

# Imatinib Mesylate as Add-On Therapy for Pulmonary Arterial Hypertension: Results of the Randomized IMPRES Study

**Running title:** *Hoepfer et al.; Imatinib in pulmonary arterial hypertension*

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**Abstract:**

**Background**—By its inhibitory effect on platelet-derived growth factor signaling, imatinib could be efficacious in treating patients with pulmonary arterial hypertension (PAH).

**Methods and Results**—IMPRES, a randomized, double-blind, placebo-controlled 24-week trial evaluated imatinib in patients with pulmonary vascular resistance (PVR)  $\geq 800$  dynes·sec·cm<sup>-5</sup> symptomatic on  $\geq 2$  PAH therapies. The primary outcome was change in 6-minute walk distance (6MWD). Secondary outcomes included changes in hemodynamics, functional class, serum levels of N-terminal brain natriuretic peptide (NT-proBNP), and time to clinical worsening (TTCW). After completion of the core study, patients could enter an open-label long-term extension study. Of 202 patients enrolled, 41% patients received 3 PAH therapies with the remainder on 2 therapies. After 24 weeks, the mean placebo-corrected treatment-effect on 6MWD was 32 m (95% confidence interval [CI], 12, 52;  $P=0.002$ ), an effect maintained in the extension study in patients remaining on imatinib. PVR decreased by 379 dynes·sec·cm<sup>-5</sup> (95% CI: -502, -255;  $P<0.001$ ; between-group difference). Functional class, TTCW and mortality did not differ between treatments. Serious adverse events and discontinuations were more frequent with imatinib than placebo (44% versus 30%, 33% versus 18% respectively). Subdural hematoma occurred in 8 patients (2 in the core study, 6 in the extension) receiving imatinib and anticoagulation.

**Conclusions**—Imatinib improved exercise capacity and hemodynamics in patients with advanced PAH but serious adverse events and study drug discontinuations were common. Further studies are needed to investigate the long-term safety and efficacy of imatinib in patients with PAH.

**Clinical Trial Registration Information**—URL: <http://www.clinicaltrials.gov>. Identifier: NCT00902174 (core study); NCT01392495 (extension).

**Key words:** hypertension, pulmonary; drugs; exercise; hemodynamics

## Introduction

Pulmonary arterial hypertension (PAH) is characterized by progressive obliteration of the pulmonary vascular bed eventually leading to right heart failure and death, if not effectively treated.<sup>1,2</sup> Although some forms of PAH are heritable or associated with other conditions such as scleroderma, many cases are idiopathic in origin.<sup>3</sup>

The median survival of patients with idiopathic or heritable PAH was less than 3 years prior to the availability of targeted PAH drugs.<sup>4</sup> Current treatment options consist of prostacyclin and its analogs, endothelin receptor antagonists (ERAs) and phosphodiesterase type-5 (PDE5) inhibitors, all of which have been shown to improve exercise capacity, hemodynamic variables and disease progression,<sup>5–10</sup> together with calcium channel blocker therapy in the rare patient responding to vasodilators and lung transplantation in the patients who are refractory to medical therapy. However, normalization of pulmonary vascular resistance (PVR) with long-term improvement is rarely achieved, even with combination treatment, and survival rates remain poor. Humbert and colleagues recently reported a 3-year survival of less than 60% in patients with newly diagnosed PAH, despite current therapy, highlighting the need for more treatment options.<sup>11,12</sup>

Once considered a consequence of abnormal pulmonary vasoconstriction, PAH is now regarded as a disease mainly caused by pulmonary vascular remodeling. Proliferation of endothelial cells and vascular smooth muscle cells with narrowing or occlusion of the vessel lumina is a histopathological hallmark of the disease.<sup>13</sup> Evidence from animal models and human disease suggest that platelet-derived growth factor (PDGF) and c-KIT signaling are important in vascular smooth muscle cell proliferation and hyperplasia.<sup>14–16</sup>

Imatinib is an anti-proliferative agent developed to target the BCR-abl tyrosine kinase in

patients with chronic myeloid leukemia. In addition, the inhibitory effects of imatinib on PDGF receptors  $\alpha$  and  $\beta$  and c-KIT suggest that it may be efficacious in PAH.<sup>15–17</sup> Imatinib reversed experimentally-induced pulmonary hypertension<sup>17</sup> and has pulmonary vasodilatory effects in animal models<sup>18</sup> and pro-apoptotic effects on pulmonary artery smooth muscle cells from patients with idiopathic PAH.<sup>19</sup> Case reports have suggested hemodynamic and clinical benefits in PAH patients.<sup>20–22</sup> A randomized, double-blind, placebo-controlled Phase II study in 59 patients reported that imatinib significantly improved pulmonary hemodynamics.<sup>23</sup> In that study, a *post hoc* subgroup analysis suggested that patients with greater hemodynamic impairment might respond better to imatinib than patients with less advanced disease. The objective of the present study was to further evaluate the safety, tolerability and efficacy of imatinib in patients with advanced PAH who were receiving at least 2 PAH therapies.

## Methods

### Patients

The study was conducted at 71 centers in 14 countries. Male and female subjects ( $\geq 18$  years) were enrolled if they had symptomatic PAH (World Health Organization [WHO] Functional Class II–IV<sup>24</sup>) and met the criteria for one of the following categories of Group 1 Pulmonary Hypertension: idiopathic or heritable PAH; PAH associated with connective tissue disease; PAH following  $\geq 1$  year repair of congenital systemic to pulmonary shunt; or PAH associated with anorexigens or other drugs.<sup>25</sup> Patients were required to be receiving at least 2 PAH therapies (ERAs, PDE5 inhibitors or prostacyclin analogs for  $\geq 3$  months) with a PVR  $\geq 800$  dynes·sec·cm<sup>-5</sup> at screening (see Online Supplementary Appendix 1). Patients with WHO Functional Class IV PAH were required to be receiving a prostanoid analog, unless shown to be intolerant. Full

details of enrolment criteria are in the protocol (Online Supplementary Appendix 2).

### **Study Design and Treatments**

IMPRES was a 24-week, multicenter, double-blind, placebo-controlled, parallel-group study.

Eligibility was determined in a 6-week screening period. Baseline 6-minute walk distance (6MWD) was derived from the mean of 2 consecutive tests with results that fell within 15% of each other.

Eligible patients were randomized in a 1:1 ratio to imatinib or placebo at an intended starting dose of 200 mg once daily (qd) (see Online Supplementary Appendix 1). The dose was increased to 400 mg qd after 2 weeks if the starting dose was tolerated; the dose could be reduced to 200 mg qd if the 400 mg dose was not well tolerated. Patients were withdrawn from the trial following dose reduction if any of the following persisted for  $\geq 2$  weeks: liver function test  $\geq 4 \times$  upper limit of normal (ULN); creatinine  $> 1.5 \times$  ULN or  $> 30\%$  versus screening value; weight gain  $> 2$  kg when due to edema and decline in right heart function; or incapacitating peripheral edema or nausea/vomiting.

All patients gave written, informed consent to participate in the study. The study protocol was approved by ethics committees and/or institutional review boards at each study center.

### **Study Assessments**

The primary efficacy endpoint was change in 6MWD from baseline to Week 24. 6MW tests (6MWT) were performed according to American Thoracic Society guidelines.<sup>26</sup> Secondary efficacy endpoints included changes in pulmonary hemodynamics and time to clinical worsening.

Hemodynamic variables were determined using right heart catheter assessments at baseline and end of study. Time to clinical worsening was determined based on time from

baseline to the first occurrence of any of the following: death; overnight hospitalization for worsening of PAH (blind adjudication); worsening of WHO functional class by at least one level; or  $\geq 15\%$  decrease from baseline in 6MWD (confirmed in 2 6MWTs at 2 consecutive visits). Blood samples were collected for laboratory assessments, including measurement of N-terminal pro-B type natriuretic peptide (NT-proBNP), at baseline and subsequent study visits. Safety assessments included echocardiographic assessment at baseline, Week 12 and Week 24, monitoring and recording of all adverse events (AEs). All deaths and unplanned overnight hospitalizations were adjudicated by an independent committee to determine whether they were due to worsening PAH. Laboratory tests and electrocardiograms (ECGs) were obtained at each visit. Patients in the core study were followed for 24 weeks after receiving the first dose of study drug.

### **Long-Term Extension Study**

After completion of the 24-week core study, patients were eligible to enter a long-term open-label extension study (ongoing). Patients who were treated with 400 mg qd of imatinib during the core study remained on 400 mg qd, those who were treated with 200 mg qd during the core study remained on 200 mg qd and those who were treated with placebo during the core study were started on 200 mg qd and then up-titrated to 400 mg qd after 2 weeks. Titration of dose between 200 and 400 mg was allowed based on drug tolerability.

### **Statistical Analyses**

Statistical power was estimated based on 6MWD, drug tolerability (dropouts), and outcomes from prior studies. Assuming a 30% dropout rate at 6 months, a sample size of 70 patients per group was calculated to detect a 50 m difference between imatinib and placebo with a standard deviation (SD) of 75 m, an alpha of 5% (2-sided), and 90% power. Additional patients were

included to enable analysis of time to clinical worsening.

Efficacy was assessed in all randomized patients who received at least 1 dose of study drug. Patients were analyzed according to randomized treatment. The assessment of 6MWD used a mixed-effects model for repeated measures, including treatment, week and country as factors, and baseline 6MWD as a covariate as well as treatment by week and 6MWD baseline by week interactions. A random effect of center within country was also included. For the primary analysis, the null hypothesis (no change in 6MWD between imatinib and placebo at Week 24) was rejected if the 2-sided *P*-value was less than 5% and the confidence interval (CI) was entirely greater than zero. Pulmonary hemodynamics were analyzed using a mixed-effects model including treatment and country as factors and baseline hemodynamic values as covariates. The random effect of center within country was also included in the model. Time to clinical worsening was analyzed using a Cox regression model, with terms for treatment and country, and baseline 6MWD as a covariate. Patients who discontinued the study were considered as censored. Full details of the statistical approach including sensitivity analyses and imputation rules for missing variables are provided in the online supplement.

## Results

### Patient Disposition, Characteristics and Drug Exposure

A total of 103 patients were randomized to imatinib and 99 to placebo (**Figure 1**) between September 17, 2009 and May 12, 2011. One patient in the placebo group was randomized, but did not receive study treatment. Baseline demographic and clinical characteristics were well balanced (**Table 1**). Long-term dose escalation (receipt of 400 mg qd for  $\geq 77$  days) was successful in 48 imatinib-treated patients (47%) and 86 placebo recipients (88%).



## Efficacy

Imatinib significantly improved 6MWD at Week 24 compared with placebo, with a mean between-group difference of 32 m (95% CI: 12, 52;  $P=0.002$ ). Sensitivity analyses including multiple imputations for missing values retained statistical significance although the treatment effects were slightly attenuated (**Table 2**). A *post-hoc* sensitivity analysis using non-parametric statistical methods and imputation for missing values similar to other published trials<sup>9</sup> was performed (treatment effect 29 m, 95% CI: 7, 50;  $P=0.010$ ) (**Table 2**, Online Supplementary Appendix 1).

Improvements in 6MWD from baseline adjusting for covariates including baseline 6MWD were statistically significant from Week 12 onwards (**Figure 2A**). A responder analysis by thresholds of improvement in 6MWD is provided in Online Supplement Appendix 3 **Table S1**). The change in 6MWD (using last observation carried forward [LOCF] to Week 24) remained significant in the subgroup of patients receiving triple combination therapy at baseline (between-group difference 34 m (95% CI: 5, 62;  $P=0.021$ , **Figure 2B**).

In the patients who remained on imatinib in the extension ( $n=66$ ), improvements in 6MWD at Week 24 of the core study were maintained at Week 24 of the extension (total 48 weeks imatinib,  $n=54$ ). In these patients, 6MWD increased by  $44.7 \pm 45.5$  m (mean  $\pm$  SD) compared to core study baseline. In comparison, in patients treated with placebo in the core study and imatinib in the extension (total 24 weeks imatinib,  $n=53$ ), the 6MWD increased by  $19.3 \pm 71.6$  m (mean  $\pm$  SD) compared to the core study baseline.

Patients receiving imatinib had greater improvements in hemodynamics. PVR decreased by  $367 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$  in imatinib-treated patients ( $n=74$ ) and increased by  $12 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$  in placebo recipients ( $n=80$ ), with a between-group difference of  $379 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$  (95% CI: –



502, -255;  $P<0.001$ ), equating to a change of -31.8% (95% CI: -42.2, -21.4;  $P<0.001$ ). In addition, mean pulmonary artery pressure (imatinib/placebo  $n=75/82$ ), cardiac output (75/81) and right atrial pressure (73/81) improved compared with placebo (all  $P\leq 0.03$ ; **Figure 3**, [further data available in Online Supplementary Appendix 3, **Table S2**]). The hemodynamic effects observed in patients with PAH associated with connective tissue disease or repaired congenital heart disease were similar to the hemodynamic changes seen in patients with idiopathic or heritable PAH, but the subgroups were too small to allow robust statistical analyses (Online Supplementary Appendix 3, **Table S3**). Similarly, improvements versus placebo were demonstrated with imatinib for 6MWD and PVR in patients in functional classes II and III [Supplementary Appendix 3, **Table S4**].

At Week 24, NT-proBNP levels (mean $\pm$ standard error) were lower in the imatinib group ( $n=68$ , 142 $\pm$ 39 pmol/L) than in the placebo group ( $n=78$ , 188 $\pm$ 40 pmol/L) with a mean difference of -45 pmol/L (95% CI: -88, -2 pmol/L;  $P=0.040$ ).

There was no significant difference in functional class at 24 weeks (imatinib  $n=70$ ; placebo  $n=83$ ). There was also no significant difference in time to first clinical worsening event (hazard ratio 1.16; 95% CI: 0.71, 1.90;  $P=0.563$ ) (**Figure 4**). During the study, 37 (36%) imatinib-treated patients had a clinical worsening event compared with 32 (33%) placebo recipients (**Table 3**). A detailed list of the timing of these events is shown in Online Supplementary Appendix 3, **Table S5**. Among the 37 clinical worsening events observed in the imatinib group, 24 occurred during the first 8 weeks. Of the 37 imatinib patients who experienced clinical worsening events, 15 continued on study drug and had a mean improvement in 6MWD of 15 m at the end of the study (Online Supplementary Appendix 3, **Figure S1**).

## Safety

All patients including withdrawals were followed for survival data until 24 weeks after receiving first dose of study drug. Five patients in each group died during the core study (2 deaths in each group while on study drug and 3 deaths in each group after discontinuation of study drug [Online Supplementary Appendix 3, **Table S6**]). One death in the imatinib group (renal failure) and 1 in the placebo group (clostridial infection) were considered by the respective investigators to be study-drug related.

During the study, 28 (27%) patients discontinued due to AEs in the imatinib group compared with 9 (9%) in the placebo group, with the majority in both groups discontinuing in the first 8 weeks. The most frequent AEs were nausea, peripheral edema, diarrhea, vomiting and periorbital edema, all known side effects of imatinib (**Table 3**; for additional data see Online Supplementary Appendix 3, **Tables S7–9**). Anemia, leucopenia and thrombocytopenia were observed in 14%, (5% severe), 2% (0% severe) and 5% (1% severe) of imatinib patients, respectively. Serious AEs (SAEs) were also more frequent with imatinib than with placebo (**Table 3**).

Echocardiographic assessments did not show any evidence of cardiac dysfunction associated with imatinib therapy (Online Supplementary Appendix 3, **Table S10**). In addition, there was no indication of renal toxicity or hepatotoxicity due to imatinib therapy.

## Long-Term Extension Study

Of the 150 patients completing the 24-week core study, 144 patients entered the extension study; 6 declined. As of March 16<sup>th</sup> 2012, of the 144 patients enrolled in the extension, 60 had withdrawn (32 of 60 due to AEs). As of October 31<sup>st</sup> 2012, a total of 18 patients had died in the extension, 8 deaths in the core imatinib group (N=66) and 10 in the core placebo group (N=78).

Fifteen of these deaths occurred while on imatinib or within 30 days of discontinuation (5 core imatinib and 10 core placebo) while 3 occurred more than 30 days after discontinuation (all from the core imatinib group). Sixteen deaths have been adjudicated and 7 have been attributed to progression of PAH (3 core imatinib and 4 core placebo patients). None of these deaths were considered to be related to imatinib toxicity by the Adjudication Committee. (Online Supplementary Appendix 3, **Tables S6 and S11**).

The most frequent AEs (>10%) during the extension were similar to those in the core study (Online Supplementary Appendix 3, **Table S12**). Fifty-three percent of patients experienced SAEs. SAEs that occurred in  $\geq 3\%$  of patients were cardiac failure (4.2%), subdural hematoma (4.2%), dyspnea (4.2%), worsening PAH (4.9%), syncope (4.9%) and device-related infection (3.5%).

Subdural hematomas occurred in 8 patients (2 of 103 imatinib patients in the core study [1.9%]; 6 of 144 patients in the extension [4.2%]), on imatinib and concomitant anticoagulation. Six patients recovered, 1 died of subdural hematoma and 1 died of unrelated causes (Online Supplementary Appendix 3, **Table S13**).

In the IMPRES core study there were no patients who received a lung transplant on imatinib and 4 patients who received lung transplantation on placebo. Six extension study patients have undergone transplantation. Patients who underwent lung transplantation were withdrawn from the study and imatinib treatment was stopped. No evidence of surgical complications attributable to imatinib has been identified. Although these discontinued patients are no longer on study, reports of 2 extension study patients with serious adverse events following the lung transplant have been received. One patient had a cerebrovascular accident 2 days after transplantation and 1 patient was reported to have died of complications related to the

transplant approximately 4.5 months following the procedure.

## Discussion

This multicenter, randomized, double-blind, placebo-controlled 24-week study demonstrates that imatinib improves exercise capacity and hemodynamics in patients with advanced PAH despite combination therapy with 2 or more PAH drugs. For all currently approved drugs, the 6MWT was the primary endpoint or part of a primary composite endpoint. Studies of 3–4 months durations in patients who were treatment-naïve to PAH therapies showed placebo-corrected changes in 6MWD of 31–50 m.<sup>7–10</sup> More recent trials in patients on a single background PAH therapy showed improvements in 6MWD of 20–26 m.<sup>27,28</sup> Unlike most previous Phase III trials, the present study enrolled patients who were receiving a combination of at least 2 PAH therapies with 41% on triple therapy including 29% on continuous parenteral prostanoid infusion. Against this background therapy, the 32 m improvement in 6MWD with imatinib after 6 months of treatment was not only statistically significant but also clinically meaningful<sup>29</sup>, especially in light of the currently available treatment options having been exhausted in many of these patients.

The present study also showed that imatinib resulted in significantly improved hemodynamic parameters. The mean placebo-adjusted improvements in cardiac output and PVR were 0.88 L/min and  $-379 \text{ dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ , respectively. The magnitude of hemodynamic improvement is remarkable given that all patients had severe PAH with an average baseline PVR around  $1200 \text{ dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$  despite already being on multiple PAH treatments. Consistent with the changes in 6MWD, these hemodynamic differences were almost entirely due to improvements in patients randomized to imatinib rather than to deterioration in the placebo group. The improvements in cardiac output were accompanied by significant decreases in serum

NT-proBNP.

Time to clinical worsening, a composite endpoint including all-cause mortality, hospitalization for worsening PAH, worsening of WHO functional class or a decrease in 6MWD of more than 15% from baseline did not differ between the 2 treatment groups. Further analysis of these events suggests that the majority of the events in the imatinib group occurred during the first 8 weeks of the study in patients who did not tolerate the study medication and who dose reduced or discontinued the study medication. A sizable proportion of the worsening events in the imatinib group were transient events associated with known imatinib side effects rather than events reflecting disease progression. Of those with clinical worsening events who continued on imatinib, improvements in 6MWD and PVR at 24 weeks were consistent with long-term improvement with imatinib therapy as opposed to PAH disease progression. The analysis method used for TTCW assumes a non-informative missing data mechanism i.e. that censoring is not related to the endpoint of interest. It is difficult to confirm this in the IMPRES study due to the difficulty in distinguishing adverse events from true clinical worsening events or signs of disease progression. Further investigations are needed to assess the effects of imatinib therapy on outcome in patients with PAH.

Most of the AEs reported in the study were similar to those previously observed in association with the use of imatinib in patients in other approved indications. The most frequent AEs were nausea, peripheral edema, diarrhea, vomiting, and periorbital edema. There were no indications of liver toxicity or impaired renal function. However, particular note should be taken of the safety profile of imatinib in PAH since certain early AEs could be mistaken for progression of right heart failure, whilst progressive venous congestion in conjunction with worsening PAH could erroneously be interpreted as an imatinib side effect.

Study-drug discontinuations were comparatively high in the present study compared with previous studies with imatinib for malignant diseases (12–44% in studies up to 24 months in duration).<sup>30,31</sup> The exact reasons for this observation are unknown but potential causes may include effects of the underlying disease and co-medications as well as a lack of experience with the use of imatinib among PAH specialists.

Subdural hematomas occurred in 4.2% of the patients treated with imatinib in the extension study, all of them in patients receiving concomitant anticoagulation. The incidence of subdural hematomas in patients receiving imatinib for oncological indications is reported to vary between 0.2 and 5.8%.<sup>32</sup> A recent study by Henkens et al. showed a relatively high incidence of bleeding complications in patients receiving oral anticoagulants for PAH, but there was only one case of central nervous system bleeding in this series.<sup>33</sup> A recent review of cases of subdural hematoma was reported from the 12-week sildenafil SUPER-1 (277 treatment-naïve patients) and the 16-week PACES-1 (267 patients stable on IV epoprostenol) clinical trials, performed among patients with mean baseline PVR of 810.5 and 952.0 dynes.sec.cm<sup>-5</sup> respectively.<sup>34</sup> Patients in both trials received open-label sildenafil for  $\geq 3$  years. The report identified only 2 cases of subdural hematoma (1 in each open-label extension), both in patients receiving oral anticoagulants. Thus, the incidence of subdural hematomas in the present study was unexpectedly high. However, the patient population was different to that of PACES-1 and SUPER-1, both in terms of hemodynamic severity and background treatment at baseline. The mechanism by which imatinib might cause subdural hematoma is unclear and requires further evaluation.

Limitations of this study include the short observation period, the relatively high dropout rates in both treatment arms and the differential dropout rates on imatinib and placebo. However,

the patient population was highly selected for disease severity and the study duration was longer than in most previous trials in the field of pulmonary hypertension. Differential dropout was anticipated and was taken into account in the pre-specified statistical analysis plan by the choice of primary analysis method and sensitivity analyses. Our statistical analyses also followed the principles identified by the National Research Council for drawing inference from incomplete data,<sup>35</sup> but the possibility cannot be excluded that the higher discontinuation rate in the imatinib group may have led to an overestimation of the treatment effect. In addition, as 75% of the study population had idiopathic or heritable PAH, our findings are not necessarily applicable to all PAH subgroups.

The target dose of 400 mg qd was selected based on the fact that this dose is widely used in patients receiving imatinib for malignant disorders. The same target dose was also used in the Phase II study of imatinib in PAH.<sup>23</sup> The present study protocol allowed dose reduction in patients not tolerating imatinib at 400 mg/day. Approximately half of the patients receiving imatinib were able to remain on the 400 mg dose. Although the number of patients was too small for a formal dose-effect analysis, the largest treatment effects were observed in patients who received a dose of 400 mg/day (Online Supplementary Appendix 3, **Table S14**), albeit this is a non-randomized comparison. There was no difference in AEs between the patients who received 400 mg daily for  $\geq 50\%$  versus  $< 50\%$  of the study. However, the minimum efficacious dose of imatinib in PAH remains unknown and needs to be determined in future trials.

Finally, the present study did not further assess the mechanisms by which imatinib acts in PAH. Understanding these mechanisms is of key importance, not only to predict the response to therapy, but also to design more targeted tyrosine kinase inhibitors for this disease. These are crucial aspects for further research, especially as broad spectrum tyrosine kinase inhibition may



have pleiotropic effects on the cardiopulmonary system. Sorafenib, for instance, had detrimental effects on cardiac output in patients with PAH<sup>36</sup> and dasatinib has been identified as a potential cause of PAH.<sup>37</sup>

In conclusion, this study provides evidence that imatinib, as the first representative of a new class of drugs for the treatment of PAH, improves exercise capacity and hemodynamics in patients with advanced PAH who remain symptomatic on at least 2 drugs of the currently available 3 drug classes. Discontinuations of study medication, and SAEs, including subdural hematomas, were more common in the imatinib group and further studies are required to assess the risk-benefit profile of imatinib in patients with advanced PAH. Until further data is available, the off-label use of imatinib for this indication is strongly discouraged.

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DQ contributed to study design and conduct, data analysis and interpretation.

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**Table 1.** Baseline Demographic and Clinical Characteristics

	<b>Imatinib (n=103)</b>	<b>Placebo (n=98)</b>
Median (range) age, years	50 (18–77)	47 (18–77)
Age distribution, n (%)		
18–39 years	28 (27)	35 (36)
40–64 years	57 (55)	54 (55)
≥65 years	18 (18)	9 (9)
Male/female gender, n (%)	20 (19) / 83 (81)	19 (19) / 79 (81)
Race, n (%)		
Caucasian	77 (75)	72 (74)
Black	4 (4)	5 (5)
Asian	19 (18)	20 (20)
Other	3 (3)	1 (1)
Median (range) PAH duration, years	3.7 (0–41)	5.1 (0–17)
Type of PAH		
Idiopathic or heritable	77 (75)	74 (76)
Associated with other conditions	26 (25)	23 (24)
Other	0	1 (1)
WHO Functional class		
Class I	1 (1)	0
Class II	23 (22)	28 (29)
Class III	71 (69)	65 (66)
Class IV	8 (8)	5 (5)
PAH-specific background therapy*		
ERA and PDE5	32 (31)	27 (28)
ERA and PG	15 (15)	10 (10)
PG and PDE5	14 (14)	20 (20)
ERA and PDE5 and PG	42 (41)	41 (42)
Median 6MWD, m (range)	355 (154–450)	366 (153–446)
Hemodynamics, mean (SD)		
Right atrial pressure, mmHg	10 (6)	10 (7)
Mean pulmonary arterial pressure, mmHg	59 (11)	60 (13)
Pulmonary capillary wedge pressure, mmHg	9 (3)	9 (3)
Cardiac output, L/min	3.5 (0.9)	3.5 (0.7)
Cardiac index, L/min/m <sup>2</sup>	2.1 (0.5)	2.1 (0.5)
Pulmonary vascular resistance, dynes·sec·cm <sup>-5</sup>	1202 (414)	1181 (360)

ERA, endothelin receptor antagonists; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type-5 inhibitors; PG, prostacyclin analogs; SD, standard deviation; WHO, World Health Organization; 6MWD, 6-minute walk distance.

