22 October 2015
EMA/CHMP/605025/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Volibris

International non-proprietary name: ambrisentan

Procedure No. EMEA/H/C/000839/II/0041

Note

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

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List of abbreviations

6MWD	6-minute walk distance
AE	adverse event
AESI	adverse event of special interest
AUC0-∞	area under the plasma concentration-time curve from zero to infinity
BCT	blinded combination therapy
BDI	Borg dyspnea index
CAMPHOR	Cambridge Pulmonary Hypertension Outcome Review
CEC	Clinical Endpoints Committee
CI	confidence interval
Cmax	maximum plasma concentration
CSR	clinical study report
eCRF	electronic case report form
EoS	End of Study
ERA	endothelin receptor antagonist
ETA	endothelin receptor type A
ETB	endothelin receptor type B
FAV	Final Assessment Visit
FC	functional class
GMR	geometric mean ratio
HR	hazard ratio
HIV	human immunodeficiency virus
HPAH	heritable pulmonary arterial hypertension
IDMC	independent data monitoring committee
IPAH	idiopathic pulmonary arterial hypertension
IP	investigational product
ITT	intent-to-treat
KM	Kaplan-Meier
LVEDP	left ventricle end-diastolic pressure
m	Module
mITT	modified intent-to-treat
MMRM	mixed models for repeated measures
mPAP	mean pulmonary artery pressure
NT-pro-BNP	N-terminal pro-B-type natriuretic peptide
OR	odds ratio
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PDE-5i	phosphodiesterase type-5 inhibitor
PH	pulmonary hypertension
PK	pharmacokinetic(s)
PP	per protocol
PVR	pulmonary vascular resistance
RAP	reporting and analysis plan
SAE	serious adverse event
SF-36	Short Form-36 (health survey)
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxo Group Ltd submitted to the European Medicines Agency on 9 December 2014 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1); as a consequence sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC were proposed to be updated. The Package leaflet is proposed to be updated accordingly. In addition, the MAH took the opportunity to update Annex II regarding a change in the PSUR cycle.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

On 11 April 2005, orphan designation (EU/3/05/273) was granted by the European Commission for ambrisentan for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0267/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-000434-PIP01-08-M03) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Radka Montoniová

Timetable	Actual dates
Submission date	9 December 2014
Start of procedure:	26 December 2014
CHMP Co-Rapporteur Assessment Report	17 February 2015
CHMP Rapporteur Assessment Report	17 March 2015
PRAC Rapporteur Assessment Report	23 February 2015
Committees comments on PRAC Rapp Advice	3 March 2015
PRAC Rapporteur Updated Assessment Report	4 March 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	12 March 2015
CHMP comments	18 March 2015
Rapporteur Revised Assessment Report	20 March 2015
Request for supplementary information (RSI)	26 March 2015
Adoption of CHMP Assessment Report for Volibris on similarity with Adempas, Opsumit and Revatio	26 March 2015
PRAC Rapporteur Assessment Report	22 June 2015
Committees comments on PRAC Rapp Advice	23 June 2015
CHMP Rapporteur Assessment Report	25 June 2015
PRAC Rapporteur Updated Assessment Report	29 June 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	9 July 2015
CHMP comments	17 July 2015
CHMP Rapporteur revised Assessment Report	17 July 2015
Request for supplementary information (RSI)	23 July 2015
PRAC Rapporteur Assessment Report	9 September 2015
CHMP Rapporteur Assessment Report	9 September 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	10 September 2015
CHMP comments	16 September 2015
Rapporteur Revised Assessment Report	n/a
Request for supplementary information (RSI)	24 September 2015
PRAC Rapporteur Assessment Report	7 October 2015
CHMP Rapporteur Assessment Report	7 October 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	8 October 2015
CHMP comments	19 October 2015

Timetable	Actual dates
Rapporteur Revised Assessment Report	16 October 2015
Opinion	22 October 2015

2. Scientific discussion

2.1. Introduction

Ambrisentan (Volibris 5 and 10 mg film-coated tablets) is an endothelin receptor antagonist that is selective for the endothelin type A.

In the European Union, the currently approved indication is as follows: "*Volibris is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease*".

On 11 April 2005, orphan designation (EU/3/05/273) was granted by the European Commission to Uppsala Medical Information System AB, Sweden, for ambrisentan for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. At the time of designation, pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension affected less than 2 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 93,000 people, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

This newly expanded therapeutic indication is based on data from the Phase 3/4 clinical study AMB112565/GS-US-300-0140 in subjects with WHO functional class (FC) II or III PAH. The study is named "AMBITION" and referred to as such hereafter. Efficacy and safety data are provided in support of the proposed prescribing information and patient information.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

Scientific advice from the European Medicines Agency (EMA) was requested by GSK for the development of ambrisentan, specifically relating to the design of the AMBITION study (08 February 2010). CHMP agreed that an event-driven study was an acceptable design for this registration study, and the planned statistical methodology was deemed acceptable. During the study, the sample size was adjusted to account for a lower than expected event rate and maintain study power, and the statistical analysis plan was adjusted to take into account EMA feedback. The CHMP did not endorse the Company's strategy to base a claim on the combination of ambrisentan and tadalafil in comparison to the pooled monotherapy arms. In order to show a benefit of both components, two comparisons, one against each monotherapy arm, were needed (Procedure EMEA/H/SA/646/1/FU/1/2010/PA/II). The definition of the primary endpoint "clinical failure" was not entirely agreed, particularly the additional fourth component of "unsatisfactory long-term clinical response") as proposed by the Company was not supported (Procedure EMEA/H/SA/646/1/FU/1/2010/PA/II).

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

The AMBITION study (n=605 patients) is the single pivotal study that provides clinical data in support of the new proposed indication for ambrisentan (Table 1).

Table 1

Type of Study	Study Number	Study Objectives	Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects	Study Population/Entry Criteria	Study Status; Type of Report
Controlled clinical study pertinent to the claimed indication	AMB112565/ GS-US-300-0140 (AMBITION)	Primary: to compare 2 treatment strategies, first-line combination therapy (with ambrisentan 10 mg once daily and tadalafil 40 mg once daily) versus monotherapy (with ambrisentan 10 mg once daily or tadalafil 40 mg once daily), in subjects with PAH Secondary: to compare the change in other clinical measures of PAH after initiating first-line combination therapy or first-line monotherapy in subjects with PAH	Phase 3/4, randomized, double-blind, event-driven, active-controlled study	Oral combination therapy: 1 x 5-mg ambrisentan tablet + 1 ambrisentan placebo tablet for 8 weeks, then 2 x 5-mg ambrisentan tablets once daily thereafter AND 1 x 20-mg tadalafil tablet + 1 tadalafil placebo tablet once daily for 4 weeks, then 2 x 20-mg tadalafil tablets once daily thereafter Oral ambrisentan monotherapy: 1 x 5-mg ambrisentan tablet + 1 ambrisentan placebo tablet + 2 tadalafil placebo tablets once daily for 8 weeks, then 2 x 5-mg ambrisentan tablets + 2 tadalafil placebo tablets once daily thereafter Oral tadalafil monotherapy: 1 x 20-mg tadalafil tablet + 1 tadalafil placebo tablet + 2 ambrisentan placebo tablets once daily for 4 weeks, then 2 x 20-mg tadalafil tablets + 2 ambrisentan placebo tablets once daily thereafter	Event-driven study (105 adjudicated clinical failure events required); minimum 24 weeks	ITT = 605 (mITT = 500, non-mITT = 105)	Adults with a diagnosis of idiopathic or heritable PAH or PAH associated with connective tissue disease, drugs or toxins, HIV infection, or congenital heart defects repaired > 1 year prior to screening; current diagnosis of WHO FC II or III; mPAP ≥ 25 mmHg, PVR ≥ 300 dyne•sec/cm^5, PCWP or LVEDP ≤ 12 mmHg if PVR ≥ 300 to < 500 dyne•sec/cm^5, or PCWP/LVEDP ≤ 15 mm Hg if PVR ≥ 500 dyne•sec/cm^5	Complete; Final Full CSR

