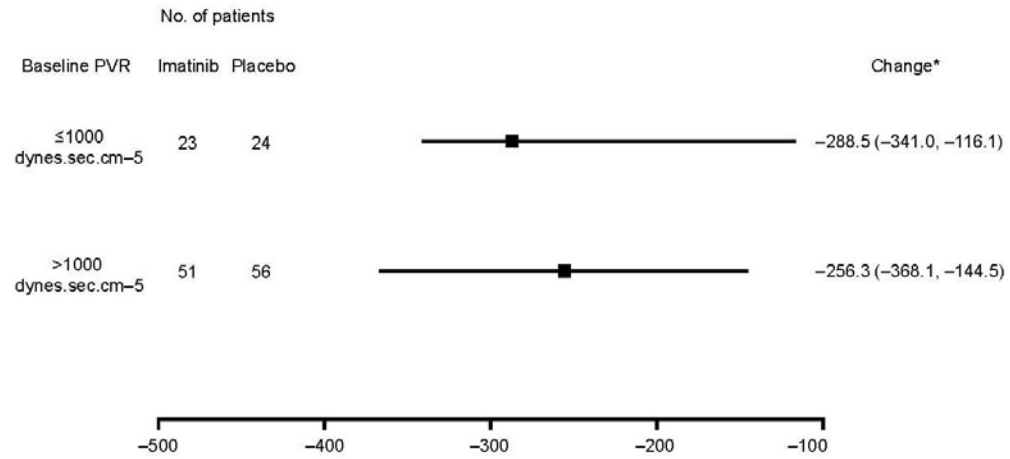


Figure E12 Between treatment differences in changes from baseline in PVR by baseline PVR

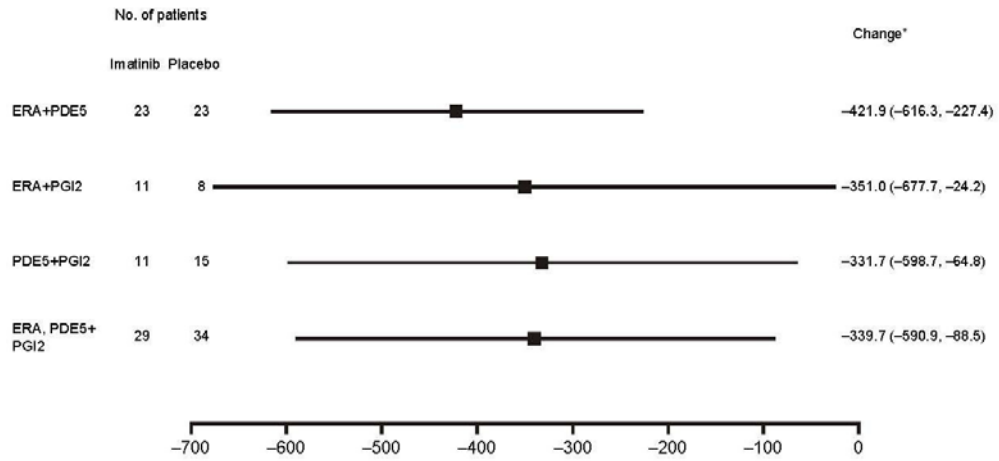


Figure E13 Between treatment differences in changes from baseline in PVR by background medication

WHO Functional class was not pre-defined as a separate endpoint, but was assessed as a component of TTCW (see above). Most subjects' WHO functional class did not change during the trial (164/200). These results are non-conclusive.

Health-related quality of life (***HRQOL***) using the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), measured in about half of the participants, did not show a relevant treatment advantage. The results are of limited value because of the limited numbers of participants.

An ***echo sub-study***, performed in about one-third of the participants, showed possible improvement in right ventricular function. However, as recognized by the applicant, the value of echo cardiology is still exploratory.

PK/PD Response and dose selection. Pre-planned analyses of 6MWD and PVR were performed by imatinib dose. A patient was defined as a long-term imatinib dose-escalator if he or she received the imatinib 400 mg QD dose for at least 77 days (50% of the planned 400 mg treatment duration) during the study (Figure E14).

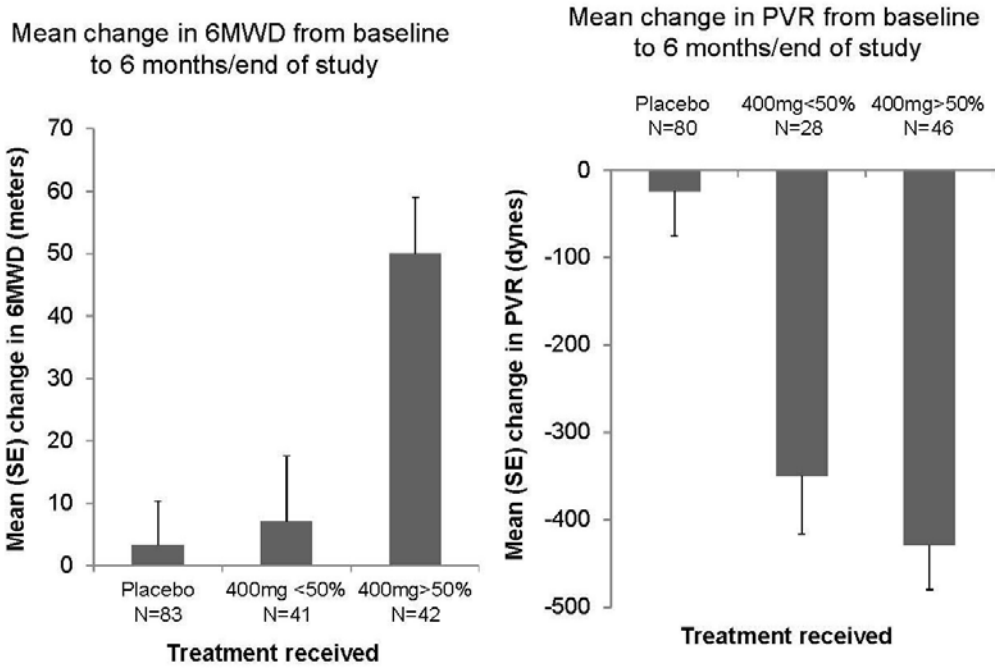


Figure E14 Change in 6MWT and PVR from baseline to end of study (LOCF) by length of exposure to 400 mg QD.

Patients who were administered imatinib 400 mg more than 50% of the time had better responses in terms of 6MWT compared to non-escalators (400 mg>50% : 59.2 ± 13.8 m, 400 mg<50%: 17.7 ± 11.7 m, placebo: 12.6 ± 11.9 m). Changes in PVR appear to be less sensitive to dose (400 mg > 50%: -455 dyn·s·cm 5, 400 mg<50%: -331 dyn·s·cm^{-5}, placebo: +19 dyn·s·cm^{-5}).

PK/PD relationships were examined to assess the relationship between exposure and efficacy in order to confirm the appropriateness of the selected dose. There was a trend for improved outcomes with higher exposure to imatinib**.**

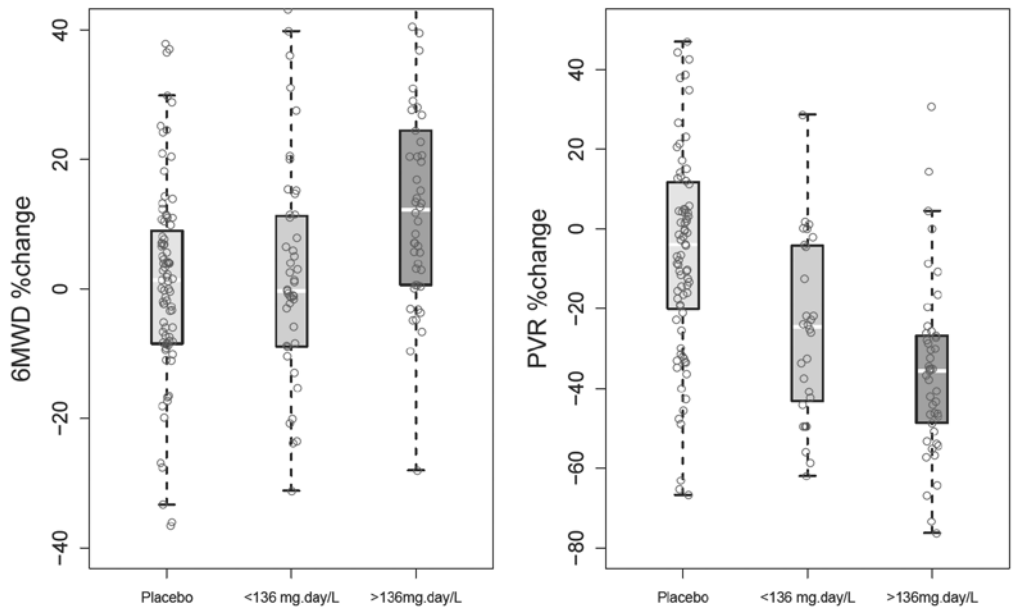


Figure E15 Change in 6MWD and PVR by cumulative exposure (Study A2301)

This analysis confirms that the full response in exercise tolerance (as measured by 6MWD) is only achieved with sufficient exposure, although a lower exposure appears sufficient for a haemodynamic response (Figure E15). It is currently concluded that the 200 mg dose is not therapeutically effective. The proposed SmPC recommends the 200 mg dose only temporarily in dose titration or (also temporarily) in case of adverse effects.

Supportive studies:

1. **E2203Ext**: Patients who completed the phase II core study were eligible for enrolment in the separate extension protocol [Study E2203Ext]. Initially these patients were offered compassionate use, but the Data Monitoring Committee recommended discontinuation of the compassionate use program and initiation of a formal extension study to ensure better safety reporting and monitoring. All patients continued in the extension at the last dose taken in the compassionate use period. Analysis of E2203Ext is severely hampered by the intermediate period of compassionate use, for which the data are much less detailed. The possible adverse effects of starting imatinib cannot be studied. Presented data of 6MWT (every 12 weeks) show that the change from baseline in 6MWD was about 50m and comparable to the change from baseline in 6MWD at end of core. The number of recruited patients is very few precluding any conclusions. The corresponding treatment duration is not clear, because of the period of compassionate use between core and extension study, but exceeds 2.5 years.

2. **A2301E1**: Patients who completed the core study could enrol in the extension, as could patients who withdrew early for non-safety reasons, if all study completion assessments were completed (no patients were enrolled using this latter criterion). The interim analysis of A2301E1 included data on 144 patients who completed the core study and were treated in the extension for a median of 275.5 days (range 6-575 days).

- **Participant flow**

The disposition of patients in the extension is summarized in Table E7. Patients who received placebo in the core study and had been switched to imatinib in the extension study experienced more discontinuations for AEs, death and for withdrawn consent than patients continuing on imatinib.

Table E7 Patient disposition in extension by core study treatment (A2301E1)

	Core imatinib (N=66) n (%)	Core placebo (N=78) n (%)
On-going in extension	53 (80.3)	43 (55.1)
Discontinued	13 (19.7)	35 (44.9)
For safety reasons		
Death	0	6 (7.7)
Adverse Event(s)	8 (12.1)	21 (26.9)
Abnormal laboratory value(s)	1 (1.5)	2 (2.6)
Abnormal test procedure result(s)	1 (1.5)	0
For insufficient efficacy	1 (1.5)	0
For administrative reasons (total)		
Subject withdrew consent	1 (1.5)	5 (6.4)
Subject's condition no longer requires study drug	1 (1.5)	1 (1.3)

- **Outcomes and estimation**

- **6MWD**

In the interim analysis, patients treated with imatinib in the phase III pivotal core study for a further 24 weeks maintained their increase in 6MWD. Patients who had been treated with placebo in the core and started imatinib showed improvements in 6MWD, as seen in Table E8 and Figure E16, but they did not reach the level of improvement seen in the patients who had taken imatinib in the core study. It seems there is an optimal starting point for imatinib. On one hand, this finding appears to be in line with data from long-term extension of a sildenafil trial (SUPER-2) showing that core placebo patients did not catch up to the core sildenafil patients (Rubin et al 2011). On the other hand, efficacy in terms of 6MWT is more evident in the more diseased patients (the higher the PVR, the better the results) further complicating the positioning of imatinib within the PAH medications.

