EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2013
EMA/CHMP/758311/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revatio

International non-proprietary name: sildenafil

Procedure No. EMEA/H/C/000638/II/0056

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 6 August 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Revatio	sildenafil	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The MAH proposed changes to the SmPC sections 4.2, 4.4, 4.5 and 5.1 based on the results of study A1481243 in order to:
- indicate that there is no data to support increasing the dose of sildenafil in combination with bosentan (section 4.2)
- include a warning on the concomitant use of sildenafil with bosentan (section 4.4)
- reflect the drug-drug interaction findings of the concomitant use of sildenafil with bosentan (section 4.5)
- describe the relevant efficacy results of study A1481243 (section 5.1)

In addition, an update of the Annex II is adopted to remove the requirement to complete the study A1481243 by June 2013.

The requested variation proposed amendments to the Summary of Product Characteristics and Annex II.

Rapporteur: Pieter de Graeff

1.2. Steps taken for the assessment

Submission date:	6 August 2013
Start of procedure:	25 August 2013
Rapporteur's preliminary assessment report circulated on:	27 September 2013
Rapporteur's updated assessment report circulated on:	18 October 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
MAH's responses submitted to the CHMP on:	18 November 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	04 December 2013
CHMP opinion:	18 December 2013

2. Scientific discussion

2.1. Introduction

Revatio was approved in 2005 (EU/1/05/318/001) for treatment of adult patients with PAH, classified as World Health Organisation (WHO) Functional Class (FC) II and III, to improve exercise capacity.

The present report pertains to study **A1481243**: a multinational, multicentre, randomised, double-blind study to assess the efficacy and safety of oral sildenafil 20 mg three times daily (TID) or placebo when added to bosentan in the treatment of subjects aged 18 years and above with PAH. This is a post-approval commitment to fulfil Follow Up Measure 006 to evaluate the safety and efficacy of the co-administration of sildenafil and bosentan in PAH patients.

The Marketing Authorisation Holder (MAH) proposes to update the SmPC to include recommendations on sildenafil and bosentan combination therapy under sections 4.2 and 4.4., 4.5 and 5.1.

The proposed changes in section 4.4 are the addition of the following:

Use of sildenafil with bosentan

In a study of PAH patients (primary PAH and secondary PAH associated with CTD) on background bosentan therapy, no incremental benefit (6-minute walk distance (6MWD)) of sildenafil co-administered with bosentan was demonstrated over bosentan alone. The results of the 6MWD were different between primary PAH and PAH associated with CTD. The mean result of the combination of sildenafil and bosentan was numerically worse than bosentan alone in patients with PAH associated with CTD but numerically better than bosentan alone in patients with primary PAH. Therefore, healthcare professionals should use their medical judgment to assess the clinical response when sildenafil is co-administered with bosentan in primary PAH. The combined use of sildenafil and bosentan in patients with PAH associated with CTD is not recommended (see Section 5.1).

2.2. Clinical Pharmacology aspects

2.2.1. Methods – analysis of data submitted

Pharmacokinetics

The drug-drug interaction between sildenafil and bosentan has been previously described in healthy volunteers. Steady-state bosentan reduced sildenafil exposure by 62.6% while steady-state sildenafil (80 mg TID) increased bosentan exposure by approximately 50%. Similarly, in PAH patients bosentan 125 mg TID reduced sildenafil exposure by 69%. Both compounds are primarily eliminated through the CYP3A4 metabolic pathway, and to a smaller extent via CYP2C9. Bosentan also induces CYP3A4, resulting in a reduction of its own exposure following multiple dosing. Sildenafil is not an inhibitor of CYP3A, however it has been shown to interfere with the hepatic uptake transporters OATP1B1/1B3 for which bosentan is a substrate.

In the current SmPC was mentioned under 4.5 Interaction with other medicinal products and other forms of interaction:

Co-administration of bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) 125 mg twice daily with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63 % decrease of sildenafil AUC. Caution is recommended in case of co-administration.

and

In a study of healthy volunteers sildenafil at steady state (80 mg three times a day) resulted in a 50 % increase in bosentan AUC (125 mg twice daily). Caution is recommended in case of co-administration

The Applicant now propose to change this text in the SmPC by:

Co-administration of bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) 125 mg twice daily with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63 % decrease of sildenafil AUC. Caution is recommended in case of co-administration. A population pharmacokinetic analysis of sildenafil data from adult PAH patients in clinical trials including a 12 week study to assess the efficacy and safety of oral sildenafil 20 mg three times a day when added to a stable dose of bosentan (62.5 mg – 125 mg twice a day) indicated a decrease in sildenafil exposure with bosentan co-administration, similar to that observed in healthy volunteers (see sections 4.2, 4.4 and 5.1).

and

A population pharmacokinetic analysis of data from a study of adult PAH patients on background bosentan therapy (62.5 mg - 125 mg twice a day) indicated an increase of bosentan AUC with co-administration of steady-state sildenafil (20 mg three times a day) of a smaller magnitude than seen in healthy volunteers when co-administered with 80 mg sildenafil three times a day (see sections 4.2, 4.4 and 5.1).

With respect to the pharmacokinetics interaction of sildenafil with bosentan in PAH patients, the Applicant did conduct a Population Pharmacokinetic analysis with data from clinical study A1481243.

In this study sildenafil was co-administered to PAH patients for 12 weeks already on bosentan therapy for more than 3 month. In this study blood samples were collected for analysis of both compounds and their respective metabolites on day 1 and day 84, with additional samples collected near trough time points on days 28 and 56.

A previous population pharmacokinetic analysis was adopted to develop a model to describe the pharmacokinetics of sildenafil in PAH patients, enriched using all available in-house data on the labelled dose of 20 mg TID in adult PAH patients.

The bosentan population pharmacokinetic model was built on published information and put in context of an earlier performed in-house trial in healthy volunteers.

In the table below an overview of the different data used for the models is given.

Table 1. Treatment and Sample Allocation of Patients Used in the Analyses

Treatment group	Analyte	A1481243		A1481244		A1481140	
		Dose (mg)	N / samples	Dose (mg)	N / samples	Dose (mg)	N / samples
Bosentan+Placebo	Bosentan	62.5/125	53 / 391	-		-	
Bosentan+Sildenafil	Bosentan	62.5/125	50 / 386	-		-	
	Sildenafil	20	50 / 379	-		-	
Sildenafil	Sildenafil	-	-	20	45 / 393	20	69 / 380

ePharm AI: 6990253

2.2.2. Results

Sildenafil Analysis.

A one-compartment population pharmacokinetic model with first-order absorption and elimination with CL/F for A1481243 estimated as a ratio of CL/F for A1481140 described the data appropriately and was considered the base model. The final model included estimation of CL/F for A1481244 as a ratio to the CL/F for A1481140 and presence of CYP3A inhibitors as a covariate. Administration of sildenafil with bosentan in A1481243 resulted in a 2.35 fold higher clearance of sildenafil. The higher clearance translates into a 57% (95% CI: 42 – 66%) lower systemic exposure (Css,ave). The observation here is consistent with the above mentioned findings where bosentan reduced systemic sildenafil exposures (AUC) at steady state by 62.6%.

Bosentan Analysis

The population PK model described allowed characterization of the bosentan concentration time profiles. The introduction of an inter-occasion variability term allowed stabilization of the parameter estimates. Introduction of the sildenafil covariate on CL/F allowed estimation of about 15% reduction in CL/F, but the confidence interval included zero, and the reduction in OFV was not significant. Likewise, the introduction of CYP3A inhibitors into the model allowed quantification of the impact on CL/F, but the confidence interval included zero, and the reduction in the OFV was also not significant. The clearance reduction was estimated with high uncertainty and would translate into an exposure increase of about 17% (95% CI: -4.7 – 52%) and about 23% (95% CI: -3.7 – 69%) for the sildenafil OATP1B1/1B3 transport and CYP3A inhibitor, respectively. The inclusion of weight on either clearance or volume of distribution did not improve the fit, aetiology had no impact on clearance, and other covariate relationships were not tested at this stage. Stratification of the bosentan PK samples according to the established stability period appears to show an increased variability for those outside the period, with the impact still being explored. The exclusion of those samples from the analyses appears to improve the precision of the estimates.

The conclusion from the Population Pharmacokinetic Analysis was:

Sildenafil exposure was reduced by about 57% at a dose of 20 mg TID when co-administered with 62.5/125 mg BID bosentan. The corresponding bosentan exposure showed a non significant increase of 17% at those dose levels with more detailed analyses to follow in the final population PK report.

During the procedure, the MAH was requested to provide further information regarding the methodology used for the PK model and corresponding results according to the PAH aetiology as detailed below:

In the linear one-compartment population pharmacokinetic model, model clearance (CL/F) was estimated for the 20 mg TID treatment arms across Studies A1481243 and A1481244 with Study A1481140 as the reference. Co-administered CYP3A inhibitors were included as covariates in the model. This model was extended to evaluate the impact of disease etiology on the exposure of sildenafil when administered at 20 mg TID.

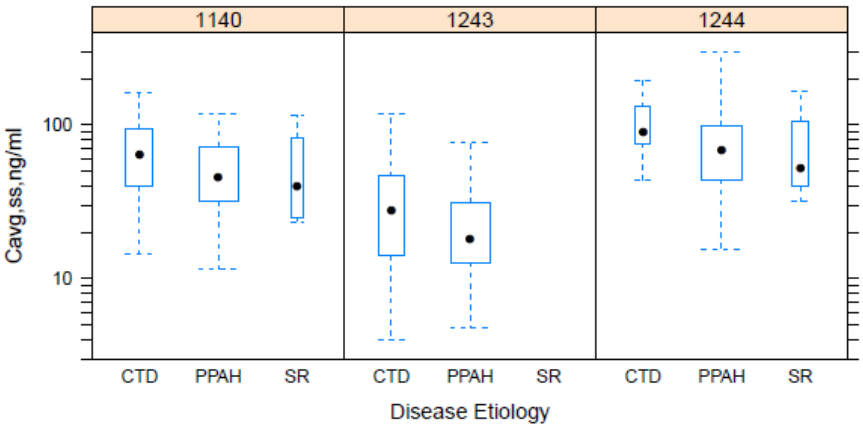
Disease etiologies of connective tissue disease (CTD), PPH and PAH associated with congenital heart disease with surgical repair (SR) were tested as covariates in the population PK model. CTD was included as a covariate individually while PPH and SR were combined into a single covariate. The size of the SR group was not sufficiently large to allow estimation of a CL/F independent from the PPH group, but since the SR group showed individual posthoc CL/F-values close to those estimated in PPH group, it was justified to combine those two groups.

To justify the inclusion of etiology in either of the population PK models using a single parameter, a reduction in the objective function value (OFV) of at least 3.85 points is necessary in comparison to the reduced model (df=1, p<0.05). The calculation of a 95% confidence interval that excludes zero, using standard errors as estimated in NONMEM and if necessary confirmed by a bootstrap, will qualify the estimate, together with a visualization of the improvement in the goodness of fit criteria.

Inclusion of disease etiology as a covariate in the population PK model for sildenafil resulted in a non-significant drop in the OFV of 3.74 points. Patients with CTD appear to have a 22% (95% CI: 1; 42) lower CL/F than patients with PPH/SR, which translates to a 28% (95% CI: 1; 74) higher average steady state concentration (Cavg,ss). Since the drop in the OFV was marginal, but the confidence interval excluded zero, we performed a bootstrap which confirmed the central tendency at 21% (95% CI: -2; 39) lower CL in CTD patients, but highlighted the uncertainty with a slightly shifted confidence interval, including zero here.

A box plot of the estimated individual Cavg,ss (Figure 1) values vs disease etiology and by Study shows large overlap between the disease etiology groups.

Figure 1. Distribution of Sildenafil Steady State Concentrations Across Protocols and Disease Etiologies



Boxplot of individual Cavg,ss estimates across Studies A1481140, A1481243 and A1481244, subdivided by disease etiology (CTD or PPAH or SR). Boxes represent the median and inter quartile ranges (IQR), with size of boxes proportional to sqrt(N), and whiskers 1.5 times the IQR. (ePharm-Artifact ID: 7467918).
CTD=Connective tissue disease, PPAH=Primary pulmonary arterial hypertension (equivalent to PPH), and SR=Surgical repair.