CSR = clinical study report; FC = Functional Class; HIV = human immunodeficiency virus; ITT = Intent-to-Treat; LVEDP = left ventricle end-diastolic pressure; mITT = modified Intent-to-Treat; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; WHO = World Health Organization

2.3.2. Pharmacokinetics

No new clinical pharmacology studies have been conducted to support the proposed new indication for ambrisentan. No new biopharmaceutical studies have been conducted to support the proposed new indication for ambrisentan, and no new formulation information is being submitted. The ambrisentan and tadalafil tablets used in the AMBITION study for which data are being submitted in this application were produced using the previously approved commercial formulations and processes.

2.4. Clinical efficacy

2.4.1. Main study

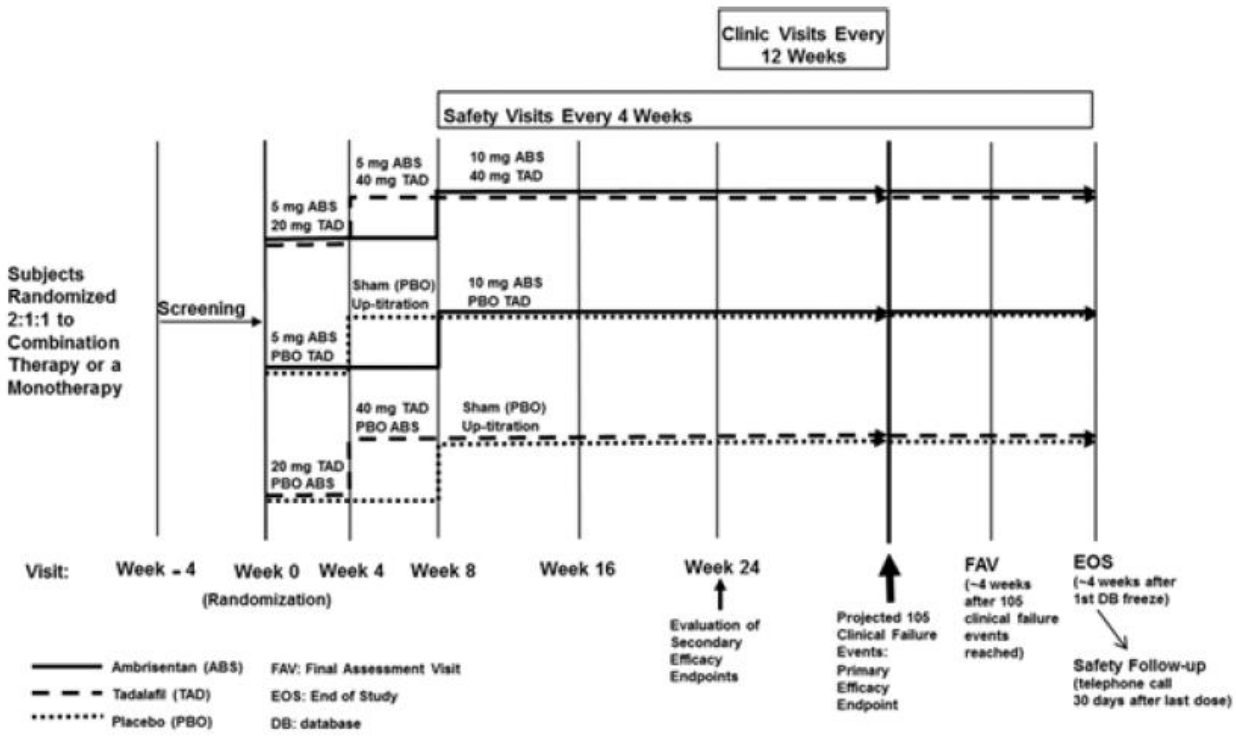
AMBITION study

The AMBITION study (n=605 patients) is the single pivotal study that provides clinical data in support of the new proposed indication for ambrisentan. This study was a Phase 3/4, randomized, double-blind, event-driven study designed to compare the safety and efficacy of initiating pharmacotherapy with a combination of ambrisentan and tadalafil to initiating pharmacotherapy with ambrisentan or tadalafil monotherapy at the same doses.

Subjects were randomized 2:1:1 to receive combination therapy (ambrisentan and tadalafil), ambrisentan monotherapy, or tadalafil monotherapy (Figure 1). Ambrisentan was uptitrated from 5 mg OD (initial dose) to 10 mg OD (target dose) after 8 weeks, and tadalafil was uptitrated from 20 mg OD (initial dose) to 40 mg OD after 4 weeks if the therapy was well tolerated. All eligible subjects were to receive a minimum of 24 weeks of therapy.

Figure 1

Methods



- **Study participants**

Inclusion criteria:
The study enrolled adults (between 18 and 75 years of age, inclusive) with a diagnosis of IPAH/HPAH or PAH associated with connective tissue disease, drugs or toxins, human immunodeficiency virus (HIV) infection, or congenital heart defects repaired > 1 year prior to screening; current diagnosis of WHO FC II or III

symptoms; mPAP ≥ 25 mm Hg, PVR ≥ 300 dyne•sec/cm5, pulmonary capillary wedge pressure (PCWP) or left ventricle end-diastolic pressure (LVEDP) ≤ 12 mm Hg if PVR ≥ 300 to < 500 dyne•sec/cm5, or PCWP/LVEDP ≤ 15 mm Hg if PVR ≥ 500 dyne•sec/cm5. The hemodynamic eligibility criteria specified here were part of the Amendment 2 changes to the protocol, which were implemented to reduce the likelihood of enrolling subjects with PH due to potential covert left ventricular diastolic dysfunction (WHO Group 2 PH).

At the time the AMBITION study was initiated, the clinical classification of PAH was based on the Dana Point guidelines [Simonneau, 2009]. The recently updated PAH classification guidelines [Simonneau, 2013] are generally consistent with the Dana Point guidelines and resulted in no difference in the PAH classification of the study subject population (Group 1 PAH).

Inclusion criteria were implemented to recruit patients in with a diagnosis of Group 1 PAH (IPAH/HPAH or PAH associated with connective tissue disease, drugs or toxins, human immunodeficiency virus (HIV) infection, or congenital heart defects repaired) > 1 year prior to screening; current diagnosis of WHO FC II or III symptoms; and several haemodynamic criteria to reduce the likelihood of enrolling subjects with PH due to potential covert left ventricular diastolic dysfunction (WHO Group 2 PH).

Exclusion criteria were quite more extensive than the contraindications already included in the SmPCs of Volibris and Adcirca, as patients with risk factors for developing adverse reactions to ambrisentan were excluded (e.g.: anemia, fluid retention, retinal problems and baseline values of ALT and/or AST>2xULN).