Table E8 6MWD long-term in extension study (Study A2301E1)

	24 weeks (end of core)		+12 weeks (ext)		+24 weeks (ext)	
6MWD ±SD	imatinib N=61	placebo N=77	Core-imatinib N=58	Core-placebo N=57	Core imatinib N=54	Core placebo N=53
Change from core baseline (m)	43 ± 55	5 ± 63	49 ± 61	16 ± 65	45 ± 46	19 ± 72

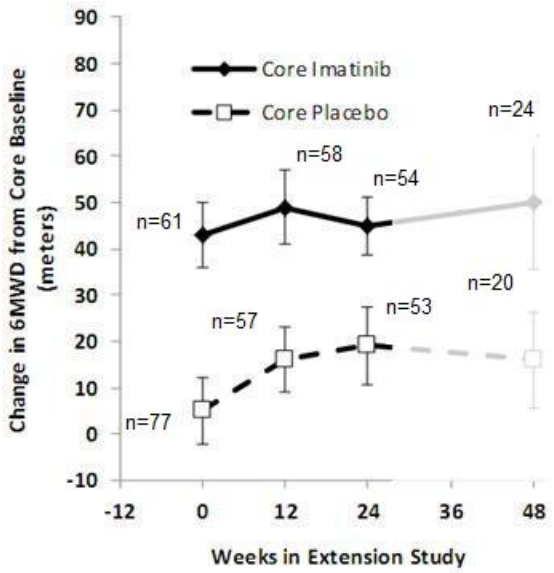


Figure E16 Change in 6MWD by core study treatment (Study A2301E1, i.a.) Only data as of Week 24 are complete on all patients. i.a. = interim analysis. Dark lines: complete data up to extension Week 24. Pale lines: partial data at later times

- **Time to clinical worsening**

Patients in the core imatinib group had slightly fewer events overall than patients in the core placebo group (Table E9).

Table E9 TTCW by core study treatment (Study A2301E1)

TTCW events	Core Imatinib N=66 n (%)	Core Placebo N=78 n (%)
all deaths	**0**	**6 (7.7)**
hospitalization for PAH (adjudicated)	18 (27.3)	15 (19.2)
worsened 6MWD (2 x ≥15% fall in 6MWD)	4 (6.1)	15 (19.2)
worsened WHO functional class	14 (21.2)	11 (14.1)
worsened WHO funct. class and 6MWD (same visit)	0	2 (2.6)
Total TTCW events	25 (37.9)	30 (38.5)

The Kaplan Meier analysis of TTCW (Figure E17) is difficult to interpret, because the analysis only includes the selection of subjects who remained in the core trial and could tolerate imatinib (or placebo). The start of the extension protocol shows a surge in TTCW events in the core placebo group. Importantly, this is driven by 6 cases of deaths in the core placebo group who switched to imatinib (discussed under safety). This is attributed by the applicant to worsening PAH during placebo treatment, but a deleterious effect of imatinib cannot be excluded. In a further analysis, no special characteristics were able to identify these patients. The applicant concluded that rapidly deteriorating patients, like the core placebo patients in the pivotal trial, should not be treated with imatinib. It seems that these patients are more vulnerable to the AEs caused by imatinib, but the underlying mechanism is not clear. This group and the definition of deterioration need to be further addressed (LOI).

The curve also shows no long term clinical advantage of imatinib treatment.

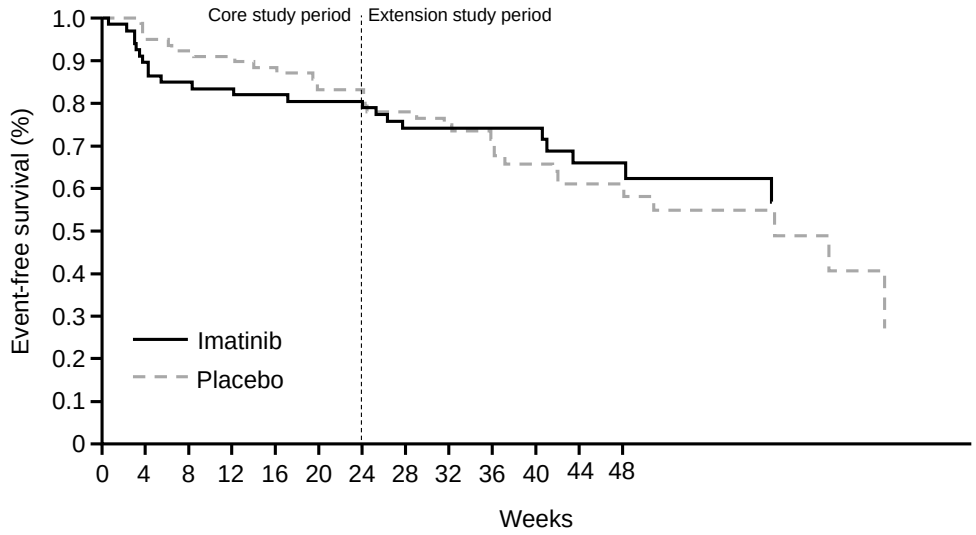


Figure E17 Kaplan-Meier plot of adjudicated TTCW events in core and extension study (Study A2301E1 i.a.)

WHO functional class. Overall, more patients were in WHO Class I and II after 48 weeks of imatinib treatment than at core baseline (Table E10). However, the extension trial was open and WHO assessment may have been biased.

Table E10 Changes in WHO Functional Class in core imatinib patients (Study A2301E1)

	WHO I	WHO Class II	WHO Class III	WHO Class IV
core baseline	1	14	41	3
at 48 weeks	4	21	30	4

Conclusions on clinical efficacy

The efficacy of imatinib in PAH is supported by a single pivotal trial and its extension. In the controlled study, administration of 400 mg QD was associated with significant improvements in the 6MWD and PVR in patients with PVR > 800 dyn·s·cm^{-5}. The clinical relevance of these changes is doubtful discussion in light of the results of the TTCW. Prevention of clinical worsening as defined by TTCW could not be shown and the trend even favoured placebo. This is especially evident in the first two months of therapy probably due to the associated AEs of imatinib. This is reflected in more hospitalisations and worsening WHO functional class. In the open-label extension, the improvement in 6MWD is maintained; however an improvement in TTCW was again not shown.

Clinical safety

This section presents relevant safety information for imatinib from the PAH program, based on the two placebo-controlled trials E2203 and A2301 and their on-going long term extensions with cut-off date, 11 Nov., 2011.

Imatinib has been used and studied in several other indications, creating a large safety database in the oncology setting. Generally, this prior exposure gives an adequate picture of the safety profile of imatinib. However, the clinical relevance of some of these identified adverse events AEs of imatinib may have a different impact in a cardiology indication, compared to an oncology indication.

Patient exposure

Relevant safety data for imatinib in PAH are retrieved from the two placebo-controlled trials E2203 and A2301 and their extensions. In study A2301, mean exposure for the recommended dose 400 mg QD for 89 patients was 93.8 ±65.3 days (Table S1).

Table S1 Overall exposure in study A2301

		Imatinib N=103	Placebo N=98
Overall exposure (days)	n	103	98
	Mean	137.2	155.8
	SD	64.15	42.98
	Median	169.0	169.0
	Min – Max	1 – 232	4 – 209
Exposure to 400 mg - days[@]	n	89	95
	Mean (SD)	93.8 (65.31)	141.8 (38.89)
	Median (range)	93.0 (2 – 198)	155.0 (9 – 195)
Exposure to 400 mg categories - days (%)	1– 7 days	8 (7.8)	0
	8 – 14 days	8 (7.8)	2 (2.0)
	15 – 28 days	7 (6.8)	2 (2.0)
	29 – 56 days	12 (11.7)	2 (2.0)
	57 – 84 days	7 (6.8)	4 (4.1)
	85 – 112 days	3 (2.9)	2 (2.0)
	113 – 140 days	9 (8.7)	7 (7.1)
	141 – 168 days	29 (28.2)	70 (71.4)
	> 168 days	6 (5.8)	6 (6.1)

The long term (1-year) exposure, achieved in E2203, A2301 and their extension studies, to 400 mg was only 51 patients. This number is rather limited in but a commitment to document further experience in a registry can address this issue (LOI).

Adverse events

Treatment with imatinib is associated with significant numbers of AEs. Most AEs are reported during the first 8 weeks of treatment. The most frequently reported AEs include abdominal complaints (nausea, vomiting, diarrhoea), fluid retention (peripheral oedema, face oedema, periorbital oedema), anaemia, hypokalaemia, muscle spasms and increased blood creatinine (Table S2). This profile is recognized from the non-PAH indications, however its impact on the benefit risk balance in the PAH indication could be different. Time course of AEs shows that the frequency of AEs decreases by time. To improve tolerability, patient education should focus on the management of these AEs, possibly by slow titration of the dose.

Table S2 AEs reported by ≥5% in the imatinib group compared with placebo (study A2301)

	Imatinib		Placebo	
	N=103	%	N=98	%
nausea	57	55,3	23	23,5
peripheral oedema	45	43,7	20	20,4
diarrhoea	36	35	19	19,4
vomiting	31	30,1	10	10,2
periorbital oedema	30	29,1	7	7,1
hypokalaemia	16	15,5	3	3,1
anaemia	14	13,6	3	3,1
face oedema	10	9,7	1	1
muscle spasms	10	9,7	2	2
increased blood creatinine	10	9,7	1	1
rash	9	8,7	2	2
alopecia	7	6,8	1	1
abdominal distension	9	8,7	3	3,1
dyspnoea	19	18,4	13	13,3

The proportion of patients with AEs that were suspected to be related to the study drug, based on investigator assessment, was 84.5% in the imatinib group and 37.8% in the placebo group. The most common suspected AEs overall were nausea (imatinib 44.7% vs. placebo 9.2%), peripheral oedema (imatinib 26.2% vs. placebo 7.1%), vomiting (imatinib 21.4% vs. placebo 2.0%), periorbital oedema (imatinib 18.4% vs. placebo 4.1%), diarrhoea (imatinib 17.5% vs. placebo 4.1%), headache (imatinib 12.6% vs. placebo 6.1%), and face oedema (imatinib 8.7% vs. placebo 1.0%).

Study E2203: AEs followed the same pattern, but nervous system disorders were reported more frequently (imatinib 17/28 = 60.7% vs. placebo 10/31=32.3%). The numbers of patients reporting headache were imatinib: 10/28 (35.7%) and placebo: 6/31 (19.4%).

Study A2301E1: The core placebo patients behaved similarly to the imatinib group in the core study (when first introduced to imatinib).

Serious adverse events and deaths

SAEs

The number of patients with SAEs in the controlled studies is shown by affected SOC and commonly occurring preferred term (≥2%) in Table S3. In Study A2301 more patients in the imatinib group than the placebo group had SAEs (43.7% vs. 29.6%). The SAEs reflected the known adverse effects of imatinib (e.g. anaemia, gastrointestinal disorders, and oedema), and the known cardiac complications of PAH (e.g. right ventricular failure).