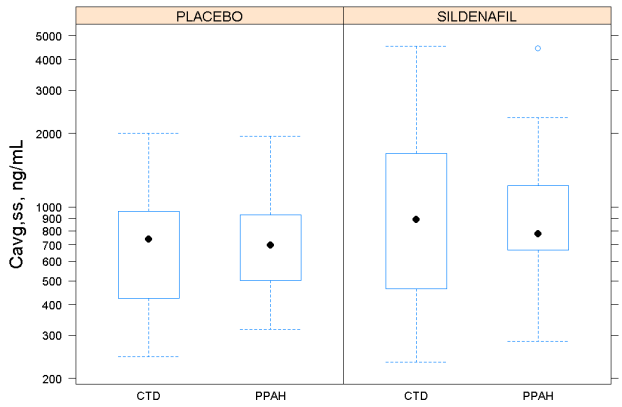
Impact of PAH Etiology on Bosentan PK

The existing bosentan population PK model, as described in the preliminary analysis memo, was also extended to test formally for a difference in CL/F and the corresponding exposure in patients belonging to either etiology, PPH or CTD, in Study A1481243. Inclusion of disease etiology as a covariate in the population PK model for bosentan resulted in a non-significant drop in the OFV of 3.11 points.

Patients with CTD appear to have a 7.4% (95% CI: -17; 32) lower clearance than patients with PPH, which translates to an 8% (95% CI: -15; 47) higher Cavg,ss.

A boxplot of the estimated individual Cavg,ss (Figure 2) values vs disease etiology shows substantial overlap between the two etiology groups.

Figure 2. Distribution of the Bosentan Steady-State Concentrations Across Treatment Groups and Etiologies in Study A1481243



Boxplot of individual Cavg,ss estimates across all subjects in Study A1481243, subdivided by treatment group (Placebo or Sildenafil) and etiology (CTD or PPAH). Boxes represent the median and inter quartile ranges (IQR), with size of boxes proportional to sqrt(N), and whiskers 1.5 times the IQR. (ePharm-Artifact ID: 7470686).
CTD=Connective tissue disease, and PPAH=Primary pulmonary arterial hypertension (equivalent to PPH).

Conclusions

These analyses address the impact the etiological background of the patient population in Study A1481243 could have had on clearance and in consequence on exposure of sildenafil and bosentan after co-administration of 20 mg sildenafil TID or placebo on bosentan background treatment of 62.5 to 125 mg BID.

For the sildenafil analyses, PK measures from Study A1481243 were compared in the modeling approach to exposures from Studies A1481140 and A1481244, while for the bosentan PK evaluation only data from Study A1481243 were used.

In the additional analyses presented here disease etiology does not appear to be of significant influence on clearance of either sildenafil or bosentan. Across all trials included in these analyses, a trend toward lower clearance in CTD patients is observed for both sildenafil and bosentan, resulting in a marginally higher exposure for each.

Therefore, it is unlikely systemic exposure differences are responsible for any difference observed in the clinical response between disease etiology subgroups as described by the primary endpoint assessment.

2.2.3. Discussion

The MAH provided the results of the PopPK analysis after incorporation of disease etiology in the model. The model performance increased only marginal. Moreover, incorporation of disease etiology in the PopPK model did not change the average concentrations of sildenafil or bosentan in a clinically significant way. No significant differences were detected between Cav of patients with PH associated with CTD or primary PAH. Therefore the conclusion by MAH that it is unlikely that differences in systemic exposure are responsible for any differences observed in the clinical response between disease etiology subgroups is endorsed by the CHMP.

The submitted population pharmacokinetic analysis confirms that bosentan reduces the exposure of sildenafil by about 60%. The analysis also showed that sildenafil in PAH patients only marginally affected the exposure of bosentan. This is in line with previously submitted data which showed that in healthy volunteers sildenafil did affect the pharmacokinetics of bosentan in a significant way but that the pharmacokinetics of bosentan in PAH patients is different from healthy volunteers and therefore the influence of sildenafil will be decreased in PAH patients.

This means that the submitted population pharmacokinetic analysis do not reveal new insight in the interaction profile of sildenafil.

The proposed text in the SmPC for section 4.5 with respect to this interaction is considered acceptable.

2.3. Clinical efficacy aspects

2.3.1. Methods – analysis of data

Literature Review of Efficacy Studies/Haemodynamic Studies conducted with Sildenafil and Bosentan

In a European trial[1] involving patients with idiopathic pulmonary arterial hypertension (IPAH), sildenafil was added when the clinical benefits of bosentan had waned in 9 patients (mean age: 39 ± 9 years). Sildenafil was added at a dose of 25 mg TID or four times daily (QID) and increased to 50 mg TID in patients with sub-optimal clinical responses to sildenafil based on pre-defined 6-minute walk distance (6MWD) and cardiopulmonary testing cut-points. Baseline 6MWD was 346 ± 66 m, which improved by 57 m to 403 ± 80 m (16%; p = 0.0003) while on bosentan. At Month 11 of bosentan monotherapy, the 6MWD had declined by 31%, to 277 m. Three months after introducing adjunctive sildenafil, however, 6MWD increased by 115 m (42%; p = 0.007), once again approaching 400 m. Cardiopulmonary exercise testing demonstrated that peak oxygen uptake rose by approximately 24% after 3 months of bosentan treatment, then fell to near baseline levels at Month 11 of treatment. However, 3 months after addition of sildenafil, peak oxygen uptake rose by 33%, to a higher level than during bosentan monotherapy. Combination therapy was well tolerated. All patients reported mild flushing and headache upon addition of sildenafil, but these adverse events (AEs) including dyspepsia proved reversible within a few days of continued sildenafil administration without dose adjustments. No patients died or had serious adverse events (SAEs) related to drug treatment. In this study, the addition of sildenafil treatment to patients with IPAH for whom the benefit of bosentan had declined resulted in clinical improvement with acceptable safety.

Gruenig (COMPASS-1 Study)[2] explored the acute haemodynamic effects of sildenafil administration. This phase II study enrolled 45 patients (≥ 18 years) with stable PAH and on bosentan treatment for at least 3 months. Patients underwent right heart catheterisation (RHC) to evaluate the acute haemodynamic effects of a) inhaled nitric oxide (iNO) and b) a single oral dose of sildenafil (25 mg). Mean PVR decreased from baseline following iNO (15%; 95% confidence interval [CI]: –21%, –8%; p = 0.0001). A statistically significant decrease from baseline in mean PVR was also observed 60 minutes following sildenafil administration (–15%; 95% CI: –21%, –10%; p < 0.0001). The reduction in PVR following sildenafil was comparable to that resulting from iNO. There were no unexpected safety findings. The pharmacodynamic (PD) effect suggested that addition of sildenafil to bosentan treatment can elicit additional haemodynamic benefits.

[1] Hoeper MM, Faulenbach C, Golpon H, et al. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. Eur Respir J 2004;24:1007–10.
[2] Gruenig E. Acute hemodynamic effects of single-dose sildenafil when added to established bosentan therapy in patients with pulmonary arterial hypertension: results of the COMPASS-1 Study. J Clin Pharmacol 2009;49:1343.

The safety, tolerability, clinical and haemodynamic impact of add-on sildenafil in patients with congenital heart disease (CHD)-related PAH and Eisenmenger physiology after failure of oral bosentan therapy was evaluated by D'Alto[3] . Thirty-two (32) CHD-related PAH patients treated with oral bosentan underwent RHC for clinical worsening. All the patients received oral sildenafil 20 mg TID in addition to bosentan after RHC. The results after 6 months of bosentan–sildenafil combination compared with baseline (bosentan monotherapy) therapy, respectively, were as follows. There was improvement seen in WHO FC (2.1 ± 0.4 vs. 2.9 ± 0.3; p = 0.042), 6MWD (360 ± 51 vs. 293 ± 68 m; p = 0.005), resting transcutaneous oxygen saturation at the end of 6MWT (72% ± 10% vs. 63% ± 15%; p = 0.047), Borg score (2.9 ± 1.5 vs. 4.4 ± 2.3; p = 0.036), serology (pro-brain natriuretic peptide [BNP] 303 ± 366 vs. 760 ± 943 pg/mL; p = 0.008), haemodynamics (pulmonary blood flow 3.4 ± 1.0 vs. 3.1 ± 1.2 L/min/m2, p = 0.002; and PVRs index 19 ± 9 vs. 24 ± 16 WU/m2, p = 0.003). Addition of sildenafil in adult patients with CHD-related PAH and Eisenmenger syndrome after oral bosentan therapy failure was safe and well tolerated at 6-month follow-up and showed improvements in the clinical status.

The effect of adding sildenafil to bosentan on 6MWD and New York Heart Association (NYHA) classification in patients with PAH who achieved inadequate improvement with bosentan monotherapy was evaluated by Porhownik et al[4]. Patients with IPAH or connective tissue disease-associated PAH who had either self-reported inadequate improvement in exercise tolerance or a decline in 6MWD after initial improvement, were included in the study (n = 10). Results were described as follows: Mean baseline 6MWD before initiation of bosentan therapy was 314.4 m (95% CI 231.6 397.2 m). Six months after initiation of bosentan, mean 6MWD increased by an average of 57.2 m (mean 6MWD 371.6 m, 95% CI 308.5 434.7 m). Mean 6MWD at the second baseline, before initiating combination therapy, was still higher than the first baseline by 24.6 m (mean 6MWD 339.0 m, 95% CI 272.6 405.4 m). Six months after the combination therapy was initiated, mean 6MWD was 62.8 m higher than the second baseline (p < 0.02) (mean 6MWD 401.8 m, 95% CI 327.0 476.6 m). The overall increase in 6MWD, six months after the combination therapy was higher than the first baseline by 87.4 m (p not significant). NYHA FC did not improve with combination therapy in all patients. In this study, initiating combination therapy in patients who achieve an inadequate improvement in exercise tolerance with monotherapy resulted in further improvement in exercise tolerance.

2.3.1. Study A1481243 - Efficacy data

Study A1481243 was a multinational, multicentre, randomised, double-blind study to evaluate the efficacy and safety of oral sildenafil 20 mg TID or placebo when added to bosentan in the treatment of subjects, aged 18 years and above, with PAH.

Study Objectives

The primary objective was to assess the effect on exercise capacity (as measured by 6MWT) after 12 weeks of treatment with sildenafil (20 mg TID) or placebo when added to subjects with PAH who were stabilised on bosentan therapy.

Study Design

Study A1481243 consisted of two phases. The initial phase of the study (Part A) was a 12 week randomised, double-blind, placebo-controlled, hospital out-patient study in which approximately 106 subjects aged 18 years and above were to be enrolled and allocated to receive either placebo or

[3] D'Alto M. Bosentan–sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol 2010.
[4] Porhownik R. Addition of sildenafil in patients with pulmonary arterial hypertension with inadequate response to bosentan monotherapy. Can Respir J 2008;15(8).

sildenafil 20 mg TID. This report presents all data for the 12-week double-blind phase of the study. The date of the last subject last visit for the double-blind phase of the study was 07 August 2012. Part B of the study is a 12-month, open label extension phase and is ongoing. All subjects had a diagnosis of PAH as confirmed by increased PAP measured by RHC within the previous 12 months and had been receiving stable treatment with bosentan for at least 3 months.

At the baseline visit, subjects were randomly assigned in a 1:1 ratio to receive either sildenafil or placebo after a 6MWT and BORG dyspnoea score. Following the baseline visit, the double-blind phase consisted of 3 clinic visits (at 4, 8 and 12 weeks post baseline) during which efficacy, PK and safety data were collected. Upon completion of the 12-week double blind phase of the study (Part A), subjects were to be given sildenafil 20 mg TID in addition to their existing bosentan therapy for further 12 months (Part B).

The ***primary endpoint*** was the distance walked during the 6 minutes at Week 12, compared to Baseline. ***Secondary endpoints*** included Borg dyspnea, time to clinical worsening, survival at one year and BNP and Pro-BNP.

Statistical methods. The primary efficacy analysis was to evaluate the difference of change from baseline in 6MWD at week 12 between treatment groups based on the ITT population. The analysis of covariance (ANCOVA) main-effects model was used which included the categorical terms for treatment, baseline 6MWD (<325 m; ≥ 325 m) and baseline etiology. Missing values were replaced according to the last observation carried forward (LOCF) approach.