\*In total, 69% imatinib patients and 72% placebo patients were treated with prostacyclin analogs. By formulation, 31% and 28% patients received intravenous, 17% and 16% patients received inhaled, 15% and 17% patients received subcutaneous and 7% and 11% patients received oral prostacyclin analogs in imatinib and placebo groups respectively.

**Table 2.** Sensitivity Analyses of the Primary Endpoint (6MWD at Week 24) including imputation for missing data. For full details of statistical methodology used to perform sensitivity analyses adjusting for missing data, please refer to Supplementary Appendix 1.

	<b>LS mean treatment difference, imatinib-placebo at Week 24, m (95% CI)</b>	<b>P value</b>
Primary analysis (repeated measures ANCOVA)	32 (12, 52)	0.002
Univariate ANCOVA using LOCF	27 (7, 47)	0.008
Univariate ANCOVA using BOCF	20 (5, 35)	0.010
Modified multiple imputation using penalties* (repeated measures ANCOVA)		
0% penalty	34 (14, 54)	0.001
2% penalty	33 (13, 53)	0.001
8% penalty	28 (8, 48)	0.005
10% penalty	27 (7, 47)	0.008
Multiple imputations using information from placebo patients (repeated measures ANCOVA) <sup>†</sup>	27 (6, 48)	0.013
Multiple imputations for specific reasons for discontinuation using information from placebo patients (repeated measures ANCOVA) <sup>‡</sup>	28 (7, 50)	0.009
Imputation based on published trials – CMH test		0.013
Imputation based on published trials – univariate ANCOVA	29 (7, 50)	0.010

ANCOVA, analysis of covariance;BOCF, baseline observation carried forward;CI, confidence interval;CMH, Cochran Mantel Haenszel test;LOCF, last observation carried forward;LS, least squares;6MWD, 6-minute walk distance.

\*Penalties were applied to patients in the imatinib arm, assuming a lower post-withdrawal 6MWD for patients who discontinued due to AEs, unsatisfactory therapeutic effect, or death than for patients that remained in the study (allowing for the possibility of data being “missing not at random”). The scenarios investigated were 98, 95, 92 and 90% lower 6MWD compared to imputations which assume the data is missing at random.

<sup>†</sup>For patients in the active arm that discontinued for any reason, missing values were imputed based on information of other patients that discontinued and placebo patients only.

<sup>‡</sup>For patients in the active arm that discontinued because of AE, unsatisfactory therapeutic effect or death, missing values were imputed based on information of other patients that discontinued for these reasons and placebo patients only.

Please see Supplementary Appendix 1 for full details.

**Table 3.** Frequency of Adverse Events

	<b>Imatinib (n=103)</b>	<b>Placebo (n=98)</b>
Adverse event, n (%) <sup>*</sup>	100 (97)	94 (96)
Nausea	57 (55)	23 (24)
Peripheral edema	45 (44)	20 (20)
Diarrhea	36 (35)	19 (19)
Vomiting	31 (30)	10 (10)
Periorbital edema	30 (29)	7 (7)
Headache	25 (24)	22 (22)
Dyspnea	19 (18)	13 (13)
Nasopharyngitis	18 (18)	19 (19)
Hypokalemia	16 (16)	3 (3)
Anemia	14 (14)	3 (3)
Cough	11 (11)	15 (15)
Fatigue	11 (11)	7 (7)
Face edema	10 (10)	1 (1)
Muscle spasms	10 (10)	2 (2)
Serious adverse events, n (%) <sup>†</sup>	45 (44)	29 (30)
Worsening of pulmonary hypertension	6 (6)	8 (8)
Anemia	7 (7)	1 (1)
Dyspnea	6 (6)	2 (2)
Edema peripheral	6 (6)	0
Presyncope	5 (5)	0
Diarrhea	3 (3)	2 (2)
Device-related infection	3 (3)	0
Syncope	1 (1)	5 (5)
Subdural hematoma	2 (2)	0 (0)
Total patients with clinical worsening, n (%)	37 (36)	32 (33)
Death (all deaths)	3 (3)	3 (3)
Hospitalization for worsening of PAH (adjudicated events)	17 (17)	13 (13)
Worsening of WHO functional class by at least 1 level	15 (15)	11 (11)
15% reduction of 6MWD on 2 consecutive occasions as compared to baseline	12 (12)	17 (17)
Worsening of WHO functional class by at least 1 level and 15% reduction in 6MWD on 2 consecutive occasions as compared to baseline	2 (2)	3 (3)

PAH, pulmonary arterial hypertension; WHO, World Health Organization; 6MWD, 6-minute walk distance.

<sup>\*</sup>Individual adverse events are shown if they occurred in >10% in the imatinib group (see online supplement for full listing).

<sup>†</sup>Individual serious adverse events are shown if they occurred in ≥3 patients in either group.

**Figure Legends:**

**Figure 1.** Patient disposition. \*Two additional deaths occurred, 1 in each group, within 30 days of study drug discontinuation;†Long-term dose-escalation was defined as  $\geq 77$  days (i.e.  $\geq 50\%$  of the 22-week period during which patients could receive imatinib 400 mg).

**Figure 2. A.** Change in 6MWD from baseline by treatment. Values are least squares means and standard errors. *P*-values are for between-group comparisons from analysis of covariance of change from baseline in 6MWD (m) at each time. 6MWD, 6-minute walk distance. N.B. Sixty-nine patients receiving imatinib and 81 patients receiving placebo completed the study. Three patients receiving imatinib and 1 patient receiving placebo did not have a 6MWD test on completion. **B.** Subgroup analysis of changes from baseline in 6MWD (m) to end of study according to background therapy. Data are least squares mean change (m) with 95% confidence intervals. ERA, endothelin receptor antagonists;PDE5, phosphodiesterase type-5 inhibitors;PG, prostacyclin analogs;6MWD, 6-minute walk distance.

**Figure 3.** Least squares (LS) mean changes from baseline to end of study in mean pulmonary artery pressure (PAP;panel A), cardiac output (CO;panel B), pulmonary vascular resistance (PVR;panel C), and right atrial pressure (RAP;panel D).  $\Delta$ , LS mean difference between groups;CI, confidence interval. N.B. Patients included in analyses of hemodynamic parameters include those who completed the study plus those who discontinued early but had a right heart catheterization performed at discontinuation.

**Figure 4.** Time to clinical worsening. CI, confidence interval. Values below the graph are the number of patients remaining in the study at each time point.

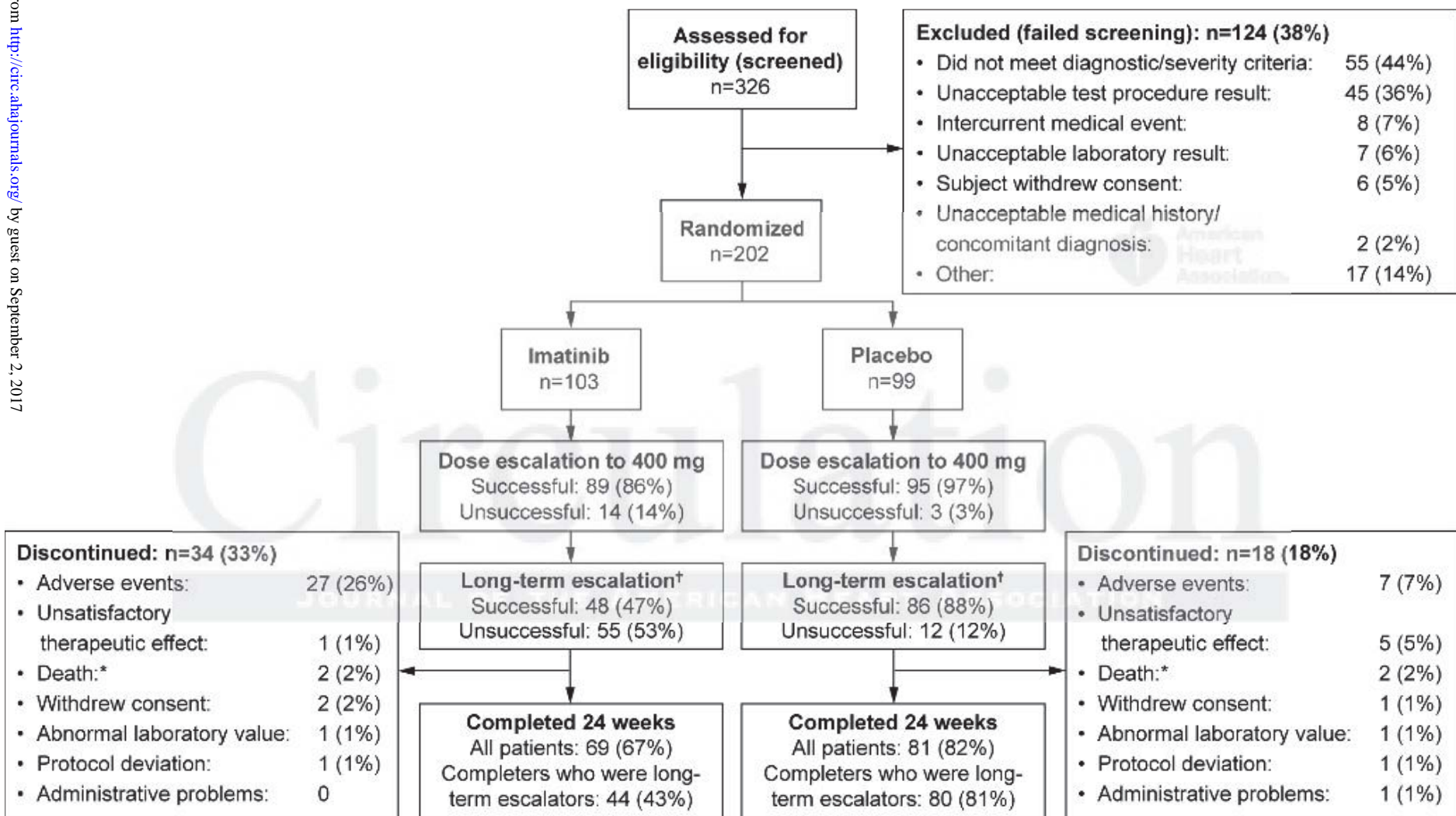


Figure 1

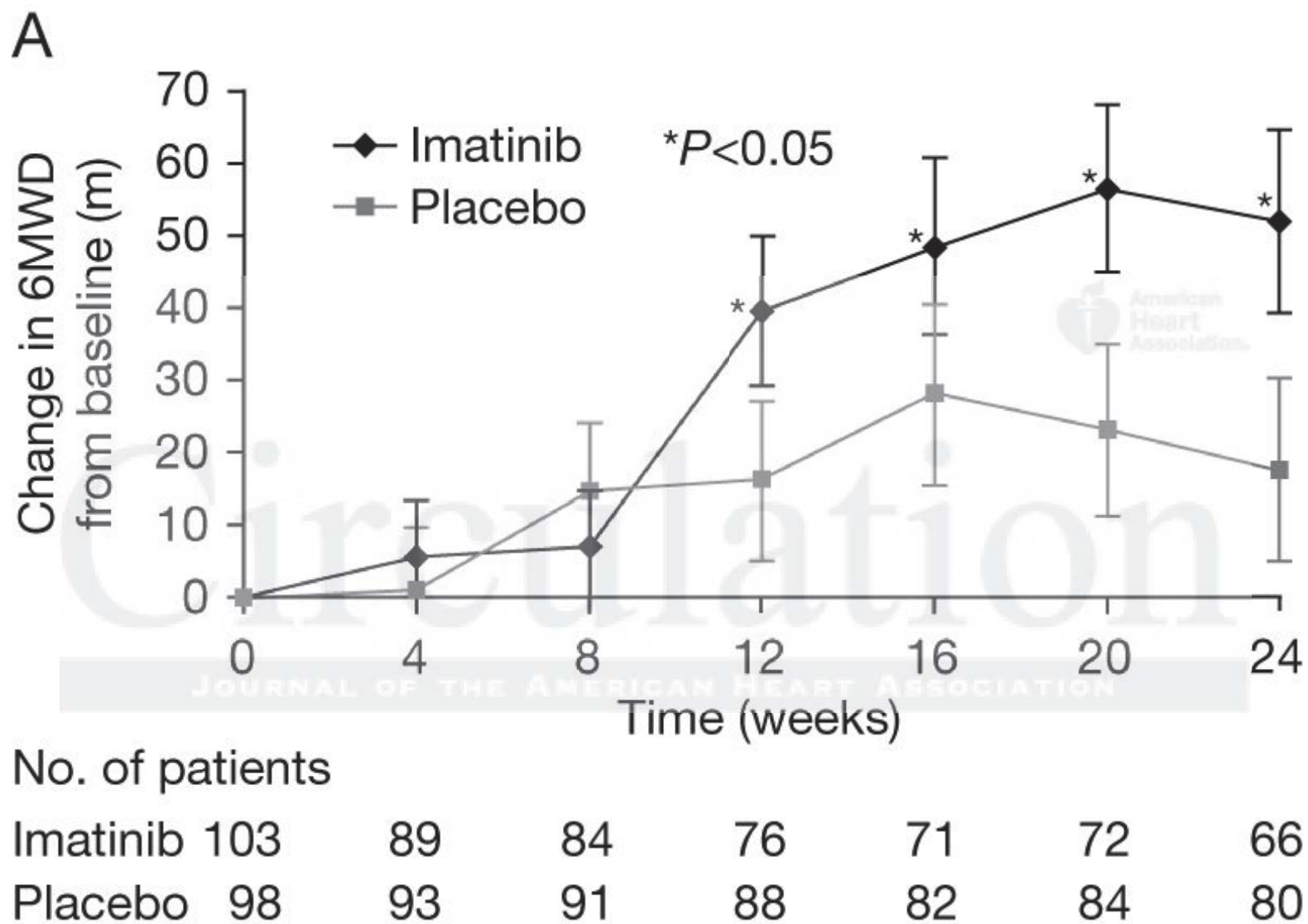


Figure 2



B

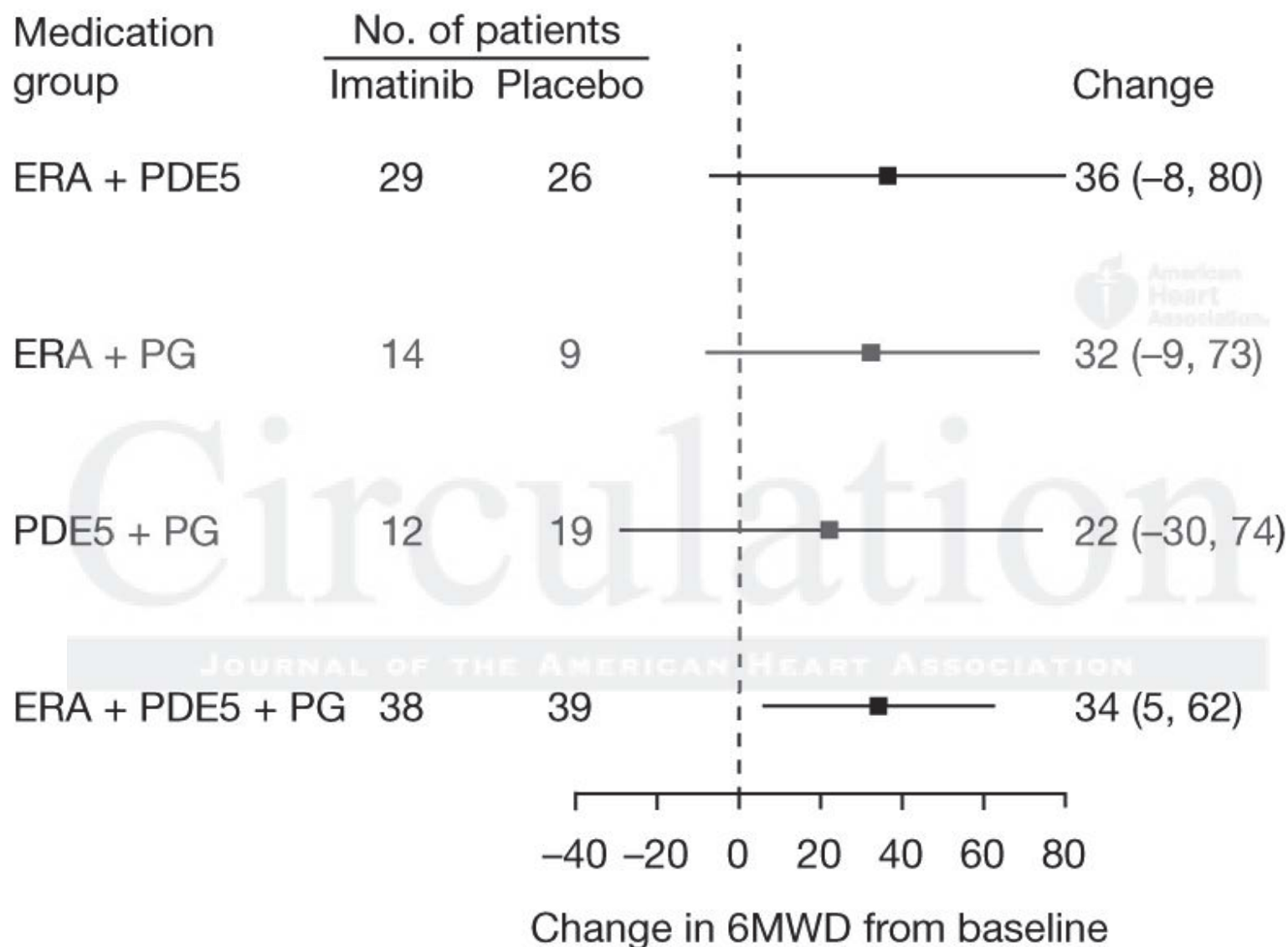


Figure 2, cont'd



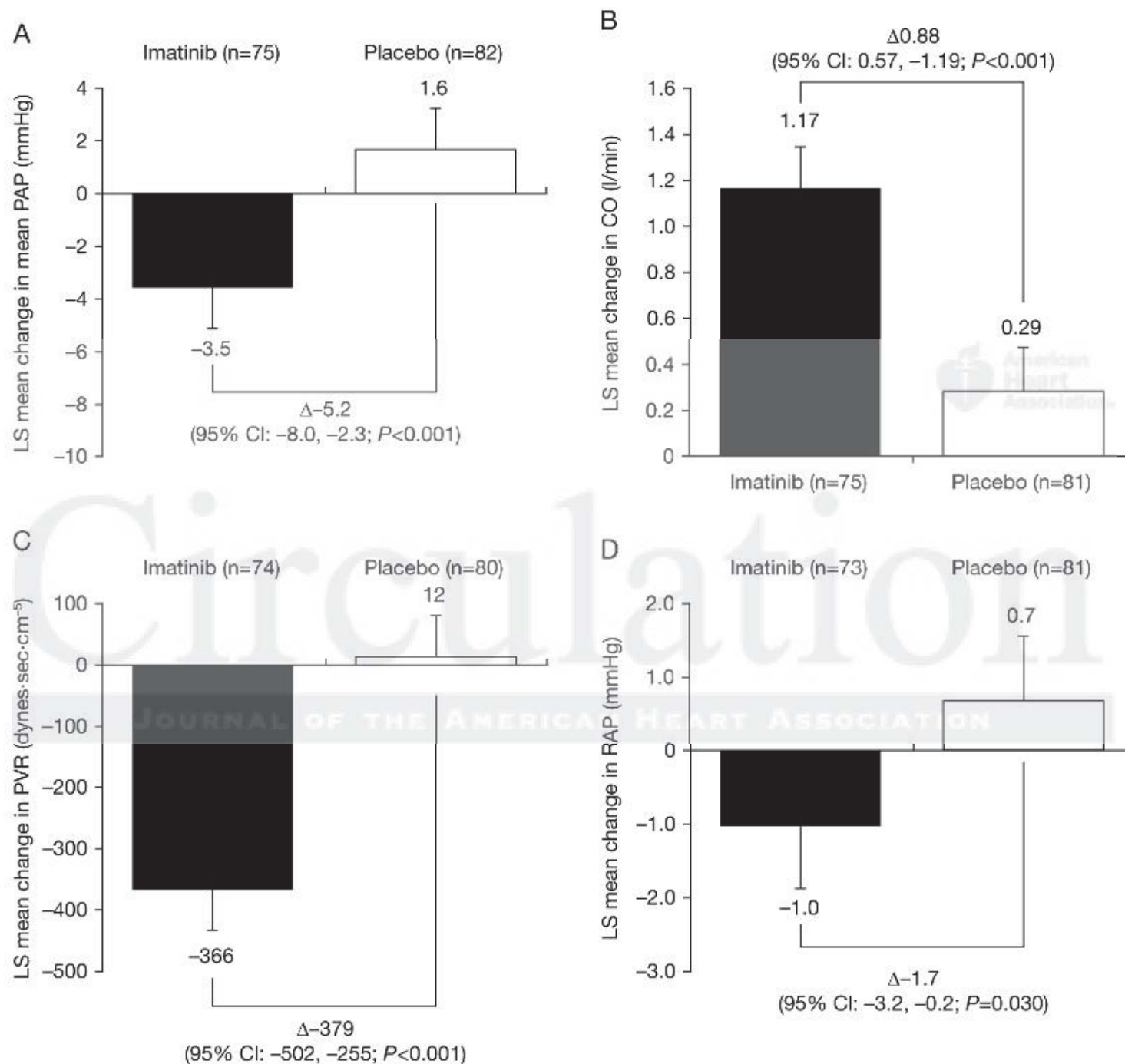
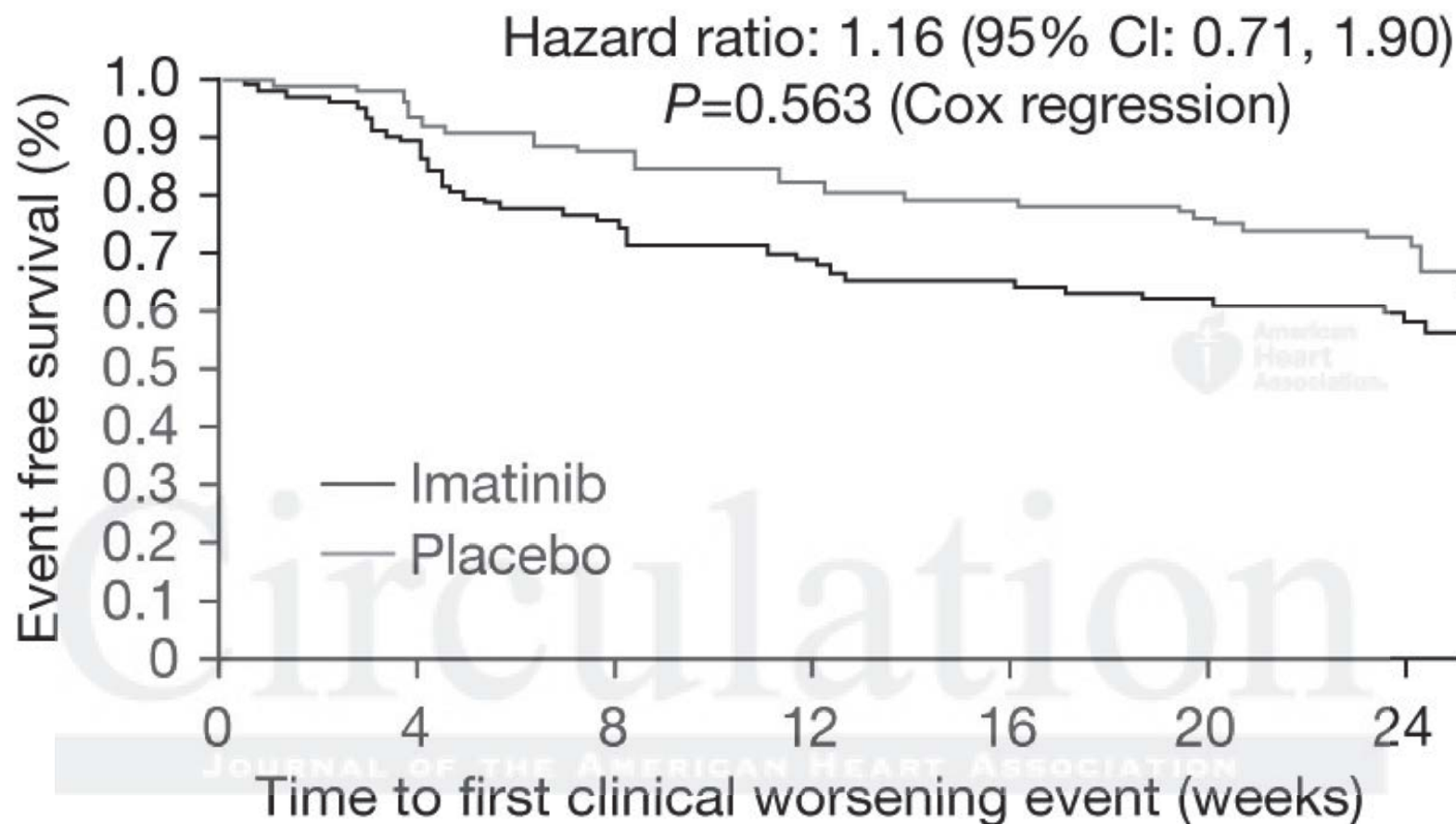


Figure 3



No. of patients

Imatinib	103	93	70	66	60	58	45
Placebo	98	91	85	80	75	72	54

Figure 4

## **Imatinib Mesylate as Add-On Therapy for Pulmonary Arterial Hypertension: Results of the Randomized IMPRES Study**

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## **Supplementary Material: Contents**

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- i) Inclusion criteria
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- iii) Sensitivity analysis of the primary endpoint
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### **Supplementary Appendix II: Study protocol**

### **Supplementary Appendix III: Results**

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## Supplementary Appendix I: Methods

### i) Inclusion criteria (to be met at the time of the screening visit and prior to randomization):

1. Male or female  $\geq 18$  years of age
2. A current diagnosis of pulmonary arterial hypertension (PAH) according to the Dana Point 2008 Meeting: World Health Organization (WHO) Diagnostic Group I, idiopathic or heritable (familial or sporadic) PAH, PAH associated with collagen vascular disease including systemic sclerosis, rheumatoid arthritis, mixed connective tissue diseases, and overlap syndrome. PAH following 1 year repair of congenital heart defect (atrial septal defect, ventricular septal defect or patent ductus arteriosus), or PAH associated with diet therapies or other drugs
3. A pulse volume recording (PVR)  $\geq 800$  dynes.sec.cm<sup>-5</sup> (as assessed by right heart catheterization at screening or in the 3 months preceding the screening) despite treatment with 2 or more specific PAH therapies, including endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE5), or subcutaneous, inhaled, intravenous or oral prostacyclin analogs for  $\geq 3$  months. Background therapy doses were to be stable for  $\geq 30$  days except for warfarin and prostacyclin analogs ( $\geq 30$  days but doses could vary even within the month before enrollment).