Table S3 Patients with SAEs by SOC (all) and preferred term (>=2%) (Studies study A2301 and E2203)

	Study A2301		Study E2203	
	Imatinib N = 103 n (%)	**Placebo** N = 98 n (%)	**Imatinib** N = 28 n (%)	**Placebo** N = 31 n (%)
Patients with SAE(s)	45 (43.7%)	29 (29.6%)	12 (42.9%)	11 (35.5%)
Blood & lymphatic disorders	**10 (9.7)**	**1 (1.0)**	**0**	**0**
Anaemia	7 (6.8)	1 (1.0)	0	0
Cardiac disorders	**10 (9.7)**	**4 (4.1)**	**3 (10.7%)**	**4 (12.9%)**
Cardiac arrest	0	0	2 (7.1%)	1 (3.2%)
Right ventricular failure	2 (1.9)	2 (2.0)	1 (3.6%)	1 (3.2%)
Angina pectoris	2 (1.9)	0 (0.0)		
Atrial flutter	2 (1.9)	1 (1.0)		
Atrial fibrillation	1 (1.0)	1 (1.0)		
Cardiac failure	1 (1.0)	0 (0.0)		
Nodal arrhythmia	1 (1.0)	0 (0.0)		
Ear & labyrinth dis.	**0**	**0**	**1 (3.6%)**	**0**
Vertigo	0	0	1 (3.6%)	0
Gastrointestinal dis.	**9 (8.7)**	**3 (3.1)**	**1 (3.6%)**	**0**
Diarrhoea	3 (2.9)	2 (2.0)	0	0
Pancreatitis	1 (3.6%)	0	0	0
General dis. & admin. Site	**10 (9.7)**	**5 (5.1)**	**1 (3.6%)**	**1 (3.2%)**
Oedema peripheral	6 (5.8)	0	0	0
Non-cardiac chest pain	0	2 (2.0)	0	0
Catheter-related complication	0	0	1 (3.6%)	0
Hepatobiliary Disorders				
Liver disorder	0	0	1 (3.6%)	0
Infections & infestations	**7 (6.8)**	**12 (12.2)**	**0**	**0**
Device related infection	3 (2.9)	0	0	0
Pneumonia	1 (1.0)	2 (2.0)	0	0
Gastroenteritis	0	2 (2.0)	0	0
Investigations	**2 (1.9)**	**1 (1.0)**	**1 (3.6%)**	**0**
Liver function test abnormal	1 (3.6%)	0	0	0
Metabolism & nutrition disorders	**6 (5.8)**	**2 (2.0)**	**0**	**1 (3.2%)**
Fluid overload / Fluid retention	1 (1.0)	1 (1.0)	0	1 (3.2%)
Nervous system disorders	**8 (7.8)**	**5 (5.1)**	**2 (7.1%)**	**1 (3.2%)**
Presyncope	5 (4.9)	0	1 (3.6%)	0
Syncope	1 (1.0)	5 (5.1)	1 (3.6%)	0
Dizziness	1 (1.0)	0	1 (3.6%)	1 (3.2%)
Resp. thoracic & mediast.	**16 (15.5)**	**11 (11.2)**	**3 (10.7%)**	**5 (16.1%)**
Dyspnoea	6 (5.8)	2 (2.0)	0	2 (6.5%)
Pulmonary arterial hypertension	4 (3.9)	4 (4.1)	2 (7.1%)	3 (9.7%)
Pulmonary hypertension	2 (1.9)	4 (4.1)	2 (7.1%)	3 (9.7%)
Respiratory failure	1 (1.0)	2 (2.0)	0	0
Haemoptysis	0	2 (2.0)	1 (3.6%)	0
Vascular disorders	**0**	**0**	**1 (3.6%)**	**0**
Arterial rupture	0	0	1 (3.6%)	0

In the long term extension study A2301E1 45.8% of the patients experienced one or more SAEs, comparable to the proportion who experienced SAEs in the core imatinib group. The SAEs were most commonly related to the SOCs of respiratory, thoracic and mediastinal disorders (13.2%), infections and infestations (11.8%), cardiac disorders (9.7%), and nervous system disorders (9.0%). The number of SAEs suspected to be related to study medication (investigator assessment), were higher in the core placebo group, than in the core imatinib group (22 events and 15 events respectively). Suspected drug-related SAEs were reported in only one patient each, with the exceptions of PAH (2 patients in the core imatinib group and one patient in the core placebo group), right ventricular failure (2 patients in the core imatinib group), leukopenia (2 patients in the core placebo group), pyrexia (2 patients in the core placebo group), vomiting (1 patient in each core treatment group) and fluid retention (2 patients in the core placebo group). There was no evidence that the type, frequency or severity of SAEs increased with long-term exposure.

Deaths

There have been 33 deaths in all studies in the PAH development program, with 32 up to the 11-Nov-2011 cut-off date for the interim analysis of the extension studies E2203Ext and A2301E1. One of these 33 deaths occurred after the cut-off date (14-Nov-2011) but has also been included here for completeness.

In both controlled studies (study A2301 and E2203), 18 deaths were recorded which occurred during the study, 30-day follow up period, or more than 30 days after discontinuation, but within 24 weeks after treatment initiation, with comparable incidence in imatinib (n=8) and placebo groups (n=10) (Table S4). The cause of death, as reported by the investigators, was PAH related in the majority of cases, which is reassuring.

Table S4 Principal cause of death in imatinib development program.

	Age/Sex/ Race	Group	Preferred term for principal cause of death	Study Day	Discon-tinued Days	Last dose (mg)	Drug relation suspected/ Adjudication PAH
Study E2203 (study & 30 day follow up, or same duration if withdrew early)							
1	54/M/Ca	Imatinib	Pulmonary hypertension	132	1	400	no
2	33/F/Ca	Imatinib	Cardiac arrest	88		400	no
3	37/M/Ca	Imatinib	Pulmonary haemorrhage	50	1	400	no
4	47/F/Ca	Placebo	Cardiac tamponade	80	2		no
5	30/F/Ca	Placebo	Cardio-respiratory arrest	31	1		no
6	50/F/Ca	Placebo	Right ventricular failure	172			yes
7	44/F/Ca	Placebo	Pulmonary hypertension	41	15		no
8	44/F/Ca	Placebo	Cardiac arrest	174	30		no
Uncontrolled compassionate use (after E2203 core and before the extension)							
9	19/M/Ca	PI-imatinib	Right ventricular failure	419		unk	yes
Study E2203 Ext (after compassionate use period)							
10	73/M/Ca	PI-imatinib	Cardiac failure	1307	1	100	no
11	26/F/Ca	PI-imatinib	Cardiac failure	1389	1	300	no
Study A2301 (study & 30 day follow up, or same duration if withdrew							

early)							
12	57/M/Ca	Imatinib	Right ventricular failure	129		400	no / PAH
13	37/M/As	Imatinib	Sepsis	4	2	200	no / not PAH
14	59/M/Ca	Imatinib	Renal failure	16	29	400	yes / PAH
15	62/F/Ca	Placebo	Right ventricular failure	23	1		no / PAH
16	68/F/Ca	Placebo	Clostridial infection	28	4		yes / not PAH
17	66/F/Ca	Placebo	Study Indication (PAH)	107	22		no / PAH
Study A2301 (more than 30 days after discontinuation but within 24 weeks after treatment initiation)							
18	64/M/Ca	Imatinib	Study indication (PAH)	31	48	400	no / PAH
19	41/M/Ca	Imatinib	Cardiac failure	61	102	400	no / -
20	35/F/Ca	Placebo	Cardiac arrest	42	51		no / PAH
21	61/F/Ca	Placebo	Pulmonary hypertension	10	41		no / PAH
Study A2301E1 (directly after core study)							
22	51/F/Ca	PI-imatinib	Cardiac failure	60	6	400	no / PAH
23	77/F/Ca	PI-imatinib	Toxicity to various agents	25		400	yes / not PAH
24	36/F/Ca	PI-imatinib	Multi-organ failure	126	11	400	yes / PAH
25	57/F/Ca	PI-imatinib	Subdural hematoma, dyspnea	13	26	400	no / -
26	58/F/Ca	PI-imatinib	Cardiac arrest, Pseudomembranous colitis, E. coli bacteremia	139	5	400	no / PAH
27	61/F/Ca	PI-imatinib	Respiratory failure (Pneumonia)	338	17	200	no / not PAH
28	37/M/Ca	PI-imatinib	Device related sepsis	57		200	no / not PAH
29	36/F/Oth	PI-imatinib	Cerebrovascular accident	47	6	400	no / not PAH
30	52/F/Bl	PI-imatinib	Right ventricular failure	64	8	200	no / PAH
31	50/F/Ca	Imatinib	Right ventricular failure	256	80	200	no / not PAH
32	45M/Ca	imatinib	Cerebral infarction	335	12	400	no / not PAH
DDI Study QTI571A2102 extension							
33	73/M/Ca	Imatinib	Septic shock				no

Patients 13-18 had TTCW events in study A2301, but death was the (first) CW event only for Patients 13 and 16.

There were 14 deaths in the two long term studies until the interim cut-off date (E2203Ext, including the compassionate use phase and study A2301E1). Of these 14 deaths, 12 had been in the core placebo group and 2 had been in the core imatinib group.

With the day 120 responses, further clarifications regarding deaths were submitted. It was shown that there was no imbalance in deaths between treatment groups in the PAH clinical studies. The overall mortality, corrected for exposure days, shows no difference between imatinib- and placebo-treated patients. The deaths per patient year are similar between placebo and imatinib-treated patients in both

the 24-week controlled studies (imatinib 0.162 deaths/year, placebo 0.183 deaths/year). These numbers may be too optimistic because inclusion in the trial was restricted to 'stable' patients and imatinib treatment may have been interrupted shortly before death. In the long-term extension studies the death rate was 0.111 deaths/year (assessor's calculation, based on Table 24-9 in the Day 150 response assessment report). These patients had proven to be more or less stable during the core trial and about half of the patients had shown to tolerate imatinib. The rate of death among all patients exposed to imatinib was 0.122 per patient year.

This death rate is comparable with the rate observed in the REVEAL registry (Benza et al 2012), where the overall cohort has a death rate of 0.085/year (assessor's calculation based on 716 deaths, 2635 patients, mean follow-up 1155 days). The Reveal registry has a wider diagnostic inclusion and imatinib patients are more 'advanced' in their disease, so the difference is considered justified.

According to the applicant, all 9 core placebo patients who initiated imatinib in the phase III extension study (A2301E1) and died during or after discontinuing A2301E1 had deterioration in either 6MWD or worsening of PVR (6 of 9 patients who died had PVR >1400 $dyn \bullet s \bullet cm^{-5}$ at the end of the core study) during the placebo phase of the core study. Four of these deaths were adjudicated as worsening of cardiac function due to PAH, whereas the remainder were adjudicated as events unrelated to PAH (e.g. device-related sepsis, suspected diazepam toxicity, cerebral vascular accident post-transplantation, pneumonia and subdural haematoma). The causality of imatinib in these deaths cannot be robustly excluded, for example in the case of subdural haematoma. According to the applicant, in the controlled phase III study, patients who were enrolled were required to be stable on 2 or more PAH therapies prior to initiation of imatinib, whereas placebo patients who initiated imatinib in the extension study were not required to meet this criterion. The applicant attributes this fatal outcome to the instability of these patients, as there were no deaths in placebo patients who had stable 6MWD and PVR values during the 24-week core study. The applicant accordingly proposes to emphasize in the SmPC that only stable patients should be initiated imatinib. The feasibility of such proposed changes in the SmPC is doubtful.

Adverse events of Special Interest. Based on the information available from Glivec, the applicant paid special attention to certain "potential and identified risks" in study A2301.

1. Cardiotoxicity. The applicant presented available safety data to discuss the cardiotoxic potential of imatinib in the oncology area. Additionally, they submitted a literature review addressing the same issue. Based on the company's sources, the cardiotoxic potential of imatinib in non-PAH indication lies is in the range of 0.04-0.5%. The SmPC of Glivec already includes a warning for patients with cardiac disease recommending close monitoring (section 4.4). The following AEs are mentioned in section 4.8 as **uncommon**: palpitations, tachycardia, cardiac failure congestive, pulmonary oedema and **rare**: arrhythmia, atrial fibrillation, cardiac arrest, myocardial infarction, angina pectoris, pericardial effusion.