To support the interpretation of the primary analysis, the analysis was repeated using the PP population rather than the ITT population. A sensitivity analysis was performed using a non-parametric approach. The stratified Wilcoxon test (Van-Elteren) was used.

The estimated sample size was based upon the primary endpoint, the change from baseline to Week 12 in the total distance walked during a 6MWT. Assuming a treatment effect for the 'sildenafil plus bosentan' arm of 30 m over the 'placebo plus bosentan' arm, and a SD of 60 m (obtained from study A1481140), a sample size of 51 subjects per treatment group would be required to detect a difference between treatments with 80% power at a one-sided significance level of 0.05.

A drop-out rate of 15% between screening and randomization and an additional drop-out rate (withdrawal) after randomization of 4% (as observed in study A1481140) was anticipated. Hence a total of approximately 128 subjects were to be screened to ensure that approximately 106 subjects would be equally randomized in order to achieve 102 evaluable subjects in two equal treatment groups of sildenafil 20 mg TID and placebo.

Results

In total, 118 subjects were screened for the study, and 104 subjects were randomly assigned into Part A (double-blind phase) of the study. Of these, 51 subjects (of which, 1 subject did not receive any treatment) were randomly assigned to the sildenafil plus bosentan group, hereafter, referred to as the sildenafil group; 53 subjects (all of whom received treatment) were randomly assigned to the placebo plus bosentan group, hereafter, referred to as the placebo group. At the completion of Part A at Week 12, of the 104 subjects initially randomly assigned, 43 subjects (84.3%) in the sildenafil group and 48 subjects (90.6%) in the placebo group completed the double-blind phase of the study.

The demographic characteristics were similar between the 2 treatment groups. The mean age of subjects in the sildenafil group was 55.2 (15.10) years and 56.9 (14.14) years in the placebo group.

The main disease characteristics are presented in table E1. The study duration for an individual subject was a maximum of 67 weeks (3-week screening phase, 12-week double-blind phase and 52-week open-label phase).

Table E1: Main disease characteristics at Baseline by Randomized Treatment Group - ITT Population

	Sildenafil (N=50)	Placebo (N=53)	Overall (N=103)
Baseline Six Minute Walk (meters) n (%)	50 (100.0)	53 (100.0)	103 (100.0)
Mean (SD)	354.44 (73.121)	350.38 (87.587)	352.35 (80.520)
Median	371.00	376.00	371.00
Range	187.0-461.0	165.0-497.5	165.0-497.5
Baseline mPAP (mmHg) n (%)	50 (100.0)	53 (100.0)	103 (100.0)
Mean (SD)	46.9 (12.47)	44.9 (13.33)	45.8 (12.89)
Median	46.0	43.0	44.0
Range	25-71	25-86	25-86
Bosentan Dose (mg/BID) n (%)			
62.5	2 (4.0)	3 (5.7)	5 (4.9)
125	47 (94.0)	49 (92.5)	96 (93.2)
Other	1 (2.0)	0	1 (1.0)
Missing	0	1 (1.9)	1 (1.0)
Duration of Bosentan Therapy (Days) n (%)	50 (100.0)	52 (98.1)	102 (99.0)
Mean (SD)	560.4 (538.12)	639.6 (604.36)	600.8 (571.41)
Median	324.0	347.0	344.0
Range	96-1987	94-2381	94-2381
Class I	0	0	0
Class II	20 (40.0)	15 (28.3)	35 (34.0)
Class III	29 (58.0)	38 (71.7)	67 (65.0)
Class IV	1 (2.0)	0	1 (1.0)
Etiology	35 (70.0)	32 (60.4)	67 (65.0)
Primary PAH	15 (30.0)	21 (39.6)	36 (35.0)
Pulmonary hypertension associated with connective tissue disease			

The majority of all subjects 71 (68.9%), had a baseline 6MWD of ≥ 325m; 35 (70%) subjects in the sildenafil group and 36 (67.9%) subjects in the placebo group. A total of 15 (30.0%) subjects in the sildenafil group and 17 (32.1%) subjects in the placebo group had a baseline walking distance of <325m.

Based on strata:

- For subjects with primary PAH and a baseline 6MWD <325m, 10 (20.0%) subjects were in the sildenafil group and 7 (13.2%) subjects were in the placebo group.
- For subjects with pulmonary hypertension associated with connective tissue disease and a baseline 6MWD <325m, 5 (10.0%) subjects were in the sildenafil group and 10 (18.9%) subjects were in the placebo group.
- For subjects with primary PAH and a baseline 6MWD ≥ 325m, 25 (50.0%) subjects were in the sildenafil group and 25 (47.2%) subjects were in the placebo group.
- For subjects with pulmonary hypertension associated with connective tissue disease and a baseline 6MWD ≥ 325m, 10 (20.0%) subjects were in the sildenafil group and 11 (20.8%) subjects were in the placebo group.

The imbalance in the two strata with baseline walking distance <325m was due to randomization stratification error. The study was designed with two stratification factors (baseline walking distance and etiology).

Primary endpoint: Both the treatment groups demonstrated mean increases from baseline 6MWD at all visits up to Week 12. The mean (SD) changes from baseline in 6MWD at Week 12 (last observation carried forward [LOCF]) for the intention-to-treat (ITT) population were 13.62 (60.950) m in the sildenafil group and 14.08 (57.557) m in the placebo group. For change from baseline to Week 12

(LOCF) in 6MWD, the least squares (LS) mean difference between the treatment groups (sildenafil minus placebo) was 2.38 m with a 90% CI of (21.843, 17.087) m. The difference between the two treatment groups was not statistically significant (1-sided p value = 0.5802) (table E2).

Table E2: Change from Baseline in Six Minute Walk Distance (meters) to Week 12 and Week 12 (LOCF) - ITT Population

	Part A	
	Sildenafil N=50	**Placebo N=53**
Baseline [a]		
n	50	53
Mean (SD)	354.44 (73.121)	350.38 (87.587)
95% CI of mean	(333.65, 375.22)	(326.24, 374.52)
Median (min, max)	371.00 (187.0, 461.0)	376.00 (165.0, 497.5)
Change from Baseline at Week 4		
n	44	52
Mean (SD)	12.26 (27.833)	11.60 (32.604)
95% CI of mean	(3.79, 20.72)	(2.52, 20.67)
Median (min, max)	11.00 (-48.0, 80.0)	6.75 (-56.5, 97.0)
Change from Baseline at Week 8		
n	44	46
Mean (SD)	22.85 (38.344)	13.36 (48.639)
95% CI of mean	(11.19, 34.51)	(-1.09, 27.80)
Median (min, max)	22.75 (-76.5, 117.0)	27.75 (-134.0, 97.0)
Change from Baseline at Week 12		
n	44	46
Mean (SD)	14.08 (63.679)	17.42 (57.270)
95% CI of mean	(-5.28, 33.44)	(0.42, 34.43)
Median (min, max)	14.25 (-275.0, 150.0)	21.00 (-160.0, 170.0)
Change from Baseline at Week 12 (LOCF) [b]		
n	49	53
Mean (SD)	13.62 (60.950)	14.08 (57.557)
95% CI of mean	(-3.89, 31.12)	(-1.78, 29.95)
Median (min, max)	12.00 (-275.0, 150.0)	16.00 (-160.0, 170.0)
ANCOVA analysis:		
Adjusted difference of mean (SE) (sildenafil-placebo)	-2.38 (11.722)	
90% CI	(-21.843, 17.087)	
1-sided P-value	0.5802	

Results from the same analysis using the per protocol (PP) population (n = 83) were similar to those from the analysis using the ITT population analysis.

There was evidence of effect modification by aetiology as observed in the subgroup analysis. For subjects with primary PAH (65% of the ITT population), a numerically greater mean increase was observed in the sildenafil group compared with the placebo group; at Week 12 (LOCF), the mean (SD) changes from baseline were 26.39 (45.67) and 11.84 (57.35) m for the sildenafil and placebo groups, respectively. However, for subjects with pulmonary hypertension associated with connective tissue disorder (35% of the ITT population), the mean (SD) changes from baseline to Week 12 (LOCF) were -18.32 (81.99) m in the sildenafil group and 17.50 (59.115) m in the placebo group.

Secondary endpoints: Overall, 98.0% of subjects in the sildenafil group and 100% of subjects in the placebo group had FC II or III PAH at baseline. During the course of the 12-week double-blind phase, the majority of subjects in each treatment group had no change in **FC**, indicating no deterioration or improvement over the 12-week treatment period.

There were few **clinical worsening** events during the 12-week double-blind phase. Two (2) subjects in the sildenafil group and 2 subjects in the placebo group were hospitalised due to PAH, and 1 subject in the sildenafil group died. During 12 weeks of treatment, the subject populations in both treatment groups were generally clinically stable.

BORG dyspnoea scores (using the modified BORG scale) were similar between treatment groups at baseline, with a median score of 4, indicating somewhat severe dyspnoea. During the 12-week double-blind phase, the mean changes from baseline in BORG dyspnoea scores were consistently negative in the sildenafil group, and positive in the placebo group, (negative shift indicated an

improvement). However, at Week 12 (LOCF), the median changes in BORG dyspnoea score were 0.00 in both treatment groups.

Tertiary endpoints: The median BNP values at baseline were 127.50 pg/mL in the sildenafil group and 112.95 pg/mL in the placebo group. At Week 12, the median changes in BNP values were 1.04 pg/mL for subjects in the sildenafil group and 7.99 pg/mL for subjects in the placebo group.

The median pro-BNP values at baseline were 575.20 pg/mL in the sildenafil group and 468.00 pg/mL in the placebo group. At Week 12, the median changes in pro BNP values were 94.10 pg/mL for subjects in the sildenafil group and 14.29 pg/mL for subjects in the placebo group.

2.3.2. discussion

The applicant presents clinical data from 4 different studies investigating the possible additive value of sildenafil when given on top of bosentan in different subtypes of PAH. Generally, some improvement in the 6 MWT or haemodynamic measurements was observed though not always of statistical significance. The difference in study results may be attributed to a difference in the PAH subtype (idiopathic, associated with connective tissue disease, congenital heart disease or Eisenmenger), the stage of the disease, or the sildenafil dose. The recruited number of patients per study is too limited precluding any robust conclusions. Also, the presented list of clinical studies is not complete. The applicant is requested to do a more thorough job and present all available studies investigating this combined use e.g the EARLY study, Mathai et al., 2007. This can help interpret the results of study A1481243.

The aim of study A1481243 was to address the efficacy and safety of combination therapy of bosentan and sildenafil. The chosen study design may not have been the most appropriate to address this aim. The design follows the standard PAH study, using the 6MWT as the primary endpoint and 12 weeks study duration. This design is already criticised in addressing the monotherapy indications, and it is doubted that it can currently be used for combination therapy, especially because of the short duration of the study. This reflected also on the recruited numbers (around 100 patients). Recruited patients were FC II (34%) and FC III (65%).

Current treatment guidelines do not recommend combination therapy for PAH patients FC II, and the margin for improvement in this less advanced patients group may be narrower than FC III. This argument is also valid for the baseline 6MWT where most recruited patients had a baseline 6MWT of >325 m. Also based on previous clinical data, by hindsight, focusing on patients with idiopathic PAH may have been a better idea.

Regarding the actual conduct of the study, the possible impact of the error in randomisation resulting in imbalance between the 2 groups in the baseline 6MWT on the results cannot be estimated. The reported results are disappointing. There is not even a trend of improvement in the sildenafil arm in the main cohort. However, a trend was shown for patients with idiopathic PAH (65%) administered sildenafil compared to placebo patients (mean change from baseline of 26.39 m compared to 11.84 m LOCF respectively). The reverse was noted for PAH associated with connective tissue disease (35%) (mean changes from baseline to Week 12 (LOCF) were -18.32 m in the sildenafil group and 17.50 m in the placebo group). There were equivocal results in WHO functional class, which are comparable to the results of 6MWT. With a short trial duration, the equivocal results of TTCW would have been expected.