The PVR restriction was initially 1000 dynes to reflect the post-hoc analysis performed for the proof-of-concept study.<sup>1</sup> The value of 1000 dynes was based on the median value observed in all patients in the proof-of-concept study. However this was lowered after the initiation of the trial (amendment made in February 2010) to more closely reflect severe PAH patients who were uncontrolled on 2 or more approved PAH therapies. The value of 800 dynes was based on the cut-off for the top 2 tertiles of PVR observed in all patients in the proof-of-concept study.

4. World Health Organization functional Class II-IV. For WHO Functional Class IV, 1 of the 2 or more specific PAH therapies was to be an inhaled, subcutaneous, intravenous or oral prostacyclin analogue, unless the subject showed intolerance of prostacyclin analogues.
5. 6MWD  $\geq$ 150 meters and  $\leq$ 450meters at screening. Distances of 2 consecutive 6MWTs were to be within 15% of one another.
6. Ability to provide written informed consent by the patient or a legal guardian.

**ii) Interactive Voice Response System**

This study utilized an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) for randomization, dispensing study drug, and study drug titration. At Visit 2 (randomization visit), the investigator or his/her delegate called the IVRS and confirmed that the patient fulfilled all the inclusion/exclusion criteria. The IVRS assigned 2 unique medication numbers to the patient that corresponded to the medication bottles assigned. The medication numbers were used to link the patient to a treatment arm.

On January 13, 2010 it was discovered that the IVRS/IWRS set-up was not consistent with protocol requirements. Specifically, the assignment of study drug to the active (imatinib) treatment arm at Visit 2 (Randomization) and the titration of study drug was not per protocol. At the time this issue was identified a total of 28 subjects had randomized into the study.

Regarding the assignment of study drug, a total of 13 subjects were affected by this issue. These 13 subjects were randomized to the active (imatinib) treatment arm and initiated treatment at imatinib 400 mg once daily (qd) instead of imatinib 200 mg qd as specified per protocol. At Visit 4 these subjects were maintained on imatinib 400 mg qd and no dose escalation occurred at this visit. No subject received more than 400 mg of imatinib. The 15 subjects randomized to the placebo treatment arm were not affected.



Regarding the titration of study drug, a total of 2 subjects were affected by this issue. These 2 subjects required an unscheduled down-titration to the 200 mg qd study drug dose (blinded treatment), however the system re-dispensed the 400 mg qd study drug dose in error. One subject received a down-titration of study medication through a manual backup system that was established to ensure appropriate dose adjustments. As corrective action to this finding, on January 14, 2010 the IVRS/IWRS was closed/turned off to new subjects. The IVRS/IWRS was subsequently re-programmed and re-validated and operational again on January 22, 2010. All subsequent subjects randomized to imatinib were started at 200 mg and dose titrations were per protocol.

As an additional follow-up action and to ensure subject safety, the Novartis Brand Safety Leader and Global Program Medical Director performed blinded internal reviews of adverse events (AEs) and serious AEs (SAEs) and did not identify any issues that required intervention. In addition, a Data Monitoring Committee (DMC) meeting was held on February 18, 2010 to review all subjects affected by this issue. Following a closed session review of blinded SAE data, the DMC recommended continuation of the study without changes.

### **iii) Sensitivity analysis of the primary endpoint**

The primary analysis for the 6-minute walk distance (6MWD) was a repeated measures analysis of covariance (ANCOVA). This method was selected as it leads to estimators with comparatively small bias (versus last observation carried forward [LOCF]), and controls Type I error rates at a nominal level in the presence of missing completely at random or missing at random (MAR) and some possibility of missing not at random (MNAR) data.<sup>2</sup> This method uses information on all existing visits to create the treatment estimate at Week 24.

A number of sensitivity analyses to impute missing data were also performed:

- a) Univariate ANCOVA analyses:
  - i) LOCF (from Week 4 onwards)

This model included all patients who had a post-baseline observation (n=92 imatinib, n=93 placebo).

ii) *Baseline observation carried forward (BOCF)*

In this model, any subject who did not reach Week 24 is assumed to have a change from baseline in 6MWD of 0 months. One hundred and three subjects on imatinib and 98 subjects on placebo were included in the analysis.

b) Multiple imputation methods used to replace missing data

All analyses included 103 subjects on imatinib and 98 subjects on placebo.

i) *Modified multiple imputation using penalties*

Multiple imputations for the missing 6MWD data were performed separately for each treatment arm under the MAR assumption and baseline 6MWD values were included in the imputation model. The imputed values after discontinuations for the imatinib arm were then modified to incorporate different MNAR penalties. The penalties applied only to patients in the imatinib arm who discontinued due to AEs, unsatisfactory therapeutic effect, or death. The modifications for the imatinib arm were specified assuming a lower post-withdrawal 6MWD for patients who discontinued due to AEs, unsatisfactory therapeutic effect, or death than for patients that remained in the study. The scenarios investigated were 98, 95, 92 and 90% lower 6MWD compared to the imputations under the MAR assumption. Imputed values under the MAR assumption for patients in the placebo arm and patients who discontinued due to other reasons remain unchanged.

ii) *Multiple imputations using the information from placebo patients*

Multiple imputations for the missing primary efficacy data were created under a MAR assumption for patients in the placebo arm. Intermittent missing values for patients in the active arm were also imputed under an MAR assumption.

For patients in the active arm that discontinued for any reason, missing values were imputed based on information of other patients that discontinued and placebo patients only. This assumed that patients after discontinuation have a similar response as a) patients in the active arm that also discontinued and b) placebo patients.

iii) *Multiple imputations for certain reasons of discontinuation using the information from placebo patients*

Multiple imputations for the missing primary efficacy data were created under a MAR assumption for patients in the placebo arm. In the active arm, intermittent missing values and missing values for patients that discontinued for reasons other than AE, unsatisfactory therapeutic effect, and death were also imputed under a MAR assumption.

For patients in the active arm that discontinued because of AE, unsatisfactory therapeutic effect or death, missing values were imputed based on information of other patients that discontinued for these reasons and placebo patients only. This method assumes that after discontinuation, patients are similar to other patients in the active arm that discontinued for the same reasons and placebo patients.

In each case, 100 data sets were created using the SAS PROC MI procedure. For scenario a) the datasets created under the MAR assumption were modified to include the penalties as described above. Each imputed dataset was then analyzed through a mixed effects model for repeated measures (MMRM) model with an unstructured covariance matrix. The MMRM model included treatment, week and country as fixed factors, center within country as a random effect, and baseline 6MWD as a covariate. Treatment by week and baseline by week interactions were also included in the model.

The results for each dataset were then combined using SAS MIANALYZE procedure to obtain a single inference that reflects the uncertainty due to missing data.

c) Imputation rule based on previously published trials

To allow comparison with previously published trials a similar imputation method was used.

Imputation rule: subjects who died or did not complete and experienced a time to clinical worsening event and discontinued study treatment within plus or minus 14 days of this event were given the worst possible change from baseline observed at any time point recorded in all patients within their treatment group. Subjects who discontinued early from study due to a treatment-related AE were given a value of 0 m for change from baseline. For all other subjects the most recent post-baseline 6MWD was carried forward to the Week 24 time-point if made at least 28 days after first dose. Subjects who did not fit into any of the categories above were assigned a change from baseline of 0 months. All subjects (103 on imatinib and 98 on placebo) were included in the analysis.

The data were analyzed in 2 ways:

- i) Using a stratified non-parametric method (the Cochran Mantel-Haenszel test) stratified by baseline 6MWD ( $\leq 325$  m versus  $> 325$  m), PAH diagnosis (idiopathic versus other) and ERA use (yes versus no). It should be noted that as this method is based on ranks, a *P*-value for significance but no mean values are produced.
- ii) Using ANCOVA to allow the production of treatment differences.

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Clinical Development & Medical Affairs

QT1571/imatinib mesylate

Clinical Study Protocol CQT1571A2301

**A 24-week randomized placebo-controlled, double-blind multi-center clinical trial evaluating the efficacy and safety of oral QT1571 as an add-on therapy in the treatment of severe pulmonary arterial hypertension: Imatinib in Pulmonary arterial hypertension, a Randomized, Efficacy Study (IMPRES)**

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## List of abbreviations

AE	adverse event
ALL	Acute Lymphoblastic Leukemia
ALT	alanine aminotransferase
AP	Accelerated Phase
ASD	Atrial Septal Defect
ASM	Aggressive Systemic Mastocytosis
AST	aspartate aminotransferase
b.i.d.	twice a day
BC	Blast Crisis
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEL	chronic Eosinophilic Leukemia
CHF	Congestive Heart Failure
CML	Chronic Myeloid Leukemia
CO	Cardiac Output
CP	Chronic Phase
CPO	Country Pharma Organization
CRD	Clinical Research and Development
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DFSP	Dermatofibrosarcoma Protuberans
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
ERA	Endothelin Receptor Antagonist
FAS	Full Analysis Set
GIST	Gastrointestinal Stromal Tumors
HES	Hypereosinophilic Syndrome
HRQOL	Health related quality-of-life
i.v.	intravenous(ly)

ICH	Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon- $\alpha$
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
MAP	Mean Arterial Pressure
o.d.	once a day
p.o.	oral(ly)
PAP	Pulmonary Arterial Pressure
PCWP	Pulmonary Capillary Wedge Pressure
PDA	Posterior Descending Artery
PDE5	Phosphodiesterase 5 inhibitor
PDGF	Platelet-derived Growth Factor
PDGFR	Platelet-derived Growth Factor Receptor
PoC	Proof Of Concept
PP	Per Protocol
PT/INR	Prothrombin Time/International Normalized Ratio
PVR	Pulmonary Vascular Resistance
QOL	Quality of life
REB	Research Ethics Board
RHC	Right Heart Catheterization
RVSP	Right Ventricular Systolic Pressure
SAE	serious adverse event
SBP	Systolic Blood Pressure
6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
SMC	Smooth Muscle Cell
SVR	Systemic Vascular Resistance
TTCW	Time To Clinical Worsening
VSD	Ventricular Septal Defect
WHO	World Health Organization

## Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Medication number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

## Protocol synopsis

**Title of study:** A 24-week randomized placebo-controlled, double-blind multi-center clinical trial evaluating the efficacy and safety of oral QTI571 as an add-on therapy in the treatment of severe pulmonary arterial hypertension: Imatinib in Pulmonary arterial hypertension, a Randomized, Efficacy Study (IMPRES).

**Purpose and rationale:** Pulmonary arterial hypertension (PAH) subjects who remain symptomatic despite specific available therapies have high morbidity and mortality. Though several therapies are now available, there is no cure. A previous Proof-of-Concept (PoC) trial evaluated the safety, tolerability, and efficacy of QTI571 (imatinib mesylate) as an adjunct to PAH specific therapy in patients with pulmonary arterial hypertension. This was a 24-week randomized, double-blind, placebo-controlled study of PAH subjects who remained symptomatic on one or more PAH therapies in WHO Functional Class II-IV.

Fifty-nine patients (40 female; 19 male) were enrolled with 42 (71.2%) completing the 6 month study. The reasons for withdrawals in the QTI571 group included death (n=3), worsening of PAH (n=2), worsening of general condition (n=1), respiratory infection (n=1), right ventricular failure (n=1), and other adverse events (n=1, loss of appetite and fatigue). The reasons for withdrawals in the placebo group included death (n=3), worsening of PAH (n=2), worsening of general condition (n=1), subject withdrew consent (n=1) and other adverse events (n=1, back pain, acid reflux, dizziness, heart flutters, chest wall pain). Baseline characteristics were similar between the two treatment groups. Overall, patients had a mean age of 44.3 years, mean weight of 68.7 kg and mean body mass index of 24.6 kg/m<sup>2</sup>. Fifty five of the 59 patients were Caucasian and 78% had idiopathic PAH. At baseline, 79% of the QTI571-group and 81% of the placebo-group patients were receiving combination therapy.

The mean ( $\pm$ SD) 6MWD did not significantly change in the imatinib group vs. placebo (+22 $\pm$ 63 vs. -1.0 $\pm$ 53 m; mean treatment difference 21.7 m; 95% CI (-13.0, 56.5; p=0.21)). There was, however, a significant decrease in PVR (mean treatment difference -230.7 dynes.sec.cm<sup>-5</sup>; 95% CI (-383.7, -77.8; p=0.004) and increase in cardiac output (CO; mean treatment difference 0.68 L/min; 95% CI (0.10, 1.26; p=0.02) in imatinib recipients compared with placebo. There was no significant difference in PAPm or change in FC between imatinib and placebo treated patients.

In a post-hoc subgroup analysis, to identify subjects who may be more responsive than others, baseline characteristics were assessed including baseline CO, PAPm, 6MWD and PVR. The beneficial changes in 6MWD were most prominent in patients with a baseline PVR > 1,000 dynes.sec.cm<sup>-5</sup>, i.e. the median PVR in the study. The greatest response was in patients on PAH specific combination therapy with a baseline PVR > 1,000 dynes.sec.cm<sup>-5</sup>, who showed a statistically significant improvement between baseline and study end for 6MWD in the imatinib group [n=5], compared with placebo [n=10] (mean +96m, 95%CI 13.2 to 179.3; p=0.027). For PVR  $\geq$  800 dynes.sec.cm<sup>-5</sup> on 2 or more specific PAH therapies there was also a statistically significant increase in 6MWD of 65 meters, (p=0.046). PAH specific combination therapy included an endothelin receptor antagonist (ERA) plus a phosphodiesterase 5 inhibitor (PDE5) such as sildenafil, or an ERA plus a prostacyclin analogue, or a PDE5 plus a prostacyclin analogue, or an ERA plus a PDE5 plus a prostacyclin analogue. The effect seen with the addition of imatinib on top of PAH specific combination therapy is clinically relevant and greater than that typically seen with other combination PAH therapies. When sildenafil was added to intravenous epoprostenol, there was an increase of 29 meters in 6MWD (Simonneau G et al. 2008). For intravenous epoprostenol added to a combination of an ERA plus a PDE5, there was a 41 meter increase in 6MWD (Jacobs W et al. 2009).

In conclusion, while the primary endpoint failed to reach statistical significance, the data are strongly suggestive of a medically significant treatment benefit associated with the use of QTI571. More specifically, the beneficial changes were most prominent in the group of patients with a PVR>1,000 dynes.sec.cm<sup>-5</sup> (as outlined above) and even more so in patients with a PVR>1,000 dynes.sec.cm<sup>-5</sup> who were uncontrolled on 2 or more PAH therapies. This latter effect was especially prominent in terms of 6MWD. The data suggested that this particularly severe group may have the greatest benefit-risk ratio and therefore further studies are warranted focusing on this group.



**Objectives:**

**Primary**

- To evaluate the efficacy of QTI571 compared to placebo as measured by the change in 6-minute walk distance (6MWD) from baseline to 24-weeks

**Secondary**

- To evaluate the time to clinical worsening (TTCW)
- To assess the safety and tolerability of QTI571.
- To evaluate change in pulmonary hemodynamics from baseline in patients after 24 weeks of treatment with QTI571 as compared to placebo.
- To assess change in Borg dyspnea score during 6-minute walk testing (6MWT), monthly, with QTI571 as compared to placebo.
- To assess the pharmacokinetics of QTI571 and the potential for interaction of QTI571 on sildenafil and bosentan.

**Exploratory**

- To assess the pharmacogenetics of QTI571.
- To assess the use of echocardiography of right ventricular performance as a measure of efficacy in treatment of PAH at selected sites.
- To assess the use of different possible definitions of time for TTCW as a measure of efficacy in treatment of PAH.
- To evaluate efficacy of QTI571 200 mg QD in subjects that are not able to tolerate 400 mg QD.
- To assess the impact of QTI571 on medical resource utilization

**Population:** The study population will consist of 200 adult males and females 18 years of age or older, with a diagnosis of severe pulmonary arterial hypertension (PAH), defined as those who remain symptomatic, i.e. WHO functional class II-IV ([section 7.4](#)), on at least two PAH specific therapies and  $PVR \geq 800 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$ . Patients are to be recruited at approximately 60 centers globally.

**Inclusion/Exclusion criteria:**

**Inclusion:**

1. Male or female 18 years of age or older
2. A current diagnosis of Pulmonary Arterial Hypertension according to the Dana Point 2008 Meeting
3. A  $PVR \geq 800 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$  despite treatment with two or more specific PAH therapies
4. WHO Functional Class II-IV
5. 6MWD  $\geq 150$  meters and  $\leq 450$  meters
6. Ability to provide written informed consent by the patient or legal guardian

**Exclusion:**

1. Women who are lactating or of child-bearing potential
2. With a QTcF  $> 450$  msec for males and  $> 470$  msec for females at screening and baseline in the absence of right bundle branch block
3. Having syncope in the 3 months prior to the screening visit
4. With a history of blood or bleeding disorder

**Investigational and reference therapy:**

- Imatinib 100 mg film coated tablets provided in 70-tablet bottles
- Placebo to match imatinib 100 mg film coated tablets in 70-tablet bottles

**Study design:** This is a multinational, multicenter, double blind, parallel group study design in patients with PAH.

Upon providing written informed consent, subjects will be screened by right heart catheterization (RHC) to determine pulmonary hemodynamics. Echocardiographies will be performed to estimate right ventricular systolic pressure (RVSP), left ventricular ejection fraction and changes in valve function, as well as electrocardiograms (ECG), safety laboratory assessments and two 6MWT. At the end of the screening period, patients will be randomized in a 1:1 ratio to receive treatment with QTI571 or placebo.

Treatment with QTI571 or matching placebo will be started at 200 mg once daily for two weeks. If well tolerated, the dose will be increased to 400 mg once daily. If the 400 mg daily dose is not well tolerated, a down titration to 200 mg once daily is permitted.

During the 24 week treatment period 6MWT will be performed monthly. ECG will be performed at each visit. Safety laboratories will be obtained weekly during dose escalation and monthly there after. An echocardiography will be performed following 3 months of treatment and repeated at the final study visit (week 24). A second right heart catheterization will also be performed at the final study visit.

**Efficacy assessments:**

- Six-minute walk test and Borg test
- Hemodynamic parameters measured/calculated from right heart catheterization
- Time to clinical worsening

**Other assessments:**

- Resource utilization
- Pharmacokinetics
- Pharmacogenetics

**Data analysis:**

The superiority of QTI571 over placebo will be evaluated by testing the following null hypothesis ( $H_0$ ) versus the alternative hypothesis ( $H_a$ ):

$H_0$ : There is no difference in the 6-MWD after 24 weeks for patients with PAH treated with QTI571 compared to placebo

$H_a$ : There is a difference in the 6-MWD after 24 weeks for patients with PAH treated with QTI571 compared to placebo

Six-minute walk distance will be analyzed using a mixed effects model for repeated measures with an unstructured covariance matrix implemented via PROC MIXED with a REPEATED statement. The primary model will include treatment, week, and country as factors, with baseline 6-MWD as a covariate. Treatment by week and baseline by week interactions will also be included in the model. The primary outcome of interest will be the comparison of QTI571 versus placebo after 24 weeks of treatment.

The primary analysis population will be the FAS. Estimated adjusted treatment differences for QTI571 minus placebo will be displayed along with the associated confidence interval and p-value (2 sided). Superiority of QTI571 over placebo will be demonstrated if the p-value (2 sided) is less than 5% significance level and the confidence interval at week 24 lies entirely to the right of (higher than) 0 meters.

## 1 Background

Pulmonary arterial hypertension is a life-threatening disease that is characterized by a marked and sustained elevation of pulmonary artery pressure, and ultimately results in right ventricular (RV) failure and death. Pulmonary arterial hypertension (PAH) subjects who fail specific available therapies have high morbidity and mortality. Though several therapies are now available, there is no cure. Although postulated for all current treatments, evidence for direct anti-proliferative effects of most approaches is missing ([Barst, et al 1996](#), [Olschewski, et al 2002](#)).

Pathological changes in the pulmonary arteries of patients with PAH include the formation of plexiform lesions, and smooth muscle and fibroblast proliferation leading to vascular obstruction ([Humbert M et al 2004](#)). Several growth factors including PDGF have been implicated in the abnormal proliferation and migration of SMCs. Platelet-derived growth factor (PDGF) is a vascular smooth muscle cell mitogen activating signal transduction pathways associated with smooth muscle hyperplasia in pulmonary hypertension ([Balasubramaniam V et al 2003](#); [Heldin CH et al 1999](#)). PDGF and its receptor (PDGFR) have been implicated in the pathobiology of pulmonary hypertension in animal studies and in patients with PAH ([Humbert M, et al 1998](#); [Balasubramaniam V, et al 2003](#); [Schermuly RT et al 2005](#)) thereby offering a potential new target for treatment.

QTI571 (imatinib mesylate, also known as STI571, formerly known as CGP 57148B) was designed to inhibit the tyrosine kinase activity of the BCR-Abl oncoprotein and is a well-established inhibitor of the stem cell factor (c-KIT) and the platelet-derived growth factor receptor (PDGF-R) kinases ([de Kogel CE et al, 2007](#)). In vitro, PDGF induced proliferation and migration of cultured human PASMCs was specifically inhibited by imatinib, through blockage of PDGFR phosphorylation ([Perros F et al, 2008](#)). Moreover, imatinib has been demonstrated to be an effective treatment in 2 well established experimental models of severe pulmonary hypertension ([Schermuly RT et al, 2005](#)). Treatment effects showed dose dependency and included a) reversal of pulmonary hypertension, b) reduction in right heart hypertrophy and improvement in cardiac output, c) reversal of pulmonary vessel proliferation, and d) an impressive survival benefit in monocrotaline-induced PAH in rats. QTI571 therefore may offer a new treatment modality for PAH, an antiproliferative agent without vasodilatory effects.

This hypothesis has been supported by case studies in patients with PAH, including a 61-year old man with rapidly progressing PAH who received imatinib in addition to bosentan, iloprost, sildenafil, oral anticoagulants and diuretics ([Ghofrani et al. 2005](#)). After 3 months, he had greatly improved exercise capacity, reduced PVR, decreased PAP, increased cardiac index, and had an improvement from class IV to class II, with no apparent adverse effects. Similar improvements in clinical condition were documented in a 52-year old man with refractory idiopathic PAH ([Patterson et al. 2006](#)) and in two patients (a 34-year old man and 65-year old woman) with PAH who received imatinib for treatment of leukaemia ([Souza et al. 2006](#)).

A previous Proof-of-Concept (PoC) trial evaluated the safety, tolerability, and efficacy of QTI571 (imatinib mesylate) as an adjunct to PAH specific therapy in patients with pulmonary

arterial hypertension. This was a 24-week randomized, double-blind, placebo-controlled study of PAH subjects who remained symptomatic on one or more PAH therapies in WHO Functional Class II-IV.

Fifty-nine patients (40 female; 19 male) were enrolled with 42 (71.2%) completing the 6 month study. The reasons for withdrawals in the treatment group included death (n=3), worsening of PAH (n=2), worsening of general condition (n=1), respiratory infection (n=1), right ventricular failure (n=1), and other adverse events (n=1, loss of appetite and fatigue). The reasons for withdrawals in the placebo group included death (n=3), worsening of PAH (n=2), worsening of general condition (n=1), subject withdrew consent (n=1) and other adverse events (n=1, back pain, acid reflux, dizziness, heart flutters, chest wall pain). Baseline characteristics were similar between the two treatment groups. Overall, patients had a mean age of 44.3 years, mean weight of 68.7 kg and mean body mass index of 24.6 kg/m<sup>2</sup>. Fifty five of the 59 patients were Caucasian and 78% had idiopathic PAH. At baseline, 79% of the QTI571-group and 81% of the placebo-group patients were receiving combination therapy.

The mean ( $\pm$ SD) 6MWD did not significantly change in the imatinib group vs. placebo (+22 $\pm$ 63 vs. -1.0 $\pm$ 53 m; mean treatment difference 21.7 m; 95% CI (-13.0, 56.5; p=0.21)). There was, however, a significant decrease in PVR (mean treatment difference -230.7 dynes.sec.cm<sup>-5</sup>; 95% CI (-383.7, -77.8; p=0.004) and increase in cardiac output (CO; mean treatment difference 0.68 L/min; 95% CI (0.10, 1.26; p=0.02) in imatinib recipients compared with placebo. There was no significant difference in PAPm or change in FC between imatinib and placebo treated patients.