In the current PAH program, two SMQs (cardiac failure and cardiomyopathy) were used to evaluate cases of potential cardiotoxicity among patients who participated in study A2301 and its extension study A2301E1. In study A2301, 101 patients had AEs captured by these two SMQs. Of these patients, 45 in the imatinib group and 20 in the placebo group had **peripheral oedema**, a very common ADR of imatinib and also a nonspecific symptom of right heart failure. The next most common preferred term in this SMQ was dyspnoea, reported in 19 patients treated with imatinib (6 serious cases) and 13 treated with placebo (2 serious cases). Of the 6 serious events in the imatinib group, 5 occurred in the setting of other adverse events that may have contributed to dyspnoea including fluid retention, pleural effusion, the patient also discontinued), tricuspid regurgitation, bleeding and anaemia (patient [PID A2301-0533-00001]). For 3 additional patients, dyspnoea was listed as a reason for study discontinuation.

Other terms in the cardiac failure SMQ include **right heart failure** (imatinib=3 vs. placebo=3) **syncope** (imatinib=1 vs. placebo=5) and **oedema** (imatinib=1 vs. placebo=3). Two patients in the imatinib-treated group reported **cardiac failure** (not otherwise specified) and 2 patients in the placebo group reported cardiac failure, cardiomegaly or ventricular dysfunction. One of the events in the imatinib group was serious and required hospitalization. No patient discontinued because of cardiac failure. One 35 year old female treated with imatinib was hospitalized on day 36 for cardiac failure, not otherwise specified, and treated with diuretics. Her cardiac output was 2.0 L/min at baseline and increased 2.6 L/min at her last study visit.

The applicant has adequately reviewed the data on cardiotoxicity of imatinib and possible consequences for this application. The problem is complicated as the adverse event profile of imatinib includes fluid retention and oedema; both are also non-specific signs of heart failure. Also, it is likely that patients with prior cardiac disease (such as PAH patients) would have a higher risk of developing cardiac damage. The review (including a report of written by external experts) concludes that the data do not point to an increased incidence of adverse cardiovascular signals in the oncology or PAH clinical development programs. While the possibility of sporadic effects of imatinib on cardiac function is difficult to exclude, the experience in the imatinib-PAH clinical program combined with the oncology experience suggest that cardiotoxicity events would be uncommon (possibly 1%). The applicant has committed to careful follow-up of patients in the extension studies, thorough cardiac examinations and submission of data.

Although the right and left ventricular function are preserved (or could even be improved) in patients using imatinib, it seems that imatinib's AE profile (e.g fluid retention and vomiting) is not well tolerated in cardially compromised patients like in PAH, with sometimes fatal outcome. This is not solved (**LOI**).

Pre-clinical data show that short-term treatment of rats with imatinib demonstrated an increase in heart weight and myocardial hypertrophy, but not at clinically relevant concentrations (3-4 µM for a dose of 400 mg/day) (Wolf et al 2010). As a result of its pharmacology, imatinib may reduce the collagen and fibronectin content in the vessel wall with also a reduction in smooth muscle cells. This may be beneficial in diseased pulmonary vessels, but could adversely affect the vessels' resistance to dilatation or rupture. This issue remains unaddressed and should be further clarified (**OC**).

2. Hepatotoxicity is an identified risk with imatinib use in the oncology indications. As stated in the SmPC (section 4.4) of Glivec: "Cases of liver injury, including hepatic failure and hepatic necrosis, have been observed with imatinib." In the pivotal study A2301, the frequencies of hepatotoxic events were comparable between the placebo (4.1%) and imatinib arms (2.9%), which can be falsely reassuring. The reported cases, eDISH analysis and the literature search conducted by the Applicant do not raise a signal of hepatotoxicity with imatinib use in PAH, based on the current limited database. Based on the imatinib profile, as known from other indications, hepatotoxicity cannot be excluded. This issue should be followed up in the RMP.

Considering that one of the major medicinal products used for the management of PAH, bosentan is associated with hepatic toxicity, the benefits of adding a product with another hepatotoxic potential should clearly outweigh this additive risk. The need to regularly monitor live functions, especially when imatinib is co-administered with bosentan is currently emphasized in the SmPC.

3. Bleeding, especially subdural haematoma (SDH). Bleedings are frequent in PAH, both as a result of the disease and the usual treatment with anticoagulants. Moreover, thrombocytopenia is a very common ADR for imatinib (in PAH study QTI771A2301 thrombocytopenia SMQ was reported in 8 patients receiving imatinib (7.9%), 3 of them with <50 x 109/L).

The overall number of imatinib patients who experienced bleeding events in A2301 was slightly higher 21/103 (20%) than that in placebo patients 16/98 (16%). There were also 6 SAEs for bleeding in the

imatinib group and 3 in the placebo group. These figures, especially for imatinib, are on the higher end of the range described above for PAH patients. Most of the bleeding events occurred in conjunction with anticoagulants and non-steroidal anti-inflammatory drugs (NSAIDs); however, in the majority of cases the INRs were not elevated. A mechanism for a possible bleeding tendency with imatinib is not clear. Preclinical data (Burton 2011) suggest that imatinib may restore endothelial function in PAH patients, but no effects on bleedings are discussed.

Nine cases of CNS haemorrhage were observed in the development program of imatinib for PAH; all in the imatinib arm and none on placebo (Table S5). Three additional cases were spontaneously reported during imatinib use for the management of PAH.

Table S5 Patients with subdural hematoma events in PAH studies A2301, A2301E1 and E2203

Patient identifier (PID) Age/ Sex/Race	Group/ Last known imatinib dosage (mg)	Preferred term for Subdural hematoma event	Study days/ days after last dose	Comments
Uncontrolled compassionate use (after STI571E2203 core and before the extension)				
[E2203ext-0003-05301] 62/F/Ca	Imatinib/ 400	**Subdural hematoma @**	Approx. 300 (including treatment in STI571E2203)	Recovered but had residual dysesthesia of the right lower arm. The patient underwent a surgical procedure and the subdural hematoma was evacuated. Patient is still active in the open-label extension phase and has received imatinib for more than 5 years.
Study QTI571A2301				
[A2301-0017-00002] 47/F/Oth	Imatinib/ 400	**Subdural hemorrhage**	15/3	Recovered. Patient did not have any residual neurological deficits and did not require surgical intervention. Subdural hematoma was associated with head trauma and an overdose of phenprocoumon.
[A2301-0524-00003] 46/F/Ca	Imatinib/ 400	**Subdural hematoma**	100	Subdural hematoma was associated with head trauma and did not require surgical intervention. The patient recovered, did not have any residual neurological deficits and completed participation in the core study.
Study QTI571A2301E1				
[A2301E1-0028-00001] 48/F/Ca	Imatinib/ 400	**Cerebral hemorrhage**	67 in ext.	The patient was discontinued from the study. Subdural hematoma due to abnormal displacement of Groshong catheter. The patient had a craniotomy and the subdural hematoma was evacuated. The patient recovered and did not have any residual neurological deficits. INR was 4.2 at the time of event.
[A2301E1-0069-00003] 57/F/Ca	Imatinib/ 400 prior to discount.	**Subdural hematoma #**	29 in ext. /16	The patient had a craniotomy and the subdural hematoma was evacuated. The patient died of subdural hematoma approx. 3 weeks after discovery of hematoma which was 16 days after imatinib discontinued. The patient was also receiving intravenous iloprost when the event occurred.
[A2301E1-0076-00002] 65/F/Ca	Imatinib/ 200	**Cerebral hemorrhage***	43 in ext.	The patient was discontinued from the study. Subdural hematoma occurred 14 days after two β-lactam antibiotics were started. The event resolved without residual neurologic effects and surgical intervention was not required.

Table S5 (continued)

[A2301E1-0022-00003] 58/F/Ca	Imatinib/ 400 prior to discount.	**Acute subdural hematoma #**	74 in ext. /1	The patient had been discontinued from the study one day before the subdural hematoma. The patient had a craniotomy and the subdural hematoma was evacuated. The patient had a history of chronic subdural hematoma. The patient recovered with sequelae (vertigo).
[A2301E1-0051-00002] 45/M/Ca	Imatinib/ 400 prior to discount.	**Subdural hematoma**	335 in ext.	The patient recovered from the subdural hematoma. The patient had a craniotomy and the subdural hematoma was evacuated. Subdural hematoma occurred in conjunction with newly diagnosed AML and thrombocytopenia. Patient died approx. 12 days after onset of subdural hematoma, due to cerebral infarction.
A2301E1-0017-00007 55/M/Ca **	Imatinib/ 100 mg	**Subdural hematoma**	377 in ext.	The patient was on phenprocoumon. Neurological examination within 24 hours of the event was normal. Treatment with imatinib was not discontinued due to the event.

The incidence of CNS bleedings in non-PAH indications is 1.1%. It is not clear why the incidence should be much higher in this indication; this cannot be attributed to the underlying disease as the placebo group did not encounter CNS haemorrhages. The patients who had CNS haemorrhages on imatinib were receiving systemic anticoagulation, but in most cases (where documented) the INR was below the target value for systemic anticoagulation. It can be agreed with the applicant that the narratives of the patients do not point to specific risk factors. It is probable that in each case, a different set of risks interplayed resulting in bleeding; however the alarming observation still stands. The use of VKA alone cannot explain the differences in frequency of SDH between the imatinib and placebo groups. Possible other mechanisms include interactions with other PAH medications, e.g prostanoids, imatinib-induced thrombocytopenia, a changed composition of the vessel wall and dura / dural cell border (less collagen and / or fibronectin) as a result of the pharmacology of imatinib (PDGF inhibition) and the possibility of endothelial damage as a result of VEGF inhibition. These possible mechanisms should be addressed (**LOI**).

The reported exposure rate is 38 subdural events per 1000 patients-year (9 events/ 211 patient years). Based on a review from studies conducted in patients with PAH receiving sildenafil + prostacyclin + anticoagulation therapy, the incidence of subdural haematomas in PAH is estimated to be around 1.5 patients/1000 years (ERS abstract 85632 - Pr Galie) and by the applicant (based on insurance claims databases) between 0.27 and 3.4 patients/1000 years; much lower than currently reported in the imatinib program..

The applicant proposes to include the following warning in section 4.4: *"In PAH patients, the risk of subdural haematoma is increased in patients taking imatinib and vitamin K antagonists. In clinical studies of Ruvise in the treatment of PAH (n=241), subdural haematomas were observed in 9 patients, all of whom were receiving vitamin K antagonists and had other contributing factors. Therefore in PAH patients treated with Ruvise, concomitant administration with vitamin K antagonists is not recommended. Treatment with Ruvise is not recommended in patients with a history of intracranial haemorrhage, including subdural haematoma, or history of elevated intracranial pressure. Patients who experience head trauma or have unexplained neurological symptoms while taking Ruvise should be evaluated for subdural haematoma."*

The warning against concomitant use of imatinib and VKA in PAH patients as proposed by the applicant could partly solve the issues related to bleedings and especially SDHs. As most PAH patients (60%) are prescribed VKA, the recommendation is not practical. Prescribers do not have data to weigh the relative benefits and risks of imatinib vs. VKA. In addition, the advice may be seen as an invitation to

switch over to novel anticoagulants, of which the benefits in PAH have not been investigated. Lastly, the possibility of a pharmacodynamic interaction of imatinib with the other PAH medications e.g. prostanoids, PDE5 and ERAs to increase bleeding risk cannot be excluded (LOI).