In summary, the CHMP considered that the importance of the results of the study is not established due to shortcomings in the study design and randomisation. Therefore the MAH was asked to discuss further the design and results of the study (PK and efficacy) and their possible consequences on

clinical practice. The applicant was also asked to present all published clinical studies addressing this co-administration.

The CHMP also considered that the proposed warnings in the SmPC also conflict with current clinical practice guidelines, which can be confusing to the prescriber, thus further clarification was requested by the CHMP.

Summary of the Applicant's Response

Study A1481243 – Key Results and Considerations for Assessment of Possible Consequences on Clinical Practice

Given the known pharmacokinetic interactions between the two drugs and the potential use of the combination in practice, as a condition of marketing authorization approvals in EU and US, the MAH designed Study A1481243 to evaluate the efficacy and safety of the combination of 20 mg TID sildenafil (approved dose) in addition to stable bosentan treatment. At the time of study planning, bosentan was the established oral therapy for PAH used as first-line treatment and the evaluation of sildenafil as add-on treatment in a 12-week trial, using 6MWD as the primary endpoint, was supported by prevailing clinical trial knowledge. In March 2006 the protocol for the study was endorsed by CHMP.

These overall efficacy results were in contrast with what was expected based on feedback from experts in this area and on current treatment guidelines. When the data were analyzed by etiology, the results were numerically better for the combination in primary pulmonary hypertension (PPH), but numerically worse for the combination in pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD). While these results add to the knowledge base addressing the use of the two drugs in combination, a number of considerations affect the interpretation of the overall results and their possible consequences on clinical practice.

Study Design

The study was designed in a way that sildenafil was added at baseline to adults with PAH who had been on a stable dose of bosentan for at least 3 months. Study results suggest that during the 12-week double-blind trial, bosentan was continuing to provide additional benefit in exercise capacity after the lead-in period of at least 3 months. This is suggested by the mean increases from baseline in 6MWD in the placebo group of 11.60 m, 13.36 m, 17.42 m at Week 4, 8 and 12 respectively. This observation, which was also seen in the PHIRST study of tadalafil added on to bosentan, puts into question whether all subjects were truly stable on bosentan treatment at baseline, as intended by the study protocol.

In addition, the study did not require that each candidate, at entry, have a clinical need for added treatment. This is in contrast with most studies reported in the literature and with the current clinical guidelines which recommend treatment combination only after an inadequate clinical response to the initial monotherapy. The consequence was that subjects who were clinically stable and not yet in need of a second agent could enter the trial. Patients responsive to bosentan monotherapy may have decreased potential for further improvement. With hindsight, a more clinically relevant approach might have been to limit the subject selection to those in need of a second agent due to lack of adequate response with the first agent, per current clinical guidelines. Retrospectively, this modification may have permitted a better alignment of the studied population with clinical practice. Furthermore, as designed the study allowed subjects of functional class (FC) II as well as FC III to enter the study. Either stratifying the population by FC at entry or more heavily weighting the population to FC III would also have provided a homogeneous PAH patient population more representative of those who are candidates for combination therapy in clinical practice.

At the time of study planning in 2006, the sildenafil exposure required in combination with bosentan to achieve beneficial effect was unknown. It was presumed at the design stage that based on data from a study in healthy volunteers where sildenafil 80 mg TID produced an approximately 50% higher bosentan exposure, a residual (<50%) increase in bosentan exposure might be observed with the approved sildenafil dose of 20 mg TID. Therefore, the study was designed to evaluate the combination administered at the labeled doses of each drug only.

The population pharmacokinetic (PK) analysis of bosentan using data only from Study A1481243 showed a non-significant increase in bosentan exposure of approximately 17% (95% CI: -4.7 – 52%) in the presence of sildenafil 20 mg TID. This was lower than anticipated based on the 50% increase in bosentan observed in the healthy volunteer study.

Also, this population PK analysis of sildenafil, using data from the 20 mg TID treatment arms across Studies A1481243 and A1481244 with Study A1481140 as the reference, confirmed an approximate 60% reduction in sildenafil exposure in the presence of bosentan in Study A1481243. This was consistent with the reduction in sildenafil exposure observed in the healthy volunteer drug-drug interaction study.

Data are limited for efficacy of sildenafil at exposures lower than that achieved with 20 mg TID. Characterization of dose-response at a lower dose range of 1, 5, and 20 mg TID in treatment-naïve PAH patients was investigated in Study A1481244 as a post-marketing commitment to FDA. Although the study was terminated prematurely with 130 subjects randomized and 129 subjects treated, the results did not demonstrate a difference between the sildenafil 20 mg and 5 mg doses; however, the equivalence of the two doses could not be inferred. The increase in 6MWD was clinically significant in the 5 mg and 20 mg groups (mean changes of 41 meters [95% CI: 25.16, 56.34] and 38 meters [95% CI: 23.77, 52.94], respectively) but smaller and not clinically significant in the 1 mg group (mean change of 14 meters [95% CI: 0.41, 28.00]).

The lower sildenafil exposure as a result of the PK drug interaction with bosentan could have contributed to the unexpected efficacy results, but is confounded by other factors in this patient population such as different baseline characteristics compared to a treatment naïve population (as studied in A1481140 and A1481244), and the potential for subjects to continue to improve their exercise capacity on bosentan background treatment after entering Part A of the study.

Furthermore, at the time of study planning the 6MWT was the gold standard utilized as primary efficacy endpoint in clinical trials in PAH. During the 6 years (2006 through 2012) required to conduct Part A of the trial, much has been learned about the limitations of the 6MWT. For example, while the 6MWT has been validated in PPH, it has not been validated in other forms of PAH, is subject to the complexities of showing less improvement in patients without advanced disease, and is confounded by the inclusion of patients on effective background therapies. In addition, there are a number of variables, such as age, height, weight, gender, motivation, test experience, co-morbidities, and concomitant medications that can impact on the performance of the 6MWT and the achieved 6MWD. These limitations have been noted especially with the CTD-associated PAH population. In retrospect, addition of hemodynamic measurements as secondary endpoints in the study could have provided a more complete picture of clinical response in the short-term trial.

Regarding the assumptions behind the sample size, the study was powered to detect a mean difference of 30 m in change of 6MWD at Week 12 between treatment groups (assuming a standard deviation of 60 m) based on the results available at the time from previous trials. A greater sample size would be required had the study been designed to detect a smaller mean difference. However, given the overall study results and the consistency of the findings across different sensitivity analyses performed (per- protocol population, non-parametric methods) and secondary efficacy endpoints, it is

unlikely that a different conclusion could be reached had more subjects been enrolled in this study assuming the study population and all other design parameters remained the same.

Study Execution

In response to the CHMP request to address the potential impact of the randomisation stratification error, the MAH believes that the error does not impact the primary efficacy analysis results and study conclusions. Multiple sensitivity analyses have confirmed the results from the primary efficacy analysis and results from analyses by actual randomisation stratification were consistent with the results from the primary efficacy analysis.

In addition to the randomisation stratification error described above, the MAH has determined that protocol deviations occurred during the conduct of the trial that resulted in some pharmacokinetic samples obtained from the placebo group being positive for sildenafil. Positive samples were detected in a total of 15 placebo-treated subjects (all at the Week 12 study visit with the exception of 1 sample from 1 subject on day 1). Sildenafil was not detected in samples from these subjects at other visits.

It is hypothesized that these positive samples occurred from the administration of an open-label sildenafil tablet (dispensed at Week 12 for the open-label phase) to these subjects prior to obtaining the PK samples and possibly before the 6MWT. Among the 14 subjects who had detectable sildenafil concentration in their PK samples at Week 12, 13 had a 6MWT at Week 12. One subject had her last 6MWT at Week 8 during the double blind phase. Statistical analyses for the primary efficacy endpoint were repeated excluding the 13 placebo subjects to investigate the impact on the primary efficacy endpoint of change in 6MWD from baseline at Week 12. The overall study results and conclusions are no different from those determined from the original primary efficacy analysis.

Furthermore, as noted in the preliminary report of the population PK analysis approximately 50% of the bosentan plasma samples were analyzed outside of the established stability period. These samples were included in the initial PK analysis. Additional long-term stability testing was recently completed extending the validated stability period to cover approximately 92% of the bosentan samples. The final population PK analysis planned for reporting in early 2014 will be conducted excluding those samples that remain outside the limits of the extended long-term stability period.

Exploratory analysis mentioned in the preliminary population PK report showed that exclusion of the samples outside of stability improved the precision but did not appreciably change the point estimates. Based on this assessment and fewer samples now falling outside long-term stability, interpretation of the population PK results is not anticipated to change from the preliminary report submitted initially in the application.

Overview of Combination Therapy in PAH – Literature Review and Current Clinical Practice

Treatment with combinations of agents targeting different pathways in the pathogenesis of the disease has been reported in the literature. Combination therapy is currently recommended in clinical guidelines for patients with an inadequate response to monotherapy, despite the lack of controlled data.

The combination of two agents such as bosentan and sildenafil is the most reported in the literature because of the ease of administration, differing mechanisms of action and tolerability. There are published clinical data investigating the combined use of bosentan and sildenafil.

The MAH searched Ovid MEDLINE, EMBASE, EMBASE DAILY, BIOSIS and DERWENT DRUG FILE for studies investigating combined use of sildenafil and bosentan. After review, eight citations met the criteria for inclusion in this review (see annex II). The MAH considered that these studies reflect the available published literature addressing the co-administration of sildenafil and bosentan.

In summary, there are some signals that are informative for interpreting the results of study (A1481243). In the studies from Hoeper et al. (2004), Porhownik et al. (2008), and D'Alto et al. (2012), patients who were clinically deteriorating on bosentan monotherapy demonstrated improvement in exercise capacity (6MWD) when sildenafil was added. However, in one randomized controlled study of patients stable on bosentan (Iversen et al., 2008), addition of sildenafil did not significantly improve 6MWD. In addition, in the EARLY study, which was limited to patients with mildly symptomatic PAH (WHO FC II), no improvement in 6MWD was observed with combined treatment. Finally, in the study by Mathai et al. (2007), IPAH patients derived greater benefit than those with scleroderma-associated PAH.

However, the limited number of patients, the different aetiologies of PAH in patients included in these studies, and the varied study designs, makes it difficult to draw meaningful clinical conclusions from the literature about the benefit of sildenafil and bosentan when used in combination.

In summary, the MAH acknowledged that clinical trial design and clinical practice in PAH have evolved since this study was designed and initiated in 2006. At the time of study planning, bosentan was the established oral therapy for PAH used as first-line treatment and the evaluation of sildenafil as add-on treatment in a 12-week trial, using 6MWD as the primary endpoint, was supported by prevailing clinical trial knowledge. Patients on a stable dose of bosentan for at least 3 months were enrolled, consistent with published literature indicating that the maximal effect of bosentan on 6MWD is achieved within the first 3-4 months of therapy.

In addition, the MAH is in agreement with the CHMP assessment that the study results can only be applied to the population and clinical setting for which the efficacy and safety of the concomitant use of sildenafil and bosentan was assessed in this clinical trial. In particular, results of this study cannot be generalised to the clinical setting where use of sequential combination therapy is currently recommended by international PAH guidelines; that is, when clinical response to initial monotherapy is inadequate.

Despite these limitations, the present study remains the only completed randomised controlled trial to date evaluating the efficacy and safety of sildenafil in patients on a stable dose of bosentan for a minimum of 3 months. Similar to more recent trials, results of this study indicate that placebo-treated patients continue to improve on bosentan alone during the double-blind portion of the trial, contrary to the early indication that maximal effect is achieved within the first 3-4 months of therapy. While sildenafil provided no incremental benefit over placebo on exercise capacity in the overall population, the study provided evidence that the effect on 6MWD differed by PAH etiology, with a more favorable, albeit modest, response in the PPH subpopulation and no improvement for the subpopulation with connective tissue disease-associated PAH. The population pharmacokinetic analyses confirmed that bosentan reduces the exposure of sildenafil by about 60%; however, for PAH patients taking sildenafil 20 mg TID, bosentan exposure was only marginally affected. There were no new or unexpected safety findings associated with the use of this combination.

As highlighted in the literature review, there are published clinical data investigating the combined use of bosentan and sildenafil; however, the limited number of patients and different etiologies of PAH included in those studies, as well as the varied study designs (the majority of which are open label), make it difficult to draw clinically meaningful conclusions.