Sample size

This event-driven study required 105 mITT subjects with an adjudicated clinical failure event in order to have approximately 97% power for the comparison of combination therapy with pooled monotherapy, and approximately 85% power for the comparison of combination therapy with individual therapy (i.e. either ambrisentan or tadalafil alone). A type 1 error rate (alpha level) of 5% (2-sided) was assumed in all power calculations for each of the three comparisons.

Original sample size calculations were based on an overall event rate of 15% (a monotherapy arm event rate of 20% per year and a combination arm event rate of approximately 10% per year). These event rates equate to a hazard ratio of 0.47 (a 53% reduction in risk).
Following a blinded review of the overall event rate after approximately 2 years of recruitment, the number of estimated adjudicated events was approximately 77% of the predicted overall event rate. Consequently, the overall event rate was re-estimated to be 12% per year. The sample size was re-estimated assuming an 8% combination arm event rate and a 16% monotherapy arm event rate per year. The revised event rate estimates maintained the original estimate of a 53% reduction in the hazard ratio of combination therapy over monotherapy.

Based on the recruitment rate at the time of re-estimation, a 148-week recruitment period and 175-week total study duration was estimated necessary to obtain 105 mITT subjects with a first event.
614 subjects would need to be enrolled to obtain 520 mITT subjects (260 subjects in the combination therapy arm and 260 in the monotherapy arm [130 subjects receiving ambrisentan and 130 subjects receiving tadalafil]). To account for the loss of subjects, a drop-out rate of 5% per treatment group per year was assumed for these calculations.

To evaluate the effects of ambrisentan on 6MWD at both maximum (peak) and minimum (trough) ambrisentan plasma concentrations, a test of the null hypothesis of no treatment group difference in change from Baseline to Week 16 in the 6MWD with 260 subjects receiving ambrisentan+tadalafil and 130 subjects receiving placebo+tadalafil yielded approximately 98% power assuming an average placebo-adjusted treatment effect of 30 m based on a 2-sample t-test and a standard deviation of 65 m.

Treatment effect and standard deviation were based on data from Phase 2 and Phase 3 clinical studies of ambrisentan. Although the sample size was calculated using a 2-sided t-test, the specified analysis for this outcome used a Wilcoxon rank sum (WRS) test; therefore, the actual power may have varied slightly.

Randomisation

Subjects were assigned to study treatment in accordance with the randomization schedule, which was generated using the Sponsor's randomization system.

The randomization of eligible subjects was stratified based on the underlying etiology of PAH (idiopathic pulmonary arterial hypertension [IPAH]/heritable pulmonary arterial hypertension [HPAH] and non-IPAH) and WHO FC (II and III). The study was event-driven and, therefore, enrollment and study duration depended on the rate of study events. Enrollment of subjects continued up until 24 weeks prior to the anticipated 105th first clinical failure event in the modified intent-to-treat (mITT).

Objectives

The primary objective of this randomized, double-blind study was to compare 2 treatment strategies: first-line combination therapy (ambrisentan and tadalafil) versus first-line monotherapy (either ambrisentan or tadalafil) in subjects with PAH. This was assessed by comparison of time to the **first clinical failure event**. A Clinical Endpoints Committee (CEC) provided adjudication of all (first and subsequent) clinical failure events reported during the study. The CEC also reviewed all cardiopulmonary serious adverse events (SAEs) to ensure that no clinical failure events were missed. Members of this committee were blinded to treatment assignment and investigator.

The secondary objectives were to compare the change in other clinical measures of PAH after initiating either first-line combination therapy or first-line monotherapy, in subjects with PAH.

Additional objectives were to assess the safety and tolerability of first-line combination therapy compared with first-line monotherapy, and to assess the effect of plasma peak and trough ambrisentan concentrations on exercise capacity in subjects with PAH.

Outcomes/endpoints

Primary endpoint:

Th definition of clinical failure events is mentioned in table 4 below:

Table 4. Definition of Clinical Failure Events

Clinical Failure Events (all events adjudicated):
Death (all-cause[a])
Hospitalization for worsening PAH (adjudicated), which comprised any of the following:
Any hospitalization for worsening PAH
Lung or heart/lung transplant
Atrial septostomy
Initiation of parenteral[b] prostanoid therapy
Disease progression (adjudicated), defined as follows:
> 15% decrease from Baseline in the 6MWD combined with WHO class III or IV symptoms (at 2 consecutive postbaseline clinic visits separated by ≥ 14 days)
Unsatisfactory long-term clinical response (adjudicated), which comprised <u>all 3 of the following:</u>
≥ 1 dose of randomized treatment received and in the study for ≥ 6 months
Decrease from Baseline in 6MWD at 2 consecutive postbaseline clinic visits separated by ≥ 14 days
Assessment of WHO class III symptoms at 2 clinic visits separated by ≥ 6 months

a. Cause of death was adjudicated into the following prespecified categories: 1. sudden cardiac death; 2. death from progressive heart failure; 3. pulmonary embolism; 4. death due to other cardiac causes; 5. death due to vascular causes (stroke); 6. death due to noncardiovascular causes; 7. cannot be determined.
b. Parenteral prostanoids were defined as intravenous or subcutaneous formulations (ie, not inhaled).

After screening and randomization assessments, subjects were assessed for efficacy and safety at Weeks 4, 8, 16, 24, and every 12 weeks thereafter. Between clinic visits, subjects had monthly laboratory safety assessments.

An independent data monitoring committee (IDMC) monitored the safety and welfare of the study subjects and reviewed the accumulated data at regular intervals. They were to recommend continuation or early termination of the study based on the criteria defined in the IDMC charter. At no time did the IDMC recommend early termination of the study. The event rate was monitored during the study using blinded data. After approximately 2 years of recruitment, a blinded review showed that the overall observed event rate (adjudicated events plus events pending adjudication adjusted for concordance) was approximately 77% of the original predicted overall 15% event rate (~12%). Consequently, the sample size was increased (from 456 to 520 subjects in the mITT population) to ensure 105 events; and to maintain power to detect a 53% reduction in the hazard ratio (HR; 97% power for the combination versus pooled monotherapy comparison and 85% power for each of the combination versus individual monotherapy comparisons), with type 1 error rate of 5% for each of the 3 comparisons).

The AMBITION study design took into account that following each subject's Final Assessment Visit (FAV), investigators needed to make decisions regarding future treatment, and future treatment decisions would be informed by knowing to what treatment group subjects had been randomized.
Therefore, investigators were unblinded at each subject's End of Study (EoS) Visit (prior to the final database lock), so they could immediately provide the appropriate treatment for each subject on completion of the study. To accommodate the requirement to maintain the study blind for final efficacy and safety assessments and freeze the database before investigators were unblinded, the study included 2 database freeze points. The initial database freeze occurred after all FAV visits were completed and cleaned data was available. At that time, the database was frozen for each subject's visit-based data through FAV, and investigators were not able to make any changes to the visit-based data through FAV unless a query had been raised by data management necessitating a change. Non-visit-based data such as adverse events

(AEs), SAEs, vital status, and clinical failure event data could be modified/added to by the investigator after the first database freeze.

- **Treatments**

Investigational products were ambrisentan, in the form of 5 mg tablets, or matching placebo; and tadalafil, in the form of 20 mg tablets, or matching placebo.

Ambrisentan or Placebo:
Ambrisentan: white, film-coated, immediate-release tablets containing 5 mg ambrisentan.
Matching placebo tablets.