4. Oedema and fluid retention are very common (71%) AEs of imatinib in non-PAH indications. In the pivotal study, the rate was 66% which is in line with the known profile of imatinib, but much higher than that of placebo group (34.7%). Most of these events (peripheral oedema, periorbital oedema, face oedema) are mild or moderate and possibly transient, but the 8 SAEs were all recorded on imatinib. Serious and severe cases in other categories (e.g. pleural and pericardial effusions) were comparable in the imatinib and placebo groups of study A2301 and were mostly associated with worsening PAH or right sided heart failure.

An adequate warning regarding intravascular volume is currently stated in section 4.4, and the relevant AEs are mentioned in section 4.8 in the SmPC. It can be agreed with the applicant that these AEs are mostly transient as indicated by the declining rate in the imatinib group in the extension study. However, considering the current target population, AEs relating to fluid retention further complicate the clinical picture. These AEs may lead to or indicate disease progression, they can be an AE of other PAH medications (bosentan), or attributed to imatinib. The possibility that these AEs are poorly tolerated by PAH patients resulting sometimes in fatal outcomes remains. This should be taken further with the overall B/R assessment.

5. Acute renal impairment. In non-PAH indications, acute renal failure was observed in 2% of patients who received imatinib and in 2.4% of patients with oedema and fluid retention who used imatinib. Acute renal failure is listed as an uncommon AE in section 4.8 of the SmPC of Glivec. Also increased blood creatinine is listed as an uncommon AE.

An imbalance in renal events occurred in study A2301 between treatment groups, mainly driven by the reported laboratory findings (“blood creatinine increased”). This can be explained by a direct effect of imatinib on renal creatinine excretion. This is currently stated as an AE in section 4.8. Still five renal events were marked serious in the imatinib groups of study A2301 and study A2301E1, versus only 1 in the placebo group. The combination of increased renal risk in a patient with a compromised cardiac function could be dangerous.

6. Myelosuppression. Serious events of erythropenia (11; 9 requiring transfusion), leucopenia (6; 4 requiring intervention) and thrombocytopenia (2; 1 died) were reported in the imatinib arm in study A2301 and its extension compared to 2 cases (both requiring transfusion) in the placebo arm.

Anaemia events may be associated with myelosuppression, which is an identified risk of imatinib. But they can also be associated with bleeding events, that might be more frequent than in oncology, because anticoagulants are in widespread use in PAH (in study A2301: 66% [A2301 CSR table 14.1-4.11]). Moreover, in patients with compromised cardiac function, the tolerance for anaemia may be lower than in CML patients. Finally, a blood transfusion may add to the fluid overload that is already present in these patients, because of PAH and medications for PAH.

Laboratory findings

Haematology. Haemoglobin is consistently lower in imatinib users compared to placebo and more exceptional values occur (see also myelosuppression). Low exceptional values also occur for WBC. Somewhat surprisingly, results for platelets are not remarkable. INR regulation during imatinib use is not problematic. During the extension study A2301E1, a comparable decrease in values is observed with the core placebo patients who started imatinib, and there is less variability in the core imatinib group which is reassuring. In the proposed SmPC, dose reductions or treatment interruptions are recommended in cases of severe neutropenia or thrombocytopenia. As the efficacy of 200 mg is

questioned, only treatment interruptions would be acceptable. This is currently implemented in the SmPC.

Clinical Chemistry. ***Creatinine*** is consistently higher in imatinib users compared to placebo starting immediately after initiation of therapy. This is an identified risk and a warning already appears in the SmPC of Glivec as well as that proposed for Ruvise saying "Mild increases in serum creatinine are commonly observed in PAH patients treated with Ruvise. Renal function should be measured at initiation of Ruvise therapy and monitored periodically, including prior to dose escalation." However, considering that also the risk of acute renal impairment exists with imatinib, the applicant currently included recommendations regarding the expected increases in creatinine.

Creatine kinase was consistently higher in imatinib users (within normal range). In the SmPC of Glivec, AEs related to muscle pain are listed as very common, whereas rhabdomyolysis is listed as rare. In the proposed SmPC of Ruvise, muscle spasm is listed as common in section 4.8. There is no warning for this risk in section 4.4; this should be implemented, together with a recommendation to measure creatine kinase if myopathy is suspected (SmPC). It is observed that ***bilirubin*** was consistently lower in imatinib users. Although not alarming with respect to safety, more understanding of this finding is required in the light of the proposed mechanism of action of imatinib (**OC**).

Vital signs. Blood pressures were different between groups at baseline, but the mixed ANCOVA model included baseline value and corrected for this. Diastolic blood pressure was lower in the imatinib-treated group in A2301 (LS Mean treatment effect 3.58 ± 1.45 mmHg; p = 0.015). Although this does not raise major concerns, it would suggest a vasodilatory effect of imatinib. The Applicant speculatively attributes this to a reduced sympathetic tone, caused by the increased cardiac output, which cannot be further confirmed currently.

Syncope is a documented ADR of imatinib, with frequency classified as uncommon (0.1% - 1%) in the SmPC. AEs of (pre)syncope occurred 11 times in study A2301, of which 6 in the imatinib group. The risk of severe and serious (pre)syncope is slightly increased in imatinib-using PAH patients; severe presyncope was reported for 4 imatinib patients and no placebo patients. From the case narratives, there was no clear signal that presyncope or syncope are aggravated with imatinib use in PAH.

Based on data about Glivec and systematic analysis of ECGs in study A2301, two cases of discontinuations due to **QT prolongation** were identified. It can be agreed with the applicant that a causal role of imatinib is not probable in these cases. However, QT prolongation has been described with other tyrosine kinase inhibitors (Kim et al. Haematologica 2012; 97: 883-99). The applicant should address this concern in the RMP (**OC**).

Safety in special populations

The effect of **renal and hepatic impairment** on imatinib plasma concentrations was determined in clinical pharmacology studies in non-PAH patients. For both conditions, AUC and Cmax values were approximately 1.5-2-fold that of the normal group at steady-state.

Exclusion criteria affected potential participation of patients with hepatic and renal impairment in the trials for PAH, this should be reflected in the SmPC. In addition, due to lack of systematic data (on encephalopathy or ascites) it was not possible to retrospectively determine a grading for hepatic impairment and analysis of the AE profile with respect to Child-Pugh classification was not possible.

Of the subjects in A2301, the numbers for normal, mild, moderate and severe renal function / impairment were 58, 113, 28 and 2 respectively. As patients with mild renal impairment constitute the largest group, the overall AE displays are mainly determined by this group. With decreasing renal function, no change in severity or frequency of AEs was observed in either imatinib or placebo groups. Only for headache a trend was observed for an increase in reporting rate with decrease in renal

function, which was comparable between imatinib and placebo treatment groups. For peripheral oedema and dyspnoea in the imatinib group, a higher proportion of moderate and severe AEs were reported with decrease in renal function, which was not seen in the placebo group.

The approved labelling of Glivec in the oncology application advises the lower end of the normal dosing range, with downward dose adjustment in case of tolerability issues.

A specific dose recommendation for hepatic impairment cannot be made, but the patients excluded from the PAH clinical trials should be mentioned in the SmPC (LOI). In the Glivec label, no dose adaptation is required, which can be acceptable in this indication as well.

Most PAH patients in the pivotal trial had mild renal impairment. In general, the AE profile of patients with different degrees of renal impairment appear to follow that of 'normal" patients, with the patients on imatinib showing a higher frequency of AEs compared to placebo. The sensitivity of patients for imatinib's fluid retention increases with declining renal function and this is intuitively acceptable. In line with the Glivec label, no dose adaptation is required.

Lung transplants. The possibility of surgical complications in imatinib patients undergoing lung transplantation is a point of discussion. Based on the limited experience, the applicant did not identify any surgical complications in the 8 patients who have undergone lung transplantation. This is reassuring. This issue should be further followed up.

Two patients who were treated with imatinib before their lung transplantation experienced SAEs. One patient had a cerebrovascular accident 5 days after withdrawal of imatinib. The relationship of imatinib use to cerebrovascular accidents is addressed in Question 25. One patient had complications of lung transplantation, including a large haemothorax, four months after transplantation and discontinuation of imatinib. Because of the time window involved a causal relationship to imatinib use is unlikely in this second case.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Imatinib may increase plasma concentration of other CYP3A4 metabolised drugs (e.g. calcium channel blockers, statins, etc.). Imatinib also inhibits CYP2C9 and CYP2C19 activity in vitro. PT prolongation was observed following co-administration with warfarin, but no relevant changes in the INR were observed in the pivotal trial. Concentrations of bosentan and sildenafil (both CYP3A4 substrates) are increased, on average, by 51% and 64% respectively in the presence of imatinib. Co-administration of imatinib, bosentan and sildenafil increases an average of 132% bosentan levels (95% CI = 46, 369%) with the subsequent increase of toxicity. These PK interactions are mentioned in SmPC section 4.5. Analysis of AEs by background therapy suggests that the triple combination of ERA, PDE5 and imatinib may be associated with an increased risk of peripheral oedema (50% vs. 22%). This may occur especially in the first 2 months of imatinib therapy. According to the applicant's analysis, there was no evidence of an increase in liver enzyme levels and no cases of hepatotoxicity were identified in patients concomitantly treated with bosentan and imatinib. However, the potentially increased risk of hepatotoxicity (with the co-administration of these drugs) should be included in the SmPC (see SmPC assessment).

Mucosal irritation and damage in the gastro-intestinal tract are caused by both local and systemic effects. The systemic effects may be related to the pharmacological activity of the compound (c-Kit inhibition), which plays a role in GI motility. In A2301 and A2301E1, diarrhoea persisted for several weeks in many patients and nausea frequently persisted for most of the study. It remains unclear if

and to what extent emesis and diarrhoea influence the PK and efficacy of concomitant medication. A2301 was not designed to address this issue. However, by the design of the population PK analysis used to describe the PK interaction in A2301, this is accounted for.

Discontinuation due to AES

Discontinuation due to AEs was more frequent with imatinib (27.2%) than with placebo group (9.2%). The reasons for discontinuation cover a broad range of the previously mentioned AEs (Table S6). The discontinuation rate in both the imatinib (33%) and the placebo arm (18%) in the pivotal trial were much higher than that reported in most of the other PAH studies, indicating a different patient population and baseline risk. The discontinuation rate in the imatinib arm is similar to those seen in trials of tyrosine kinase inhibitors in pulmonary fibrosis (30%).The applicant proposes to address these AEs and discontinuations through an educational program, which is detailed in the RMP.

- **Table S6 Adverse events leading to permanent discontinuation of study drug considered suspected to be related to study medication – n (%) of patients (Safety set) in A2301**

Preferred term	Imatinib N=103 n (%)	Placebo N=98 n (%)
Patients with any AE (irrespective of causality) leading to permanent discontinuation of study drug	28 (27.2)	9 (9.2)
AEs suspected to be related to study medication		
Edema peripheral	3 (2.9)	0
Electrocardiogram QT prolonged	2 (1.9)	0
Coagulopathy	1 (1.0)	0
Neutropenia	1 (1.0)	0
Thrombocytopenia	1 (1.0)	0
Periorbital edema	1 (1.0)	0
Diarrhea	1 (1.0)	0
Nausea	1 (1.0)	0
Vomiting	1 (1.0)	1 (1.0)
Pyrexia	1 (1.0)	0
Jaundice	1 (1.0)	0
Blood creatinine increased	1 (1.0)	0
International normalised ratio increased	1 (1.0)	0
Platelet count decreased	1 (1.0)	0
Presyncope	1 (1.0)	0
Renal failure acute	1 (1.0)	0
Dyspnea	1 (1.0)	0
Pleural effusion	1 (1.0)	1 (1.0)
Pneumonitis	1 (1.0)	0
Pulmonary veno-occlusive disease	1 (1.0)	0
Rash	1 (1.0)	0
Anemia	0	1 (1.0)
Right ventricular failure	0	1 (1.0)
Edema	0	1 (1.0)
Clostridial infection	0	1 (1.0)

Conclusions on clinical safety

Imatinib use is associated with an identified risk for significant adverse events namely: GI disorders, fluid retention, myelosuppression, liver and kidney impairment. These AEs appear to be tolerated in the context of an oncology indication. However, the clinical implications of these AEs in a cardiology setting may be seriously different. Adverse events like vomiting and fluid retention can impact the compromised haemodynamic state in PAH patients leading to hospitalizations. A higher risk of bleeding and anaemia could further aggravate the cardiac condition. It is not clear of better AE management, after an educational program or through experience with imatinib in PAH patients, will effectively mitigate these risks.