While the MAH acknowledges the limitations of the study given the evolution of the PAH clinical trial design, currently ongoing trials will provide complementary data and support overall interpretation. In COMPASS-2, patients receiving sildenafil therapy are randomised to bosentan or placebo and assessed with respect to time to a first morbidity/mortality event as well as change in 6MWD. Additionally, the

event-driven AMBITION trial is expected to shed light on the value of initial (i.e., combination therapy from the outset) versus sequential combination therapy in treatment-naïve patients.

CHMP comments

In their response, the applicant acknowledged the shortcomings of the study, which could explain the results and consequently limit the extrapolation of the results to clinical practice. For example, the study did not require that patients have a clinical need for added treatment. This is in contrast to clinical treatment guidelines which recommend starting a new treatment sequentially after the first therapy has shown failure.

The study also allowed patients from FC WHO II and III. It is known that FC WHO II has a lower potential for improvement. Thus patients with more advanced disease, or showing signs of clinical deterioration could have been a more appropriate study population. In addition, study results suggest that during the 12 weeks period, the placebo group (on bosentan only) still showed improvement in 6MWT. Comparable results were shown in the PHIRST study. In PHIRST, a subgroup of patients were administered another PDE5.I (tadalafil) on top of bosentan. There was less improvement shown in the 6MWT in the subgroup co-administered tadalafil on top of bosentan of 17 metres (p=0.09; 95 % CI: : -7.1, 43.0) compared to tadalafil on top of placebo (39 metres (p<0.01, 95 % CI:13.0, 66.0). This resulted in a warning in section 4.4 that "The efficacy of tadalafil in patients already on bosentan therapy has not been conclusively demonstrated." It cannot be excluded that in PHIRST, study population was also not the most adequate to show a response of combined. A comparable warning is accordingly considered appropriate.

Regarding the randomization errors, the applicant explains that several sensitivity analyses have confirmed the results from the primary efficacy analysis and results from analyses by actual randomisation stratification were consistent with the results from the primary efficacy analysis.

Addressing the PK analysis, comparable results in exposure between primary and secondary PAH do not support that this can be the underlying reason for a difference in efficacy (see Q2 for details). PK results in healthy volunteers are comparable to results obtained in the current study regarding exposure of sildenafil. It was shown in both studies that exposure to sildenafil is reduced when co-administered with bosentan. However, this only cannot explain the results. In one study efficacy in terms of 6MWT using the 20 mg and 5 mg TID sildenafil were shown to be comparable, though results were not conclusive. On the other hand, there was a lower increase in exposure in bosentan (17%) when sildenafil 20 mg TID is administered in the current study compared to 50% increase previously reported when sildenafil 80 mg TID is administered. The possible influence of this difference is not known.

The company identified 8 published studies addressing the combined use of sildenafil and bosentan in PAH. Their results generally corroborate the above findings, mainly the high dependence of the response on the studied population. For example, in the studies from Hoeper et al. (2004), Porhownik et al. (2008), and D'Alto et al. (2012), patients who were clinically deteriorating on bosentan monotherapy demonstrated improvement in 6MWD when sildenafil was added, but not when they are stable on bosentan (Iversen et al., 2008) or with mild symptoms (EARLY study). In the study by Mathai et al. (2007), IPAH patients derived greater benefit than those with scleroderma-associated PAH.

In conclusion, the MAH is in agreement with the CHMP assessment that the study results can only be applied to the population and clinical setting for which the efficacy and safety of the concomitant use of sildenafil and bosentan was assessed.

The MAH acknowledged that the results of this study are not generalisable to the clinical setting where use of sequential combination therapy is currently recommended by international PAH guidelines; that is, when clinical response to initial monotherapy is inadequate.

An explicit non-recommendation for the use of sildenafil and bosentan in PAH associated with CTD is not supported by the CHMP. In view of the above described shortcomings in the study and the limited numbers of patients with PAH associated with CTD (n=36) such a recommendation is not considered justified. The data are not considered robust enough.

However, the data should still be adequately described in section 5.1 to allow the healthcare professionals to draw conclusions. It is now proposed to amend the text under section 4.4 similar to that of tadalafil, with further amendments of the other sections (4.4, 4.5 and 5.1 and editorial changes in section 4.2).

In section 4.4, some specific warnings regarding the subgroups of primary PAH and PAH associated with CTD are now proposed.

The updated SmPC proposal received after the Request for supplementary Information was overall acceptable by the CHMP. The details on the final SmPC are described in the product information section.

2.4. Clinical safety aspects

2.4.1. Introduction

Review of Safety with Sildenafil and Bosentan Combination Therapy from Other Studies

In Study A1481149, a randomised, double-blind, placebo-controlled, parallel-group trial, a total of 55 healthy male volunteers were randomised to one of 3 treatment arms for 18 days, sildenafil plus placebo, bosentan plus placebo or sildenafil plus bosentan. Safety results indicated that bosentan and sildenafil in combination were well tolerated, with no SAEs reported. All AEs were of mild or moderate intensity. In addition, literature reports of combination therapy of sildenafil and bosentan (presented under efficacy) did not report any major safety concerns. Addition of sildenafil after oral bosentan therapy failure was safe and well tolerated.

2.4.2. Results

Safety Information from Study A1481243

A total of 34 (68.0%) subjects in the sildenafil group and 41 (77.4%) in the placebo group experienced at least 1 all-causality treatment-emergent adverse event (TEAE). Seventeen (34.0%) subjects in the sildenafil group and 13 (24.5%) in the placebo group experienced treatment-related TEAEs. For the sildenafil group, the most frequently reported treatment-related TEAEs was headache (6 [12.0%] subjects) and flushing (5 [10.0%] subjects). The number of subjects with severe all-causality TEAEs was 4 (8.0%) in the sildenafil group compared with 10 (18.9%) in the placebo group. No subjects in the sildenafil group reported a severe treatment-related TEAE, compared with 2 (3.8%) subjects in the placebo group.

The incidence of treatment-emergent serious SAEs in the sildenafil group was numerically lower compared with the placebo group; 9 (18.0%) in the sildenafil group and 12 (22.6%) in the placebo group. One subject (2.0%) in the sildenafil group had an SAE (acute coronary syndrome), which was considered to be treatment-related (the investigator considered this event related to study drug; the

sponsor considered the event was most likely attributed to the subject's pre-existing 3-vessel coronary disease, with underlying diabetes mellitus and hypertension; however, due to temporal association, a possible contributory role of the study drug could not be excluded). No subjects in the placebo group experienced SAE that was considered to be treatment related.

There was one death among subjects who participated in the double-blind phase of the study that was in the sildenafil treatment group.

A 59 year old female with a 6 month history of pulmonary hypertension secondary to connective tissue disease was enrolled and randomly assigned to the sildenafil group. Her past medical history included congestive heart failure, rheumatoid arthritis, hypoxia and hypertension. She received sildenafil until her death at Day 13. The cause of death was sudden death (unknown cause; autopsy not performed), and both the investigator and sponsor assessed the event to be unrelated to the study drug. The event was considered to be due to progression of the underlying disease of pulmonary hypertension.

Additionally, at the time of data cut-off for the Clinical Study Report (CSR), 3 out of 6 deaths had occurred in the open-label phase (Part B) due to arrhythmia, pancreatic neoplasm and pulmonary hypertension and 3 deaths (all were considered to be the result of the underlying disease, pulmonary hypertension) were reported through survival data collection after discontinuation from the study. Three deaths occurred in subjects' originally assigned to the sildenafil group and 3 in subjects' originally assigned to the placebo group. Causes of death were PAH (4), pancreatic neoplasm (1) and cardiac arrhythmia (1). None of the deaths were considered to be related to the study drug (table S1)

Table S1: Summary Listing of Deaths

Age at death (years)/Sex	Treatment Group, DB/OL	Phase event occurred/Day of last dose of study drug	Day of onset of event	Day of death	MedDRA Preferred Term for event	Investigator Sponsor Causality
59/F	Sildenafil/-	Double-blind/ Day 13	13	13	Sudden death	Unrelated Disease under study
49/F	Sildenafil/ Sildenafil	Open-label post-therapy/Day 453	480	480	Arrhythmia	Unrelated Disease under study
60/F	Sildenafil/ Sildenafil	Open-label/ Day 446	441	766	Pancreatic neoplasm	Unrelated Disease under study
24/F	Sildenafil/ Sildenafil	Open-label /Day 107	86	110	Pulmonary hypertension	Unrelated Other -unknown
68/F	Placebo/ Sildenafil	Post-Study /Day 281	260	324	Pulmonary hypertension	Unrelated Disease under study
75/F	Placebo/ Sildenafil	Post-Study /Day 419	626	630	Pulmonary hypertension	Unrelated Disease under study
75/M	Placebo/ Sildenafil	Post-Study/ Day 253	253	341	Pulmonary hypertension	Unrelated Disease under study

Four (8.0%) subjects in the sildenafil group and 4 (7.5%) in the placebo group had at least one TEAE leading to discontinuation. There was no trend in the causes of discontinuations; no AE term appeared more than once. A total of 4 (8.0%) sildenafil-treated subjects and 1 (1.9%) placebo-treated subject had all-causality TEAEs leading to dose reduction or temporary discontinuation. A total of 2 (4.0%) subjects from the sildenafil group and 1 (1.9%) subject from the placebo group had treatment-related TEAEs leading to dose reduction or temporary discontinuation.

During the procedure, the details of the two cases of treatment-related TEAEs leading to dose reduction or temporary discontinuation in the sildenafil arm were requested and provided by the MAH.

Summary of the Applicant's Response

The MAH provided the requested information and also information related to one additional death reported since the data snapshot for Part A was performed in February 2013. This death occurred in a subject originally assigned placebo, 2 months after he had completed both Part A and Part B of the study. A narrative of this additional death is also included.

Protocol: A1481243
A 47-year old female subject with a five month history of idiopathic pulmonary arterial hypertension was enrolled in the study. The subject was randomized to double blind sildenafil and received treatment for 84 days; the first dose was administered on study Day 1 and the last dose of double blind treatment was administered on Day 84. The subject began open label sildenafil on Day 85 and took the final dose on Day 449.

At the time of screening, her past medical conditions included atrial flutter, bacteraemia, gastric ulcer, headache, large intestine polyp, oedema peripheral, pericardial effusion, pleural effusion and vomiting (dates not reported). The subject's present medical conditions included anaemia, apnoea, cardiac failure congestive, cardiac murmur, cardiomegaly, cough, deep vein thrombosis, dizziness, duodenal ulcer, gastrooesophageal reflux disease, hepatic cyst, hepatic steatosis, hypokalaemia, jugular vein distension, large intestine polyp, pulmonary arteriopathy, pulmonary valve incompetence, syphilis, tricuspid valve incompetence, vasodilatation (dates not reported) and no known drug allergies.

Concomitant medications (in addition to bosentan 125 mg bid Day -132 to ongoing) included amiodarone hydrochloride, digoxin, dimeticone, activated, furosemide, hydrotalcite, potassium chloride, spironolactone, trichlormethiazide.

On Day 8, the subject experienced a non-serious adverse event of flushing which was considered moderate in intensity by the investigator. On Day 8 the subject's total daily dose of study drug was reduced from 60mg to 40mg due to this event. On day 35, her study drug dose was increased back to 60mg. Causality is noted as related to study drug. The event resolved on Day 17.

The subject completed the study on Day 449.

Protocol: A1481243
A 64-year old Asian female subject with a 13 year and 11 month history of idiopathic pulmonary arterial hypertension was enrolled. The subject was randomized to double blind sildenafil 20 mg tid and received treatment for 29 days; the first dose was administered on Study Day 1 and the last dose of blinded treatment was administered on Day 29.

The ongoing medical conditions at the time of screening included hypothyroidism , nasal polyps, exertional dyspnoea, palpitations, oedema and fatigue, disturbance in attention, headaches and hypertension, chest pain, snoring, coughs and seasonal allergies, dizziness, abdominal distension, macular degeneration, nasal congestion, and flatulence, oropharyngeal pain, throat irritation, constipation and hyperlipidaemia, and dysphonia, arthritis, dyspepsia, nocturia, clubbing of nails,

upper airway cough syndrome, decreased weight and breast mass. Concomitant medications (in addition to bosentan 125 mg bid) included benzonatate, clavulin, levofloxacin, sodium alendronate, vitamin C, calcium carbonate, digoxin, diltiazem hydrochloride, estropipate, ezetimibe, furosemide, sodium levothyroxine, macrogol, plain multivitamins, spironolactone, tocopherol and warfarin (all ongoing).