In a post-hoc subgroup analysis, to identify subjects who may be more responsive than others, baseline characteristics were assessed including baseline CO, PAPm, 6MWD and PVR. The beneficial changes in 6MWD were most prominent in patients with a baseline PVR > 1,000 dynes.sec.cm<sup>-5</sup>, i.e. the median PVR in the study. The greatest response was in patients on PAH specific combination therapy with a baseline PVR > 1,000 dynes.sec.cm<sup>-5</sup>, who showed a statistically significant improvement between baseline and study end for 6MWD in the imatinib group [n=5], compared with placebo [n=10] (mean +96m, 95%CI 13.2 to 179.3; p=0.027). For PVR  $\geq$  800 dynes.sec.cm<sup>-5</sup> on 2 or more specific PAH therapies there was also a statistically significant increase in 6MWD of 65 meters, (p=0.046). PAH specific combination therapy included an endothelin receptor antagonist (ERA) plus a phosphodiesterase 5 inhibitor (PDE5) such as sildenafil, or an ERA plus a prostacyclin analogue, or a PDE5 plus a prostacyclin analogue, or an ERA plus a PDE5 plus a prostacyclin analogue. The effect seen with the addition of imatinib on top of PAH specific combination therapy is clinically relevant and greater than that typically seen with other combination PAH therapies. When sildenafil was added to intravenous epoprostenol there was an increase of 29 meters in 6MWD ([Simonneau G et al. 2008](#)). For intravenous epoprostenol added to a combination of an ERA plus a PDE5 there was a 41 meter increase in 6MWD ([Jacobs W et al. 2009](#)).

In conclusion, while the primary endpoint failed to reach statistical significance, the data are strongly suggestive of a medical significant treatment benefit associated with the use of QTI571. More specifically, the beneficial changes were most prominent in the group of

patients with a  $PVR > 1,000 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$  (as outlined above) and even more so in patients with a  $PVR > 1,000 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$  who were uncontrolled on 2 or more PAH therapies.

## Clinical Safety

Since 10-May-2001, imatinib is approved in over 99 countries under the names Glivec® and Gleevec® for the treatment of both hematological malignancies and solid tumors. It is indicated for the treatment of patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase (CP), blast crisis (BC), accelerated phase (AP), and CP after failure of interferon- $\alpha$  (IFN). It is also approved for patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL), hypereosinophilic syndrome (HES) / chronic eosinophilic leukemia (CEL), myelodysplastic/myeloproliferative diseases (MDS/MPD), and aggressive systemic mastocytosis (ASM). For solid tumors, imatinib is indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) and for inoperable or recurrent dermatofibrosarcoma protuberans (DFSP).

As of May 19, 2007 a total of 12,035 patients had received imatinib in clinical studies initiated by Novartis in adults and children with Ph+ leukemias and in adults with solid tumors. No healthy volunteers have been exposed to the drug. The duration and the follow up phase of these studies ranged as long as 84+ months. Additionally, 2,500 patients have received imatinib in non-Novartis studies. No carcinogenicity has been reported.

Treatment with imatinib mesylate is thought to be well-tolerated and safe. Most of the side effects of imatinib mesylate are of mild severity and usually manifest during the first month of therapy. The following adverse events have each been reported as SAE in <4% of patients across the pooled experience: edema/fluid retention, neutropenia, thrombocytopenia, exfoliative rash, hepatotoxicity, upper gastrointestinal tract bleeding and central nervous system hemorrhages.

In August 2006, 10 cases of congestive heart failure (CHF) in patients receiving imatinib were reported ([Kerkala R et al, 2006](#)). However, many had pre-existing risk factors including hypertension (7 of 10) and diabetes (4 of 10). This prompted Novartis to review the clinical safety data base. Novartis reviewed 2,347 subjects in 6 registration trials who received imatinib ([Hatfield A et al, 2007](#)). Twelve cases of incident CHF (no predisposing factors) were identified (0.5%). In a study comparing imatinib to interferon- $\alpha$  plus cytosine arabinoside for the treatment of CML in chronic phase, 0.04% of the subjects (1 case in 2,309 years of patient exposure) receiving imatinib developed cardiac failure with left ventricular dysfunction compared to 0.75% of the subjects (4 cases in 536 years of patient exposure) receiving interferon- $\alpha$  plus cytosine arabinoside.

There have been no reports of QT prolongation in any of the imatinib clinical studies. There were no cases of prolonged QT in the PAH PoC study. Noratinib, a related tyrosine kinase inhibitor, has been found to have a QTcF prolongation on average of 7.5 ms.

In the PAH PoC study, the most common adverse events (AEs) reported in the imatinib group were nausea (N=14; 50%; 17 events), headache (N=10; 35.7%; 14 events) and peripheral edema (N=7; 25.0%; 13 events). These AEs were expected in this population and this treatment, and did not lead to discontinuation of study drug. Nausea was controlled by taking

the medication with food. A total of 21 (75%) patients in the imatinib group reported AEs of mild intensity, 20 (71%) reported AEs of moderate intensity, and 9 (32%) patients reported AEs of severe intensity. Of the patients in the placebo group 24 (77%) reported AEs of mild intensity, 19 (61%) reported AEs of moderate intensity, and 5 (16%) patients reported AEs of severe intensity. Neutropenia, thrombocytopenia, exfoliative rash, upper gastrointestinal tract bleeding and central nervous system hemorrhages were not seen in the PoC study.

Serious AEs (SAEs) were reported for 11 imatinib recipients (39%) and 7 placebo recipients (23%). SAEs in the imatinib group included cardiac arrest (N=2), vertigo (n=1), pancreatitis (N=1), catheter related complication (N=1), liver dysfunction (N=2), dizziness (N=1), presyncope (N=1), syncope (N=1), haemoptysis (N=1), worsening pulmonary hypertension (N=3), and arterial rupture (N=1). SAEs in the placebo group included atrial flutter (N=1), cardiac arrest (N=2), right ventricular failure (N=2), general physical health deterioration (N=1), fluid retention (N=1), dizziness (N=1), and worsening pulmonary hypertension (N=3).

Overall there was a fall in the hemoglobin levels with imatinib ( $151 \pm 14$  to  $128 \pm 16$  g/L, SD) and a rise in hemoglobin levels with placebo ( $143 \pm 25$  to  $152 \pm 25$  g/L). There were no clinically significant changes of blood chemistry variables over time.

There were three deaths in each group. Two additional patients died in the placebo group within 2 months of completing the study. One patient in the imatinib group and one patient in the placebo group had rupture of the pulmonary artery (fatal in both cases).

Subjects enrolled in PoC were offered open label compassionate use imatinib when they finished study participation. The open label extension study was added to the protocol to record the long-term safety of imatinib and to determine long-term response. Twenty one subjects have enrolled in the open-label extension. Preliminary data has been collected. All subjects have been treated with imatinib for at least one year, and the majority for two years. The doses in these subjects have ranged from 200 mg to 500 mg. The fall in hemoglobin has stabilized in these subjects, with lowest hemoglobin of 100 g/L. As of April 2009, there have been two serious adverse events since the beginning of the extension study in August 2008. One case of hyponatremia, and one subject hospitalized for worsening of PAH. Only one subject has had a fall in 6MWD as compared to baseline.

The aim of this study is to provide pivotal confirmation of the efficacy, safety and tolerability of imatinib in patients with severe PAH.

## **1.1 History of Amendments**

### **Amendment #1**

Protocol amended per request of Japan PMDA. This amendment is only applicable to Japan.

### **Amendment #2**

Protocol amended per request of French, Belgian, and United Kingdom Health Authorities.

This amendment is applicable to all participating countries.

### **Amendment #3**

Protocol amended per request of the French Health Authorities. This amendment is only applicable to France.

### **Amendment #4**

This amendment is applicable to all participating countries.

## **2 Purpose and rationale**

The purpose of this study is to confirm the PoC trial findings and provide pivotal confirmation of the efficacy, safety and tolerability of QTI571 for registration of QTI571 in the treatment of severe pulmonary arterial hypertension defined as subjects who remain symptomatic on a least two PAH specific therapies and have a PVR  $\geq 800$  dynes.sec.cm<sup>-5</sup>.

### **Primary Endpoint – 6MWD**

The 6MWT (including distance walked, change in oxygenation, Borg Dyspnea Score and number of stops) is a practical and simple assessment of functional capacity, reflective of activities of daily living, used for pretreatment and post treatment comparisons in patients with PAH (Solvay et al, 2001; American Thoracic Society, 2002). The 6MWD has been shown to correlate with WHO functional class, cardiac output and pulmonary vascular resistance, exercise tolerance, survival, and response to therapy (Miyamoto et al, 2000; Sitbon O et al, 2002; Provencher S et al, 2006).

Improvement in 6-MWD has been the most frequently used endpoint in the pivotal studies for the registration of PAH therapies. Furthermore, 6MWD continues to be considered an appropriate endpoint in investigating drugs for PAH when the proposed indication is improvement in exercise capacity.

### **Dose Rationale**

The dose for the phase III trial will be the same as for the PoC study. The target dose for patients in PoC was chosen as 400 mg QD, the lowest recommended dose in the treatment of CML. In order to avoid fluid retention or the risk of other adverse effects associated with imatinib (such as nausea) which could be potentially detrimental to this study population, dosing started at 200 mg QD (or placebo) and increased, after two weeks of treatment, to 400 mg QD (or placebo) if tolerated. Dose reduction was allowed if a subject did not tolerate 400 mg.

Twenty of the 28 subjects on QTI571 tolerated dose escalation to 400 mg QD and remained on 400 mg throughout the study. Of the twenty patients who tolerated 400 mg throughout the study, 14 subjects completed 6 months of treatment. Eight subjects did not tolerate 400mg as per protocol and were down titrated to 200 mg at some point during the study. Of these 5 completed 6 months of treatment on any QTI571 dose. Twenty-three of 31 patients randomized to placebo also completed 6 months of treatment. The subjects who tolerated 400 mg QD throughout the study had a higher mean (SE) improvement in 6MWD as compared with those who did not tolerate 400 mg throughout the study (+42m (18) vs. +18m (9)).



In previous studies, the efficacy of imatinib for 10 different indications has been shown to be correlated with imatinib dose and concentrations, higher doses correlate with greater efficacy. Higher imatinib trough levels (1000 ng/ml) were associated with a better rate of major molecular response or cytogenetic response in CML patients and improved clinical benefit for GIST patient (Larson RA et al, 2008; Picard S et al, 2007). Doses lower than 400 mg/day would result in only 27% of the subjects reaching a clinically significant trough level of 1000 ng/ml.

Higher doses of imatinib than 400 mg QD may increase the risk of Grade 3-4 nausea, vomiting, anemia, and fluid retention. These adverse side effects could lead to dehydration, decreased oxygen carrying capacity or fluid overload, which are particularly undesirable in PAH subjects, so higher doses than 400 mg are not warranted.

Patients on PAH specific combination therapy and high PVR have high mortality and few treatment options. These patients warrant the use of the highest tolerated and safe dose (400 mg QD) to provide the highest possibility of benefit from the anti-proliferative effects of imatinib in the shortest possible timeframe.

### **3 Objectives**

#### **3.1 Primary objectives**

To evaluate the efficacy of QTI571 compared to placebo as measured by the change in 6-minute walk distance (6MWD) from baseline to 24 weeks.

#### **3.2 Secondary objectives**

- To evaluate the time to clinical worsening (TTCW), defined as all cause mortality, overnight hospitalization for worsening PAH (established by external adjudication committee), worsening of WHO functional class or a drop in 6MWD by 15% during 24 weeks of treatment with QTI571 as compared to placebo.
- To assess the safety and tolerability of QTI571.
- To evaluate change in pulmonary hemodynamics from baseline in patients after 24 weeks of treatment with QTI571 as compared to placebo.
- To assess change in Borg dyspnea score during 6-minute walk testing (6MWT), monthly, with QTI571 as compared to placebo.
- To assess the pharmacokinetics of QTI571 and the potential for interaction of QTI571 on sildenafil and bosentan.
- To assess changes in health-related quality of life after 24 weeks of treatment (using CAMPHOR) with QTI571 compared with placebo.

#### **3.3 Exploratory objectives**

- To assess the pharmacogenetics of QTI571.
- To assess the use of echocardiography of right ventricular performance as a measure of efficacy in treatment of PAH at selected sites.

- To assess the use of different possible definitions of time TTCW as a measure of efficacy in treatment of PAH.
- To evaluate efficacy of QTI571 200 mg QD in subjects that are not able to tolerate 400 mg QD.
- To assess the impact of QTI571 on medical resource utilization.

## 4 Study design

This is a multinational, multicenter, double blind, parallel group study design in patients with PAH.

Upon providing written informed consent, subjects will be screened by right heart catheterization (RHC) to determine pulmonary hemodynamics. During the screening period, an echocardiography will be performed to estimate RVSP, LVEF, as well as note the presence or absence of pericardial effusion, left atrial dilation, right ventricle dilation, right ventricle hypertrophy and any other abnormality. An electrocardiogram (ECG) in triplicate, safety laboratory assessments and two 6MWTs will also be performed. Patients receiving treatment for PAH as specified in the protocol who have undergone RHC in the 3 months prior to the screening visit may forgo this procedure at screening, provided that all required pulmonary hemodynamic measurements were assessed at that time and the subject complied with eligibility criteria at the time of the RHC. At the end of the screening period, patients will be randomized in a 1:1 ratio to receive treatment with QTI571 or placebo.

Treatment with QTI571 or matching placebo will be started at 200 mg once daily for two weeks. If well tolerated, the dose will be increased to 400 mg once daily. If the 400 mg daily dose is not well tolerated, a down titration to 200 mg once daily is permitted. All patients will be instructed to take four tablets of study drug once daily for the duration of the study.

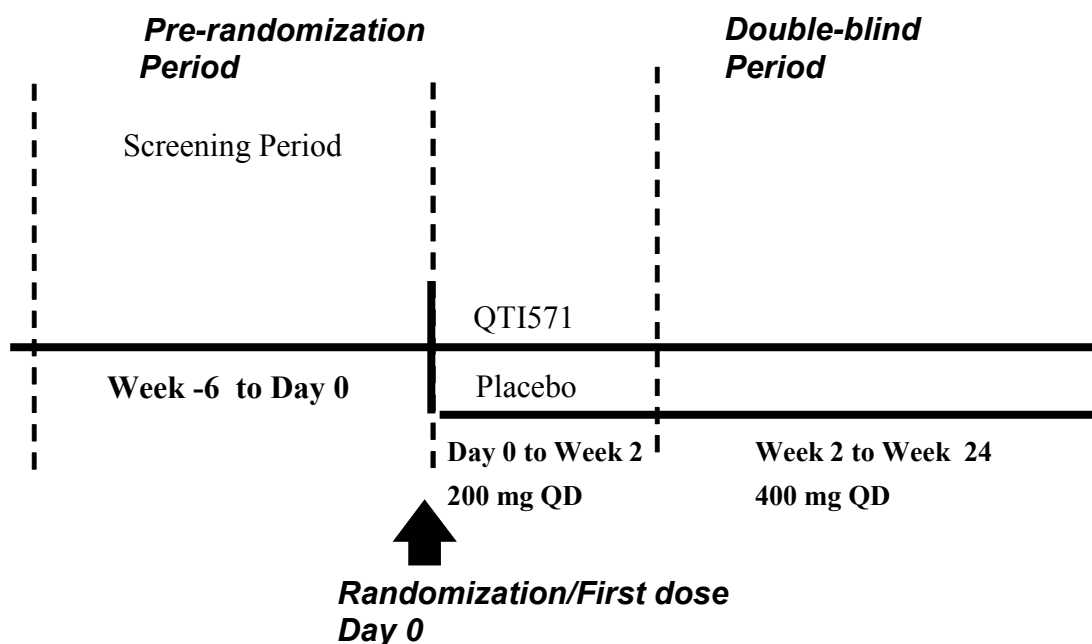
During the 24 week treatment period 6MWT will be performed monthly. ECG will be performed at each visit. Safety laboratories will be obtained weekly during dose escalation and monthly thereafter. An echocardiography will be performed following 3 months of treatment and repeated at the final study visit (week 24). A second right heart catheterization will also be performed at the final study visit.

Subjects who complete the study will be eligible for enrollment in the separate extension protocol CQT1571A2301E1 once Study Completion assessments are obtained at week 24. Subjects who complete the study and decline participation in extension protocol CQT1571A2301E1 must return four weeks after the final dose for safety evaluations, including laboratory assessments and physical exam. Any patient who withdraws from the study prematurely must return to the site for Study Completion assessments (see [Section 7.5](#)). Mortality at 24 weeks after first dose should be ascertained for these subjects. These subjects may be eligible for the separate extension protocol CQT1571A2301E1 six months after date of first dose of study drug.

The extension protocol CQT1571A2301E1 will assess long term safety, morbidity and mortality, including echocardiography, 6MWT, safety laboratories, ECG, TTCW end points, as well as adverse event reporting. No additional right heart catheterizations will be performed. The subject treatment in the core study will remain blinded, so it will not be

known if the subject is on QTI571 or placebo. Details on the dosing regimen are detailed in extension protocol CQT1571A2301E1. Safety laboratories and ECG will be checked before dose escalation. Patients may remain in extension protocol CQT1571A2301E1 at the maximum tolerated dose until QTI571 is approved for this indication or the program is discontinued. Active subjects unable to pay for drug after registration may be eligible for a treatment assistance program.

**Figure 4-1 Study design**



## 5 Population

The study population will consist of 200 adult males and females 18 years of age or older, with a diagnosis of severe pulmonary arterial hypertension (PAH), defined as those who remain symptomatic, i.e. WHO functional class II-IV ([section 7](#)), on at least two PAH specific therapies and  $PVR \geq 800 \text{ dynes} \cdot \text{sec} \cdot \text{cm}^{-5}$ . PAH may be either idiopathic or heritable (familial or sporadic), associated with collagen vascular disease including systemic sclerosis, rheumatoid arthritis, mixed connective tissue diseases, and overlap syndrome, associated with the use of appetite suppressants or toxic compounds or associated with congenital heart disease ( $\geq$  one year post complete repair ASD, VSD or PDA). Patients are to be recruited at approximately 60 centers globally.

### 5.1 Inclusion criteria

Each patient will meet the following inclusion criteria at the time of the Screening Visit and prior to randomization:

1. Male or female 18 years of age or older

2. A current diagnosis of Pulmonary Arterial Hypertension according to the Dana Point 2008 Meeting: WHO Diagnostic Group I, idiopathic or heritable (familial or sporadic) PAH, PAH associated with collagen vascular disease including systemic sclerosis, rheumatoid arthritis, mixed connective tissue diseases, and overlap syndrome. PAH following one year repair of congenital heart defect (ASD, VSD or PDA), or PAH associated with diet therapies or other drugs
3. A PVR  $\geq 800$  dynes.sec.cm<sup>-5</sup> (as assessed by RHC at screening or in the 3 months preceding the screening visit as described in [section 7.3.2](#)) despite treatment with two or more specific PAH therapies, including endothelin receptor antagonists (ERA), phosphodiesterase 5 inhibitors (PDE5), or subcutaneous, inhaled, intravenous or oral prostacyclin analogues for  $\geq 3$  months. Background therapy doses must be stable for  $\geq 30$  days except for warfarin and prostacyclin analogues ( $\geq 30$  days but doses can vary even within the month before enrollment).
4. WHO Functional Class II-IV. For WHO Functional Class IV, one of the 2 or more specific PAH therapies must be an inhaled, subcutaneous, intravenous or oral prostacyclin analogue, unless the subject has been shown to be intolerant of prostacyclin analogues.
5. 6MWD  $\geq 150$  meters and  $\leq 450$  meters **at screening**. Distances of two consecutive 6MWTs **should be within 15% of one another**.
6. Ability to provide written informed consent by the patient or a legal guardian.

## 5.2 Exclusion criteria

The following patients will be excluded from participation in the study:

1. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant. **UNLESS** they are:
  - women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner
  - women whose partners have been sterilized by vasectomy or other means
  - two birth control methods. The two methods can be a double barrier method or a barrier method plus a hormonal method. Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test ( $> 5$  mIU/ml)
3. Have previously received treatment with imatinib
4. In treatment with chronic nitric oxide therapy
5. With a diagnosis of pre-existing lung disease including parasitic diseases affecting lungs, congenital abnormalities of the lungs, thorax or diaphragm or bronchial asthma that may significantly contribute to severity of PAH in the opinion of the investigator

6. With a pulmonary capillary wedge pressure > 15 mm Hg to rule out PAH secondary to left ventricular dysfunction. If pulmonary capillary wedge pressure is not attainable, then a left atrial pressure measurement may be used in its place. [In France, left atrial pressure measurement may not be used in place of pulmonary capillary wedge pressure.]
7. With a diagnosis of pulmonary artery or vein stenosis
8. With other diagnosis of PAH in WHO Diagnostic Group 1 or 1' are excluded including congenital systemic to pulmonary shunts (large, small that are not surgically repaired), portal hypertension, HIV infection, hereditary hemorrhagic telangiectasia, hemoglobinopathies, veno-occlusive disease)
9. With a diagnosis of PAH associated with: venous hypertension (WHO Diagnostic Group II, including LVEF < 45%), hypoxia (WHO Diagnostic Group III), chronic pulmonary thromboembolic disease (WHO Diagnostic Group IV) or other miscellaneous causes (WHO Diagnostic Class V, which includes sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels, glycogen storage disease, Gaucher's disease, myeloproliferative disorders).
10. With deficient thrombocyte function, thrombocytopenia <  $50 \times 10^9/L$  ( $50 \times 10^3/\mu L$ )
11. With a history of left heart failure in the past 3 months.
12. With uncontrolled systemic arterial hypertension, systolic > 160 mmHg or diastolic > 90 mmHg
13. With hemoglobin < 100 g/L (10 g/dL)
14. With deficiencies of blood coagulation, inherited or acquired blood coagulation disorders, factor XII, factor XIII; decreased generation of coagulation factors due to acute or chronic liver diseases, efficient coagulation due to auto-antibodies against coagulation factors such as in lupus anticoagulant
15. With disseminated intravascular coagulation (DIC)
16. With evidence of major bleeding or intracranial hemorrhage
17. With a history of elevated intracranial pressure
18. With a history of latent bleeding risk such as diabetic retinopathy, gastrointestinal bleeding due to gastric or duodenal ulcers, or colitis ulcerosa
19. With a history of moderate or greater hepatic insufficiency transaminase levels > 4 times the upper limit of normal or a bilirubin > 2 times the upper limit of normal
20. With a history of renal insufficiency (serum creatinine > 200  $\mu\text{mol/l}$  or 2.6 mg/dl)
21. Previous therapeutic radiation of lungs or mediastinum
22. With a history of sickle cell anemia
23. With a QTcF > 450 msec for males and > 470 msec for females at screening and baseline in the absence of right bundle branch block.
24. With a history of ventricular tachycardia, ventricular fibrillation or ventricular flutter
25. Having syncope in the 3 months prior to the screening visit
26. With a history of Torsades de Pointes
27. With a history of long QT syndrome

28. Having undergone atrial septostomy in the 3 months prior to the screening visit
29. Having undergone radiofrequency catheter ablation for atrial or sinus arrhythmias in the 3 months prior to screening visit
30. With an advanced, severe, or unstable disease of any type that may interfere with the primary and secondary endpoint evaluations
31. With a history of immunodeficiency diseases, including HIV
32. With a known hypersensitivity to QTI571 or drugs similar to the study drug
33. With a disability that may prevent the patient from completing all study requirements and in particular, interfere with the 6MWT assessment
34. With a life expectancy of 6 months or less
35. Having used other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
36. With a history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
37. With a diagnosis of Hepatitis B or C.
38. With a history of alcohol abuse within 6 months of screening.
39. With a history of illicit drug abuse within 6 months of screening.
40. Male subjects must be using two acceptable methods of contraception, (e.g. spermicidal gel plus condom) for the entire duration of the study, up to the Study Completion visit, and refrain from fathering a child in the three months following the last study drug administration. Periodic abstinence and withdrawal are not acceptable methods of contraception.
41. Patients with a diagnosis of systemic sclerosis, with the exception of those who can provide results from a pulmonary function test conducted within the 6 months preceding enrollment, showing total lung capacity (TLC)  $> 70\%$ . If  $TLC \leq 70\%$ , a chest CT showing minimal lung parenchymal involvement must be produced.
42. [(France only) Patients for whom a lung transplant is indicated in the next 6 months.]

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Patients who fail to meet all inclusion/exclusion criteria may be re-screened. All re-screened patients must be assigned a new subject number.

## **6 Treatment**

### **6.1 Investigational and control drugs**

- Imatinib 100 mg film coated tablets provided in 70-tablet bottles
- Placebo to match imatinib 100 mg film coated tablets in 70-tablet bottles

### **6.2 Treatment arms**

Patients will be assigned to one of 2 treatment arms in a 1:1 ratio:

- Imatinib 400 mg QD
- Placebo

### **6.3 Treatment assignment**

At Visit 2 all eligible patients will be given a randomization number that assigns them to one of the treatment arms. The investigator or his/her delegate will call the Interactive Voice Response System (IVRS) and confirm that the patient fulfills all the inclusion/exclusion criteria. The IVRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs.

The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

### **6.4 Treatment blinding**

Randomized double-blind treatment will remain blind to patients, investigator staff, persons performing the assessments, and data analysts from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions. The bioanalyst will have access to the randomization list to identify subjects who have received imatinib to avoid the unnecessary analysis of samples from placebo group subjects. The bioanalyst will not reveal any information from the randomization list to any other party involved in the trial prior to database lock. An external independent statistician and an independent programmer will produce interim analysis results for review by the DMC. The data monitoring committee (DMC) will be semi-unblinded and may be fully unblinded if they feel it is necessary ([Section 8.4](#)). (2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor. All patients will be dispensed two 70-tablet bottles of study drug, and will be instructed to take 2 tablets from each bottle for each daily dose.

Unblinding will only occur in the case of patient emergencies (see [Section 6.5.9](#)) and at the conclusion of the study.