Pharmacovigilance system

There were no concerns regarding the pharmacovigilance system. The applicant has provided documents that set out a detailed description of the system of pharmacovigilance for Novartis version 11 dated 22 December 2011. The Rapporteur considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk management plan

The applicant submitted responses to the questions regarding the risk management plan and submitted an updated version of the risk management plan version 5, dated 2 October 2012.

The safety profile of imatinib has been quite established due to the experience in the oncology indication, and most risks of oncology are also safety concerns for the PAH indication. Nevertheless, the implications of the risks of imatinib in PAH patients are different than in oncology patients. Anemia is related with myelosuppression and this may be tolerated less in patients with compromised cardiac function than in oncology patients. Moreover, a blood transfusion may contribute to the fluid overload that is a risk in the PAH patients, because of compromised myocardial function and the cardiovascular medication given for PAH. It is likely that the patients with prior cardiac disease (such as PAH patients) have a higher risk of developing cardiac damage as compared to oncology patients. At the present time, this risk cannot be excluded. This may negatively affect the clinical course of the disease and will necessitate continuous careful monitoring of such events.

The incidence of CNS bleedings is considerably higher in the PAH indication (4.8%) as compared to the oncology-indications (1.1%). Patients who experience CNS or GI hemorrhage may require emergency hospitalization and treatment and the events can be life-threatening. The reason is unknown and warrants further discussion. Altough the available data do not show elevated liver enzymes during combined use of bosentan and imatinib, both drugs are known to cause hepatic events. Furthermore, when the drugs are co-administered their plasma level increases. The interaction between bosentan and imatinib is covered in the RMP as potential risk and hepatotoxicity is included as important identified risk in the RMP.

Important identified risks in PAH patients are: “edema and fluid retention,” “myelosuppression,” “CNS and GI haemorrhages,” “hepatotoxicity,” “renal failure” and “cardiac failure”. The applicant added “low tolerability” as important identified risk as requested since the overall tolerability in the clinical trials was low, with a drop-out rate of 30%. Frequently reported events headache, dyspnea, nausea,

vomiting, peripheral edema, and periorbital edema especially during the first 8 weeks of treatment led to discontinuation. Based on non-clinical data and studies in oncology patients is “Secondary malignancies” included as potential risk in the RMP as requested. QT prolongation should be included as an important potential risk because the chronic use of imatinib in PAH patients, the known hypokalemia related to imatinib use and the known QT/QTc prolongation for other tyrosine kinase inhibitors. Appropriate pharmacovigilance activities and risk minimisation measures should be proposed.

The following table provides an overall summary of the risk management plan.

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Important identified risks		
Myelosuppression	Routine pharmacovigilance activities including cumulative analysis in PSUR. Targeted follow-up with the use of a myelosuppression checklist for CTCAE grade 3 and 4 myelosuppression serious and non-serious spontaneous cases.	**SmPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects. 5.3 Preclinical safety data **Additional risk minimization activity:** Educational materials to educate patients and physicians about the need for appropriate monitoring of hematological parameters and management of myelosuppression with dose reduction or dose interruption, and, in rare cases, discontinuation of treatment.
Edema and Fluid Retention	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects **Additional risk minimization activity:** Educational materials to educate patients and physicians about the need for appropriate monitoring (patient should be weighed and clinically evaluated periodically for signs and symptoms of a change in intravascular volume status).
CNS and GI Hemorrhages	Routine pharmacovigilance activities including cumulative analysis in PSUR. Targeted follow-up with the use of a cerebral hemorrhage checklist for all serious and nonserious spontaneous cases.	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects. **Additional risk minimization activity:** Educational materials to educate the patients and physicians about the need for appropriate monitoring of hematological parameters and abnormal bleeding as well as early signs and symptoms of cerebral bleeding event (e.g., severe headache and/or decreased level of consciousness).
Hepatotoxicity	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects. 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties 5.3 Preclinical safety data
Skin Rashes and Severe Cutaneous Reactions	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section:** 4.8 Undesirable effects.
Hypothyroidism	Routine pharmacovigilance	**SmPC Section:**

	activities including cumulative analysis in PSUR. Thyroid hormone level measurements in patients without a thyroid history are included in ongoing Study AMN107A2404	4.4 Special Warning and Precautions for Use
Cardiac Failure	Routine pharmacovigilance activities including cumulative analysis in PSUR. Subclinical LVD monitored by 2-D echocardiography in the nilotinib registration studies with imatinib as an active comparator (Study AMN107A2303). Targeted follow-up with the use of a Cardiac failure with the use of Acute and Congestive Heart Failure checklist for all serious reactions, serious and non-serious spontaneous cases.	**SmPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.
Acute Renal Failure	Routine pharmacovigilance activities including cumulative analysis inPSUR. Targeted follow-up with the use of a renal failure checklist for all serious and non-serious spontaneous cases.	**SmPC Sections:** 4.2 Posology and method of administration, Renalinsufficiency 4.4 Special warnings and precautions for use 4.8 Undesirable effects. 5.2 Pharmacokinetic properties, Organ functionimpairment 5.3 Preclinical safety data **Additional risk minimization activity**: Educational materials to educate patients and physicians about the need for appropriate monitoring of renal function and evaluation of clinically significant increases in serum creatinine.
Severe Respiratory Adverse Reactions	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section:** 4.8 Undesirable effects.
Rhabdomyolysis and Myopathy	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section:** 4.8 Undesirable effects
Ovarian Hemorrhage and Hemorrhagic Ovarian Cyst	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section** 4.8 Undesirable effects.
Low tolerability		These include the events of nausea, peripheral edema, diarrhea, vomiting, periorbital edema, headache, and dyspnea. This item will be appropriately communicated through the educational materials. The details on the risk of peri-orbital- and peripheral edema are described in the specific section on the risk of Edema and Fluid Retention.
Important potential risks		
Disseminated Intravascular Coagulation	Routine pharmacovigilance activities including cumulative analysis in PSUR.	No risk minimization activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimization activities may be proposed if necessary.

Hypoglycemia	Routine pharmacovigilance activities including cumulative analysis in PSUR.	No risk minimization activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labelling and additional risk minimization activities may be proposed if necessary.
Suicidality	Routine pharmacovigilance activities including cumulative analysis in PSUR.	No risk minimization activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labeling and additional risk minimization activities may be proposed if necessary.
Tolerability during Pregnancy and Pregnancy Outcomes	Routine pharmacovigilance activities including cumulative analysis in PSUR. Pregnancy registry for imatinib and nilotinib (CSTI571A2403).	**SmPC Sections:** 4.6 Pregnancy and lactation and 5.3 Preclinical safety data.
Hypophosphatemia	Routine pharmacovigilance activities including cumulative analysis in PSUR. Phosphate assessment as a function of dose in registration study (STI571K2301). Bone metabolism abnormalities and evaluation of dose dependency of parameters of bone metabolism e.g. serum phosphate (Study STI571EUS252)	**SmPC Section** 4.8 Undesirable effects.
Interactions with Strong CYP3A4 Inhibitors	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section:** 4.5 Interactions
Interactions with Strong CYP3A4 Inducers	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section:** 4.5 Interactions
Interactions with Drugs eliminated by CYP3A4	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section:** 4.5 Interactions
Interactions with Drugs Eliminated by CYP2C9, CYP2C19 and CYP2D6	Routine pharmacovigilance activities including cumulative analysis in PSUR.	**SmPC Section:** 4.5 Interactions
Interactions with Acetaminophen/ paracetamol	Routine pharmacovigilance activities including cumulative analysis in PSUR.	No risk minimization activities are proposed. This item was removed from the CDS labeling of Glivec 24 Sept 2010. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labeling and additional risk minimization activities may be proposed if necessary.
Important missing information		
Pediatric patients: Long-term follow up	Routine pharmacovigilance activities including cumulative analysis in PSUR. An open-label extension (QTI571A2306E1) will be conducted in children (aged 6 months to < 18 years of age) with PAH to obtain long-term safety data in accordance with the PIP for PAH	**SmPC Sections:** 4.4 Special warnings and precautions for Use 4.8 Undesirable effects. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities and pediatric studies identify additional data, the risk will be communicated through the labeling and additional risk minimization activities may be proposed if necessary.
Pediatric patients below 2 year of age	Routine pharmacovigilance activities.	**SmPC Section** 4.2 Posology and method of administration.

	A double-blind study (CQTI571A2306) and open-label extension (CQTI571A2306E1)	Should routine pharmacovigilance activities and/or double-blind study (CQTI571A2306) and open-label extension (CQTI571A2306E1) uncover additional data, this risk will be communicated through will be communicated through the IB, CDS, and EU-SmPC and additional risk minimization activities may be proposed if necessary.
Pediatric patients < 18 years	Routine pharmacovigilance activities. A double-blind study (CQTI571A2306) and open-label extension (CQTI571A2306E1)	**SmPC Sections** 4.2 Posology and method of administration. Should routine pharmacovigilance activities and/or double-blind study (CQTI571A2306) and open-label extension (CQTI571A2306E1) uncover additional data, this risk will be communicated through will be communicated through the IB, CDS, and EU-SmPC and additional risk minimization activities may be proposed if necessary.
Renal impairment	Routine pharmacovigilance activities.	**SmPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.2 Pharmacokinetic properties 5.3 Preclinical safety data
Hepatic impairment	Routine pharmacovigilance activities.	**SmPC Sections:** 4.2 Posology and method of administration, 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties 5.3 Preclinical safety data
Elderly patients	Routine pharmacovigilance activities.	**SmPC Section** 4.2 Posology and method of administration.

Targeted follow up of serious and non-serious cases (additional pharmacovigilance activity) is proposed for the following safety concerns: “myelosuppresion”, “CNS and GI hemorrhages” , “acute renal failure”, “cardiac failure”, and for “hepatotoxicity” by the concomitant use of bosentan and imatinib in PAH. Safety studies as additional pharmcovigilance activity study hypothyroidism, cardiac failure, hypophosphatemia and a pregnancy registry for imatinib to study tolerability during pregnancy and pregnancy outcomes. A comment on the imatinib registry for PAH patients which is only described in the educational program is expected.

The risks of imatinib may not easily be manageable in a cardiology patient population, and they may even aggravate the disease process.

Educational material (additional risk minimization activities) are proposed for the following safety concerns: “myelosuppression,” “edema and fluid retention,” “CNS and GI bleeding”, “acute renal failure” and “low tolerability”. Hepatotoxicity is an important identified risk with impact and physicians should be aware of the management of this safety concern in patients treated with imatinib. For this reason hepatotoxicity should also be addressed with educational material.

The educational program includes recommendations regarding temporarily dose titration to 200mg/day for an extended period to treat possible events in the first 8 weeks of treatment to minimize the risk on treatment discontinuation. The dose titration is however a temporarily solution to create tolerability because the efficacy of imatinib with a dose of 200mg per day is doubtful.Furthermore, intensive patient monitoring has been proposed including measurements prior to and during imatinib treatment

to monitor the renal function, blood counts and body weight. These aim to detect events in early stage to be able to treat patients early or even discontinue imatinib if necessary. No contra-indications are proposed. To further strengthen the risk minimisation for bleedings the warning that warfarin and other coumarins are not recommended during imatinib treatment should be extended to 'any anticoagulatory drug'. However, the feasibility of the warning in clinical practice may be difficult since the majority of the PAH patients is using anticoagulants. Based on feasibility of the recommendations in clinical practice and the not fully known mechanism of the bleedings, only known risk factors of the bleedings can be minimised and the risk of bleeding remains a concern. There are still some requests regarding information to be included in the RMP and the evaluation of the educational program.