On Day 10, the subject experienced a non-serious adverse event (AE) of blurred vision. The event was considered to be of moderate intensity by the investigator. On the same day the subject also experienced non-serious AEs of ocular hyperaemia and sensory disturbance which were considered to be of moderate intensity. On Day 20 the study drug was reduced to 40 mg total dose per day, and the AEs of ocular hyperaemia and sensory disturbance were resolved on this day. The subject was referred to an ophthalmologist for further investigation. The study drug was permanently discontinued on Day 29 due to the event of blurred vision. On Day 31, the event of blurred vision was resolved. On 20 Sep 2007 the subject permanently withdrew from the study.

The investigator assessed the causality of the non-serious AEs of blurred vision, ocular hyperaemia and sensory disturbance as related to the study drug.

Protocol: A1481243

A 70-year old-male subject with an eleven month history of idiopathic pulmonary arterial hypertension was enrolled in the study. The subject was randomized to double blind placebo and received treatment for 84 days; the first dose was administered on Study Day 1 and the last dose of double blind treatment was administered on Day 84. The subject began open label sildenafil on Day 85 to Day 283 and again from Day 309 and took the final dose on Day 451.

At the time of screening, his ongoing medical conditions included ex-smoker, atrial fibrillation, cardiac operation, mitral valve disease and mitral valve repair.

Concomitant medications (in addition to bosentan 125 mg bid Day 1 to 85) included acetylsalicylic acid, bisoprolol, duovent, mirtazapine, osyrol-lasix, ramipril, tamsulosin hydrochloride, tiotropium bromide and torasemide.

On Day 81, the subject experienced a non-serious adverse event of respiratory disorder (short breathing) which was considered mild in intensity by the investigator. No action was taken with the study drug and the subject continued to receive treatment. Causality is noted as other viral infection. The event resolved on the same day at Day 81.

On Day 105, the subject experienced a non-serious adverse event of nasopharyngitis which was considered mild in intensity by the investigator. No action was taken with the study drug and the subject was seen by a pulmonary consultant. Causality is noted as other illness-chronic bronchitis. The event was ongoing at the end of the study (Day 505).

On Day 182 the subject experienced a non-serious adverse event of infective exacerbation COPD which was considered moderate in intensity by the investigator. No action was taken with the study drug and the subject was seen by a pulmonary consultant. Causality is noted as other illness-chronic bronchitis. The event was ongoing at the end of the study (Day 505).

The subject completed the study on Day 504. During post-study follow up it was discovered the patient died on Day 584 due to pulmonary embolism or sudden cardiac death. The investigator did not attribute the patient's death to the blinded study drug, nor to open-label sildenafil, concomitant drug or clinical trial procedure.

The study was un-blinded on 15 Oct 2013 and revealed that the subject was randomized to receive placebo during the 12-week double-blind period and then received sildenafil during the 12-month open-label.

Based on the information available, the Company (Pfizer, Inc.) concurred with the investigator that there was no information to suggest that the reported event "embolism pulmonary or sudden cardiac death" with fatal outcome was related to the blinded study drug, sildenafil, concomitant drug or clinical trial procedure. The ongoing medical condition of pulmonary hypertension was assessed as the most likely contributory factor to the reported fatal outcome event.

Assessment of the Applicant's Response

The requested narratives were submitted as requested and the assessment did not reveal any new safety issues.

Finally, the majority of subjects did not have laboratory abnormalities during the study, and the proportion of subjects with laboratory abnormalities appeared similar in both treatment groups. Minimal changes from baseline vital sign values were observed.

2.4.3. Discussion

Generally, submitted safety data from study A1481243 do not reveal any specific safety issues when sildenafil is co-administered with bosentan. One case of treatment emergent serious adverse event of acute coronary syndrome was reported in the sildenafil arm. It can be agreed that causality is confounded with the past history of the patient. It is also difficult to assess causality in the reported cases of deaths reported in the study (one case in the sildenafil arm in the DB period, and 6 cases thereafter), due to the underlying CV disease and its progression. The conclusions of the MAH, regarding the lack of causality of the study medications to the reported deaths can be supported, based on the submitted narratives.

2.5. Changes to the Product Information

During the procedure, the CHMP requested further amendments to the PI as discussed in detail above.

Proposed additions by the MAH are indicated underlined, proposed deletions by the MAH are indicated with ~~strikethrough~~.

2.5.1. SmPC

- **Section 4.2 Posology and method of administration**

The proposed changes submitted by the MAH are highlighted below:

In general, any dose adjustment should be administered only after a careful benefit-risk assessment. A downward dose adjustment to 20 mg twice daily should be considered when sildenafil is co-administered to patients already receiving CYP3A4 inhibitors like erythromycin or saquinavir. A downward dose adjustment to 20 mg once daily is recommended in case of co-administration with more potent CYP3A4 inhibitors clarithromycin, telithromycin and nefazodone. For the use of sildenafil with the most potent CYP3A4 inhibitors, see section 4.3. Dose adjustments ~~of~~ for sildenafil may be required when co-administered with CYP3A4 inducers (see section 4.5). However, there are no data to support increasing the dose of sildenafil in combination with bosentan (see sections 4.4, 4.5, and 5.1).~~For the use of sildenafil with the most potent CYP3A4 inhibitors, see section 4.3.~~

CHMP comments

The proposed modification in section 4.2 regarding the interaction with bosentan is not accepted by the CHMP. This addition refers to dose adjustments in case sildenafil is co-administrated with bosentan, a combination which did not show a robust clinical benefit in the first place, and for which a warning is proposed. Such comment is not considered relevant to be placed in section 4.2. In addition, in case the combination is still used off-label, the PK data show significant changes in the kinetics of at least sildenafil.

The company proposed however, a minor editorial change (removing of the brackets) in the current paragraph, which is acceptable.

- **Section 4.4 Special warnings and precautions for use**

Use of sildenafil with bosentan

In a study of PAH patients (primary PAH and secondary PAH associated with CTD) on background bosentan therapy, no incremental benefit (6-minute walk distance (6MWD)) of sildenafil co-administered with bosentan was demonstrated over bosentan alone. The results of the 6MWD were different between primary PAH and PAH associated with CTD. The mean result of the combination of sildenafil and bosentan was numerically worse than bosentan alone in patients with PAH associated with CTD but numerically better than bosentan alone in patients with primary PAH. Therefore, healthcare professionals should use their medical judgment to assess the clinical response when sildenafil is co-administered with bosentan in primary PAH. The combined use of sildenafil and bosentan in patients with PAH associated with CTD is not recommended (see Section 5.1).

CHMP comments

In line with the assessment, it is preferred to make a more general warning in section 4.4, with a cross reference to section 5.1., similar to the text of tadalafil. This would allow a more balanced interpretation of the data, considering the limitations of the study.

The CHMP proposed the following warning for consideration by the MAH:

Use of sildenafil with bosentan:

The efficacy of sildenafil in patients already on bosentan therapy has not been conclusively demonstrated (see sections 4.5 and 5.1).

This proposal has been accepted by the MAH and is implemented in this variation.

- **Section 4.5 Interaction with other medicinal products and other forms of interaction**

MAH proposal

The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg, ~~bosentan~~ *ambrisentan*, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration. ~~There is a pharmacokinetic interaction between sildenafil and bosentan (see below information on the interaction with CYP3A4 inducers and effects of sildenafil on other medicinal products).~~

…

Co-administration of bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) 125 mg twice daily with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63 % decrease of sildenafil AUC. ~~Caution is recommended in case of co-administration.~~ A population pharmacokinetic analysis of sildenafil data from adult PAH patients in clinical trials including a 12 week study to assess the efficacy and safety of oral sildenafil 20 mg three times a day when added to a stable dose of bosentan (62.5 mg – 125 mg twice a day) indicated a decrease in sildenafil exposure with bosentan co-administration, similar to that observed in healthy volunteers (see Sections 4.2, 4.4 and 5.1).

…

In a study of healthy volunteers sildenafil at steady state (80 mg three times a day) resulted in a 50 % increase in bosentan AUC (125 mg twice daily~~). Caution is recommended in case of co-administration.~~ A population pharmacokinetic analysis of data from a study of adult PAH patients on background bosentan therapy (62.5 mg - 125 mg twice a day) indicated an increase of bosentan AUC with co-administration of steady-state sildenafil (20 mg three times a day) of a smaller magnitude than seen in healthy volunteers when co-administered with 80 mg sildenafil three times a day (see Sections 4.2, 4.4 and 5.1).

CHMP comments

The proposed changes could be acceptable, after deleting cross-reference to section 4.2. In addition, the exact figure reported in bosentan exposure (17%) observed in the study should be included.

These comments were accepted by the MAH. The approved text is mentioned below:

The efficacy and safety of sildenafil co-administered with other treatments for pulmonary arterial hypertension (eg, ~~bosentan~~ *ambrisentan*, iloprost) has not been studied in controlled clinical trials. Therefore, caution is recommended in case of co-administration. ~~There is a pharmacokinetic interaction between sildenafil and bosentan (see below information on the interaction with CYP3A4 inducers and effects of sildenafil on other medicinal products).~~

…

Co-administration of bosentan (a moderate inducer of CYP3A4, CYP2C9 and possibly of CYP2C19) 125 mg twice daily with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63 % decrease of sildenafil AUC. ~~Caution is recommended in case of co-administration.~~ A population pharmacokinetic analysis of sildenafil data from adult PAH patients in clinical trials including a 12 week study to assess the efficacy and safety of oral sildenafil 20 mg three times a day when added to a stable dose of bosentan (62.5 mg – 125 mg twice a day) indicated a decrease in sildenafil exposure with bosentan co-administration, similar to that observed in healthy volunteers (see Sections 4.4 and 5.1).

…

In a study of healthy volunteers sildenafil at steady state (80 mg three times a day) resulted in a 50 % increase in bosentan AUC (125 mg twice daily~~). Caution is recommended in case of co-administration.~~ A population pharmacokinetic analysis of data from a study of adult PAH patients on background bosentan therapy (62.5 mg - 125 mg twice a day) indicated an increase of bosentan AUC with co-administration of steady-state sildenafil (20 mg three times a day) of a smaller magnitude than seen in healthy volunteers when co-administered with 80 mg sildenafil three times a day (see Sections 4.4 and 5.1).

- **Section 5.1 Pharmacodynamic properties**

Efficacy and safety in adult patients with PAH (when used in combination with bosentan)

A randomized, double-blind, placebo controlled study was conducted in 103 subjects with PAH who were on bosentan therapy for a minimum of three months. The PAH patients included those with primary PAH, and PAH associated with CTD. Patients were randomized to placebo or sildenafil (20 mg three times a day) in combination with bosentan (62.5 125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 6MWD. The results indicate that there is no significant difference in mean change from baseline on 6MWD observed between sildenafil 20 mg and placebo (13.62 m and 14.08 m, respectively).

Differences in 6MWD were observed between patients with primary PAH and PAH associated with CTD. For subjects with primary PAH (67 subjects), mean changes from baseline were 26.39 m and 11.84 m for the sildenafil and placebo groups, respectively. However, for subjects with PAH associated with CTD (36 subjects) mean changes from baseline were -18.32 m and 17.50 m for the sildenafil and placebo groups, respectively.

Overall, the adverse events were generally similar between the two treatment groups (sildenafil plus bosentan vs. bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy (see Sections 4.2, 4.4, 4.5).”

CHMP comments

This section can be accepted, after implementing the following changes to give more informative data to the prescriber (results with 95% CI should be added).