## **6.5 Treating the patient**

### **6.5.1 Patient numbering**

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). The investigator or his/her staff will contact the IVRS/IWRS and provide the requested identifying information for the patient to register them into the IVRS/IWRS. For studies using eCRFs, patient numbers are already entered on the data entry screen. Patient number chosen must be the number assigned to the patient upon entering the study. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized for any reason, the IVRS/IWRS must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should also be completed.

Each study site will be supplied by Novartis with study drug in packaging of identical appearance.

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a dose. Investigator staff will identify the study drug package to dispense to the patient by calling the IVRS and obtaining the medication number. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document for that patient.

### **6.5.2 Study drug supply, storage and tracking**

Each study site will be supplied by Novartis with study drug in packaging of identical appearance.

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug, but no information about the patient except for the medication number.

Patients will be dispensed 2 bottles of study medication at Visit 2 and Visit 4 and monthly thereafter. New study medication will also be dispensed at every dose down-titration and escalation. Patients will be instructed to take two tablets from each bottle for their daily dose throughout the study.

At Visit 2, subjects randomized to receive imatinib 200 mg will be dispensed a 70-tablet bottle of imatinib and a 70-tablet bottle of placebo and those randomized to placebo will receive two 70-tablet bottles of placebo. At Visit 4, dose escalation to 400 mg in patients

receiving study drug will be achieved by dispensing two 70-tablet bottles of imatinib. The subjects receiving placebo will again be dispensed two 70-tablet bottles of placebo.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

### **6.5.3 Instructions for prescribing and taking the study drug**

Eligible patients will be randomized at Visit 2 to receive treatment with QTI571 or matching placebo at an initial dose of 200 mg once daily. All patients will be instructed to take four tablets of study drug (two tablets from each bottle dispensed) once daily with a meal and an 8 oz/200mL glass of water, for the duration of the study. Patients must be instructed not to chew the medication, but to swallow it whole.

Patients will receive the first dose of study medication at the site during Visit 2 once all assessments scheduled prior to dosing have been performed. After dosing, the patient will undergo post-dosing assessments. Subjects will remain on the initial daily dose for two weeks. If well tolerated, the dose will be increased to 400 mg once daily at Visit 4. The first 400 mg dose will be administered at the site during the visit. After dosing, the patient will undergo post-dosing assessments.

**It is critical for pharmacokinetic assessments that patients refrain from taking study drug prior to site visit on the day of Visit 4, Visit 6 and Visit 11. It may be advisable to contact the patient on the day prior to the study with a reminder to this effect.**

Dose reduction to 200 mg should take place if any of the following occur:

- Increase in liver function tests >4x upper limit of normal
- Increase in creatinine >50% over the upper limit of normal or a 30% increase over the screening level for subjects with pre-existing abnormalities in renal function
- Weight gain >2 kg with physical exam consistent with fluid overload and evidence of decline in right heart function by echocardiogram
- Any subject experiencing a degree of peripheral edema (with no right heart dysfunction) or nausea/vomiting that in the judgment of the investigator and/or patient himself/herself is sufficiently incapacitating.

Study drug should be discontinued if any of the above criteria occur during the initial two weeks of study drug administration.

Patients will be withdrawn from the study if, two weeks after the reduction/down-titration in dose to 200 mg QD, these criteria persist.

Dose escalation back to 400 mg is permitted if, in the investigator's clinical judgment, it is safe to do so. Efficacy in all other indications has been shown to increase with dose. Subjects should be maintained at 400 mg whenever possible.

Dose escalations and reductions may take place at a scheduled visit or at unscheduled visits. A follow up visit should be scheduled no later than 2 weeks after any change in dose.

All dosages prescribed and dispensed to the patient and all dose changes during the study will be recorded in the IVRS, as well as the Dosage Administration Record eCRF.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

#### **6.5.4 Permitted study drug dose adjustments and interruptions**

QTI571 will be initiated at a dose level of 200 mg per day during the two weeks of treatment. If treatment is well tolerated, the daily dose will be increased to 400 mg at Visit 4. Treatment will continue at 400 mg daily for the duration of the study. If, in the judgment of the investigator, at any time during trial participation the patient's 400 mg daily dose is not well tolerated, the dose may be decreased to 200 mg daily. The daily dose may subsequently be increased to 400 mg if deemed advisable by the investigator.

All dose changes must be called into the IVRS. The IVRS will identify a new study drug package to dispense to the patient at each dose change.

Additionally, dosing with study medication should be stopped immediately for the following reasons:

- Thrombocytopenia of less than 50,000/mm<sup>3</sup> or neutropenia of less than 1,000/mm<sup>3</sup>.  
Dosing can be restarted only when the platelet count is above 75,000/mm<sup>3</sup> or the neutrophil count is over 1,500/mm.
- Receipt of a lung transplant
- All events of syncope. The patient should return to the site for an unscheduled visit to perform the following assessments:
  - 1) Holter monitor to rule out:
    - Significant high degree atrioventricular blocks (ie. Second degree atrioventricular blocks Mobitz type 1 and 2, and third degree atrioventricular block)
    - Sinus pause greater than 2 seconds
    - Sino-atrial block (dropped p wave)
  - 2) Echocardiogram to rule out LV dysfunction (LVEF < 45%)

If significant arrhythmia or LV dysfunction is diagnosed, the patient should be prematurely discontinued from the study. If no significant arrhythmia or LV dysfunction is found, the patient may resume study drug at the discretion of the investigator.

### 6.5.5 Rescue medication

Subjects who experience worsening of PAH requiring hospitalization may require the use of diuretics and supplemental oxygen. If severe, subjects may require intensive care treatment and use of vasopressors.

PAH therapies, not used at time of enrollment, such as ERA, PDEV, or subcutaneous, oral, inhaled or intravenous prostacyclin derivatives, should only be added if the subject meets a TTCW event, including hospitalization for worsening of PAH for more than 24 hours, worsening of WHO functional class by one or more levels, or a decrease in 6MWD of 15% measured on two occasions. Subjects who achieve a TTCW event will remain in the study and perform monthly and end of study assessments.

### 6.5.6 Concomitant PAH medication

All concomitant medications used to treat PAH, both specific and background, that are taken 4 weeks prior to Visit 1 and during the study must be collected on the Concomitant PAH medication eCRF with the dose of medication. The patient should notify the study site of any dose changes to concomitant PAH medication doses and must be captured on the Concomitant PAH medication eCRF throughout the study. Patients must be on a stable dose of all concomitant PAH medications prior to each scheduled pharmacokinetic blood draw for at least 3 days.

Specific PAH medications include: all endothelin receptor antagonists, phosphodiesterase 5 inhibitors and inhaled, oral, intravenous, or subcutaneous prostacyclin analogues.

Background PAH therapies include: oxygen, digoxin, all diuretics, calcium channel blockers and warfarin. Background PAH therapies may be adjusted as necessary during the study.

The following describes possible interactions of QTI571 and PAH medications.

- Bosentan may decrease the exposure to QTI571 by a mean max of 50%; therefore no change to the dose of QTI571 is anticipated. QTI571 will increase the exposure to Bosentan by a mean max of less than 2 fold. Therefore, Bosentan side effects may occur more frequently and a down titration of Bosentan may be considered necessary.
- QTI571 may cause an increase in the exposure to Sildenafil. Powerful inhibitors of CYP3A4 and may cause a significant increase in exposure to Sildenafil. It is predicted that co prescription of QTI571 and Sildenafil may lead to approximately a doubling in exposure to Sildenafil.
- Warfarin is a substrate of both CYP2C9 and CYP3A4 (R-warfarin (a CYP3A4 substrate) and S-warfarin (a CYP2C9 substrate and pharmacologically more active enantiomer)). Patients receiving warfarin and imatinib concomitantly have demonstrated both increases and decreases in international normalized ratio ([Peng et al, 2005](#)). All patients receiving treatment with oral anticoagulants will have Prothrombin Time (PT)/International Normalized Ratio (INR) testing performed at every visit.
- No interactions are expected with prostacyclin analogues.
- Approximately 50-70% of digoxin is excreted by the kidneys unchanged. No interactions are expected with digoxin. Digoxin levels will be monitored.
- No interactions with calcium channel blockers are expected.

### **6.5.7 Other concomitant treatment**

The investigator should instruct the patient to notify the study site about any dose changes or new medications taken after the start of the study drug. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered 4 weeks prior to Visit 1 and during the study must be collected on the Non-PAH Concomitant medication eCRF.

All con-medications that are inhibitors, inducers or substrates of CYP3A4 and CYP2D6 should be used with caution.

QTI571 is an inhibitor of CYP3A4, CYP2D6 and CYP2C in vitro. The inhibition of CYP3A4 and CYP2D6 occur at pharmacological concentration and drug interactions would be predicted for drugs metabolized by these CYPs, the inhibition of CYP2C9 occurs at 3-4 fold the levels for CYP3A4 and CYP2D6, therefore interactions with CYP 2C9 metabolized drugs would be possible.

The following describes possible interactions of QTI571 and con-medications that are inhibitors, inducers or substrates of CYP3A4:

- CYP3A4 inhibitors are expected to give small increases to QTI571 exposure and should be closely monitored. Examples of such drugs are: Amiodarone, Diltiazem, Verapamil, macrolide antibiotics, Itraconazole and Ketoconazole. Clinical studies have shown CYP3A4 inhibition with ketoconazole increases QTI571 exposure by approx 40%.
- CYP3A4 inducers are expected to give significant decreases in QTI571 exposure. Examples of such drugs are: carbamazepine, rifampicin, some reverse transcriptase inhibitors.
- CYP3A4 substrates are expected to give modest increases in exposure of the substrate. They should be used with caution as their toxic effects may become more pronounced. Therefore a decrease in dose (cessation of therapy) of the substrate and/or more careful monitoring should be considered. Examples of such drugs are: Simvastatin carbamazepine, cyclosporine, some statins, HIV protease inhibitors and Triazolam. Subjects with HIV are excluded, therefore all HIV protease inhibitors are not allowed. These agents especially with a narrow therapeutic margin should be used with caution as there toxic effects may become more pronounced. Therefore a decrease in dose (cessation of therapy) of the substrate and/or more careful monitoring should be considered. Examples of such drugs are: Amitryptiline, clomipramine, fluoxetine, metoprolol.

QTI571 may increase paracetamol levels. Caution should be exercised when using imatinib and paracetamol concomitantly, especially with high doses of paracetamol.

### **6.5.8 Study drug discontinuation and premature patient withdrawal**

Patients will be withdrawn from the study if the following criteria persist two weeks after down-titration to 200 mg QD:

- Increase in liver function tests >4x upper limit of normal
- Increase in creatinine >50% over the upper limit of normal or a 30% increase over the screening level for subjects with pre-existing abnormalities in renal function

- Weight gain >2 kg with physical exam consistent with fluid overload and evidence of decline in right heart function by echocardiogram
- Any subject experiencing a degree of peripheral edema (with no right heart dysfunction) or nausea/vomiting that in the judgment of the investigator and/or patient himself/herself is sufficiently incapacitating.

In addition, the following circumstances **require** study drug discontinuation:

- Withdrawal of informed consent
- Pregnancy
- Left Ventricular Ejection Fraction (LVEF) drops to  $\leq 45\%$
- QTc is prolonged by more than 60 msec as compared with the baseline value, or if the QTc value is in excess of 500 msec as confirmed by the central ECG vendor
- If significant arrhythmia or LV dysfunction is diagnosed or conduction disorder, including:
  - Significant high degree atrioventricular blocks (ie. second degree atrioventricular blocks Mobitz type 1 and 2, and third degree atrioventricular block)
  - Sinus pause greater than 2 seconds
  - Sino-atrial block (dropped p wave)
- Any other significant risk to the patient's safety in the clinical judgment of the investigator
- [(France only) Any patient whose condition worsens during the study to such an extent that lung transplantation is indicated.]

The subject should be withdrawn from the study.

In addition to these requirements, the investigator should discontinue study drug for a given patient if, on balance, continuation of study treatment would be detrimental to the patient's well-being.

The investigator must notify the IVRS of the study drug discontinuation.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion eCRF. The investigator must notify the IVRS of the premature withdrawal.

All patients who withdraw from the study prematurely must return to the site for Study Completion assessments, including 6MWT, right heart catheterization, echocardiogram, ECG and safety laboratories. Mortality at 24 weeks after first dose should be ascertained. All subjects that withdraw may be eligible for the separate extension protocol CQT1571A2301E1 no sooner than 24 weeks after their first dose of study drug intake

Those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw will be considered lost to follow-up. The investigator should

show "due diligence" by detailing in source documents all steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

#### **6.5.9 Emergency unblinding of treatment assignment**

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IVRS. When the investigator telephones the system to unblind a patient, he/she must provide the requested patient identifying information and the date, time, and reason for unblinding. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Head that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, patient number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding. Study drug also must be discontinued for any patient whose treatment code has been broken inadvertently or for any non-emergency reason.

#### **6.5.10 Study completion and post-study treatment**

Subjects who complete the study will be eligible for enrollment in the separate extension protocol CQT1571A2301E1 once Study Completion assessments are obtained at week 24. Subjects who complete the study and decline participation in extension protocol CQT1571A2301E1 must return for Visit 12, four weeks after the final dose (Visit 11) for safety evaluations, including laboratory assessments and physical exam. Any patient who withdraws from the study prematurely and does not participate in extension protocol CQT1571A2301E1 must return to the site for Study Completion assessments (see [Section 7](#)). In addition, mortality at 24 weeks after first dose should be ascertained for these subjects.

The extension protocol CQT1571A2301E1 will assess long term safety, morbidity and mortality, including echocardiography, 6MWT, safety laboratories, ECG, TTCW end points, as well as adverse event reporting. No additional right heart catheterizations will be performed. The subject's treatment in the core study will remain blinded, so it will not be known if the subject is on QT1571 or placebo. Subjects who complete study participation and have signed the extension Informed Consent, will be dispensed extension study drug at Visit 1 of the QT1571A2301E1 trial (which occurs on the same day as Visit 11 of the core trial). Safety laboratories and ECG will be checked before dose escalation. Subjects who complete the study, or who discontinue the study early, and decline participation in extension protocol

CQTI571A2301E1 must return four weeks after the final dose to complete Visit 12 during which safety evaluations, including laboratory assessments and physical exam will be performed. Patients may remain in extension protocol CQTI571A2301E1 at the maximum tolerated dose until QTI571 is approved for this indication or the program is discontinued. Active subjects unable to pay for drug after registration may be eligible for a treatment assistance program.

### **6.5.11 Early study termination**

The study can be terminated at any time for any reason by Novartis Pharmaceuticals. Should this be necessary, the patient should be seen as soon as possible and treated as described in [Section 7](#) for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

### **6.5.12 Lung transplantation considerations**

Data from the Novartis global safety database does not suggest that treatment with imatinib increases the potential for adverse events following pulmonary transplantation. Thirty cases were identified in a search of preferred terms including heart and lung transplantation, lung lobectomy, lung neoplasm surgery, lung operation, lung transplantation, pneumonectomy and thoracotomy. Within these cases, one heart lung transplantation and one lung transplantation were included. Among the reports of thoracic surgery, no intra operative or postoperative complications were described. A single case was identified in which imatinib was associated with an episode of hypotension after coadministration with anesthetic agents. Concomitant medications associated with hypotension were also administered. Spontaneous cases do not suggest increased risk of hypotension or cardiotoxicity in patients post pulmonary transplantation. The search also included GIST patients on imatinib that frequently need emergent surgery; no post operative complications have been identified in this population.

Oncological use of imatinib does not suggest that concomitant use with immunosuppressive agents will pose risks apart from those currently described in the SmPC. Of the 298 drug-drug interactions reported in the safety database, 3 described concomitant use of imatinib and calcineurin inhibitors. In two of the cases, increased concentrations of cyclosporin were described, no other events were described. Imatinib treatment for PAH will cease at the time of lung transplantation and they will be removed from the study.

Overall, current data does not suggest that PAH patients requiring pulmonary transplantation are at risk of worse outcomes after receiving imatinib treatment, though unknown adverse events cannot be ruled out.

In the treatment of CML, pharmacodynamic effects are closely related to pharmacokinetic blood levels. Pharmacokinetic washout requires 5 days. When assessing patients for enrolment in the trial, appropriate consideration should be given to whether this washout period can be achieved according to local protocols, procedures and time on waiting list for pulmonary transplantation. If appropriate, patients may need to be suspended from an active transplant list before entering the study. The risk to benefit ratio for an individual patient



should be considered when assessing patients on the transplant list for enrolment or continued participation in the trial.

## 7 Visit schedule and assessments

Patients will have the status of their pulmonary hypertension assessed for eligibility and throughout the conduct of the study according to the World Health Organization (WHO) classification (modified after the New York Association Functional Classification) as detailed below:

**Class I** – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

**Class II** – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

**Class III** – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

**Class IV** – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

All study assessments required during the conduct of the study are listed on [Table 7-1](#), which indicates with an “x” the visits at which they are performed.

Patients should be seen for all visits on the designated day with a visit window of  $\pm 3$  days at Visit 2 through Visit 6, and a visit window of  $\pm 7$  days at Visits 7 through Visit 12.

Patients, who discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of end-of-study assessments that are required at Visit 11, as identified in [Table 7-1](#), should be performed.

If the patient refuses to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to ascertain mortality 24 weeks after the first dose of study drug.

At a minimum, patients will be contacted for safety evaluations during and up to the 30 days following the last dose of study. Documentation of attempts to contact the patient should be recorded in the source documentation.

**Table 7-1      Assessment schedule**

[illegible]

- 1 Screening visit can occur up to 6 weeks prior to randomization; visits 3-6 will have a 3-day window, subsequent visits will have a 7-day window
- 2 Only patients who complete the study and decline participation in extension protocol CQT1571A2301E1 will return for Visit 12
- 3 Including all PAH treatments with dosing, including warfarin dosing
- 4 At Visit 2 blood samples for laboratory evaluations should be drawn and vital signs and edema evaluations performed prior to dosing
- 5 ECGs must be performed prior to the 6MWT
- 6 At Visit 2, questionnaire should be completed prior to 1st dose of study drug.
- 7 Patients resting values of oxygen saturation (%), heart rate (b/min), blood pressure (mm Hg), and Borg score are to be recorded on the eCRF before the test, at the end of the test, and two minutes after the end of the test.
  - \* Or at time of discontinuation of study
  - \*\* ECGs to be performed in triplicate at 5 minute intervals at Visit 1, as well as prior to dosing at Visit 2, Visit 4, and Visit 6. At Visit 2, ECGs should be performed prior to contacting IVRS for randomization and dosing the patient.
  - \*\*\* If abnormalities are identified, urine sample to be collected for analysis by central laboratory
- ◆ ECG to be conducted 0.5-3 hr post dosing
- † During screening two consecutive 6MWTs should be assessed at least 2 hours apart in a single day. The 6MWT should be repeated until two consecutive tests are within 15% of each other at Day -3 (Day -6 to Day 0 window allowance) and if 6MWD are not within 15% of one another. The average of the 2 tests should be used as the baseline but will not be calculated. Individual qualifying test results will be captured by the site on the eCRF. After screening measurements, single 6MWT will be performed monthly.
- Θ Dose increase to 400 mg QD if 200 mg QD dose well tolerated
- \$ QTI571, bosentan, sildenafil and their active metabolites in plasma samples will be assayed and the blood sampling time points can be seen from the blood log table
- ♣ PG blood draw recommended after randomization at Visit 2 to avoid patient discontinuation prior to PG sample collection; PG blood draw can be performed at any visit prior to study completion or discontinuation
- ± Visit 12 follow-up/survival visit required only for completed or discontinued patients who do not consent to participate in extension protocol CQT1571A2301E1.

## 7.1 Information to be collected on screening failures

Patients may discontinue from the study prior to randomization from Visit 1 and Visit 2, prior to any double-blind medication being administered.

Patients discontinuing prior to randomization are considered screening failures.

If a patient discontinues before receiving study drug, only the demographic information and Screening Log entry with the precise reason for screen failure, should be completed on the eCRF. Patient demographics to be collected on all patients include: date of birth, age, sex, race, ethnicity and source of patient referral.

## 7.2 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient.

Dose Administration Record eCRF will be completed by the site staff at each visit.

## 7.3 Efficacy

### 7.3.1 Six-minute walk test and Borg Scale

A standardized Six-Minute Walk Test (6MWT) will be performed in accordance with the guidelines of the ([American Thoracic Society 2002](#)). The six minute walk will be carried out

by a trained technician according to the guidelines in [Appendix 3](#). The 6MWT must be performed after all ECGs have been completed. It should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length. The length of the corridor should be marked every 3 m. The turnaround points should be visibly marked. A starting line, which marks the beginning and end of each 60-m lap, should be clearly marked on the floor.

During the walk the patient is connected to a portable pulse oximeter via a finger probe.

Patients will be instructed to walk at a comfortable speed for as far as they can manage in six minutes, resting whenever they need to but will not be permitted to sit. Patients should use their usual walking aids during the test (cane, walker, etc). However, no additional assistive devices will be permitted. The test will be terminated if the patient becomes too distressed or if the SpO2% falls below 60%. As soon as the test is complete the patient will be asked to sit down, the SpO2%, heart rate and Borg score values will be recorded, and recovery will be monitored.

Patients resting values of oxygen saturation (%), heart rate (b/min), blood pressure (mm Hg) and Borg Questionnaire score will be recorded in the eCRF before the test, at the end of the test and two minutes after the end of the test. Total distance walked (meters), the number and duration of any stops and whether the patient completed the test will also be recorded in the eCRF. If the patient discontinues the test prematurely, the time (minutes/seconds) and distance walked will be recorded.

Requirement of rescue medication including requirement of oxygen therapy and any adverse events occurring during the 6MWT will be recorded. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate (and at the same rate during each 6MWT procedure) or as directed by the investigator.

During screening 6MWTs at least 2 hours apart on day -3 (Day -6 to Day 0 window allowance) will be performed and must be within 15% of one another; if not within 15% of each other, additional 6MWT may be performed until 2 consecutive six minute walk distances are within 15% of one another (maximum of 4 tests may be performed). Subjects who cannot produce two 6MWT within 15% of each other after 4 tries should be considered a screening failure.

The average of the 2 consecutive qualifying tests will be used as the baseline; however, this average will not be calculated at the site. Results from both of these 6MWTs will be recorded in the eCRF.

After screening measurements, single 6MWTs will be performed monthly. Every attempt should be made to conduct the 6MWT about the same time of day to avoid diurnal variation. The environment in which the test is carried out should have adequate temperature to avoid additional burdens to the patient by heat or cold air.

Additional instructions for the 6MWT are provided in [Appendix 3](#). A copy of the Borg Scale Questionnaire is included in [Appendix 4](#).

### **7.3.2 Hemodynamic parameters measured/calculated from right heart catheterization**

The right heart catheter assessment is performed to assess several prognostic hemodynamic variables in pulmonary hypertension, including right atrial pressure (RA), mean pulmonary arterial pressure (mean PAP), mean Pulmonary Capillary Wedge pressure (mean PCWP), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and Cardiac Output (CO), Mean Arterial Blood Pressure (MAP), Pulmonary Vascular Resistance (PVR) and Systemic Vascular Resistance (SVR).

Patients receiving treatment for PAH as specified in the protocol who have undergone RHC in the 3 months prior to the screening visit may forgo this procedure at screening, if all the following criteria are met:

- All required pulmonary hemodynamic measurements were assessed at that time.
- Subject complied with eligibility criteria at the time of the RHC
- Subject was on the same PAH specific therapies that the subject will be taking upon entering the study for 3 months at the time of the RHC.
- Subject was on the same PAH background therapies that the subject will be taking upon entering the study for 30 days at the time of the RHC.
- The dose of the PAH specific and PAH background therapies (except for warfarin) have not changed since the time of the RHC

**The above criteria should be recorded in the source documents. If the above criteria are not met the subject must undergo RHC during screening**

Right heart catheterization will be performed according to the local hospital procedures. The following hemodynamic parameters will be assessed when the patient is in a stable hemodynamic rest state (as demonstrated by three consecutive Mean PAP and CO measurements within 10% of each other) whilst the patient is breathing ambient air or oxygen:

- RA, mean PAP, mean PCWP, SBP, DBP, HR
- CO measured in triplicate by the thermodilution technique or by the Fick method (the same method must be used at screening and end of study for each subject).

PVR, SVR and MAP will be calculated and populated in the eCRF automatically.

Right ventricle pressure data from the right heart catheterization with simultaneously recorded ECG recordings may be collected and digitally stored at selected sites. The measurement of RV pressures is a standard part of the right heart catheterization and do not add to patient burden.

Instructions for shipment of digitally collected and stored ECG recordings will be provided to participating sites and will be identified in the monitoring plan.

### **7.3.3 Time to clinical worsening (TTCW)**

TTCW events, as a secondary objective, will include all cause mortality, overnight hospitalization for worsening of PAH, a worsening of WHO functional class by at least one level, or a 15% decrease in the 6MWD as compared to baseline confirmed by two 6MWTs at

two consecutive study visits. The time of the first 15% decrease will be the TTCW once it is confirmed on the following visit.

Overnight hospitalization will be adjudicated by an external Adjudication Committee to confirm the hospitalization was due to worsening of PAH. The external Adjudication Committee will consist of three MDs with expertise in the treatment of PAH. The events will be reviewed in a blinded manner. The detailed tasks, necessary data transfers, and criteria needed to establish that the hospitalization was for worsening of PAH will be included in the charter.

In addition as an exploratory endpoint, other possible definitions for TTCW for this population will be explored. This analysis will be determined by the Adjudication Committee. Other possible TTCW to be considered, may include but is not limited to: other cut offs for decline in 6MWD, addition of a third PAH therapy, or change in Borg Score.

The study site **should make every attempt** to obtain any necessary hospital records including discharge summaries. In the case of mortality, autopsies should be encouraged **and every effort should be made to obtain autopsy reports**.

#### **7.3.4 Appropriateness of efficacy measurements**

The efficacy variables selected are standard for this indication/patient population.