Tadalafil or Placebo:
Tadalafil: dark yellow tablet, containing 20 mg tadalafil.
Matching placebo tablets
Investigational product dosing:
The target doses of investigational product were 10 mg ambrisentan once daily and 40 mg tadalafil once daily (Table 3).

Table 3. Investigational product dosing

Therapy Arm	Initial Dose	Titrated Dose	Notes
Combination therapy arm	**One tablet of 5 mg ambrisentan** and one tablet of ambrisentan-matching placebo **(5 mg once daily for the first 8 weeks)** **and** One tablet of **20 mg tadalafil** and one tablet of tadalafil-matching placebo **(20 mg once daily for the first 4 weeks)**	**Two tablets of 5 mg ambrisentan**[1] **(10 mg once daily)** **and** **Two tablets of 20 mg tadalafil (40 mg once daily)**	Subjects with mild to moderate renal impairment (creatinine clearance >30 mL/min and <80 mL/min) were assessed for tolerability at the Week 4 visit and a risk:benefit decision made by the investigator whether the subject remain on tadalafil 20 mg once daily or up-titrate to tadalafil 40 mg once daily
Monotherapy arm: ambrisentan group	**One tablet of 5 mg ambrisentan**[1] and one tablet of ambrisentan-matching placebo **(5 mg once daily for the first 8 weeks)** **and** Two tablets of tadalafil-matching placebo	**Two tablets of 5 mg ambrisentan (10 mg once daily)** **and** Two tablets of tadalafil-matching placebo	No renal function criteria were applied.
Monotherapy arm: tadalafil group	**One tablet of 20 mg tadalafil** and one tablet of tadalafil-matching placebo **(20 mg once daily for the first 4 weeks)** **and** Two tablets of ambrisentan-matching placebo	**Two tablets of 20 mg tadalafil (40 mg once daily)** **and** Two tablets of ambrisentan-matching placebo	Subjects with mild to moderate renal impairment (creatinine clearance >30 mL/min and <80 mL/min) were assessed for tolerability at the Week 4 visit and a risk:benefit decision made by the investigator whether the subject remain on tadalafil 20 mg once daily or up-titrate to tadalafil 40 mg once daily

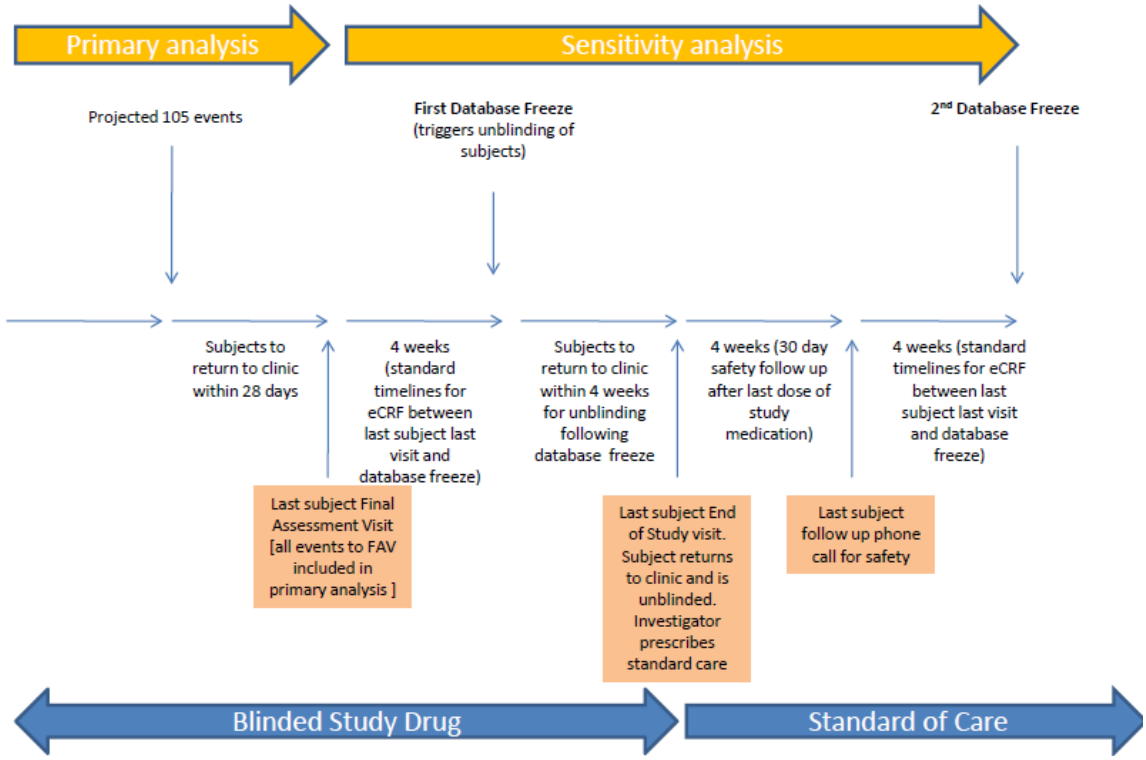
1. Subjects in whom the investigator was concerned about tolerability at 5 mg of ambrisentan had the option to remain on this dose given as one tablet of 5 mg ambrisentan and one tablet of ambrisentan matching placebo.

Treatment following a clinical failure event:
Following the declaration of a clinical failure event by the investigator, investigators could assign the subject to blinded combination therapy (BCT) or add non-parenteral prostanoids (not provided by the sponsor) to their current therapy, if deemed appropriate. Investigators did not have to await outcome from the adjudication committee prior to initiating BCT or adding non-parenteral prostanoids. For the former option, subjects randomized to monotherapy had the other drug of the combination added to their medication regimen. Subjects randomized to combination therapy and uptitrated per protocol at Week 4 and Week 8 effectively continued to receive blinded combination therapy, where no new drug was added to the subject's medication regimen. Note that these interventions were optional and that the investigator did not have to choose either one.

Permitted Medications and Non-Drug Therapies:
Standard medical treatment(s) taken by the subject upon study entry were permitted to be maintained throughout the study. Coadministration of tadalafil with alpha blockers was permitted, with caution exercised due to the possibility of additive effects on blood pressure. It was recommended that subjects participating in the study limit alcohol consumption [per the Adcirca USPI, 2014].

Drugs prohibited while receiving investigational product:
1) Other ERAs (such as Bosentan [Tracleer] and Sitaxentan [Thelin]); 2) Commercial ambrisentan (Volibris or Letairis); 3) Inhaled nitric oxide; 4) Intravenous inotropes (e.g., dopamine, dobutamine); 5) PDE-5i (such as sildenafil [Revatio or Viagra] and vardenafil [Levitra]); 6) Commercial tadalafil (Adcirca or Cialis); 7) Any other investigational therapy; 8) All forms of prostanoids were prohibited unless the investigator determined the subject met the definition of clinical failure; 9) Nitrates; 10) Potent inhibitors of CYP3A4 (e.g., protease inhibitors, systemic ketoconazole, or systemic itraconazole); 11) Potent inducers of CYP3A4 (e.g., rifampicin); 12) Cyclosporine A (except ophthalmic formulation).

Treatment/ blinding during the study
Subjects continued to receive their randomized treatment until their EoS visit. At the EoS visit, randomized treatment assignment was unblinded and subjects were treated at the discretion of the investigator. In some instances investigators may have been unblinded after a subject's FAV and before their EoS visit to enable investigators to make decisions regarding future treatment and necessary preparations regarding those treatments (eg, reimbursement). An additional prespecified analysis for all events through EoS was performed to support the primary analyses. A follow-up telephone call to check safety was performed 30 days after the subject's last dose of IP, after which the data were cleaned, and a second database freeze and final database lock were performed.