The approved text is mentioned below:

Efficacy and safety in adult patients with PAH (when used in combination with bosentan)

A randomized, double-blind, placebo controlled study was conducted in 103 clinically stable subjects with PAH (WHO FC II and III) who were on bosentan therapy for a minimum of three months. The PAH patients included those with primary PAH, and PAH associated with CTD. Patients were randomized to placebo or sildenafil (20 mg three times a day) in combination with bosentan (62.5-125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 6MWD. The results indicate that there is no significant difference in mean change from baseline on 6MWD observed between sildenafil (20 mg three times a day) and placebo (13.62 m (95% CI: -3.89 to 31.12) and 14.08 m (95% CI: -1.78 to 29.95), respectively).

Differences in 6MWD were observed between patients with primary PAH and PAH associated with CTD. For subjects with primary PAH (67 subjects), mean changes from baseline were 26.39 m (95% CI: 10.70 to 42.08) and 11.84 m (95% CI: -8.83 to 32.52) for the sildenafil and placebo groups, respectively. However, for subjects with PAH associated with CTD (36 subjects) mean changes from baseline were -18.32 m (95% CI: -65.66 to 29.02) and 17.50 m (95% CI: -9.41 to 44.41) for the sildenafil and placebo groups, respectively.

Overall, the adverse events were generally similar between the two treatment groups (sildenafil plus bosentan vs. bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy (see sections 4.4 and 4.5).

2.5.2. Package Leaflet

No changes to the Package Leaflet are proposed by the MAH. The current wording in the Package Leaflet is:

Section 2 Other medicines and Revatio

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
…

- Therapies for pulmonary hypertension (e.g. bosentan, iloprost)

The MAH does not propose any changes to the wording in the Package Leaflet. This is agreed by the CHMP.

3. Overall conclusion and impact on the benefit/risk balance

Study A1481243, a randomised double-blind, placebo-controlled study of sildenafil (20 mg TID) or placebo added to stable background bosentan therapy (62.5–125 mg twice daily [BID]) in adults with PAH, was designed to evaluate the efficacy, safety and clinical relevance of concomitant therapy given the PK interaction between sildenafil and bosentan.

Pharmacokinetics

The submitted population pharmacokinetic analysis shows that bosentan reduces the exposure of sildenafil by about 60%. The analysis also showed that sildenafil 20 mg TID only marginally affected the exposure of bosentan (17%). This is unlike sildenafil 80 mg TID where exposure to bosentan was increased up to 50%.

Efficacy

Primary endpoint. There was a comparable non-significant gain in 6MWD at Week 12 (LOCF) for ITT population of 13.62±60.95 m in the sildenafil group and 14.08±57.56 m in the placebo group. The difference between the two treatment groups was not statistically significant (1-sided p value = 0.5802). Results of Per protocol analysis were comparable.

Subgroups. A pre-specified subgroup analysis showed that for subjects with primary PAH (65% of the ITT population), a numerically greater mean increase was observed in the sildenafil group compared with the placebo group; at Week 12 (LOCF), the mean changes from baseline were 26.39±45.67 m and 11.84±57.45 m for the sildenafil and placebo groups, respectively. For subjects with pulmonary hypertension associated with connective tissue disease (35% of the ITT population), the mean 6MWT decreased by Week 12 (LOCF) to -18.32±81.996 m in the sildenafil group and 17.50±59.11 m in the placebo group.

Secondary endpoints. The majority of subjects in each treatment group had no change in **WHO functional class**. There were few **clinical worsening** events during the 12-week double-blind phase. Two patients in the sildenafil group and 2 patients in the placebo group were hospitalised due to PAH, and 1 subject in the sildenafil group died. At Week 12 (LOCF), there were minimal changes recorded in **BORG dyspnoea** score in both treatment groups..

The chosen study design may not have been the most appropriate to investigate the value of combination therapy. The study design follows the standard PAH study design, using the 6MWT as the primary endpoint and 12 weeks study duration. This design is already criticised in addressing the monotherapy indications, and it is doubted that it can currently be used for combination therapy, especially because of the short duration of the study. This reflected also on the recruited numbers (around 100 patients). Recruited patients were FC II (34%) and FC III (65%). It is doubtful of significant improvements would have been shown in FC II. This argument is also valid for the baseline 6MWT where most recruited patients had a baseline 6MWT of >325 m. Also based on previous clinical data, by hindsight, focusing on patients with idiopathic PAH may have been a better idea.

Safety

In the double-blind phase of the study, the median treatment duration was 84 days for both treatment groups.

Seventeen (34.0%) patients in the sildenafil group and 13 (24.5%) in the placebo group experienced treatment-related TEAEs. For the sildenafil group, the most frequently reported treatment-related TEAEs was headache (6 [12.0%] subjects) and flushing (5 [10.0%] subjects).

The incidence of treatment-emergent serious **SAEs** in the sildenafil group was numerically lower compared with the placebo group; 9 (18.0%) in the sildenafil group and 12 (22.6%) in the placebo group. One subject (2.0%) in the sildenafil group had an SAE (acute coronary syndrome), which was considered to be treatment-related.

There was one death reported in the sildenafil treatment group. The cause of death was sudden death (unknown cause; autopsy not performed), and both the investigator and sponsor assessed the event

to be unrelated to the study drug. The event was considered to be due to progression of the underlying disease of pulmonary hypertension.

Additionally, at the time of data cut-off for this report, 3 out of 6 deaths had occurred in the open-label phase (Part B) due to arrhythmia, pancreatic neoplasm and pulmonary hypertension and 3 deaths (all were considered to be the result of the underlying disease, pulmonary hypertension) were reported through survival data collection after discontinuation from the study. Causes of death were PAH (4), pancreatic neoplasm (1) and cardiac arrhythmia (1). None of the deaths were considered to be related to the study drug.

Four (8.0%) subjects in the sildenafil group and 4 (7.5%) in the placebo group had at least one TEAE leading to discontinuation. There was no trend in the causes of discontinuations; no AE term appeared more than once. A total of 4 (8.0%) sildenafil-treated subjects and 1 (1.9%) placebo-treated subject had all-causality TEAEs leading to dose reduction or temporary discontinuation. A total of 2 (4.0%) subjects from the sildenafil group and 1 (1.9%) subject from the placebo group had treatment-related TEAEs leading to dose reduction or temporary discontinuation. Submitted data about these cases did not reveal any new safety issues.

Discussion

Study A1481243 addresses an important issue in the management of PAH which is combination treatment. Both bosentan and sildenafil are very commonly prescribed in the management of PAH for longer than 10 years. As they act on different pathways both producing pulmonary vasodilation, there are pharmacological merits in their combination. Their co-administration is accordingly recommended in clinical guidelines in more advanced cases of PAH. The class of recommendations for combination therapies in general are IIa-C for FC II, and IIa-B for FC III. These are based on expert opinion and not investigated in large scale RCT. Study A1481243 is the first RCT for regulatory assessment addressing this issue. The study aimed to investigate this combination strategy regarding the PK interaction, efficacy and safety. The results do not indicate any benefits for the combination in the general cohort, some improvement in the idiopathic PAH subgroup and some deterioration in the subgroup of PAH associated with CTD.

This lack of additive efficacy in the general cohort could probably be attributed to the inappropriate study population. The recruited patients were stable, heterogenous group of WHO FC II and III. They were still improving on bosentan, even after 3 months. This observation was already seen in the PHIRST study, which also failed to show additive improvement of tadalafil when administered on top of bosentan, investigated in a subgroup of the study. This is not the population recommended for sequential combination therapy as per clinical treatment guidelines.

A PK interaction between sildenafil and bosentan (bosentan decreases exposure to sildenafil by 60% and sildenafil increases exposure to bosentan) is already described in healthy volunteers and included in the labelling. This interaction is further confirmed in study A1481243, but with less significant results on bosentan exposure in PAH patients. Considering that sildenafil is only authorised as 20 mg tid, a possible decreased effect when co-administered with bosentan that results in a 60% less exposure can not be excluded. However, some clinical data show that efficacy of sildenafil can still be observed with doses as low as 5 mg TID. No robust conclusions can be drawn. On the other hand, the expected increased exposure of bosentan up to 50% when co-administered with 80 mg TID sildenafil was not achieved in the current study, showing only 17% increase with 20 mg TID sildenafil. Importantly, there was no significant difference in exposure between patients with primary and secondary PAH which could explain the difference in their response.

Available published data generally corroborate the above findings regarding the study population. For example, in the studies from Hoeper et al. (2004), Porhownik et al. (2008), and D'Alto et al. (2012), patients who were clinically deteriorating on bosentan monotherapy demonstrated improvement in 6MWD when sildenafil was added, but not when they are stable on bosentan (Iversen et al., 2008) or with mild symptoms (EARLY study). In the study by Mathai et al. (2007), IPAH patients derived greater benefit than those with scleroderma-associated PAH.

In summary, the results of this study cannot automatically be extrapolated to the clinical setting where use of sequential combination therapy is currently recommended by international PAH guidelines; that is, when clinical response to initial monotherapy is inadequate. In addition, an explicit non-recommendation against co-administration of revatio on top of bosentan in patients with PAH associated with CTD is not considered justified, due to the study shortcomings, and the limited size of this subgroup (n=36). The ongoing AMBITION study (RCT to study the combination of ERA and PDE5.I sequentially or upfront in an event driven design) may be more relevant to address this important question. It is proposed therefore to mention only that the efficacy of sildenafil in patients already on bosentan therapy has not been conclusively demonstrated in section 4.4, with cross-reference to sections 4.5 and 5.1 of the SmPC and to refrain from any recommendations.

The co-administration of sildenafil and bosentan is commonly practiced in more advanced PAH, based on expert opinion. Accordingly, including relevant clinical data addressing this issue is more than welcome. The PK between the two products is long investigated and already included in their respective SmPCs. Currently the applicant is proposing the addition of a warning about the lack of efficacy of the combination, especially for PAH associated with CTD.

Considering the importance of the data, the CHMP had asked for thorough overview of available medical literature before a decision can be made and accordingly decide on the appropriate SmPC recommendations.

However any change in the warning section, should only be based on robust and sound clinical data. As presented and acknowledged, the study has many flaws and it was important to investigate these limitations and how they could have affected the results.

Conclusion

In the current variation, the results of study A1481243 can be included in the labelling, provided the limitations of the studied population are adequately mentioned. The changes in sections 4.4, 4.5 and 5.1 submitted in the Request for Supplementary information are overall acceptable. The minor editorial change in section 4.2 is acknowledged.

The data submitted in this application do not change the benefit/risk balance for the approved indication. The MAH has fulfilled the request to submit the data from the study A1481243 and it is therefore accepted to update the annex II to remove this information.

It is recommended that the MAH updates the current RMP at the next regulatory opportunity, in order to reflect the data submitted in this variation and introduce the removal of the request to submit the A1481243 study results.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Update of sections 4.2, 4.4, 4.5 and 5.1 of the SmPC based on the results of study A1481243 in order to:
- include a warning on the concomitant use of sildenafil with bosentan (section 4.4)
- reflect the drug-drug interaction data on the concomitant use of sildenafil with bosentan (section 4.5)
- describe the relevant efficacy results of study A1481243 (section 5.1)

A minor editorial change is also introduced in section 4.2.

In addition, an update of the Annex II is adopted to remove the requirement to complete the study A1481243 by June 2013.

The requested variation proposed amendments to the Summary of Product Characteristics and Annex II.

5. EPAR changes

The EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Update of sections 4.2, 4.4, 4.5 and 5.1 of the SmPC based on the results of study A1481243 in order to:
- include a warning on the concomitant use of sildenafil with bosentan (section 4.4)
- reflect the drug-drug interaction data on the concomitant use of sildenafil with bosentan (section 4.5)
- describe the relevant efficacy results of study A1481243 (section 5.1)

A minor editorial change is also introduced in section 4.2.

In addition, an update of the Annex II is adopted to remove the requirement to complete the study A1481243 by June 2013.

Summary

The MAH submitted results of the A1481243 study, a randomised double-blind, placebo-controlled study of sildenafil (20 mg TID) or placebo added to stable background bosentan therapy (62.5–125 mg twice daily [BID]) in adults with PAH. This study was designed to evaluate the efficacy, safety and clinical relevance of concomitant therapy given the PK interaction between sildenafil and bosentan.

It is acknowledged that the results of this study are not generalisable to the clinical setting where use of sequential combination therapy is currently recommended by international PAH guidelines; that is, when clinical response to initial monotherapy is inadequate.

A main summary of the information is provided below.