### **7.4 Safety**

#### **7.4.1 Physical examination**

A complete physical examination will be performed at Visit 1, Visit 11 and Visit 12, if applicable. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

#### **7.4.2 Vital signs**

Vital signs, including respiratory rate and temperature, will be assessed at every visit. In addition, BP and pulse measurements will be obtained at each visit after the patient has been sitting for five minutes, with back supported and both feet placed on the floor. Systolic and diastolic blood pressure will be measured manually or by using an automated validated device, with an appropriately sized cuff.

Height in centimeters (cm) will be measured at Visit 1.

All vital sign assessments at Visit 2 should be performed prior to dosing.

Body weight to be recorded to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes, will be measured at Visit 1 through Visit 11, as well as Visit 12, if applicable.

#### **7.4.3 Edema**

Periorbital and peripheral edema will be assessed at each visit. At Visit 2 assessment should be performed prior to dosing.

#### **7.4.4 Laboratory evaluations**

A central laboratory will be used for analysis of all specimens collected, with the exception of Prothrombin Time (PT) and International Normalized Ratio (INR). PT and INR analysis will be conducted at a local laboratory identified by the site.

Blood samples for laboratory evaluations at Visit 2 should be drawn prior to dosing.

Instructions on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

##### **7.4.4.1 Hematology**

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and microscopy, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), RBC morphology, and platelet count will be measured at all study visits, including the end of study or premature discontinuation visit.

##### **7.4.4.2 Clinical chemistry**

Blood urea, creatinine, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, phosphorous, total protein, albumin, cholesterol, creatinine kinase, GGT, glucose, LDH, magnesium, total CO<sub>2</sub>, triglycerides, and uric acid will be measured at all study visits, including the end of study or premature discontinuation visit. Digoxin levels will be measured at Visits 2, 3 and 5 for those patients currently taking digoxin.

##### **7.4.4.3 N-terminal pro-b type Natriuretic Peptide (NT-proBNP)**

NT-proBNP will be collected at Visit 2 and Visit 6 through Visit 12.

##### **7.4.4.4 Urinalysis**

Dipstick measurements for specific gravity, protein, glucose and blood will be done. WBC and RBC sediments will also be measured. If any abnormalities are identified, a urine sample will be collected for analysis by the central laboratory where urine macroscopy and microscopy will be analyzed.

#### **7.4.5 Electrocardiogram (ECG)**

A central ECG organization will be collecting all ECG readings; however, results must be reviewed by the investigator to monitor patient safety. Each site will be provided with 12-lead ECG equipment. Instruction on equipment operation and handling of results will be provided by the ECG vendor.

All ECGs must be performed prior to the 6MWT.

At Visit 1, patients will undergo three consecutive ECGs conducted at 5-minute intervals.

At Visit 2 and Visit 4, three consecutive ECGs will be conducted at 5-minute intervals prior to the patient's first dose of study drug. At Visit 2, the pre-dose ECGs should be performed prior to contacting IVRS for randomization.. An additional ECG will be performed 0.5 hr to 3 hr after the patient received the first dose. The post-dose ECG should be conducted in coordination with the post-dose PK blood draw (see [section 7.5.2](#)) at each of these visits.

At Visit 6, three consecutive ECGs will be conducted at 5-minute intervals prior to the patient's dose of study drug.

At Visit 3, Visit 5 and Visits 7 through 11, a standard 12-lead ECG will be conducted. Drug dosing does not occur at these visits.

[Table 7-2](#) summarizes the schedule of ECGs conducted throughout the study:

**Table 7-2 Electrocardiogram schedule**

Visit	1	2	3	4	5	6	7	8	9	10	11	12
Triplicate ECG at 5-minute intervals	X	X		X		X						
0.5 – 3.0 hour POST-DOSE ECG		X		X								
Standard ECG			X		X		X	X	X	X	X	X

#### 7.4.6 Echocardiogram

Echocardiograms will be performed at baseline, 3 months and at EOS as a safety assessment of ventricular function. At the site, the estimated RVSP, LVEF, presence or absence of pericardial effusion, left atrial dilation, right ventricle dilation, right ventricle hypertrophy and any other noted abnormality will be recorded on the eCRF. Additionally, LVEF will also be assessed if heart failure is suspected or syncope occurs.

In addition, as an exploratory objective at selected sites, digital images will be collected and sent to a central facility for exploratory analyses of RV function. These assessments will include, but are not limited to: Doppler estimate of pulmonary vascular resistance (see [Appendix 5](#) for possible calculation), fractional area change of the right ventricle, tricuspid annular motion/tricuspid annular plane systolic excursion, and Tei index. The images required for this analysis are part of the standard procedures of echocardiograms and do not add to the burden of the patient.

A separate operating manual will be developed by the central facility with input for investigators participating in the project to included specifics of the techniques to obtain the images and the analyses plan.

#### 7.4.7 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Visit 1 and Visit 11. If positive, the patient must be discontinued from the trial. An optional urine pregnancy test can be performed locally at Visit 1, prior to the right heart



catheterization, and at Visit 2, prior to randomization. This information should only be captured in the source documentation at the site.

#### **7.4.8 Appropriateness of safety measurements**

The safety assessments selected are standard for this indication/patient population.

### **7.5 Other assessments**

#### **7.5.1 Resource utilization**

For the purpose of economic evaluation, medical healthcare resource utilization (RU) will be recorded.

At the screening visit (Visit 1), patients will be asked about the number of hospitalizations, ER visits and outpatient visits in the previous year. At each visit thereafter (Visit 2 through Visit 11), the investigator will record the patient's RU in terms of number of hospitalizations and outpatient medical care, including ER visits, since the previous scheduled visit. The collection of RU will continue during extension protocol CQT1571A2301E1, as longer term data is preferred for economic evaluations.

A hospitalization is defined as any visit to the hospital requiring an overnight stay. The frequency and duration of any inpatient hospitalization will be recorded along with the primary reason for the hospitalization and the primary and secondary diagnosis at discharge. For each hospitalization the duration spent in each of the following will be recorded: intensive care unit, general ward, emergency room, other, along with the type of physician consulted.

The frequency of unscheduled outpatient visits will be recorded along with the type of provider and type of facility visited, including the ER. An unscheduled outpatient visit is defined as any visit with a medical practitioner, in the office or at home, apart from the study visits.

Additionally, any procedures conducted during hospitalization or unscheduled outpatient visit will be recorded in the eCRF.

RU forms should be reviewed by the investigator for potential adverse events. If AEs or SAEs are confirmed then the investigator must record the events as per instructions given in [Section 8](#) of the protocol.

#### **7.5.2 Pharmacokinetics**

##### **7.5.2.1 Pharmacokinetics collection and processing**

##### **Blood collection for QT1571, bosentan and sildenafil**

Population pharmacokinetic methodology will be utilized to assess the PK of QT1571 and the potential for interaction of QT1571 on bosentan and sildenafil. Samples will be collected from all eligible patients randomized to active and placebo treatment groups in this trial. In addition to enable the evaluation of DDI, a complete history of their concomitant medications

will be captured in the eCRF at each visit and will be captured prior to blood draw at the scheduled PK sampling visit.

Blood collection for PK assessments (QTI571, sildenafil and bosentan): 6.0 mL blood will be taken at the following sampling windows:

- Day 0 (week 0, 1<sup>st</sup> 200 mg QD): at predose, between 0.5 - 3 hour (~ T<sub>max</sub>) post dose.
- Day 14 (week 2, 1<sup>st</sup> 400 QD): at predose, between 0.5 - 3 hour (~ T<sub>max</sub>) post dose.
- Day 28 (week 4, QTI571 drug concentration at steady-state): at predose, between 0.5 - 3 hour (~ T<sub>max</sub>) post dose
- Day 168 (week 24): at predose, between 0.5 – 3 hour (~T<sub>max</sub>) post dose, between 3 – 6 hour post dose and between 6 – 8 hour post dose

All samples must be taken by either direct venipuncture or via indwelling cannula inserted in a forearm vein. For each plasma sample, 6.00 mL of blood must be collected into a tube containing heparin, inverted several times and centrifuged at 1100-x g for at least 10 minutes. Plasma samples must be separated into polypropylene screw-cap tubes and frozen at -20C. All tubes must be kept frozen until shipment to Novartis. All samples must be carefully packed in suitable packing material containing sufficient dry ice to keep them frozen during shipment.

Refer to [section 10.5.4](#) for pharmacokinetic parameter estimation. Instructions for pharmacokinetic blood sample handling and shipment are found will be detailed in the central laboratory manual.

### 7.5.2.2 Pharmacokinetic analytical methods

#### Analytical methods for QTI571, bosentan, sildenafil and their active metabolites

The parent compound QTI571 and its active metabolite, CGP74588, will be measured in plasma by validated HPLC-MS/MS assay.

Bosentan is metabolized in the liver by CYP3A4 and CYP2C9 resulting in three metabolites, one of which, Ro 48-5033, is pharmacologically active and may contribute 10 to 20% to the total activity of the parent compound. Bosentan is an inducer of CYP2C9, CYP3A4 and possibly CYP2C19. Therefore, the parent drug bosentan and its major active metabolite, Ro 48-5033, will be determined by validated HPLC-MS/MS assays.

Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients with PAH, however, the ratio of the metabolite to sildenafil is higher. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours. Therefore, the parent drug sildenafil and its active metabolite, N-desmethylation of sildenafil, will be determined by validated HPLC-MS/MS assays.

## **Analytical method for measurement of digoxin levels for those patients on this co-medication**

Pharmacokinetic interactions are not expected with digoxin. In addition, given the safety profile for digoxin, digoxin levels will also be monitored at baseline and at steady state with 200mg and 400 mg QD dosing (after 7 days of exposure) by the central lab. An exploratory analysis will be carried out to see whether or not QTI571 will have an impact on digoxin PK.

## **Pharmacokinetics**

The key population PK analysis will be focused on the parent drugs QTI571, bosentan and sildenafil. The concentration ratio between parent drugs and their active metabolites will be determined.

### **7.5.3 Pharmacogenetics**

To study the effects of human genetic variation on drug response, exploratory pharmacogenetic research studies will be conducted as a sub-study to this protocol. Instructions on collection, storage and shipment of samples are described in the central laboratory manual.

Pharmacogenetics will be limited to mutations in BMPR2 receptor, and polymorphisms that are part of the TGF beta super family, or associated pathways. Pharmacogenetics will only be measured in those subjects who provide separate informed consent for a blood draw at any time after screening and prior to study completion or premature discontinuation. Pharmacogenetic studies are not required for entry into study.

### **7.5.4 Health related quality-of-life**

Health-related quality of life (HRQOL) will be measured using the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), the only disease-specific measure of HRQOL (McKenna 2006) and health status (McKenna 2008; Meads 2008) in pulmonary hypertension.

The CAMPHOR has been fully validated in the UK (McKenna 2006), USA (Gomberg-Maitland 2008) and Canada (Coffin 2008) in PAH patients between 18-80 years of age who qualified for all NYHA functional classes. The CAMPHOR consists of 65 items and 3 scales. Two scales measure HRQOL: 1) Impairment (Symptoms) consists of 25 items and is intended to measure any loss or abnormality of psychological, physiological or anatomical structure or function, equating to symptoms; it is further sub-divided into 3 subscales - energy, breathlessness and mood, and 2) disability (functioning), which consists of 15 items and is intended to measure any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being. The third scale is a separate QOL measure, which consists of 25 items and relies on the needs-based model of QOL defined as the individual's perceived ability and capacity to satisfy his/her needs. Impairment and disability, both consequences of disease, are major influences on QOL (McKenna 2006).

Patients are asked to report their responses of how they feel at the moment. The 25-item Symptom and QOL scales are scored from 0-25, with a higher score indicating the presence of more symptoms and poor QOL, respectively. Both scales consist of dichotomous answers (Yes/No for Symptoms and True/Not true for QOL). The 15-item Functioning scale is scored

from 0-30 and has a three-point answer (Able to do on own without difficulty / Able to do on own with difficulty / Unable to do on own); a higher score indicates poor functioning.

The CAMPHOR has good internal consistency ( $\alpha = 0.90 - 0.92$ ) and reproducibility (test-retest correlations =  $0.86 - 0.92$ ) and has shown convergent, divergent and known groups validity. However, no responsiveness or interpretability (i.e, meaningfulness of change) have been established so far (Chen 2008).

The CAMPHOR questionnaire will be applied to patients in the countries for which a translation is available.

The CAMPHOR should be administered prior to any medical assessments on visits 1 (screen) and 2 (randomization) and bi-monthly thereafter (visits 7, 9 and 11).

The patient should be given sufficient space and time to complete the questionnaire. Patients should complete the questionnaire in the language they are most familiar with.

The study coordinator should check the questionnaire for completeness and encourage the patient to complete any missing responses. Patient responses to the CAMPHOR questionnaire will be transcribed onto the eCRF by the study coordinator.

Completed questionnaires will be reviewed and examined by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the patient. If AEs or SAEs are confirmed then the physician must record the events as per instructions given in Section 8.1 and Section 8.2 of the protocol. Investigators should not encourage the patients to change the responses reported in the completed questionnaires.

## **8 Safety monitoring**

### **8.1 Adverse events**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events eCRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)

3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- syncope

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see [Section 8.2](#).**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

## **8.2 Serious adverse event reporting**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study

participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

**It is mandatory that all events of Syncope be reported as a Serious Adverse Event.**

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Clinical Safety & Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety & Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

### **8.3 Pregnancies**

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Clinical Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the

possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

## **8.4 Data Monitoring Committee**

An external DMC will be appointed to monitor the safety of the patients during the study. The DMC will review on an ad hoc basis all reports of deaths during the study. SAEs will also be reviewed on an ad hoc basis if considered necessary. The DMC will also perform a pre-planned review of additional pre-defined safety data when 50% patients have completed 3 months of treatment. The membership of the DMC and the responsibilities of the DMC and Novartis will be defined in a separate 'Data Monitoring Committee Charter' document. The DMC Charter will include information about data flow, purpose and timings of DMC meetings, communication strategy, procedures for ensuring confidentiality, procedures to address conflicts of interest and statistical monitoring guidelines.

## **8.5 Adjudication committee**

Overnight hospitalizations will be adjudicated by an external Adjudication Committee to confirm the hospitalization was due to worsening of PAH. Additionally, if any patient dies during the study the specific cause of death will be adjudicated. Members of the external Adjudication Committee will include physicians with expertise in the treatment of PAH who are not involved in the study conduct. The events will be reviewed in a blinded manner.

# **9 Data review and database management**

## **9.1 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs

are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

## **9.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

## **9.3 Database management and quality control**

Novartis staff, or CRO working on behalf of Novartis, review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Obvious errors are corrected by Novartis personnel, or CRO working on behalf of Novartis. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO) with the exception of the PT/INR and dipstick urinalysis that will be performed locally.

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drugs dispensed to the patient and all dosage changes will be tracked using an Interactive Voice Randomization System. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After this action has been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biostatistics and Statistical Reporting and the Global Therapeutic Area Head.



## **10 Data analysis**

All analyses will be performed when all patients have either completed 24 weeks of treatment, been discontinued or withdrawn early from the study.

### **10.1 Populations for analysis**

The Full Analysis Set (FAS) will include all randomized patients who received at least one dose of study drug. To fulfill the intention to treat criterion patients will be analyzed according to the treatment group allocated at randomization.

The per-protocol (PP) population will include all patients in the FAS without any major protocol violations. Patients will be analyzed according to the treatment they received. Major protocol violations will be defined in the validation analysis plan prior to data base lock and the unblinding of the study.

The Safety Population will consist of all patients that received at least one dose of study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. The safety population allows the inclusion of non-randomized patients who receive study drug in error.

The primary analysis population for efficacy will be the FAS. The PP population will be used for supportive analysis of the primary variable. The Safety population will be used in the analysis of all safety variables.

### **10.2 Patient demographics/other baseline characteristics**

Demographic and baseline characteristics including age, gender, race, ethnicity, height, weight, body mass index (BMI), relevant medical history, screening pulmonary hemodynamics and 6-MWD, duration of PAH, prior concomitant medications (PAH related and non-PAH related), vital signs (body temperature, respiratory rate, systolic and diastolic blood pressure and radial pulse rate), QTc and ECG will be summarized for the safety population.

### **10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)**

The number of patients and the length of time (in days) exposed to the study drug will be summarized by treatment for the Safety population.

Concomitant medications will be summarized by treatment for the Safety population. Concomitant PAH related medications will be summarized by pre-specified categories recorded on the CRF and preferred term. Concomitant medications not related to PAH will be summarized by preferred term.

Treatment compliance will be summarized by treatment for the FAS.

### **10.4 Analysis of the primary objective(s)**

The primary objective is to determine if QTI571 is superior to placebo with respect to 6-MWD in patients with PAH following 24 weeks (Visit 11) of treatment.

#### **10.4.1 Variable**

Six-minute walk distance is measured in the clinic at Visits 6-11 (weeks 4, 8, 12, 16, 20 and 24). All time points will be included in the analysis model but the primary timepoint of interest is the 6MWD after 24 weeks of treatment.

The baseline measurement is defined as the average of two 6MWD values taken in the clinic during screening (Visit 1), one performed at day -3 ( $\pm 3$  days).

#### **10.4.2 Statistical hypothesis, model, and method of analysis**

The superiority of QTI571 over placebo will be evaluated by testing the following null hypothesis ( $H_0$ ) versus the alternative hypothesis ( $H_a$ ):

$H_0$ : There is no difference in the 6-MWD after 24 weeks for patients with PAH treated with QTI571 compared to placebo

$H_a$ : There is a difference in the 6-MWD after 24 weeks for patients with PAH treated with QTI571 compared to placebo

The primary variable will be analyzed using a mixed effects model for repeated measures with an unstructured covariance matrix implemented via PROC MIXED with a REPEATED statement. The primary model will include treatment, week, and country as factors, with baseline 6-MWD as a covariate. Treatment by week and baseline by week interactions will also be included in the model. The primary outcome of interest will be the comparison of QTI571 versus placebo after 24 weeks of treatment.

The primary analysis population will be the FAS. Estimated adjusted treatment differences for QTI571 minus placebo will be displayed along with the associated confidence interval and p-value (2 sided). Superiority of QTI571 over placebo will be demonstrated if the p-value (2 sided) is less than 5% significance level and the confidence interval lies entirely to the right of (higher than) 0 meters.

#### **10.4.3 Handling of missing values/censoring/discontinuations**

Every effort will be made to ensure missing values are kept to a minimum. However, some missing data is inevitable in this serious illness. To some extent missing data are less of a problem, when repeated measures mixed models are used, unless there are very substantial between-treatment group differences with respect to the pattern of drop-out. Missing values are less problematical as observations at each time point influence estimates of treatment effects at every other time point, due to the specification of the covariance pattern. Patients whose observations are limited to early time points because of drop-out will nevertheless be taken into account when estimates are made of treatment effects at later time points. These individuals will not influence treatment estimates as greatly as individuals whose data is complete, so the pattern of missing data cannot be completely ignored.

To assess the robustness of the conclusions from the primary analysis model multiple sensitivity analyses using parametric and non-parametric methods will be performed under varying missing data distributions. These will be specified in the statistical analysis plan.

#### **10.4.4 Supportive analyses**

The primary analyses for the 6MWD at 24 weeks will be repeated for the PP population.

Supportive analysis to assess the impact of missing data will be performed as specified in the statistical analysis plan. This sensitivity analysis framework will be used to assess the robustness of the results under various missingness assumptions.

The analysis of subgroups of patients may be considered and any subgroups will be predefined and specified in the statistical analysis plan.

### **10.5 Analysis of secondary objectives**

#### **10.5.1 Efficacy (secondary)**

##### **10.5.1.1 Time to Clinical Worsening**

To determine if QTI571 is superior to placebo with respect to time to clinical worsening following 24 weeks of treatment.

Time to clinical worsening is defined as the first of the following events to occur: all cause mortality; overnight hospitalization for worsening of PAH; worsening of WHO functional class by one level; or a 15% decline in 6MWD measured on two consecutive occasions. The time of the first 15% decrease will be the TTCW once it is confirmed on the following visit. TTCW events will be adjudicated in a blinded fashion by an independent committee. The primary analysis of this endpoint will be performed based on events agreed by the adjudication committee; however, the analysis will also be repeated including all events reported locally.

The time to clinical worsening will be analyzed using a Cox regression model for the FAS. The model will include terms for treatment and country. The model will also contain the baseline 6MWD as a covariate. An adjusted hazard ratio will be displayed along with its associated 95% confidence interval and p-value (2 sided).

The model assumptions will be checked and if needed alternative methods will be used as appropriate.

The analysis will be repeated each individual component of the TTCW (without multiplicity adjustment). These results will be considered as supportive evidence.

##### **10.5.1.2 Procedure to handle multiplicity**

A hierarchical testing approach to the analyses will be taken for the primary endpoint (6-MWD) and time to clinical worsening

Primary: 6-MWD QTI571 superiority comparison vs. placebo  
(2-sided  $\alpha=0.05$ )

Secondary: Time to clinical worsening QTI571 superiority comparison vs. placebo  
(2-sided  $\alpha=0.05$ )

This procedure will control the family-wise type I error rate at level alpha for the primary endpoint and the secondary endpoint, time to clinical worsening.

### **10.5.1.3 Other secondary variables**

Other secondary variables and time-points are grouped below in no particular order. All variables will be summarized and analyzed by treatment for the FAS unless stated otherwise.

The model assumptions will be checked and if needed alternative methods will be used as appropriate.

No adjustment for multiplicity will be made.

#### **(A) 6-minute walk test**

All aspects of the 6MWT (total distance walked, number of stops, total duration of stops, oxygen saturation, systolic and diastolic blood pressure, heart rate and Borg score) will be summarized at each time point. In addition all data from the 6MWT will be analyzed at each time point using a mixed model. The model will contain treatment as a fixed effect with the appropriate baseline value as a covariate. To reflect the randomization scheme the model will also include country as a fixed effect with center nested within country as a random effect.

Estimates of adjusted treatment effect and estimates of treatment contrast for QT1571 minus placebo will be displayed along with the associated confidence intervals and two-sided p-values.

#### **(B) Pulmonary hemodynamics**

Several prognostic hemodynamic variables for pulmonary hypertension, including right atrial pressure (RA), mean pulmonary arterial pressure (mean PAP), mean Pulmonary Capillary Wedge pressure (mean PCWP), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) Heart Rate (HR), Cardiac Output (CO), Cardiac Index (CI), Mean Arterial Blood Pressure (MAP), Pulmonary Vascular Resistance (PVR) and Systemic Vascular Resistance (SVR) will be measured at screening and study completion. Cardiac Index will be calculated as CO/BSA. BSA will be calculated at baseline using Dubois formula (Dubois & Dubois, 1916). All variables will be summarized at each time point. In addition all parameters will be analyzed using a mixed model. The model will contain treatment as a fixed effect with the appropriate hemodynamic parameter baseline value as a covariate. To reflect the randomization scheme the model will also include country as a fixed effect with center nested within country as a random effect.

Estimates of adjusted treatment effect and estimates of treatment contrast for QT1571 minus placebo will be displayed along with the associated confidence intervals and two-sided p-values.

#### **(C) World Health Organization classification of functional status**

Functional status at each time point will be reported by treatment.

## **10.5.2 Safety**

All safety endpoints will be summarized by treatment for all patients in the safety population. Additional subgroups may be analyzed and these will be specified in the statistical analysis plan.

### **Adverse events**

All study emergent adverse events will be recorded and listed. Adverse events starting on or after the time of the first use of study drug will be classified as a treatment emergent adverse event. Any adverse events that started during the study before the time of the first use of study drug will be reported as medical history in the CRF.

The following treatment emergent adverse event summaries will be produced, overall by system organ class and preferred term, overall by system organ class, preferred term and maximum severity, suspected drug-related adverse events by system organ class and preferred term, serious adverse events by system organ class and preferred term, and adverse events leading to permanent discontinuation of study-drug by system organ class and preferred term. The number and % of patients with the most frequent AEs (>5% for any treatment) will be summarized by treatment.

Selected adverse events may be summarized over time.

The following prior adverse event summaries will be produced, overall by system organ class and preferred term, serious adverse events by system organ class and preferred term, and adverse events leading to withdrawal from the study by system organ class and preferred term. Alternatively if the number of prior adverse events is low, listings will be used instead of summaries.

### **Electrocardiogram (ECG) and vital signs**

Data from the electrocardiogram and vital signs will be summarized by treatment at each timepoint. The baseline measurement will be the average of the -10 minute, -5 minute and immediately pre-dose measurement at Visit 2. The maximum (QTc, systolic blood pressure, pulse rate and heart rate) or minimum (diastolic blood pressure) post first dosing (i.e. post baseline) value will also be summarized. Changes from baseline will also be summarized by treatment.

QTc, heart rate and vital signs at all time-points during each visit, the maximum (QTc, systolic blood pressure, pulse rate, heart rate) or minimum (diastolic blood pressure) post first dosing value will be analyzed using a similar mixed model as for pulmonary hemodynamics.

Notable values for vital signs and change from baseline will be summarized. A notable value is defined as follows: pulse rate of <40 and >90 bpm; systolic blood pressure of <90 and >140 mm Hg; diastolic blood pressure of <50 and >90 mm Hg.

Notable QTc values and change in QTc from pre to post-dose will be summarized. A notable value is defined as a QTc interval of greater than 450 ms for males and greater than 470 ms for females. The categories used for the change in QTc from pre to post-dose are less than 30 ms, 30 to 60 ms and greater than 60 ms.

QTc will be calculated from the QT interval and RR (in seconds) using Fridericia's formula:

$QTc = QT / \sqrt[3]{RR}$ , where  $\sqrt[3]{}$  denotes the cube root.

## **Laboratory data**

Hemoglobin, platelets, neutrophils, total bilirubin, proBNP and AST/ALT will be summarized by treatment at each visit. Changes from baseline will also be summarized by treatment. The baseline measurement will be the pre-dose measurement at Visit 2.