Statistical methods

- **Statistical methods**

The primary comparison of interest was between the hazard rates of time to clinical failure in the combination therapy arm (ambrisentan and tadalafil) and the pooled monotherapy arm (ambrisentan and

placebo plus tadalafil and placebo) following the final assessment visit for each subject. The mITT population was utilized for this comparison. The comparison was made at a 5% significance level (2-sided).

Secondary comparisons were of the combination therapy with the individual monotherapy arms. These comparisons were only performed if the comparison of the combination arm vs. pooled monotherapy arms was significant (5% significance level, 2-sided).

All randomized subjects included in this study were included in the analyses according to the analysis populations defined in Table 5.

Table 5. Efficacy Analysis Populations

Analysis Population	Definition	Notes
ITT	All randomized subjects who received ≥ 1 dose of IP	Subjects were analyzed according to their randomized treatment group. This was the primary analysis population for assessing **safety**.
mITT	All randomized subjects who received ≥ 1 dose of IP and met the PAH diagnosis and inclusion/exclusion criteria defined in Protocol Amendment No. 2	Inclusion criteria 3 and 6 were revised in Protocol Amendment No. 2 on the recommendation of the external Scientific Steering Committee to prevent potential covert left ventricle disease confounding the diagnosis of PAH. Subjects were analyzed according to their randomized treatment group. This was the primary analysis population for assessing **efficacy**.
Non-mITT	All randomized subjects who received ≥ 1 dose of IP and who failed to meet the inclusion/exclusion criteria defined in Protocol Amendment No. 2	Subjects were analyzed according to their randomized treatment group.
PP (Per Protocol)[a]	The subset of subjects in the mITT without any major protocol violation	If the PP population was greater than 85% of the mITT population or less than 50% of the mITT population, a PP analysis was not performed.
Peak/Trough	Subjects in the mITT population who were randomized to combination therapy or tadalafil monotherapy at Baseline and who were included in the peak/trough randomization at Week 16	This population only includes subjects who had not had any medical intervention or a down-titration of ambrisentan or tadalafil by Week 16. **This population was only used in the Peak / Trough assessment of the 6MWD.**

a Because only 17 (3%) subjects in the mITT population had inclusion/exclusion criteria deviations leading to exclusion from the per protocol population, the per protocol analyses were not performed.

For time-to-event endpoints, all lost to follow-up subjects were censored at their last known date in the study. For other endpoints, multiple statistical methods of imputation were applied as sensitivity analyses. Among them were Mixed Models Repeated Measures (MMRM) as well as imputations methods for missing data. Among the imputation methods applied were Worst Rank Score Analysis, Worst Case and Last Observation Carried Forward (LOCF).

Primary Analysis: Time to clinical failure was displayed as Kaplan-Meier event-free curves from randomization to individual subject's FAV. Events that occurred after individual subject's FAV were not used in the primary analysis but were included in the EoS analyses.

Supportive Analysis of the Primary Endpoint:

Supportive analyses of time to first clinical worsening (TtCW) event (death, hospitalization for PAH, and disease progression) and time to each of the components of the primary endpoint (death, hospitalisation, disease progression, and unsatisfactory long-term clinical response) up to FAV (first database freeze) were also performed.

Multiple Comparisons and Multiplicity: A step-down procedure was adopted among the outcomes. If the primary outcome for the combination versus pooled monotherapy comparison was statistically significant, inferences on the first secondary outcome were evaluated. If the first secondary outcome for the combination versus pooled monotherapy comparison was found to be significant, inferences on the second secondary outcome were evaluated.
The gate keeping approach was implemented for the primary analysis of all secondary outcomes in the predefined order below:

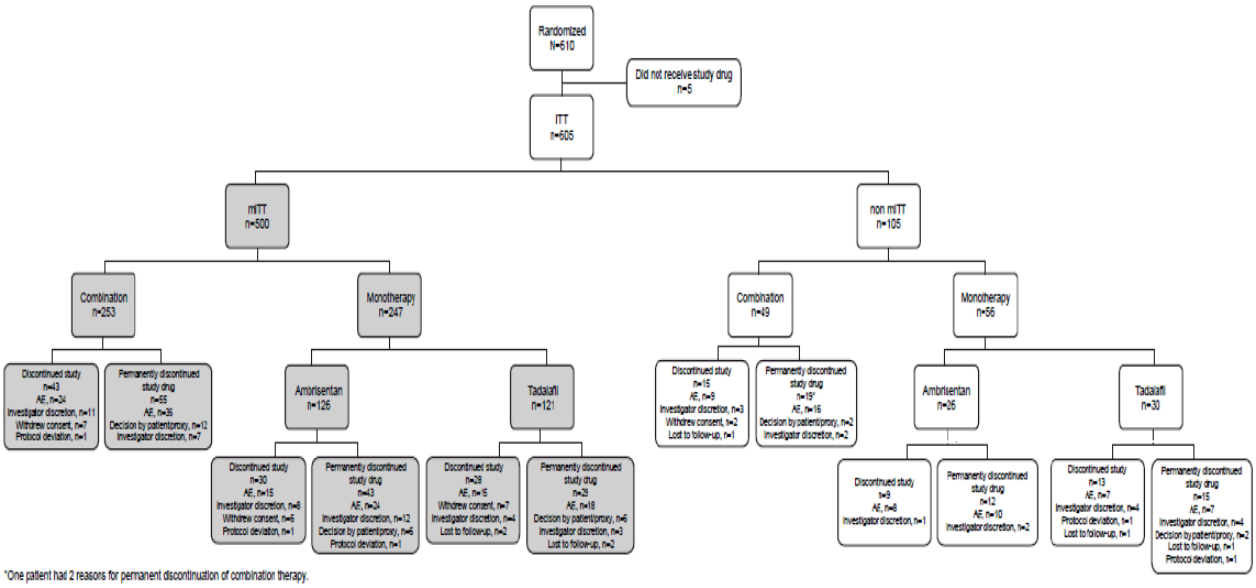
1. Change from Baseline at Week 24 in NT-pro-BNP was summarized and analyzed as the geometric mean and the geometric mean ratio and tested using analysis of covariance with terms for PAH etiology and WHO functional class.
2. The percentage of subjects with satisfactory clinical response at Week 24 was summarized and response (yes, no) analyzed as a binary endpoint using logistic regression, with PAH etiology and WHO functional class as covariates.
3. Change from Baseline in 6MWD test at Week 24 was analyzed using the Wilcoxon rank sum test stratified by PAH etiology and WHO functional class.
4. Change from Baseline in WHO functional class at Week 24 was analyzed between treatments using a Wilcoxon rank sum test, stratified by PAH etiology and WHO functional class at Baseline.
5. Change from Baseline in BDI immediately following exercise at Week 24 was analyzed using the Wilcoxon rank sum test stratified by PAH etiology and WHO functional class.

Additionally, for each outcome where the combination treatment arm was demonstrated as significantly improved compared with pooled monotherapy, comparisons of combination treatment versus each individual monotherapy treatment were performed. The significance level for all comparisons was 5% (two-sided). The gate-keeping approach was used for the primary statistical method for the primary and each secondary endpoint. The gate-keeping approach was not used for sensitivity analyses as assessed by alternative statistical methods.