- *Section 4.4*

Use of sildenafil with bosentan:

The efficacy of sildenafil in patients already on bosentan therapy has not been conclusively demonstrated (see sections 4.5 and 5.1).

- *Section 4.5*

A population pharmacokinetic analysis of sildenafil data from adult PAH patients in clinical trials including a 12 week study to assess the efficacy and safety of oral sildenafil 20 mg three times a day when added to a stable dose of bosentan (62.5 mg – 125 mg twice a day) indicated a decrease in sildenafil exposure with bosentan co-administration, similar to that observed in healthy volunteers (see Sections 4.4 and 5.1).

A population pharmacokinetic analysis of data from a study of adult PAH patients on background bosentan therapy (62.5 mg - 125 mg twice a day) indicated an increase of bosentan AUC with co-administration of steady-state sildenafil (20 mg three times a day) of a smaller magnitude than seen in healthy volunteers when co-administered with 80 mg sildenafil three times a day (see Sections 4.4 and 5.1).

- Section 5.1

Efficacy and safety in adult patients with PAH (when used in combination with bosentan)

A randomized, double-blind, placebo controlled study was conducted in 103 clinically stable subjects with PAH (WHO FC II and III) who were on bosentan therapy for a minimum of three months. The PAH patients included those with primary PAH, and PAH associated with CTD. Patients were randomized to placebo or sildenafil (20 mg three times a day) in combination with bosentan (62.5-125 mg twice a day). The primary efficacy endpoint was the change from baseline at Week 12 in 6MWD. The results indicate that there is no significant difference in mean change from baseline on 6MWD observed between sildenafil (20 mg three times a day) and placebo (13.62 m (95% CI: -3.89 to 31.12) and 14.08 m (95% CI: -1.78 to 29.95), respectively).

Differences in 6MWD were observed between patients with primary PAH and PAH associated with CTD. For subjects with primary PAH (67 subjects), mean changes from baseline were 26.39 m (95% CI: 10.70 to 42.08) and 11.84 m (95% CI: -8.83 to 32.52) for the sildenafil and placebo groups, respectively. However, for subjects with PAH associated with CTD (36 subjects) mean changes from baseline were -18.32 m (95% CI: -65.66 to 29.02) and 17.50 m (95% CI: -9.41 to 44.41) for the sildenafil and placebo groups, respectively.

Overall, the adverse events were generally similar between the two treatment groups (sildenafil plus bosentan vs. bosentan alone), and consistent with the known safety profile of sildenafil when used as monotherapy (see sections 4.4 and 4.5).

6. Attachments

1. Appendix 1

Appendix I

Table 1. Overview of Published Literature on Combination Use of Sildenafil and Bosentan in PAH

Study	Design	Study Treatments	Primary Outcome Measure	Number of Subjects	Results
Safety/Efficacy					
Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension (Hoeper et al. Eur Respir J 2004; 24: 1007–1010)	Single center, open label study	Oral bosentan 62.5 mg BID for 4 weeks followed by 125 mg BID either first-line therapy or add-on to a prostanoid (inh/ IV iloprost, or beraprost). Patients not reaching goals (6MWD, CPET) received sildenafil 25 mg TID, increased after 4–12 weeks to 50 mg TID if response insufficient	Treatment efficacy monitored by 6MWD and CPET, and targeted to reach pre-defined goals (6MWD>380 m and peak oxygen uptake >10.4 $mL.min^{-1}.kg^{-1}$)	N=58 total/ 9 of 58 patients with IPAH, initially treated with bosentan or a combination of bosentan and a prostanoid, received sildenafil	Baseline 6MWD (346±66 m) improved on bosentan by 57 m to 403±80 m (p=0.0003). After 11±5 months, 6MWD declined to 277±80 m. After 3 months of sildenafil added to bosentan, 6MWD increased to 392±61 m (p=0.007) and remained stable throughout follow-up (median 9 months)

Table 1. Overview of Published Literature on Combination Use of Sildenafil and Bosentan in PAH

Study	Design	Study Treatments	Primary Outcome Measure	Number of Subjects	Results
Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension (Mathai at al. Eur Respir J 2007; 29: 469–475)	Single-centre, open-label, retrospective review	Bosentan therapy at recommended doses, Sildenafil added in cases of clinical deterioration (sildenafil 25 mg TID, increased to 50 or 100 mg TID as tolerated, or 20 mg TID after Revatio approval) Bosentan failure: worsening symptoms, decline in NYHA FC or decline 6MWD by >30 m	Change from baseline (initiation of bosentan) in NYHA FC and 6MWD after 3 months of combination therapy with bosentan and sildenafil	N= total 82 with IPAH and PAH-SSc/ 25 received combination therapy (IPAH-13, PAH-SSc-12)	5/13 IPAH patients improved by at least one FC after addition of sildenafil to bosentan, vs 2/12 PAH-SSc patients (p=0.22). After 3 months of combination therapy, mean 6MWD increased significantly in IPAH (294$\pm$104 vs. 340$\pm$141 m; p=0.05) but no change in 6MWD in SSc-PAH patients.

Table 1. Overview of Published Literature on Combination Use of Sildenafil and Bosentan in PAH

Study	Design	Study Treatments	Primary Outcome Measure	Number of Subjects	Results
EARLY: Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial (Galie et al., Lancet 2008; 371: 2093–2100)	Multicenter, randomized, placebo-controlled study, 24 weeks WHO FC II patients only	Bosentan initial dose of 62.5 mg BID, up-titrated to 125 mg BID after 4 weeks, or placebo (Protocol amended to allow sildenafil use after regulatory approval)	Co-primary endpoints: change to month 6 in PVR at rest, (% of baseline value), and change from baseline to month 6 in 6MWD	N=185 total/ 29 on background sildenafil (bosentan group, 14 [15%], placebo group, 15 [16%])	PVR: Similar effect in patients +/- sildenafil (with sildenafil: −20·4%, 95% CI −43·9 to 13·0, p=0·0478, 13 patients in bosentan group, 15 in placebo group; without sildenafil: −23·1%, −35·1 to −8·9, p<0·0001, 67 patients in bosentan group, 73 in placebo group). 6MWD: In patients with sildenafil, mean bosentan treatment effect was –17·3 m (95% CI –105·7 to 71·1; p=0·8551; 13 patients in the bosentan group; 15 in the placebo group) and 25·7 m (3·8–47·6; p=0·0795; 73 patients in the bosentan group, 76 in the placebo group) in those without sildenafil. The median treatment effect with sildenafil was 5·0 m (95% CI –43·1 to 53·9) and 15·0 m (–1·6 to 32·2) without.

Table 1. Overview of Published Literature on Combination Use of Sildenafil and Bosentan in PAH

Study	Design	Study Treatments	Primary Outcome Measure	Number of Subjects	Results
Addition of sildenafil in patients with pulmonary arterial hypertension with inadequate response to bosentan monotherapy (Porhownik et al., Can Respir J. 2008; 15(8) 427-430)	Open-label, single-centre	Patients on background bosentan, addition of sildenafil in case inadequate clinical response (either self-reported or not reaching 6MWD treatment goals)	Mean change from baseline (start of combination therapy) in 6MWD	N=10 with IPAH (8) or CTD-PAH (2)	Mean 6MWD before initiating combination therapy was 339.0 m. Six months after the combination therapy was initiated, mean 6MWD was 62.8 m higher ($p < 0.02$) (mean 6MWD 401.8 m, 95% CI 327.0-476.6 m).
Bosentan–sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology (D'Alto et al. Int J Cardiology 2012; 155:378–382)	Single-centre, open-label, single-arm, prospective study	Bosentan 125 mg BID (or 62.5 mg BID if needed for side effects) plus sildenafil 20 mg TID after clinical deterioration on bosentan monotherapy	The changes in clinical, exercise tolerance, haematological variables and haemodynamics from baseline to 6 months of bosentan-sildenafil therapy	N=32, 29/32 (91%) on bosentan 125 mg BID and 3/30 (9%) on bosentan 62.5 mg BID, plus sildenafil 20 mg TID	After 6 months of combination therapy, an improvement in clinical status (WHO FC), 6MWD, SpO2 at the end of 6MWT, Borg dyspnoea index, proBNP and haemodynamics (pulmonary blood flow and PVR) was observed

Table 1. Overview of Published Literature on Combination Use of Sildenafil and Bosentan in PAH

Study	Design	Study Treatments	Primary Outcome Measure	Number of Subjects	Results
Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial (Iversen et al. Eur Heart J. 2010; 31: 1124-1131)	Randomized, placebo-controlled, double-blinded, cross-over design	Patients were treated open label with bosentan (62.5/125 mg BID) for 9 months. After 3 months, sildenafil (25/50 mg TID)/ placebo was added for 3 months, and a cross-over was performed for the last 3 months.	The primary endpoint was change from baseline in 6MWD	N = 21 patients with Eisenmenger syndrome	Bosentan improved the 6MWD (377 vs. 414 m, P<0.01), PVR (28 vs. 22 wood, P=0.01), and pulmonary blood flow (2.6 vs. 3.5 L/min, P=0.01). Adding sildenafil to bosentan did not improve the 6MWD significantly (21 vs. 8 m, P =0.48), but increased saturation at rest (2.9 vs. –1.8%, P<0.01).
First experience with an oral combination therapy using bosentan and sildenafil for pulmonary arterial hypertension (Lunze et al. European Journal of Clinical Investigation 2006; 36 (Suppl. 3), 32–38)	Observational, open-label, prospective single-centre study	Patients stable on bosentan, dosage was 0.75 mg/kg BID for 4 weeks then doubled, corresponding to the standard adult dose of 125 mg BID. Sildenafil dosage 0.5 mg/kg 3-4 times/day.	Clinical status, exercise capacity, and haemodynamics were assessed at baseline and at the end of the observation period after a mean follow-up time of 1·1 years (0·5–2·5 years).	N=11 (median age 12·9 years, range 5·5–54·7 years). Idiopathic PAH (n= 4), secondary to congenital heart disease (n= 5), CTEPH (n= 1), and radiotherapy (n= 1).	Clinical improvement was about one NYHA class (mean 2·8 ± 0·4 – 1·6 ± 0·8, P= 0·001), increase of transcutaneous oxygen saturation (89·9 ± 9·9 – 92·3 ± 7·1%; P= 0·037), maximum oxygen uptake (18·1 ± 6·8 – 22·8 ± 10·4 mL/kg*min; P= 0·043), and 6MWD (351 ± 58 – 451 ± 119 m; P= 0·039). mPAP measured invasively decreased (62 ± 12–46 ± 18 mmHg; P= 0·041).

Table 1. Overview of Published Literature on Combination Use of Sildenafil and Bosentan in PAH

Study	Design	Study Treatments	Primary Outcome Measure	Number of Subjects	Results
Pharmacokinetics/Pharmacodynamics					
COMPASS 1: Acute hemodynamic effects of single-dose sildenafil when added to established bosentan therapy in patients with pulmonary arterial hypertension (Gruenig et al., J Clin Pharmacol 2009 49: 1343-52)	Prospective, open-label, noncomparative, multicenter, phase II study	All patients on background bosentan for ≥12 weeks Acute, single dose of sildenafil (25 mg)	Percent change in PVR from baseline to 60 minutes after sildenafil administration	N=44/44 as single dose sildenafil	A statistically significant decrease from baseline in mean PVR was observed 60 minutes following sildenafil (-15%; 95% CI: -21%, -10%; P < .0001, n=37).

6MWD=6-minute walk distance, 6MWT=6-minute walk test, BID=Twice daily, CI=Confidence interval, CPET=Cardiopulmonary exercise testing, CTD-PAH=Connective tissue disease-associated pulmonary arterial hypertension, CTEPH=Chronic thromboembolic pulmonary hypertension, IPAH=Idiopathic pulmonary arterial hypertension, mPAP=Mean pulmonary arterial pressure, N=Number of subjects, NYHA FC=New York Heart Association functional class, PAH=Pulmonary arterial hypertension, PAH-SSc=Pulmonary arterial hypertension associated with systemic sclerosis, proBNP=Pro-brain natriuretic peptide, PVR=Pulmonary vascular resistance, SpO2=Saturation of peripheral oxygen, TID=Three times daily, and WHO FC=World Health Organization functional class.