These will also be analyzed using a similar mixed model as for pulmonary hemodynamics.

All other laboratory data will be listed with abnormal values flagged. The laboratory values and the change from baseline for continuous laboratory parameters will be summarized at each time-point and visit. A frequency table of results for categorical laboratory parameters will be produced by time-point and visit. Shift tables relative to the normal reference ranges will be used to summarize the change from baseline to each time-point and visit as well as the worse case post first dosing for each laboratory parameter.

## **Echocardiography**

Echocardiograms will be performed at baseline, 3 months and at EOS as a safety assessment of ventricular function.

The incidence of specific abnormalities (presence or absence of pericardial effusion, left atrial dilation, right ventricle dilation, right ventricle hypertrophy and any other abnormality noted on the eCRF) will be reported.

RVSP and LVEF will be summarized at each visit. Changes from baseline will also be summarized by treatment. These will also be analyzed using a similar mixed model to that used for the pulmonary hemodynamic analysis (with the screening value used as baseline).

In addition, as an exploratory objective at selected sites, digital images will be collected and sent to a central facility for exploratory analyses of RV function. These assessments will include, but are not limited to: Doppler estimate of pulmonary vascular resistance, fractional area change of the right ventricle, tricuspid annular motion/tricuspid annular plane systolic excursion, and Tei index. Analyses of these results will be pre-specified in the statistical analysis plan.

## **Edema**

The incidence and severity of edema will be summarized at each visit by treatment.

## **Time to premature discontinuation**

Time to premature discontinuation due to the primary reason of PAH related adverse event or unsatisfactory therapeutic effect will be displayed graphically for each treatment group using a Kaplan-Meier curve for the safety population. Patients who did not experience a discontinuation due to a PAH related adverse event or unsatisfactory therapeutic effect will be censored at Visit 11. Patients who withdrew from the study for any other reason will be censored at the date of withdrawal.

The time to premature discontinuation due to a PAH related adverse event or unsatisfactory therapeutic effect will be analyzed for the safety population using the same Cox regression model as specified for time to clinical worsening.

### 10.5.3 Resource utilization

Data relating to Resource Utilization will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity. Only descriptive statistics of Resource Utilization data will be given in the study report.

Data collected during the screening visit (Visit 1) will be analyzed for those patients who entered the study only.

The number of hospital admissions, number of ER visits and number of unscheduled doctor's visits during the whole treatment period will be tabulated separately by treatment group.

The mean duration of hospitalization and its 95% confidence interval will be calculated for each treatment group.

In addition the number of patients with 0 or  $\geq 1$  hospital admissions, the number of patients with 0 or  $\geq 1$  ER visits, the number of patients with 0 or  $\geq 1$  unscheduled doctor's visits will be tabulated by treatment group.

### 10.5.4 Pharmacokinetics

Population modeling will be undertaken to evaluate QTI571 pharmacokinetics in this patient population. A one-compartment model has been previously employed to describe imatinib pharmacokinetics in other patient populations (e.g. [Schmidli et al 2005](#), [Judson et al 2005](#)) and will be considered to estimate pharmacokinetic parameters such as  $k_a$ ,  $CL/F$ ,  $V/F$ ) and characterize interindividual variability. A covariate analysis will be conducted to identify relevant variables impacting pharmacokinetics of each compound. This will include demographic variables (age, weight, gender, and race), laboratory test values (e.g. Hb, WBC, TBIL, etc), and co-medication classes.

A similar approach will be used to characterize bosentan and sildenafil pharmacokinetics. This will be restricted to patients receiving QTI571-matched placebo. One-compartment models will be considered but more complex models (e.g. two-compartment) will be tested, if appropriate. To evaluate the potential for interaction of QTI571 on sildenafil and bosentan pharmacokinetics, the final models will be analyzed on the full set of concentrations (all patients) and extended by adding indicator variables to represent a QTI571 effect on clearance and volume. AUC over the dosing interval (AUC<sub>tau</sub>) and C<sub>max</sub> values will be simulated from the model in order to characterize their distribution under the presence or absence of QTI571 and evaluate the potential for interaction on those medications. A post-hoc power calculation will be conducted to assess the size of interaction effect that the analysis would be able to detect with sufficient confidence. This will help interpret the meaningfulness of the results in light of the data collected.

### **10.5.5 Pharmacogenetics/pharmacogenomics**

The incidence of specific mutations will be reported. If numbers permit additional analyses will be performed on mutation subgroups. These analyses will be pre-specified in the statistical analysis plan.

### **10.5.6 PK/PD**

An exploratory PK/PD analysis will be performed if data permit.

### **10.5.7 Health related quality-of-life**

The CAMPHOR will be scored in accordance with the developers scoring algorithm. All scales and subscales of the questionnaire will be summarized by treatment at each time point.

## **10.6 Sample size calculation**

A total of 200 patients will be randomized.

A difference of 50 meters or greater in 6MWD distance is considered to be clinically relevant in subjects who remain symptomatic on a least two PAH specific therapies and have a PVR  $\geq$  800 dynes sec-cm-5 after 6 months treatment. The analysis of E2203 (proof-of-concept trial) after 6 months treatment suggested a standard deviation (SD) of the difference in treatment effect between QTI571 and placebo of approximately 56 meters. This SD has an associated 95% confidence interval of 46 to 72 meters. As this SD is based on a relatively small sample size it was decided to use 75 meters for the purposes of sample size calculation. A value of 75 meters or less has a probability of over 95% of being the true SD. Patients will be randomized in a ratio of 1:1 to QTI571 or placebo. A sample size of 49 evaluable patients on QTI571 and 49 on placebo would be needed to detect a 50 meter difference between QTI571 and placebo as statistically significant at the 5% significance level (2 sided) with 90% power.

In this group of seriously ill patients a proportion are likely to drop-out early. Therefore, assuming a drop out rate of 30% over 6 months of treatment a minimum sample size of 140 patients (70 patients receiving QTI571 and 70 patients receiving placebo) is required.

For TTCW, assuming a 9 month accrual period, and an event free survival rate at 24 weeks of 94% for QTI571 and 82% for placebo (similar to that seen in a published study of combination PAH therapy – [Simonneau et al](#)), 100 patients per group are required to detect this difference with 90% power and an alpha 0.05.

Although an interim analysis is planned the type I error criterion is so extreme (see [Section 10.8](#)) that there would be minimal impact on the power/sample size.

Sample size was calculated using nQuery 6.01.

## **10.7 Power for analysis of critical secondary variables**

The sample size in [Section 10.6](#) includes consideration of the power for the analysis of time to clinical worsening (TTCW).



## **10.8 Interim analysis**

An independent Data Monitoring Committee (DMC) will receive reports of all deaths that occur during the study. Initially these will be provided in a blinded fashion. At their own discretion, the DMC may request the treatment information for these patients. In addition the DMC will review partially blinded (Group A vs. Group B) safety and mortality data when 50% of subjects have completed 3 months of treatment. Based on parameters established in a DMC charter, additional reviews may be scheduled at the discretion of the DMC.

The details of the information flow, confidentiality and specific analyses required for the safety interim will be documented in the DMC Charter. The Charter will be finalized prior to unblinding the data for the IA. The IA will be performed by an external Independent Statistician and an Independent Programmer. The data will be reviewed by an independent and partially unblinded Data Monitoring Committee (DMC) ([Section 8.4](#)). Persons directly involved in the conduct of the clinical trial will not be involved in performing the IA or reviewing the results.

As recommended by [Koch et al, 1998](#) a nominal adjustment to final p-values for the primary endpoint (6-MWT) and time to clinical worsening of 0.0001 will be made to allow for the interim analysis. Further adjustments of 0.0001 will be made for each review if additional unblinded data reviews are requested by the DMC.

## **11 Ethical considerations**

### **11.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **11.2 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a

copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

### **11.3 Responsibilities of the investigator and IRB/IEC/REB**

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

### **11.4 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as [clinicaltrials.gov](http://clinicaltrials.gov). In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **12 Protocol adherence**

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **12.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety

of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

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## **14      Appendix 1: Clinically notable laboratory values and vital signs**

There are no specific criteria for this study, however, the Central Laboratory will flag laboratory values falling outside of the normal ranges on the Central Laboratory Report (which the investigator should review and sign off) and the investigator will report any values considered clinically significant in the eCRF.

For ECGs a notable QTc value is defined as a QTc interval of greater than 450 ms for males and greater than 470 ms for females – all such ECGs will be flagged by the Central CRO's cardiologist and require assessment for clinical relevance by the Investigator.

## 15 Appendix 2: PK blood log

Study Phase		Time (week)	Time Window (hrs)	PK BLOOD SAMPLES		
				QTI571		
				PK Col No	Sample No	(mL)
Visit 2 (Day 0) First 200mg QD dose	Predose	0	0 hr	1	1	6
	Postdose		0.5 - 3 hr	1	2	6
Visit 4 (Day 14)	Predose	2	0	2	3	6
First 400mg QD dose	Postdose		0.5 - 3 hr	2	4	6
Visit 6 (Day 28)	Predose	4	0	3	5	6
	Postdose		0.5 - 3 hr	3	6	6
Visit 11 (Day 168)	Predose	24	0 hr	4	7	6
	Postdose		0.5 - 3 hr	4	8	6
			3 - 6 hr	4	9	6
			6 - 8 hr	4	10	6
Total (mL)						60



## **16      Appendix 3: Six minute walk test and oximetry (oxygen saturation , SpO<sub>2</sub>)**

A standardized Six-Minute Walk Test (6MWT) will be performed in accordance with the guidelines of the (American Thoracic Society 2003). The patient's resting values of oxygen saturation (%), heart rate (b/min), blood pressure (mm Hg) and Borg Questionnaire score are to be recorded on the eCRF before the test, at the end of the test, and two minutes after the end of the test.

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 30 m in length. The length of the corridor should be marked every 3 m. The turnaround points should be marked (e.g. with a cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor e.g. using brightly colored tape.

The distance walked in six minutes (6MWD) will be calculated and recorded. If the patient discontinues the test prematurely, the time (mm:ss) and distance walked will be recorded.

Requirement of rescue medication including requirement of oxygen therapy and any adverse events occurring during the 6MWT will be recorded. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by the investigator.

During the study the 6MWT should be done about the same time of day to avoid diurnal variation. If ECG is to be recorded at the same visit, this must be done prior to the 6MWT.

### **REQUIRED EQUIPMENT**

- 1) Countdown timer (or stopwatch)
- 2) Mechanical lap counter
- 3) Two small cones to mark the turnaround points
- 4) A chair that can be easily moved along the walking course
- 5) Worksheets on a clipboard
- 6) A source of oxygen
- 7) Sphygmomanometer
- 8) Telephone
- 9) Automated electronic defibrillator
- 10) Portable pulse oximeter

### **PATIENT PREPARATION**

- 1) Comfortable clothing should be worn.
- 2) Appropriate shoes for walking should be worn.
- 3) Patients should use their usual walking aids during the test (cane, walker, etc.).
- 4) The patient's usual medical regimen should be continued.
- 5) A light meal is acceptable before early morning or early afternoon tests.
- 6) Patients should not have exercised vigorously within 2 hours of beginning the test.

## MEASUREMENTS

- 1) Repeat testing should be performed about the same time of day to minimize intraday variability.
- 2) A "warm-up" period before the test should not be performed.
- 3) The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete portion of CRF.
- 4) Measure and record baseline heart rate and oxygen saturation (SpO<sub>2</sub>) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact. Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

### Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

- 1) Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
- 2) Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

- 1) Post-test: Record the postwalk Borg dyspnea and fatigue levels
- 2) Measure SpO<sub>2</sub> and pulse rate from the oximeter and then remove the sensor.
- 3) Record the number of laps from the counter
- 4) Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
- 5) Congratulate the patient on good effort and offer a drink of water.

## References:

([American Thoracic Society, 2003](#))

## 17 Appendix 4: Borg Scale

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- 0 Nothing at all
  - 0.5 Very, very slight (just noticeable)
  - 1 Very slight
  - 2 Slight (light)
  - 3 Moderate
  - 4 Somewhat severe
  - 5 Severe (heavy)
  - 6
  - 7 Very severe
  - 8
  - 9
  - 10 Very, very severe (maximal)
- 

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

([American Thoracic Society, 2003](#))

## 18      **Appendix 5: Echocardiographic estimation of pulmonary vascular resistance**

### **Required views:**

- 1 – Parasternal short axis view at the aortic valve level: Obtain the right ventricular outflow tract time-velocity integral (RVOT-TVI) (cm) by placing a 1- to 2-mm pulsed wave Doppler sample volume in the proximal right ventricular outflow tract just within the pulmonary valve. The sample volume location should be adjusted so that the closing but not opening click of the pulmonary valve was visualized.
- 2 – Obtain the peak tricuspid regurgitant velocity (TRV) (m/s) using Continuous wave Doppler from the parasternal short axis, apical 4-chamber, subcostal.

Tips: Agitated saline can be used to enhance suboptimal Doppler signals.

### **Measurements:**

In patients with atrial fibrillation, the average of five measurements should be used.

- 1 – TRV: Measure peak tricuspid regurgitation velocity. The highest TR velocity obtained from multiple views (parasternal short axis, apical 4-chamber, subcostal) should be recorded.
- 2 – TRPG: Measure peak tricuspid regurgitation gradient. The highest TR gradient obtained from multiple views (parasternal short axis, apical 4-chamber, subcostal) should be recorded.
- 3 – Trace RVOT-TVI.

### **Calculations:**

$$\text{PVR}_{(\text{Wood units})} = 10 \times \text{TRV}_{(\text{m/s})} / \text{RVOT-TVI}_{(\text{cm})} + 0.16 \quad [1]$$

$$\text{PVR}_{(\text{dyne s cm}^{-5})} = 187 + \text{TRPG}_{(\text{m/s})} / \text{RVOT-TVI}_{(\text{cm})} \times 118 \quad [2]^*$$

\*Validated in patients with Pulmonary Arterial Hypertension.

### **References**

[1] ([Abbas et al.](#))

[2] ([Kouzu et al.](#))

([American Journal of Cardiology, 2009](#))

## **Supplementary Appendix III: Results**

### **i) Supplemental Tables**

**Table I. Responder Analysis: Proportion of Patients Achieving Absolute and Relative Increases in 6MWD**

	<b>Imatinib</b>	<b>Placebo</b>	
<b>Increase from Baseline to End of</b>	<b>n=103</b>	<b>n=98</b>	
<b>Study</b>	<b>n (%)</b>	<b>n (%)</b>	<b>P value</b>
<b>Number of patients*</b>	93	93	
<b>Absolute change</b>			
≤−45 m	9 ( 9.7)	16 (17.2)	0.196
≤−40 m	10 (10.8)	19 (20.4)	0.105
≤−35 m	12 (12.9)	21 (22.6)	0.124
≤−30 m	12 (12.9)	26 (28.0)	0.017
≤−25 m	13 (14.0)	27 (29.0)	0.020
≤−20 m	16 (17.2)	31 (33.3)	0.018
≤−15 m	17 (18.3)	32 (34.4)	0.019
≤−10 m	21 (22.6)	35 (37.6)	0.037
<0 m	32 (34.4)	43 (46.2)	0.135
≥0 m	61 (65.6)	50 (53.8)	0.135
> 0 m	54 (58.1)	41 (44.1)	0.078
>15 m	51 (54.8)	37 (39.8)	0.056
>20 m	48 (51.6)	32 (34.4)	0.026
>25 m	42 (45.2)	31 (33.3)	0.133
≥30 m	38 (40.9)	28 (30.1)	0.168
>35 m	37 (39.8)	25 (26.9)	0.087
>40 m	36 (38.7)	22 (23.7)	0.039
>45 m	34 (36.6)	14 (15.1)	0.001
>50 m	30 (32.3)	12 (12.9)	0.003
>55 m	29 (31.2)	12 (12.9)	0.004

>60 m	23 (24.7)	11 (11.8)	0.036
<b>Relative change</b>			
≥5%	49 (53)	33 (36)	0.026
≥10%	39 (42)	23 (25)	0.019
≥15%	28 (30)	13 (14)	0.013
≥20%	23 (25)	12 (13)	0.060
≥25%	16 (17)	7 (8)	0.073
≥30%	11 (12)	4 (4)	0.104
≥35%	9 (10)	4 (4)	0.249
≥40%	5 (5)	1 (1)	0.211
≥45%	3 (3)	1 (1)	0.621

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\*Includes all patients with at least one 6MWD measurement performed ≥28 days post-baseline after first dose. Analysis is on last post-baseline distance carried forward.

6MWD, 6-minute walk distance.

Percentages of patients achieving ≥5%, ≥10% or ≥15% increases in 6MWD from baseline through Week 24 (using last observation carried forward [LOCF] analysis) were significantly higher in the imatinib group, compared with placebo (53% versus 36%, 42% versus 25% and 30% versus 14%, respectively; all  $P \leq 0.026$ ).



**Table II. Analysis of Covariance of Change from Baseline at end of Study in Hemodynamic Parameters from Right Heart Catheterization at End of Study\***

		Treatment Difference (imatinib-placebo)			
Treatment	n	LS mean (SE)	LS mean (SE)	95% CI	P value
Right atrial pressure (mmHg)					
Imatinib	73	−1.0 (0.9)	−1.7 (0.8)	−3.2, −0.2	0.030
Placebo	81	0.7 (0.9)			
Mean pulmonary arterial pressure (mmHg)					
Imatinib	75	−3.5 (1.6)	−5.2 (1.4)	−8.0, −2.3	<0.001
Placebo	82	1.6 (1.6)			
Mean pulmonary capillary wedge pressure (mmHg)					
Imatinib	74	0.9 (0.7)	1.0 (0.7)	−0.3, 2.3	0.135
Placebo	80	−0.05 (0.7)			
Cardiac output (L/min)					
Imatinib	75	1.2 (0.2)	0.9 (0.2)	0.6, 1.2	<0.001
Placebo	81	0.3 (0.2)			
Systemic vascular resistance (dynes·sec·cm <sup>−5</sup> ) <sup>†</sup>					
Imatinib	71	−467.8 (78.6)	−379.8 (74.1)	−526.2, −233.3	<0.001
Placebo	76	−88.1 (77.2)			
Pulmonary vascular resistance (PVR) (dynes·sec·cm <sup>−5</sup> ) <sup>‡</sup>					
Imatinib	74	−366.5 (67.7)	−378.6 (62.4)	−501.9, −255.3	<0.001
Placebo	80	12.1 (69.0)			

\*End of study value = treatment + country + baseline value + error with center within country as random effect.

<sup>†</sup>Systemic vascular resistance was calculated as (mean arterial blood pressure – right atrial pressure) / cardiac output \* 80.

<sup>‡</sup>PVR was calculated as (pulmonary artery mean pressure – mean pulmonary capillary wedge pressure) / cardiac output \* 80.

CI, confidence interval; LS mean, least squares mean; SE, standard error of the mean.

**Table III. Summary of Pulmonary Vascular Resistance (PVR) Results by Type of Pulmonary Arterial Hypertension (PAH) and Treatment**

PAH type	Imatinib			Placebo		
	Difference from baseline			Difference from baseline		
	Baseline	Week 24	Last post-	Baseline	Week 24	Last post-
			baseline value			baseline value
IPAH	n=56	n=53	n=56	n=60	n=60	n=60
Dynes·sec·cm <sup>-5</sup> (SD)*	1185.3 (328.0)	−388.4 (334.2)	−384.3 (332.2)	1176.5 (351.2)	4.4 (492.2)	4.4 (492.2)
APAH	n=18	n=16	n=18	n=19	n=18	n=19
Dynes·sec·cm <sup>-5</sup> (SD)*	1271.1 (634.2)	−480.1 (406.1)	−446.0 (394.5)	1118.7 (270.6)	−55.8 (307.2)	−95.7 (345.5)
Other	n=0			n=1	n=1	n=1
Dynes·sec·cm <sup>-5</sup> (SD)*				1263.7	−376.0	−376.0

Only patients with measurements at baseline and post-baseline visit are shown. \*PVR was calculated as (pulmonary artery mean pressure – mean pulmonary capillary wedge pressure) / cardiac output \* 80.

APAH, associated pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; SD, standard deviation.

**Table IV. Summary Statistics of Change from Baseline in 6MWD (m) and PVR at 24 Weeks in Patients who Completed the Study, by WHO Functional Class and Treatment**

Endpoint	WHO functional		n	Mean (SD)
	class	Treatment		
6MWD, m	II	Imatinib	17	39 (59)
		Placebo	26	22 (54)
	III	Imatinib	45	41 (53)
		Placebo	50	-2 (68)
	IV	Imatinib	3	-10 (65)
		Placebo	4	-5 (8)
PVR, dynes·sec·cm <sup>-5</sup>	II	Imatinib	16	-476 (487)
		Placebo	26	-61 (337)
	III	Imatinib	49	-391 (307)
		Placebo	49	10 (518)
	IV	Imatinib	3	-361 (316)
		Placebo	4	-12 (311)

SE, standard error of the mean; 6MWD, 6-minute walk distance; PVR, Pulmonary Vascular Resistance; WHO, World Health Organisation

**Table V. Time to Clinical Worsening (TTCW) Events in Patients Receiving Imatinib by Time of First Occurrence**

	Timing of First Occurrence of Event				Total n
	=8 weeks (n=103)	>8–16 weeks (n=91)	>16–24 weeks (n=76)	>24 weeks (n=72)	
<b>Imatinib patients</b>					
TTCW events	24	6	5	2	37
Hospitalization for PAH	9	2	2	0	13
Worsened function					
15% fall in 6MWD	7	1	1	2	11
Worsened WHO					
functional class	9	3	2	0	14

N.B. Some patients had more than one TTCW event on the same day.

PAH, pulmonary arterial hypertension; WHO, World Health Organization; 6MWD, 6-minute walk distance.

**Table VI. Listing of Reported Deaths: IMPRES Core Study and Extension**

<b>Treatment group</b>	<b>Age/sex</b>	<b>Initial timing of onset of SAE(s)/timing of death</b>	<b>Principal cause of death</b>
<b>Core study</b>			
Placebo	68/F	After 3 weeks of placebo	Clostridium difficile infection
Placebo	66/F	After 4 months of placebo/21 days following discontinuation	Worsening PAH
Placebo	62/F	19 days following discontinuation	Right ventricular failure
Placebo	61/F	After 5 days of placebo/14 days following discontinuation	Pulmonary hypertension (following complications of pneumonia, diarrhea and disease progression)
Placebo	35/F	After 1 and 2 months of placebo/2 months following discontinuation	Cardiac arrest (following pulmonary hemorrhage and tracheobronchial aspergillosis)
Imatinib 200 mg	37/M	After 3 days of imatinib	Sepsis
Imatinib 400 mg	57/M	After 4 months of imatinib	Right ventricular failure
Imatinib 400 mg	59/M	After 16 days of imatinib/16 days following discontinuation	Renal failure

<b>Treatment group</b>	<b>Age/sex</b>	<b>Initial timing of onset of SAE(s)/timing of death</b>	<b>Principal cause of death</b>
Imatinib 400 mg	41/M	After 2 months of imatinib/2 months following discontinuation	Cardiac failure
Imatinib 400 mg	64/M	After 1 month of imatinib/25 days following discontinuation	Worsening PAH (hypoxemic respiratory failure)
<b>Open-label extension (Deaths reported as of Oct 31<sup>st</sup> 2012)</b>			
Placebo/Imatinib 200 mg	61/F	After 11 months of imatinib	Pneumonia
Placebo/imatinib 400 mg	36/F	After 4 months of imatinib	Multi-organ failure (worsening pulmonary hypertension and pericardial infusion)
Placebo/imatinib 400 mg	51/F	After 1 month of imatinib	Cardiac failure
Placebo/imatinib 400 mg	59/F	After 4 months of imatinib/5 days following discontinuation	Cardiac arrest, pseudomonas colitis, E. coli bacteremia
Placebo/imatinib 400 mg	57/F	After 12 days of imatinib and 16 days following discontinuation/25 days following discontinuation	Subdural hematoma and respiratory failure
Placebo/imatinib 400 mg	77/F	After 1 month of imatinib	Toxicity to various agents (possible diazepam intoxication)
Placebo/imatinib 200 mg	37/M	After 7 weeks of imatinib	Device-related sepsis

<b>Treatment group</b>	<b>Age/sex</b>	<b>Initial timing of onset of SAE(s)/timing of death</b>	<b>Principal cause of death</b>
Placebo/imatinib 400 mg	36/F	After 2 months of imatinib/5 days following discontinuation	Cerebrovascular accident
Placebo/imatinib 200 mg	52/F	After 2 months of imatinib	Right ventricular failure
Placebo/imatinib 400 mg	72/F	After 16 months of imatinib	Pneumonia, worsening PAH, interstitial lung disease
Imatinib/imatinib 200 mg	50/F	After 14 months of imatinib/approx 3 months following discontinuation	Right ventricular failure (with worsening PAH)
Imatinib/imatinib 400 mg	45/M	After 11 months of imatinib/approx 2 weeks following discontinuation	Cerebral Infarction
Imatinib/imatinib 200 mg	47/F	After 17 months of imatinib	Right ventricular failure
Imatinib/imatinib 400 mg	73/M	After 8 months of imatinib	Sudden cardiac death
Imatinib/imatinib 200 mg	65/F	After 2 months of imatinib/approx 8 months following discontinuation	Right ventricular failure
Imatinib/imatinib 200 mg	63/F	After 23 months of imatinib	Respiratory failure
Imatinib/imatinib 400 mg	60/M	After 19 months of imatinib/4 months following discontinuation	Complications from lung transplantation



<b>Treatment group</b>	<b>Age/sex</b>	<b>Initial timing of onset of SAE(s)/timing of death</b>	<b>Principal cause of death</b>
Imatinib/imatinib 200 mg	74/F	After 28 months of imatinib/21 days following discontinuation	Multi-organ failure
PAH, pulmonary arterial hypertension; SAE, serious adverse event.			

Tables VII–IX summarize data from the study safety population and are sorted by descending order of frequency in the imatinib treatment group. Adverse events are recorded by preferred term using the Medical Dictionary for Regulatory Activities (MeDRA).