Results

This study was conducted at 120 centers in 14 countries. A total of 764 subjects were screened and 610 subjects were subsequently randomized to IP. There were 605 randomized subjects across all treatment groups who received at least one dose of IP. Figure 3 displays the subject disposition information.

Participant flow (figure 3)



*One patient had 2 reasons for permanent discontinuation of combination therapy.

Source: m5.3.5.1, AMB112565/GS-US-300-0140, Source Table 1.1, Source Table 1.2, Source Table 3.1, and Source Table 3.2.

mITT population to FAV

From Baseline to Study Day 28, 8% of subjects in the combination therapy group discontinued IP compared with 3% of subjects in the ambrisentan monotherapy group, and 2% of subjects in the tadalafil monotherapy group. The difference in early discontinuation of IP appears to be driven by a higher number of subjects discontinuing IP due to AEs in the combination therapy group (n=19), compared with pooled monotherapy group (n=5). The events types leading to IP discontinuation in the combination therapy group were diverse; however the most common AE leading to IP discontinuation was edema/fluid retention, which led to 7 subjects discontinuing IP in the combination therapy group, compared with 1 subject in the pooled monotherapy group.

The percentage of subjects in the mITT population who withdrew from the study up to FAV was 17% in the combination therapy group, 24% in the ambrisentan monotherapy group, and 23% in the tadalafil monotherapy group. (table7).

The most frequently reported reason for study withdrawal up to FAV in all 3 treatment groups was AE, which was reported in 9% of subjects in the combination therapy group and in 12% of subjects in each of the monotherapy groups. The percentage of subjects who discontinued IP prematurely up to FAV was 22% in the combination therapy group, 34% in the ambrisentan monotherapy group, and 24% in the tadalafil monotherapy group. Adverse event was the most frequently reported reason for premature treatment discontinuation up to FAV in all 3 treatment groups. The percentage of subjects who discontinued IP up to FAV due to an AE was 14% in the combination therapy group, 19% in the ambrisentan monotherapy group, and 15% in the tadalafil monotherapy group.

Table 7. Subject Disposition to FAV; mITT (Randomized Treatment) Population

	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		BCT Initiated N=83		Total N=500	
Subject Status	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Withdrawn from Study	43	(17)	58	(23)	30	(24)	28	(23)	15	(18)	101	(20)
Primary reason for study withdrawal												
Adverse event	24	(9)	30	(12)	15	(12)	15	(12)	13	(16)	54	(11)
Protocol deviation	1	(<1)	1	(<1)	1	(<1)	0	-	0	-	2	(<1)
Lost to follow-up	0	-	2	(<1)	0	-	2	(2)	0	-	2	(<1)
Investigator discretion	11	(4)	12	(5)	8	(6)	4	(3)	2	(2)	23	(5)
Withdrew consent	7	(3)	13	(5)	6	(5)	7	(6)	0	-	20	(4)
IP stopped permanently/prematurely												
Yes	55	(22)	72	(29)	43	(34)	29	(24)	20	(24)	127	(25)
Primary reason for IP discontinuation												
Adverse event	36	(14)	42	(17)	24	(19)	18	(15)	19	(23)	78	(16)
Protocol deviation	0	-	1	(<1)	1	(<1)	0	-	0	-	1	(<1)
Lost to follow-up	0	-	2	(<1)	0	-	2	(2)	0	-	2	(<1)
Investigator discretion	7	(3)	15	(6)	12	(10)	3	(2)	0	-	22	(4)
Decision by subject or proxy	12	(5)	12	(5)	6	(5)	6	(5)	1	(1)	24	(5)

Source: Table 1.1 and Table 1.2

- **Recruitment**

Following a blinded review of the overall event rate after approximately 2 years of recruitment, the number of estimated adjudicated events was approximately 77% of the predicted overall event rate. Consequently, the overall event rate was re-estimated to be 12% per year. The sample size was re-estimated assuming an 8% combination arm event rate and a 16% monotherapy arm event rate per year. The revised event rate estimates maintained the original estimate of a 53% reduction in the hazard ratio of combination therapy over monotherapy. Based on the recruitment rate at the time of re-estimation, a 148-week recruitment period (based on a recruitment rate of 4.9 subjects per week prior to implementation of Protocol Amendment No.2 and 3.4 subjects per week thereafter), and 175-week total study duration, it was estimated that to obtain 105 mITT subjects with a first event, 614 subjects would need to be enrolled to obtain 520 mITT subjects (260 subjects in the combination therapy arm and 260 in the monotherapy arm [130 subjects receiving ambrisentan and 130 subjects receiving tadalafil]).

Conduct of the study

Methods used for blinding/masking are acceptable.

Given the possibility of unblinding due to the different safety profiles of ambrisentan and tadalafil, the applicant was requested to provide main efficacy outcome separately for patients with and without adverse events related to study medication by the investigator including separate analysis for patients who tolerated the full investigational doses versus those who did not tolerate uptitration to the full investigational doses.

Post-hoc analyses restricted to the patients who experienced one or more drug-related adverse events were generally consistent with the primary analyses. In summary, bias due to potential unblinding due to the different safety profiles of ambrisentan and tadalafil can reasonably ruled out with the ancillary analyses provided by the applicant.

The most relevant amendment occurred upon scientific advice and consultation. The original inclusion and exclusion criteria inadvertently permitted enrolment of subjects with potential left heart failure into the study. Amendment 2 revised the inclusion exclusion to exclude such subjects. This group is referred to as the non-mITT population. The results in this subpopulation were similar to those in the mITT population (see efficacy discussion).

Statistical methods used were generally appropriate. However, some issues are further discussed later in the efficacy discussion part in relation to "data censoring" and lack of a "per protocol analysis" .

Baseline data

Demographic characteristics

mITT population (n=500): demographic and baseline characteristics were generally similar across the randomized treatment groups (Table 8). The mean age in each of the 3 treatment groups was approximately 54 years, 32% of the population was >65 yrs old and only 2% was ≥75 yrs. Most subjects in the mITT population were female (78%). Approximately 90% of all subjects were white. Most subjects had a diagnosis of IPAH/HPAH with a WHO FC score of III. Subjects were generally equally divided between North America and the rest of the world (94% of subjects (257) in rest of the world were from Europe). Most subjects (65%-71% across treatment groups) were not on concomitant calcium channel blockers. Three subjects, 2 in the combination therapy group and 1 in the ambrisentan monotherapy group, had severe renal impairment. The median baseline 6MWD (range: 357.00 to 368.50 meters), BDI score (range: 3.5 to 4.0) and pro-BNP (range: 869.0 to 1171.0 ng/L) were similar across treatment groups.