3. ORPHAN MEDICINAL PRODUCTS

N/A

4. BENEFIT RISK ASSESSMENT

Imatinib is a tyrosine kinase inhibitor that is currently approved in the EU for the management of several oncological indications. In the current application, imatinib is investigated for use in pulmonary arterial hypertension (PAH). It is claimed that Ruvise (imatinib) improves exercise capacity in stable patients with pulmonary vascular resistance PVR $\geq$ 800 dyn·s·cm $^{-5}$ and who remain symptomatic despite receiving maximum tolerated PAH-specific therapy.

Benefits

Beneficial effects

The pivotal study (A2301) investigated the ***primary endpoint*** of 6-Minute Walking Distance (6MWD) after 24 weeks in a population comparable to the proposed indication. The investigated endpoint is in line with the recommendation of the relevant CHMP guideline (EMEA/CHMP/EWP/356954/2008) to support a claim of improved exercise capacity. Imatinib 400 mg QD (n=103) showed superiority over placebo (n=98) in the add-on setting in the primary analysis [LS mean treatment effect: 31.8 m (95% CI: 11.8-51.8; p = 0.002)]. For the predefined clinically relevant threshold of 50 m improvement, responders were 32% in the imatinib group vs. 13% in the placebo group (p = 0.003). Long term data in the extension study showed maintenance of efficacy in terms of 6MWD in patients administered imatinib for 24 months.

Haemodynamic parameters were measured as a ***secondary endpoint***. Treatment difference for pulmonary vascular resistance (PVR) was -379 dyn·s·cm^{-5} (95% CI: -502, - 255; p<0.001). A PVR response of at least 30% was achieved by 56.8% in the imatinib vs. 20.0% in the placebo group. The improvement in PVR was confirmed by a sensitivity analysis. The decrease in PVR was accompanied by a significant reduction in pulmonary artery pressure (PAP) [treatment difference -5.18 mmHg (95%CI: -8.02, +2.34; p<0.001)] and a significant increase in cardiac output (CO) [treatment difference +0.88 L/min (95%CI: 0.57 - 1.19; p<0.001)].

Exploratory analyses showed improvement of echocardiographic parameters of right ventricular function and NT-proBNP as marker of PAH severity, right ventricular function and left sided heart-failure.

Results of the primary endpoint in the main cohort were consistent in the **subgroups** with idiopathic PAH, WHO functional class III, and on top of combinations of two or more different PAH specialised therapies (endothelin receptor antagonists, phosphodiesterase 5 inhibitors or prostacyclins).

Dose Selection. The maintenance dose of 400 mg was selected based on tolerability and an expectation of effectiveness, but was not further supported by a dose-ranging trial. In the subgroup of patients who were not administered the 400 mg dose for ≥50% of study duration, efficacy is not shown in terms of 6MWT (400mg>50%: 59.2 ± 13.8 m, 400mg<50%: 17.7 ± 11.7 m, placebo: 12.6 ± 11.9 m). The relevance of sufficient exposure is further confirmed in the PK/PD analysis. The proposed SmPC now reflects that the dose of 200 mg is considered not effective and only 400 mg can be recommended.

Uncertainty in the knowledge about the beneficial effects

Mode of action. Submitted preclinical data show some support to an anti-proliferative mechanism of action, but there is lack of clinical data to further substantiate such claims. A direct vasodilatory effect cannot be excluded. The contribution of a PK interaction between imatinib and the co-administered bosentan and sildenafil resulting in an increase in exposure of these 2 drugs cannot be ruled out. In study A2301, systemic blood pressure was lower in imatinib treated patients (LS Mean treatment effect on diastolic blood pressure Week 24: -3.58 mmHg; 95% CI: -6.45, -0.71; p= 0.015). Pulmonary and systemic vascular resistance both decreased, with a comparable magnitude (PVR: -378 $dyn \cdot s \cdot cm^{-5}$ (95% CI: -502, -255; p<0.001); SVR: -380 $dyn \cdot s \cdot cm^{-5}$ (95% CI: -526, - 233; p<0.001). These observations suggest a direct vasodilatory action. The applicant's claim that this is caused by reduced sympathetic tone as a result of increased cardiac output cannot currently be confirmed.

***Efficacy*.** The effect on **6MWT** was confirmed in the per protocol analysis, but the treatment difference was smaller (23 m). Although a beneficial effect is further confirmed by sensitivity analyses of the full analyses set, the estimates of the magnitude of the effect range from 12 to 35 m. This is related to the high discontinuation rate (33%) in the imatinib group. The choice of the method to manage these missing values is complicated. When applying conservative imputation methods, statistical significance is lost.

The observed improvements in 6MWT and haemodynamic parameters were accompanied with conflicting results in the Time to clinical worsening (TTCW), which was investigated as a ***secondary endpoint*** in the pivotal study. More events were reported in the imatinib arm [n=37 (35.9%)] compared to the placebo arm [n=32 (32.7%); HR= 1.16; 95% CI: 0.705, 1.902; p = 0.563)].There were comparable numbers of deaths reported. Events of hospitalization and worsening of WHO functional class occurred more frequently with imatinib (16.5% and 14.6% respectively) compared to placebo (13.3% and 11.2% respectively). Hospitalisations in the imatinib arm were shown to be mainly related to the adverse event profile of imatinib during the first 8-16 weeks; but are not due to cardiotoxicity . The hospitalisations indicate that the AE profile of imatinib is not well tolerated by PAH patients.

In the on-going extension study (A2301E1) all patients were administered imatinib. In the interim analysis, patients in the core imatinib group who continued imatinib had slightly fewer TTCW events than patients in the core placebo group who initiated imatinib: 25/66 (37.9%) vs. 30/78 (38.5%), respectively. Importantly, more deaths were reported in the core placebo group who switched to imatinib (total of 9 deaths), compared to the core imatinib group (total of 2 deaths) (discussed below). Also, the core placebo patients who switched to imatinib in the extension study showed only modest improvements in 6MWT (19 ± 72 m in Week 24).

Target population. The definition of the severity of PAH in the target population was based on high PVR, as investigated in the proof of concept study. This is not in line with the accepted definition based on WHO FC, and used in the registration of other PAH medications. There was no correlation seen between PVR and WHO FC. Exploring the baseline characteristics and medical history of responders (in

terms of both 6MWD and PVR) did not reveal any specific factor possibly contributing to a favourable response: of 17 responder patients, 14 were treated with 400 mg daily for more than 50% of the study (77 days). Also female gender and IPAH predicted being a responder. However, no robust recommendations can be made based on these factors.

The applicant further defined a subgroup of high risk patients (6MWD of <300 m, cardiac index (CI) <2.0 or PVR >2000 dyn·s·cm^{-5}); twelve of seventeen of these responders (71%) were in this high-risk group. On the other hand, all 9 core placebo patients who initiated imatinib in the phase III extension study and died had deterioration in either 6MWD or worsening of PVR (6 of 9 patients who died had PVR >1400 dyn•s•cm^{-5} at the end of the core study). This questions the use of PVR only as a prognostic tool to a beneficial response to imatinib. Other undefined characteristics appear to determine the response.

Subgroups. Results show a better response in the subgroup with PVR > 1000 dyn·s·cm^{-5} [LS mean treatment difference in 6MWD= 31.4 (95%CI: 8.2 - 54.6)] than in the subgroup with PVR< 1000 dyn·s·cm^{-5} [11.0 (95%CI: -25.4 - 47.3)]. Improvement is also less evident in ***WHO FC II*** [LS mean treatment difference= 15 m (-20.85 - 50.85; p=0.401)] than WHO III (LS mean treatment difference in 6MWD=33.92 m (9.35 - 58.5; p=0.0074). However, there was limited representation in the study (n=51). There is limited representation of the subgroup of associated PAH (***APAH)*** (n=43) and a modest efficacy is shown (LS mean treatment difference in 6MWD =14.9 m (95%CI: -28.1 - 57.8). Further analysis is needed to address efficacy in these subgroups.

Medication errors in A2301. After the inclusion of the first 28 patients, it was discovered that the Interactive Voice Response System malfunctioned and these patients (including 13 randomised to imatinib and 15 to placebo) had received 400 mg QD instead of 200 mg QD as planned during the dose titration phase. These 28 patients contribute to the 48 patients who were excluded from the per protocol analysis. The issue is related to failure of the computer system validation, which is a GCP element. This may have impacted the tolerability of the investigational treatment, but the trial's data are not compromised.

Risks

Unfavourable effects

Relevant safety data for imatinib in PAH are retrieved from the two placebo-controlled trials E2203 and A2301 and their extensions. In the clinical development program for PAH, 221 patients were exposed to imatinib. In the pivotal study A2301, mean exposure for the recommended dose 400 mg QD for 89 patients was 93.8 ±65.3 days.

Treatment with imatinib is associated with significant numbers of **AEs**. Most AEs are reported during the first 8-16 weeks of treatment. The proportion of patients with AEs that were suspected to be related to the study drug based on investigator assessment was 84.5% in the imatinib group and 37.8% in the placebo group. The most common suspected AEs overall were nausea (imatinib 44.7% vs. placebo 9.2%), peripheral oedema (imatinib 26.2% vs. placebo 7.1%), vomiting (imatinib 21.4% vs. placebo 2.0%), periorbital oedema (imatinib 18.4% vs. placebo 4.1%), diarrhoea (imatinib 17.5% vs. placebo 4.1%), headache (imatinib 12.6% vs. placebo 6.1%), and face oedema (imatinib 8.7% vs. placebo 1.0%).

Serious AEs. In Study A2301 more patients in the imatinib group (43.7%) than the placebo group (29.6%) had SAEs. The SAEs reflected the known adverse effects of imatinib (e.g. anaemia, gastrointestinal disorders, and oedema), and the known cardiac complications of PAH (e.g. right

ventricular failure). In the long term extension study **A2301E1,** the AE profile of placebo patients who switched to imatinib was in line with that experienced by imatinib users in the core study, except for the increased numbers of deaths.

Serious events of ***erythropenia*** (11; 9 requiring transfusion), ***leucopenia*** (6; 4 requiring intervention) and ***thrombocytopenia*** (2; 1 died) were reported in the imatinib arm in study A2301 and its extension compared to 2 cases (both requiring transfusion) in the placebo arm.

Deaths. Thirty three deaths were reported in the PAH development program (n=18 in the controlled studies; 8 in the imatinib group and 10 in the placebo group; 14 in the extension studies, and 1 in a DDI study). Comparable numbers of deaths were reported in the controlled studies. In most (20/33) cases of death, (right) cardiac failure, cardiac arrest or PAH were mentioned as cause of death.

The issue of possible ***cardiotoxicity*** was addressed by the applicant. The submitted data do not point to an increased incidence of direct cardiotoxicity in the oncology or PAH clinical development programs. While the possibility of anecdotal effects of imatinib on cardiac function is difficult to exclude, the experience in the imatinib-PAH clinical program combined with the oncology experience suggest that cardiotoxicity events would be uncommon (possibly 1%).

No significant differences were seen in ***QT/QTc prolongation*** in study A2301. However, certain points indicate that the study may not reflect the clinical setting in which imatinib may eventually be used: patients were excluded if QTcF was greater than 450 ms and if electrolytes were not within normal ranges, electrolytes were to be corrected and then the patient re-screened for QTc. In addition, hypokalemia is a very common adverse event reported with imatinib (15.5%) and a well known risk factor for this kind of arrhythmias. Finally QT/QTc prolongation has been described for the majority of tyrosine kinase inhibitors and warnings have been included in their respective SmPCs. All these issues suggest that QT/QTc prolongation could be a potential risk for the PAH population treated with imatinib. This should be reflected in the RMP.