**Table VII. Frequency of Adverse Events (AEs), (>5.0% in Any Treatment Group) by Preferred Term**

	<b>Imatinib</b>	<b>Placebo</b>
	<b>n=103</b>	<b>n=98</b>
	<b>n (%)</b>	<b>n (%)</b>
Patients with any AE(s)	100 (97)	94 (96)
Nausea	57 (55)	23 (24)
Edema peripheral	45 (44)	20 (20)
Diarrhea	36 (35)	19 (19)
Vomiting	31 (30)	10 (10)
Periorbital edema	30 (29)	7 (7)
Headache	25 (24)	22 (22)
Dyspnea	19 (18)	13 (13)
Nasopharyngitis	18 (18)	19 (19)
Hypokalemia	16 (16)	3 (3)
Anemia	14 (14)	3 (3)
Cough	11 (11)	15 (15)
Fatigue	11 (11)	7 (7)
Face edema	10 (10)	1 (1)
Muscle spasms	10 (10)	2 (2)
Abdominal distension	9 (9)	3 (3)
Blood creatinine increased	9 (9)	1 (1)
Dizziness	9 (9)	5 (5)
Oropharyngeal pain	9 (9)	6 (6)
Rash	9 (9)	2 (2)
Dyspepsia	8 (8)	5 (5)
Epistaxis	8 (8)	7 (7)

	<b>Imatinib</b>	<b>Placebo</b>
	<b>n=103</b>	<b>n=98</b>
	<b>n (%)</b>	<b>n (%)</b>
Alopecia	7 (7)	1 (1)
Pulmonary arterial hypertension	7 (7)	6 (6)
Pyrexia	7 (7)	3 (3)
Abdominal pain	6 (6)	3 (3)
Nasal congestion	6 (6)	4 (4)
Pain in extremity	5 (5)	6 (6)
Upper respiratory tract infection	5 (5)	7 (7)
Device-related infection	4 (4)	5 (5)
Palpitations	4 (4)	7 (7)
Urinary tract infection	4 (4)	5 (5)
Non-cardiac chest pain	3 (3)	7 (7)
Pruritus	3 (3)	5 (5)
Respiratory tract infection	3 (3)	8 (8)
Abdominal pain upper	2 (2)	6 (6)
Influenza	2 (2)	5 (5)
Sinusitis	2 (2)	6 (6)
Syncope	1 (1)	5 (5)

**Table VIIIa. Frequency of Adverse Events (AEs) (>10% in Any Treatment Group), by First Occurrence Period**

	Imatinib (n=103)				
	Total n (%)	≤8 weeks n	>8–16	>16–24	>24
			weeks	weeks	weeks
			n	n	n
Number of patients evaluated	103	103	91	76	72
Patients with AEs	100 (97)	95	5	0	0
Deaths	3 (3)	2	0	1	0
Patients with non-fatal SAEs	44 (43)	30	10	4	0
Patients with SAEs including deaths	45 (44)	31	10	4	0
Discontinuations due to AEs	28 (27)	20	6	2	0
<b>Preferred term</b>					
Nausea	57 (55)	54	2	0	1
Edema peripheral	45 (44)	31	7	7	0
Diarrhea	36 (35)	31	2	3	0
Vomiting	31 (30)	26	3	1	1
Periorbital edema	30 (29)	21	6	2	1
Headache	25 (24)	19	5	1	0
Dyspnea	19 (18)	14	5	0	0
Nasopharyngitis	18 (18)	13	3	2	0
Hypokalemia	16 (16)	9	2	4	1
Anemia	14 (14)	5	9	0	0
Cough	11 (11)	7	3	1	0
Fatigue	11 (11)	7	2	2	0

	Placebo (n=98)				
		≤8	>8–16	>16–24	>24
	Total	weeks	weeks	weeks	weeks
	n (%)	n	n	n	n
Number of patients evaluated	98	98	95	89	85
Patients with AEs	94 (96)	69	8	14	3
Deaths	3 (3)	2	0	1	0
Patients with non-fatal SAEs	27 (28)	13	7	5	2
Patients with SAEs including deaths	29 (30)	15	7	5	2
Discontinuations due to AEs	9 (9)	7	2	0	0
<b>Preferred term</b>					
Nausea	23 (24)	18	1	2	2
Edema peripheral	20 (20)	11	3	5	1
Diarrhea	19 (19)	13	4	2	0
Vomiting	10 (10)	4	2	3	1
Headache	22 (22)	14	4	4	0
Dyspnea	13 (13)	7	5	1	0
Nasopharyngitis	19 (19)	9	6	4	0
Cough	15 (15)	11	1	2	1

For patients with multiple occurrences of an AE, the first occurrence was considered in the table.

Only treatment-emergent AEs (within last dose +7 days for AEs and +30 days for SAEs) are summarized. A patient was evaluated in a period if a treatment-emergent (serious) AE could have happened in the period. Numbers for evaluated patients and discontinuations may not add up.

SAE, serious adverse event.

**Table VIIIb. Most Frequent Adverse Events (AEs) (>10 in Any Treatment Group), by Occurrence Period, Adjusted for Exposure**

	Imatinib (n=103)				
	Total	≤8 weeks	>8–16	>16–24	>24
			weeks	weeks	weeks
	n (%)	n	n	n	n
Number of patients evaluated	103	103	91	76	72
Total exposure in period (patient years)	38.7	14.1	11.8	10.9	1.9
AEs (per patient year)	1011 (26.1)	622 (44.0)	224 (19.0)	143 (13.1)	22 (11.6)
Deaths (per patient year)	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Non-fatal SAEs (per patient year)	110 (2.8)	58 (4.1)	43 (3.7)	7 (0.6)	2 (1.1)
Patients with SAEs including deaths	112 (2.9)	59 (4.2)	43 (3.7)	8 (0.7)	2 (1.1)
Discontinuations due to AEs	34 (0.9)	25 (1.8)	7 (0.6)	2 (0.2)	0 (0.0)
<b>Preferred term</b>					
Nausea	73 (1.9)	65 (4.6)	4 (0.3)	3 (0.3)	1 (0.5)
Edema peripheral	71 (1.8)	45 (3.2)	14 (1.2)	10 (0.9)	2 (1.1)
Diarrhea	51 (1.3)	39 (2.8)	5 (0.4)	7 (0.6)	0 (0.0)
Vomiting	50 (1.3)	35 (2.5)	7 (0.6)	6 (0.6)	2 (1.1)
Headache	43 (1.1)	24 (1.7)	13 (1.1)	6 (0.6)	0 (0.0)
Periorbital edema	38 (1.0)	25 (1.8)	9 (0.8)	3 (0.3)	1 (0.5)
Nasopharyngitis	25 (0.6)	13 (0.9)	5 (0.4)	6 (0.6)	1 (0.5)
Dyspnea	21 (0.5)	14 (1.0)	5 (0.4)	1 (0.1)	1 (0.5)
Hypokalemia	21 (0.5)	9 (0.6)	3 (0.3)	8 (0.7)	1 (0.5)

Cough	17 (0.4)	8 (0.6)	4 (0.3)	5 (0.5)	0 (0.0)
Oropharyngeal pain	17 (0.4)	8 (0.6)	7 (0.6)	2 (0.2)	0 (0.0)
Anemia	15 (0.4)	5 (0.4)	9 (0.8)	1 (0.1)	0 (0.0)
Face edema	12 (0.3)	7 (0.5)	2 (0.2)	3 (0.3)	0 (0.0)
Blood creatinine increased	11 (0.3)	8 (0.6)	0 (0.0)	3 (0.3)	0 (0.0)
Dizziness	11 (0.3)	7 (0.5)	3 (0.3)	1 (0.1)	0 (0.0)
Dyspepsia	11 (0.3)	9 (0.6)	1 (0.1)	1 (0.1)	0 (0.0)
Fatigue	11 (0.3)	7 (0.5)	2 (0.2)	2 (0.2)	0 (0.0)
Muscle spasms	11 (0.3)	11 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Placebo (n=98)</b>					
		<b>≤8</b>	<b>&gt;8–16</b>	<b>&gt;16–24</b>	<b>&gt;24</b>
	<b>Total</b>	<b>weeks</b>	<b>weeks</b>	<b>weeks</b>	<b>weeks</b>
	<b>n (%)</b>	<b>n</b>	<b>n</b>	<b>n</b>	<b>n</b>
Number of patients evaluated	98	98	95	89	85
Total exposure in period (patient years)	41.8	14.4	13.6	12.7	1.1
AEs (per patient year)	593 (14.2)	288 (20.0)	152 (11.2)	130 (10.3)	23 (20.0)
Deaths (per patient year)	3 (0.1)	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Non-fatal SAEs (per patient year)	66 (1.6)	26 (1.8)	20 (1.5)	17 (1.3)	3 (2.6)
Patients with SAEs including deaths	68 (1.6)	28 (1.9)	20 (1.5)	17 (1.3)	3 (2.6)
Discontinuations due to AEs	10 (0.2)	8 (0.6)	2 (0.1)	0 (0.0)	0 (0.0)
<b>Preferred term</b>					
Nausea	26 (0.6)	18 (1.3)	2 (0.1)	4 (0.3)	2 (1.7)
Edema peripheral	25 (0.6)	13 (0.9)	6 (0.4)	5 (0.4)	1 (0.9)



Diarrhea	22 (0.5)	13 (0.9)	6 (0.4)	3 (0.2)	0 (0.0)
Vomiting	10 (0.2)	4 (0.3)	2 (0.1)	3 (0.2)	1 (0.9)
Headache	22 (0.5)	14 (1.0)	4 (0.3)	4 (0.3)	0 (0.0)
Periorbital edema	8 (0.2)	5 (0.3)	1 (0.1)	2 (0.2)	0 (0.0)
Nasopharyngitis	24 (0.6)	9 (0.6)	10 (0.7)	5 (0.4)	0 (0.0)
Dyspnea	16 (0.4)	8 (0.6)	6 (0.4)	2 (0.2)	0 (0.0)
Hypokalemia	3 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)
Cough	16 (0.4)	11 (0.8)	2 (0.1)	2 (0.2)	1 (0.9)
Oropharyngeal pain	7 (0.2)	2 (0.1)	2 (0.1)	2 (0.2)	1 (0.9)
Anemia	5 (0.1)	1 (0.1)	2 (0.1)	2 (0.2)	0 (0.0)
Face edema	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increased	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	8 (0.2)	5 (0.3)	1 (0.1)	2 (0.2)	0 (0.0)
Dyspepsia	8 (0.2)	4 (0.3)	1 (0.1)	3 (0.2)	0 (0.0)
Fatigue	7 (0.2)	4 (0.3)	3 (0.2)	0 (0.0)	0 (0.0)
Muscle spasms	2 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)

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Data are number of AEs (patient years adjusted for exposure). All occurrences of an AE are considered in the table.

Only treatment-emergent AEs (within last dose +7 days for AEs and +30 days for SAEs) are summarized.

Total exposure is calculated as the sum of each patient's treatment exposure in each respective period. A patient was evaluated in a period if a treatment-emergent (serious) AE could have happened in the period.

SAE, serious adverse event.

**Table IX. Frequency of Serious Adverse Events (SAEs), (>1.0% in Any Treatment Group), Including Deaths, by Primary System Organ Class and Preferred Term**

	<b>Imatinib</b>	<b>Placebo</b>
	<b>n=103</b>	<b>n=98</b>
	<b>n (%)</b>	<b>n (%)</b>
Patients with any SAE(s)	45 (44)	29 (30)
Blood and lymphatic system disorders	10 (10)	1 (1)
Anemia	7 (7)	1 (1)
Neutropenia	2 (2)	0 (0)
Thrombocytopenia	2 (2)	0 (0)
Cardiac disorders	10 (10)	4 (4)
Angina pectoris	2 (2)	0 (0)
Atrial flutter	2 (2)	1 (1)
Right ventricular failure	2 (2)	2 (2.0)
Gastrointestinal disorders	9 (9)	3 (3)
Diarrhea	3 (3)	2 (2.0)
Nausea	2 (2)	1 (1)
General disorders and administration site conditions	10 (10)	5 (5)
Edema peripheral	6 (6)	0 (0)
Non-cardiac chest pain	0 (0)	2 (2)
Infections and infestations	7 (7)	12 (12)
Device-related infection	3 (3)	0 (0)
Sepsis	2 (2)	0 (0)
Pneumonia	1 (1)	2 (2)
Gastroenteritis	0 (0)	2 (2)
Metabolism and nutrition disorders	6 (6)	2 (2)
Hypokalemia	2 (2)	0 (0)

	<b>Imatinib</b>	<b>Placebo</b>
	<b>n=103</b>	<b>n=98</b>
	<b>n (%)</b>	<b>n (%)</b>
Nervous system disorders	8 (8)	5 (5)
Presyncope	5 (5)	0 (0)
Syncope	1 (1)	5 (5)
Respiratory, thoracic and mediastinal disorders	16 (16)	11 (11)
Dyspnea	6 (6)	2 (2)
Pulmonary arterial hypertension	4 (4)	4 (4)
Pleural effusion	2 (2)	1 (1)
Pulmonary hypertension	2 (2)	4 (4)
Respiratory failure	1 (1)	2 (2)
Hemoptysis	0 (0)	2 (2)

**Table X. Echocardiogram Results: Left Ventricular Ejection Fraction at End of Study**

	Absolute value, %		Change from baseline, %	
	Imatinib	Placebo	Imatinib	Placebo
	n=103	n=98	n=103	n=98
n	67	83	67	83
Mean	68	67	2	1
SD	10	10	10	9
Median	66	65	0	0
Minimum to maximum	50 to 97	45 to 98	−23 to 31	−35 to 20

Data are last post-baseline observation carried forward if made at least 28 days after first dose.

SD, standard deviation.

**Table XI. Extension Study: Summary of Disposition of Patients (as of March 16 2012)**

	<b>Core</b>	<b>Core</b>	<b>Total</b>
	<b>Imatinib</b>	<b>Placebo</b>	<b>n=144</b>
	<b>n=66</b>	<b>n=78</b>	<b>n (%)</b>
	<b>n (%)</b>	<b>n (%)</b>	
Entered extension	66 (100)	78 (100)	144 (100)
Completed core study	66 (100)	78 (100)	144 (100)
Discontinued core study	0 (0)	0 (0)	0 (0)
Ongoing in extension	44 (67)	40 (51)	84 (58)
Discontinued extension	22 (33)	38 (49)	60 (42)
Primary reason for premature study drug discontinuation			
Adverse event(s)	10 (15)	22 (28)	32 (22)
Subject withdrew consent	1 (2)	5 (6)	6 (4)
Death*	4 (6)	6 (8)	10 (7)
Abnormal laboratory value(s)	1 (2)	3 (4)	4 (3)
Subject's condition no longer requires study drug	1 (2)	1 (1)	2 (1)
Abnormal test procedure result(s)	2 (3)	0 (0)	2 (1)
Unsatisfactory therapeutic effect	2 (3)	1 (1)	1 (1)
Lost to follow-up	1 (2)	0 (0)	1 (1)

\*As of October 31<sup>st</sup> 2012, a further 3 deaths were reported as the primary reason for study drug discontinuation (n=1 core placebo; n=2 core imatinib)

**Table XII. Frequency of Adverse Events Recorded in Extension Study (as of March 16, 2012)**

	<b>Core Imatinib</b>	<b>Core Placebo</b>	<b>Total</b>
	<b>(n=66)</b>	<b>(n=78)</b>	<b>(n=144)</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Patients with any AE*	58 (87.9)	76 (97.4)	134 (93.1)
Nausea	17 (25.8)	38 (48.7)	55 (38.2)
Edema peripheral	17 (25.8)	27 (34.6)	44 (30.6)
Periorbital edema	13 (19.7)	22 (28.2)	35 (24.3)
Diarrhoea	11 (16.7)	23 (29.5)	34 (23.6)
Nasopharyngitis	14 (21.2)	20 (25.6)	34 (23.6)
Vomiting	11 (16.7)	23 (29.5)	34 (23.6)
Headache	7 (10.6)	20 (25.6)	27 (18.8)
Cough	15 (22.7)	6 (7.7)	21 (14.6)
Anemia	6 (9.1)	9 (11.5)	15 (10.4)
Dyspnea	10 (15.2)	5 (6.4)	15 (10.4)
Muscle spasms	5 (7.6)	10 (12.8)	15 (10.4)
Pyrexia	8 (12.1)	7 (9.0)	15 (10.4)
Fatigue	5 (7.6)	9 (11.5)	14 (9.7)
Rash	2 (3.0)	12 (15.4)	14 (9.7)
Upper respiratory tract infection	5 (7.6)	8 (10.3)	13 (9.0)
Epistaxis	6 (9.1)	5 (6.4)	11 (7.6)
Hypokalemia	3 (4.5)	8 (10.3)	11 (7.6)
Pulmonary arterial hypertension	6 (9.1)	5 (6.4)	11 (7.6)
Leukopenia	1 (1.5)	9 (11.5)	10 (6.9)
Iron deficiency anemia	3 (4.5)	6 ( 7.7)	9 (6.3)

	<b>Core Imatinib</b>	<b>Core Placebo</b>	<b>Total</b>
	<b>(n=66)</b>	<b>(n=78)</b>	<b>(n=144)</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Oropharyngeal pain	8 (12.1)	1 ( 1.3)	9 (6.3)
Thrombocytopenia	3 (4.5)	6 ( 7.7)	9 (6.3)
Bronchitis	1 (1.5)	7 ( 9.0)	8 (5.6)
Dizziness	4 (6.1)	4 ( 5.1)	8 (5.6)
Hypotension	5 (7.6)	3 ( 3.8)	8 (5.6)
Pain in extremity	3 (4.5)	5 ( 6.4)	8 (5.6)
Abdominal pain	3 (4.5)	4 ( 5.1)	7 (4.9)
Abdominal pain upper	2 (3.0)	5 ( 6.4)	7 (4.9)
Arthralgia	1 (1.5)	6 ( 7.7)	7 (4.9)
Hypoxia	2 (3.0)	5 ( 6.4)	7 (4.9)
Non-cardiac chest pain	3 (4.5)	4 ( 5.1)	7 (4.9)
Pruritus	1 (1.5)	6 ( 7.7)	7 (4.9)
Syncope	1 (1.5)	6 ( 7.7)	7 (4.9)
Abdominal discomfort	2 (3.0)	4 ( 5.1)	6 (4.2)
Alopecia	2 (3.0)	4 ( 5.1)	6 (4.2)
Cardiac failure <sup>1</sup>	1 (1.5)	5 ( 6.4)	6 (4.2)
Device related infection	4 (6.1)	2 ( 2.6)	6 (4.2)
Dyspepsia	2 (3.0)	4 ( 5.1)	6 (4.2)
Flushing	1 (1.5)	5 ( 6.4)	6 (4.2)
Urinary tract infection	0 (0.0)	6 ( 7.7)	6 (4.2)
Face edema	1 (1.5)	4 ( 5.1)	5 (3.5)
Right ventricular failure	5 (7.6)	0 ( 0.0)	5 (3.5)
Decreased appetite	0 (0.0)	4 ( 5.1)	4 (2.8)
Fluid retention	0 (0.0)	4 ( 5.1)	4 (2.8)

	<b>Core Imatinib</b>	<b>Core Placebo</b>	<b>Total</b>
	<b>(n=66)</b>	<b>(n=78)</b>	<b>(n=144)</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
Gastritis	0 (0.0)	4 ( 5.1)	4 (2.8)
Patients with any SAE <sup>†</sup>	32 (49)	44 (56)	76 (53)
PAH	4 (6)	3 (4)	7 (5)
Dyspnea	3 (5)	3 (4)	6 (4)
Syncope	1 (2)	6 (8)	7 (5)
Device related infection	4 (6)	1 (1)	5 (4)
Cardiac failure <sup>‡</sup>	1 (2)	5 (6)	6 (4)
Right ventricular failure	4 (6)	0	4 (3)
Pyrexia	1 (2)	3 (4)	4 (3)

\*Individual AEs are shown if they occurred in >5% patients in any core treatment

group; <sup>†</sup>Individual serious adverse events are shown if they occurred in ≥3 patients in any

core treatment group; <sup>‡</sup>All cases of cardiac failure as reported by investigator were confirmed to be right ventricular failure.

Three additional patients in the core imatinib and 3 in the core placebo group died after discontinuing from the study and are not reported in this table.

The core imatinib and core placebo group patients all received imatinib treatment in the extension study, regardless of core study treatment assigned. The overall exposure to extension study treatment was a mean of 342 days in the total group, 392 days in the core imatinib group and 300 days in the core placebo group. The mean exposure to imatinib, including both core and extension study treatment, was 569 days in the core imatinib group, and 300 days in the core placebo group.

AE, adverse event; PAH, pulmonary arterial hypertension; SAE, serious adverse event.



**Table XIII. Listing of Cases of Subdural Hematoma Reported for Patients Receiving Imatinib for Pulmonary Arterial Hypertension (PAH)**

Study	Diagnosis	Age/ sex	Dose	Use of anticoagulation therapy	Other PAH- specific therapies	Other predisposing factors	Outcome/Intervention
			/duration of use of imatinib				
IMPRES core study	Subdural bleed with increase in INR up to 8.0	47/ female	200 mg/ 12 days	Phenprocoumon	Sildenafil  Sitaxentan	Post-traumatic brain injury due to a car accident, history of seizure disorder	No surgical intervention required  Patient recovered with no residual neurological deficits (patient did not die)
IMPRES core study	Post-traumatic subacute subdural hematoma	47/ female	400 mg/ 3 months	Warfarin	Epoprostenol  Ambrisentan	Head trauma	No surgical intervention required  Patient recovered with no residual neurological deficits and completed participation in core study

Study	Diagnosis	Age/ sex	Dose	Use of anticoagulation therapy	Other PAH- specific therapies	Other predisposing factors	Outcome/Intervention
			/duration of use of imatinib				
							(patient did not die)
IMPRES extension study	Subdural hematoma INR up to 4.8	50/ female	400 mg/ 2 months	Warfarin	Sildenafil  Epoprostenol	Displacement of Groshong catheter for epoprostenol in omental vein	Patient had a craniotomy and the Subdural hematoma was evacuated  Patient recovered with no residual neurological deficits (patient did not die)
IMPRES extension study	Renal impairment Subdural hematoma, general deterioration in	57/ female	400 mg/ 12 days	Warfarin	Iloprost  Sildenafil  Ambrisentan	Event occurred during intravenous infusion of iloprost	Patient had a craniotomy and subdural hematoma was evacuated  Patient died of subdural hematoma and respiratory failure 16 days after

Study	Diagnosis	Age/ sex	Dose	Use of anticoagulation therapy	Other PAH- specific therapies	Other predisposing factors	Outcome/Intervention
			/duration of use of imatinib				
	health						discontinuing imatinib
IMPRES extension study	Subdural hemorrhage	66/ female	200 mg/ 7 months	Enoxaparin, Warfarin	Sildenafil  Bosentan  Epoprostenol	Two $\beta$ -lactam antibiotics were started 2 weeks prior to the event	No surgical intervention required  Patient recovered with no residual neurological deficits  Patient died of right heart failure 8 months after the subdural hematoma
IMPRES extension study	Chronic subdural hematoma	59/ female	400 mg/ 2 months	Phenprocoumon	Iloprost  Sildenafil  Ambrisentan	History of chronic subdural hematoma and syncope	Patient had a craniotomy and the subdural hematoma was evacuated  Patient recovered with sequelae (vertigo)

Study	Diagnosis	Age/ sex	Dose	Use of anticoagulation therapy	Other PAH- specific therapies	Other predisposing factors	Outcome/Intervention
			/duration of use of imatinib				
							(patient did not die)
IMPRES extension study	Acute subdural hematoma	47/ male	400 mg/ 18 months	Acenocoumarol	Sildenafil  Bosentan	Acute myeloid leukemia, cerebral infarction, thrombocytopenia	Patient had a craniotomy and the subdural hematoma was evacuated  Patient recovered from the subdural hematoma but died of a cerebral infarction 12 days after the event
IMPRES extension study	Subdural hematoma	55/ male	400 mg/ one year	Phenprocoumon	Sildenafil  Bosentan	No identified factor	Patient had a craniotomy and the subdural hematoma was evacuated  Patient had a normal neurological exam with 24

Study	Diagnosis	Age/ sex	Dose  /duration of use of imatinib	Use of  anticoagulation therapy	Other PAH-  specific therapies	Other  predisposing factors	Outcome/Intervention
							hours of the event and completely recovered (patient did not die)

N.B. one additional case of subdural hematoma has been reported within the compassionate use program following participation in the Phase II proof-of-concept study. This 63-year-old female patient had been receiving imatinib 400 mg for 10 months at the time of the event. Concomitant medication included phenprocoumon, sildenafil and bosentan. Following the event the patient continued to receive imatinib.

INR, International Normalized Ratio (normalized Prothrombin Time ratio).

**Table XIV. Summary Statistics of Change from Baseline in 6MWD (m) and PVR at 24 Weeks in Patients who Completed the Study, by Treatment (Long-Term Imatinib dose Escalation [Successful Versus not successful\*] and Placebo)**

Endpoint	Treatment	n	mean (SE)
6MWD, m	Imatinib (long-term dose escalation successful)	40	50 (9)
	Imatinib (long-term dose escalation not successful)	24	22 (10)
	Placebo	79	5 (7)
PVR, dynes·sec·cm <sup>-5</sup>	Imatinib (long-term dose escalation successful)	44	−437 (53)
	Imatinib (long-term dose escalation not successful)	23	−371 (77)
	Placebo	78	−10 (52)

\*Successful long-term dose escalation refers to sustained dose escalation to 400 mg for ≥50% of the treatment period.

SE, standard error of the mean; 6MWD, 6-minute walk distance; PVR, Pulmonary Vascular Resistance

ii) **Supplemental Figures**

**Figure I. Effect of Clinical Worsening (CW) Events on Outcomes for Patients who Completed the Study at 24 Weeks.** PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance. Data shown are mean±standard error.