Table 8. Demographic and Baseline Characteristics (by Randomized Treatment [mITT Population])

	Combination Therapy (N=253)		Monotherapy Pooled (N=247)		Ambrisentan Monotherapy (N=126)		Tadalafil Monotherapy (N=121)		Total (N=500)	
Age (yrs): Mean (SD)	54.5 (14.29)		54.2 (14.89)		53.9 (14.70)		54.5 (15.15)		54.4 (14.58)	
Age Categories	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
<65	172	(68)	167	(68)	89	(71)	78	(64)	339	(68)
65 to <75	75	(30)	78	(32)	35	(28)	43	(36)	153	(31)
≥75	6	(2)	2	(<1)	2	(2)	0	-	8	(2)
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Sex: Female	188	(74)	200	(81)	100	(79)	100	(83)	388	(78)
Post-menopausal	92	(49)	104	(52)	52	(52)	52	(52)	196	(51)
Sterile (of childbearing age)	40	(21)	36	(18)	18	(18)	18	(18)	76	(20)
Potentially able to bear children	56	(30)	60	(30)	30	(30)	30	(30)	116	(30)
Ethnicity: Not Hispanic/Latino	223	(88)	226	(91)	113	(90)	113	(93)	449	(90)
Region: North America	116	(46)	112	(45)	51	(40)	61	(50)	228	(46)
Region: Rest of the World	137	(54)	135	(55)	75	(60)	60	(50)	272	(54)
Concomitant calcium channel blockers: Yes	77	(30)	79	(32)	37	(29)	42	(35)	156	(31)
Creatinine Clearance (renal impairment), n	251		247		126		121		498	
≤30 mL/min/1.73 m^2 (severe)	2	(<1)	1	(<1)	1	(<1)	0	-	3	(<1)
>30 to <80 mL/min/1.73 m^2 (mild to moderate)	105	(42)	118	(48)	64	(51)	54	(45)	223	(45)
≥80 mL/min/1.73 m^2 (normal)	144	(57)	128	(52)	61	(48)	67	(55)	272	(55)

	Combination Therapy (N=253)		Monotherapy Pooled (N=247)		Ambrisentan Monotherapy (N=126)		Tadalafil Monotherapy (N=121)		Total (N=500)	
WHO FC Score II	76	(30)	79	(32)	38	(30)	41	(34)	155	(31)
WHO FC Score III	177	(70)	168	(68)	88	(70)	80	(66)	345	(69)
Etiology of PAH										
Idiopathic PAH	127	(50)	138	(56)	72	(57)	66	(55)	265	(53)
Heritable PAH	7	(3)	7	(3)	3	(2)	4	(3)	14	(3)
Associated PAH	119	(47)	102	(41)	51	(40)	51	(42)	221	(44)
Associated with, n:	119		102		51		51		221	
Connective tissue disease	103	(87)	84	(82)	44	(86)	40	(78)	187	(85)
Limited scleroderma	52	(44)	30	(29)	17	(33)	13	(25)	82	(37)
Baseline 6 Minute Walk Distance (meters): Mean (SD)	353.50 (87.888)		351.72 (91.827)		354.19 (92.317)		349.15 (91.626)		352.62 (89.770)	
Baseline BDI Scores; Mean (SD)	4.44 (2.343)		4.31 (2.298)		4.50 (2.412)		4.11 (2.164)		4.38 (2.319)	
Baseline N-Terminal Pro-B-Type Natriuretic Peptide (ng/L)[a]: Mean (SD)	1606.1 (1752.70)		1504.9 (2287.30)		1570.2 (1585.19)		1437.9 (2838.87)		1555.6 (2035.48)	
Time (days) from diagnosis to 1st IP administration, n										
Q1 (1st quartile)	8.0		10.0		9.0		12.0		10.0	
Median	20.0		25.0		20.5		29.0		22.0	
Q3 (3rd quartile)	48.0		62.0		47.0		65.0		52.0	

Notes: Percentages are based on number of subjects with Baseline data for each parameter. Etiology of PAH and WHO FC Scores are from electronic case report form (eCRF) data. Ethnicity and race are not available for some subjects. In France ethnicity and race are not required to be collected. Baseline is the last value prior to dosing.

a. Baseline values for Subject Numbers 079329-706, 08132-751, 083132-802, 083132-803 were not included as they were not made available until the second database freeze.

Subjects from Europe represented just over 50% of the total mITT population (257 subjects out of 500). The demographic and baseline characteristics of European subjects were similar to the characteristics of the total population.

The mean age of European subjects was approximately 56 years. Most subjects in each treatment group were female (range of 68 – 79% across groups) and white (90%). Most subjects had a diagnosis of IPAH (58%) with a WHO FC score of III (74%). Most subjects (70%) were not on concomitant calcium channel blockers. The median baseline 6MWD (range: 368 to 381 meters), BDI score (4 in all groups) and pro-BNP (range: 747 to 1055 ng/L) were similar across treatment groups.

Non-mITT population (n= 105):

subjects in the non-mITT population were slightly older (mean 62 yrs), somewhat more likely to be male (30%), and had worse exercise capacity (based on the mean baseline 6-minute walk distance: median 331 m), and had substantially more comorbidities than subjects in the mITT population.

The mean age was 54 yrs (range: 18-75) with predominance of female gender (78%), as expected. Most subjects had a diagnosis of IPAH/HPAH (95%) and only 3% (14 patients) had heritable PAH.

There was a high proportion of patients initially diagnosed as the WHO functional class III (compared to WHO functional II) enrolled into the AMBITION study. Most patients had a WHO FC score of III (69%). Therefore, PAH was advanced in many patients at the time of initial diagnosis. In Europe (257 subjects out of 500 in the mITT population), this proportion was even higher, with 74% of European patients being on WHO FC III at enrolment in AMBITION. This is entirely consistent with the 75% of patients that are in WHO FC III at enrollment in European registries (Hoeper et al. The COMPERA registry. Int J Cardiol. 2013;168: 871-80).

Numbers analysed

ITT population (population for the safety analysis): Subjects who received at least one dose of IP comprise the ITT population; 5 subjects did not receive at least one dose of IP (Table 9).

mITT population (population for the main efficacy analysis): Over 80% of the ITT population met the PAH diagnosis and classification eligibility criteria defined in Protocol Amendment No. 2. These subjects comprise the mITT population which is the population of primary interest for all safety and efficacy analyses in this report. The difference between the ITT and mITT populations (subjects who received at least one dose of IP but did not meet the PAH diagnosis and classification eligibility criteria defined in Protocol Amendment No. 2) comprise the non-mITT population.

Table 9. Study Populations (All Randomized Subjects)

Population (N-bolded)	Randomized Treatment									
	Combination Therapy (N=306)		Monotherapy Pooled (N=304)		Ambrisentan Monotherapy (N=152)		Tadalafil Monotherapy (N=152)		Total (N=610)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Randomized subjects who did not receive one dose of IP	4/306	(1)	1/304	(<1)	0	-	1/152	(<1)	5/610	(<1)
ITT population	**302**/306	(99)	**303**/304	(100)	**152**/152	(100)	**151**/152	(99)	**605**/610	(99)
mITT population*	**253**/302	(84)	**247**/303	(82)	**126**/152	(83)	**121**/151	(80)	**500**/605	(83)
Non-mITT population	**49**/302	(16)	**56**/303	(18)	**26**/152	(17)	**30**/151	(20)	**105**/605	(17)

*Because only 17 (3%) subjects in the mITT population had inclusion/exclusion criteria deviations leading to exclusion from the per protocol population, the per protocol analyses were not performed.

Important protocol deviations during the study are summarized in Table 10.