Creatinine is consistently higher in imatinib users compared to placebo starting immediately after initiation of therapy. This is an identified risk from the oncology program and is thought to be related to an inhibitory effect of imatinib on creatinine secretion on the basolateral membrane of the proximal tubule. There is also a risk of ***acute renal failure*** with imatinib identified in the oncology setting; one case is reported in the PAH program, leading to discontinuation.

In non-PAH indications, ***hepatotoxicity*** is an identified risk with imatinib use. In the pivotal study A2301, the frequencies of hepatotoxic events were comparable between the placebo (4.1%) and imatinib arms (2.9%). Assessment of three cases of hepatotoxicity reported with imatinib use did not support causality. Based on the current limited database, there is no signal of hepatotoxicity with imatinib use in PAH, but considering imatinib's profile in, other indications, hepatotoxicity cannot be excluded. This issue should be followed up in the RMP.

The effect of ***renal*** and ***hepatic impairment*** on imatinib plasma concentrations was determined in clinical pharmacology studies in non-PAH patients. For both conditions, AUC and Cmax values were approximately 1.5-2-fold that of the normal group at steady-state. Due to lack of systematic data (on encephalopathy or ascites) it was not possible to retrospectively determine a grading for hepatic impairment and analysis of the AE profile with respect to Child-Pugh classification was not possible.

Most PAH patients in the pivotal trial had mild renal impairment. In general, the AE profile of patients with different degrees of renal impairment appear to follow that of 'normal" patients, with the patients on imatinib showing a higher frequency of AEs compared to placebo. The sensitivity of patients for fluid retention caused by imatinib increases with declining renal function and this is intuitively acceptable.

Withdrawals. In study A2301, discontinuation due to AEs was more frequent with imatinib (27.2%) than with placebo group (9.2%). The reasons for discontinuation were diverse, including well-known adverse reactions of imatinib like fluid retention (5 vs 1), cytopenia (3 vs 1) and nausea (2 vs 1).

Uncertainty in the knowledge about the unfavourable effects

The extent of long-term exposure is very limited as only 51 patients used the recommended dose of 400 mg for at least one year. The PAH database is too small to detect rare events; although the safety profile of imatinib in the oncology indication is well described.

Deaths. In the extension study A2301E1, 9 deaths were reported in the core placebo group, versus 2 patients who used imatinib in the core trial. Of these core placebo patients, 6 died within 3 months from the switch to imatinib. Of these deaths, 4 were adjudicated as worsening of cardiac function due to PAH, whereas the remainder were adjudicated as events unrelated to PAH. The causality of imatinib in these deaths cannot be excluded, for example in the case of subdural haematoma. The applicant attributes this fatal outcome to the instability of these patients. According to the applicant, in the controlled phase III study, recruited patients were required to be stable on 2 or more PAH therapies prior to initiation of imatinib, whereas placebo patients who initiated imatinib in the extension study were not required to meet this criterion. In addition, no deaths were reported in placebo patients who had stable 6MWD and PVR values during the 24-week core study. The applicant accordingly proposes to emphasize in the SmPC that only stable patients should be initiated imatinib. However, the mechanism that makes such patients more vulnerable to imatinib is not further discussed. It can not be excluded that the AE profile of imatinib (e.g fluid retention and oedema) can have a serious negative impact on some patients. The feasibility such proposed changes in the SmPC is doubtful.

Subdural haematomas were reported 9 times in imatinib group vs. nil in the placebo group in the controlled trials; three additional cases were subsequently spontaneously reported. The mechanism of this increased risk of SDH in PAH administered imatinib is not explained. One factor could be the co-administration of VKA. The contribution of other mechanisms, such as interaction with other PAH drugs like prostanoids, or a direct vascular effect cannot be excluded.

Interactions. Polypharmacy is common in the claimed PAH patients who typically use a bosentan, sildenafil and/or a prostacyclin, in addition to an anticoagulant. PK interactions are therefore potentially relevant as imatinib is a CYP3A4 inhibitor, increasing the exposure of bosentan and sildenafil by 51% and 64% respectively. Also there is an increased exposure of statins. PD interactions can also not be excluded, including oedema and liver toxicity when used with bosentan and increased bleeding tendency when used with prostacyclins or anticoagulants. A higher incidence of oedema was reported when imatinib was co-administered with bosentan, but not liver toxicity. No increased risks were seen when imatinib was co-administered with sildenafil.

Data on patients who underwent ***lung transplant*** are too sparse to allow for a definite conclusion on the potential risks of using imatinib in patients scheduled for lung transplant, but so far no specific risks were identified.

Balance

Importance of favourable and unfavourable effects

The mainstay of current treatment strategies of PAH are pulmonary specific vasodilators. The rationale of investigating a medicinal product with a new **mode of action** is welcome, especially in the setting of advanced disease. There are some preclinical data indicating that imatinib may have an anti-

proliferative action in PAH, but this is not supported by any clinical data. It would have been more supportive of the application if an anti-proliferative mechanism is clearly shown.

Imatinib is investigated as ***add-on therapy*** in patients with PVR≥ 800 dyn·s·cm^{-5} on top of 2 or 3 PAH specific medications. Although add-on therapy is practiced in PAH, none of these combinations is licensed. This emphasises the importance of this clinical program. The above benefits were obtained in a population using at least 2 drugs for PAH and still in need of additional therapy. The proposed indication clearly focuses on patients for whom no other options exist.

The ***primary endpoint*** of 6MWD is in line with the relevant CHMP guideline, although the value of basing efficacy claim solely on this endpoint is currently debated; improvement in 6MWT has not been shown to correlate with survival. In the pivotal study, the gain of 30 m in 6MWD achieved by imatinib should be viewed in the context of other add-on trials. Increases of around 29 m (PACES), 20 m (TRIUMPH) and 17 m (PHIRST) were observed in different studies, on top of only one PAH specialised therapy. However, further analysis of the data undermines the results: the pre-specified clinically relevant 50 m was only achieved in one third of the imatinib patients. The effect size is uncertain with estimates between 12 and 35 m.

Such limited symptomatic efficacy was accompanied by improvements only in pulmonary haemodynamics, but not in clinical events. This further weakens the observed primary efficacy endpoint.

The value of ***pulmonary haemodynamics*** is currently limited to a secondary endpoint. There is some evidence that a reduction in PVR by 30% is correlated to prolonged survival; this was achieved in around half of the imatinib group. Some patients show an increase in right ventricular function, which is not always true with other PAH medications. However, this improvement in right ventricular function did not translate into benefits in clinical outcomes.

The relevant CHMP guideline already underscored the importance of investigating more clinically relevant endpoints like ***time to clinical worsening*** besides the effect on 6MWT. Previous experience in measuring TTCW shows that it is possible to show meaningful reductions in clinical outcomes in a 3-months trial. However, in the currently submitted pivotal trial, the reported benefits did not translate into any delay in clinical worsening.

It is observed that the results of TTCW were mainly driven by short term hospitalisations due to the AE profile of imatinib such as oedema and fluid retention. Analysis of data adequately excluded a direct cardiotoxic potential for imatinib. However, it appears that PAH patients are more vulnerable to the AE profile of imatinib than the oncology patients. In short, although TTCW is an efficacy endpoint meant to investigate improvements in clinical outcomes associated with the new intervention, no such improvements were seen with imatinib. On the contrary, the endpoint captured the heavy AE profile of imatinib.

The ***database*** of exposure is very limited, but could be acceptable considering the orphan indication and the specific proposed indication. Also, previous experience in the oncology indications gives a good understanding of the identified risks. However, this experience was not applied in the pivotal study, resulting in a high dropout rate in the imatinib arm and also increased hospitalisations in the first 8-16 weeks.

Although ***mortality*** results are balanced in the pivotal study, a surge of early mortality in the core placebo patients who initiate imatinib in the extension study occurred. No specific characteristics could identify these patients. A high PVR is shared by a ‘responder' and patient with a fatal outcome. The applicant attributes this higher mortality in some patients to their instability, but without any further

explanations about the underlying mechanisms. It cannot be excluded that the AE profile of imatinib (oedema and fluid retention) may be particularly harmful to some patients, leading to this fatal outcome.

The unexplained higher risk of ***subdural haematoma*** with imatinib is another unresolved serious issue. Considering that imatinib is proposed to be a last resort for terminally ill patients, it is problematic to increase their disease burden by such a serious AE.

Relevant PK and/or PD interactions with bosentan, sildenafil and prostacyclins cannot be excluded based on the current database. Such risks need to adequately covered in the SmPC and the RMP.

Many patients with different degrees of ***hepatic or renal impairment*** were excluded from the clinical trials. A specific dose recommendation for hepatic impairment cannot be made, but the patients excluded from the PAH clinical trials should be mentioned in the SmPC. In the Glivec label, no dose adaptation is required in patients with hepatic or renal impairment, which can be acceptable in this indication as well.

Benefit-risk balance

The limited benefit in terms of gain in 6MWT cannot balance the negative safety profile of imatinib in PAH. Imatinib not only failed to prevent clinical deterioration, it has a significant role in the causality of more hospitalisations and deterioration in functional class, as a consequence of the AE profile (fluid retention, vomiting, diarrhoea, anaemia and bleeding). Imatinib use is also associated with an unexplained higher risk of SDH, which is not considered acceptable in severely sick patients.

This is further compounded by the difficulty in the selection of the target population, that leaves doubt as to which patients may benefit and which patients will be at risk of severe and even fatal AEs.

Discussion on the benefit-risk assessment

In this population of PAH patients who have no other therapeutic options, while using at maximum other PAH specific drugs, there is an unmet medical need and a new treatment option would be highly welcome. Imatinib shows benefits in terms of improvement in exercise capacity and pulmonary haemodynamics; the clinical relevance and the robustness of these results are questioned. Efficacy in certain subgroups (e.g males, WHO FC II, males, PVR at baseline < 1.000 dyn.s.cm^{-5}) needs to be further addressed. Moreover, the exact MoA is not well described. The applicant agreed to remove a reference to the anti-proliferative MoA in the indication, but it would have been more supportive to the application if such an MoA could have been clinically verified.

The described benefits were not accompanied by a delay in clinical events; on the contrary, initiation of imatinib may even have a negative impact on safety in some patients due to its heavy AE profile. This questions the tolerability. Currently the applicant proposes to temporarily down titrate the dose to 200 mg to improve tolerability. This is accepted as the currently proposed SmPC clearly indicates that such dose reductions are temporary and that patients should be maintained on the 400 mg dose, which is the only therapeutic dose. The applicant also proposes an educational program in the RMP to educate the health care providers about the management of these AEs. Considering that such measures were not implemented in the pivotal study, there remain doubts regarding their implementation and effectiveness in actual clinical practice.

Safety of imatinib is also not established in the PAH population. In certain PAH patients, administration of imatinib led to a fatal outcome. The susceptibility and the exaggerated reaction of these PAH patients to the AE profile of imatinib is not further discussed. This is a serious issue, as patients who do

not respond to imatinib, may suffer serious AEs like SDH or even death. The applicant currently proposes to modify the indication to stable patients who are already receiving all tolerated therapies at maximum. The feasibility of such "SmPC" restrictions is doubted. More precise criteria should be given to distinguish the target population.

To minimise the risk of SDH, the applicant proposes to include a warning, 'not recommending' the concomitant use of imatinib and VKAs. As the exact mechanism of SDH is not identified, this measure may only partly reduce the risk. In addition, considering that around 60% of PAH patients are prescribed VKA, such a recommendation would deprive patients of an established therapy, at an unknown cost. Other contributing mechanisms such as interactions with prostanoids or a direct vascular effect cannot be excluded.

Conclusions

The overall B/R of Ruvise is negative.