Table 10. Important Protocol Deviations; mITT (Randomized Treatment) Population

	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		BCT Initiated N=88		Total N=500	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any important protocol deviations	**45**	**(18)**	**36**	**(15)**	**12**	**(10)**	**24**	**(20)**	**18**	**(20)**	**81**	**(16)**
Eligibility criteria not met	24	(9)	12	(5)	4	(3)	8	(7)	5	(6)	36	(7)
Received wrong treatment or incorrect dose	14	(6)	21	(9)	6	(5)	15	(12)	11	(13)	35	(7)
Prohibited medication or device	6	(2)	3	(1)	1	(<1)	2	(2)	2	(2)	9	(2)
Not withdrawn after developing withdrawal criteria/Not discontinued from study treatment	3	(1)	2	(<1)	1	(<1)	1	(<1)	0	-	5	(1)
Other protocol deviation category	1	(<1)	3	(1)	1	(<1)	2	(2)	2	(2)	4	(<1)

Source: Table 1000.7

The CHMP considered that the populations definitions are not entirely endorsed. The defined ITT population should correspond with the randomised population, but really corresponds to the safety population (randomised patients who received at least one dose of study drug). Anyway the difference between the randomised and ITT population is only 5 patients who did not receive at least one dose of study drug and therefore the definition has no impact on the analyses.

The mITT population comprises 83% of the ITT population, and excludes patients who did not meet the eligibility criteria. This is endorsed.

The applicant states that a per-protocol analysis was not performed because only 17 (3%) subjects in the mITT population had inclusion/exclusion criteria deviations leading to exclusion from the PP population. This

is not endorsed as "eligibility criteria not met" is only one of the types of "important protocol deviations" defined in the AMBITION study report. Important protocol deviations were detected in 16% of the AMBITION study population. Although it is recognized that ITT analysis is the main analysis for the demonstration of superiority, the applicant was requested to provide with a PP analysis excluding the 81 patients with important protocol deviations.

Time to First Adjudicated Clinical Failure Event (Baseline to Final Assessment Visit) (by Randomized Treatment [mITT Population]) patients without important protocol deviations

	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121	
Subjects with Event	n	(%)	n	(%)	n	(%)	n	(%)
Number of Subjects without important protocol deviations	208		211		114		97	
First Clinical Failure Event	35	17	62	29	39	34	23	24
Death (all-cause)	7	3	7	3	2	2	5	5
Hospitalization for worsening PAH	9	4	24	11	16	14	8	8
Disease progression	5	2	11	5	10	9	1	1
Unsatisfactory long-term clinical response	14	7	20	9	11	10	9	9
Analysis of time to first clinical failure event	35	17	62	29	39	34	23	24
Number of subjects censored	173	83	149	71	75	66	74	76
Hazard Ratio (Cox Model)			0.479		0.423		0.570	
95% CI			0.315 – 0.729		0.266 – 0.672		0.334 – 0.971	
Stratified log-rank test p-value			0.0004		0.0002		0.0360	
Source Tables 44.0101 and 44.0301								

The CHMP considered that the TTCF for combination vs pooled monotherapy analysis for the mITT population excluding the 81 patients with important deviations was consistent with the overall mITT population analyses, with statistically significant reductions with the CT in comparison with pooled monotherapies and each of the monotherapies separately.

Outcomes and estimation

The combination demonstrated a statistically significantly reduction in TTCF in comparison to pooled monotherapy (HR 0.55, 95% CI (0.36, 0.85) p=0.0055).

The comparison to ambrisentan monotherapy was also statistically significant (HR 0.49, 95% CI (0.30, 0.79) p=0.0029) but the comparison to tadalafil monotherapy was not statistically significant (HR 0.65, 95% CI ((0.37, 1.14) p=0.1296). Similarly, an analysis of TTCF for patients without an adverse event assessed as related to IP by the investigator was performed. The combination demonstrated a statistically significantly reduction in TTCF in comparison to pooled monotherapy (HR 0.40, 95% CI (0.18, 0.85) p=0.0147)). The comparison to ambrisentan monotherapy (HR 0.42, 95% CI (0.17, 1.02) p=0.0485) and the comparison to tadalafil monotherapy (HR 0.36, 95% CI(0.16, 0.85) p=0.0152) were statistically significant.

An analysis of patients who experienced an adverse event of fluid retention (irrespective of relationship to IP) was also performed. The combination demonstrated a statistically significantly reduction in TTCF in comparison to pooled monotherapy [HR 0.34, 95% CI (0.21, 0.54) p<0.0001]. The comparisons to ambrisentan monotherapy (HR 0.37, 95% CI (0.22, 0.62) p<0.0001) and to tadalafil monotherapy were statistically significant (HR 0.29, 95% CI (0.17, 0.52) p<0.0001). An analysis of the patients who did not experience and adverse event of fluid retention did not provide sufficient power to detect a statistically

significant treatment effect due to low event rate. However, the direction of benefit favoured combination therapy.

Primary endpoint

***Time to First Clinical Failure Event (Adjudicated)* mITT Population**

The primary endpoint for the study was time to first adjudicated clinical failure event from Baseline to FAV. This was a composite endpoint consisting of: death, hospitalization for worsening PAH, disease progression and unsatisfactory long term clinical response. In the mITT population, the difference between the first-line combination therapy group (ambrisentan plus tadalafil) and the pooled monotherapy group (ambrisentan or tadalafil) was statistically significant (log-rank p-value = 0.0002) (Table 11). The reduction in risk of a first adjudicated clinical failure event was 50% for subjects in the combination therapy group (hazard ratio [HR] from Cox proportional hazards model = 0.502 [95% CI: 0.348, 0.724]). The differences between the combination therapy group and each of the individual monotherapy were also statistically significant (log-rank p-value = 0.0004; HR = 0.477 [95% CI: 0.314, 0.723] for the ambrisentan monotherapy group and log-rank p-value = 0.0045; HR = 0.528 [95% CI: 0.338, 0.827] for the tadalafil monotherapy group). The 1-, 2-, and 3-year KM probabilities of having a first adjudicated clinical failure event were lower with combination therapy compared with pooled monotherapy and with each monotherapy.

Table 11. Time to First Adjudicated Clinical Failure Event (Baseline to Final Assessment Visit) (by Randomized Treatment [mITT Population])

	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		Total N=500	
Subjects with Event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
First Clinical Failure Event	46	(18)	77	(31)	43	(34)	34	(28)	123	(25)
Death (all-cause)	9	(4)	8	(3)	2	(2)	6	(5)	17	(3)
Hospitalization for worsening PAH	10	(4)	30	(12)	18	(14)	12	(10)	40	(8)
Any hospitalization for worsening PAH	6	(2)	21	(9)	12	(10)	9	(7)	27	(5)
Initiation of parenteral prostanoid therapy	4	(2)	9	(4)	6	(5)	3	(2)	13	(3)
Lung or heart/lung transplant	0		0		0		0		0	
Atrial septostomy	0		0		0		0		0	
Disease progression	10	(4)	16	(6)	12	(10)	4	(3)	26	(5)
Unsatisfactory long-term clinical response	17	(7)	23	(9)	11	(9)	12	(10)	40	(8)
Analysis of time to first clinical failure event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**		
Number of subjects censored	207	(82)	170	(69)	83	(66)	87	(72)		
K-M probability of event by 1 yr (%)	11.09		24.47		24.04		24.87			
95% CI	(7.62, 16.01)		(19.28, 30.76)		(17.12, 33.13)		(17.71, 34.27)			
K-M probability of event by 2 yrs (%)	20.28		36.77		38.84		34.34			
95% CI	(15.07, 27.00)		(30.07, 44.42)		(29.66, 49.69)		(25.22, 45.60)			
K-M probability of event by 3 yrs (%)	32.41		43.89		47.85		39.39			
95% CI	(23.23, 44.03)		(35.57, 53.21)		(36.77, 60.34)		(27.53, 54.09)			

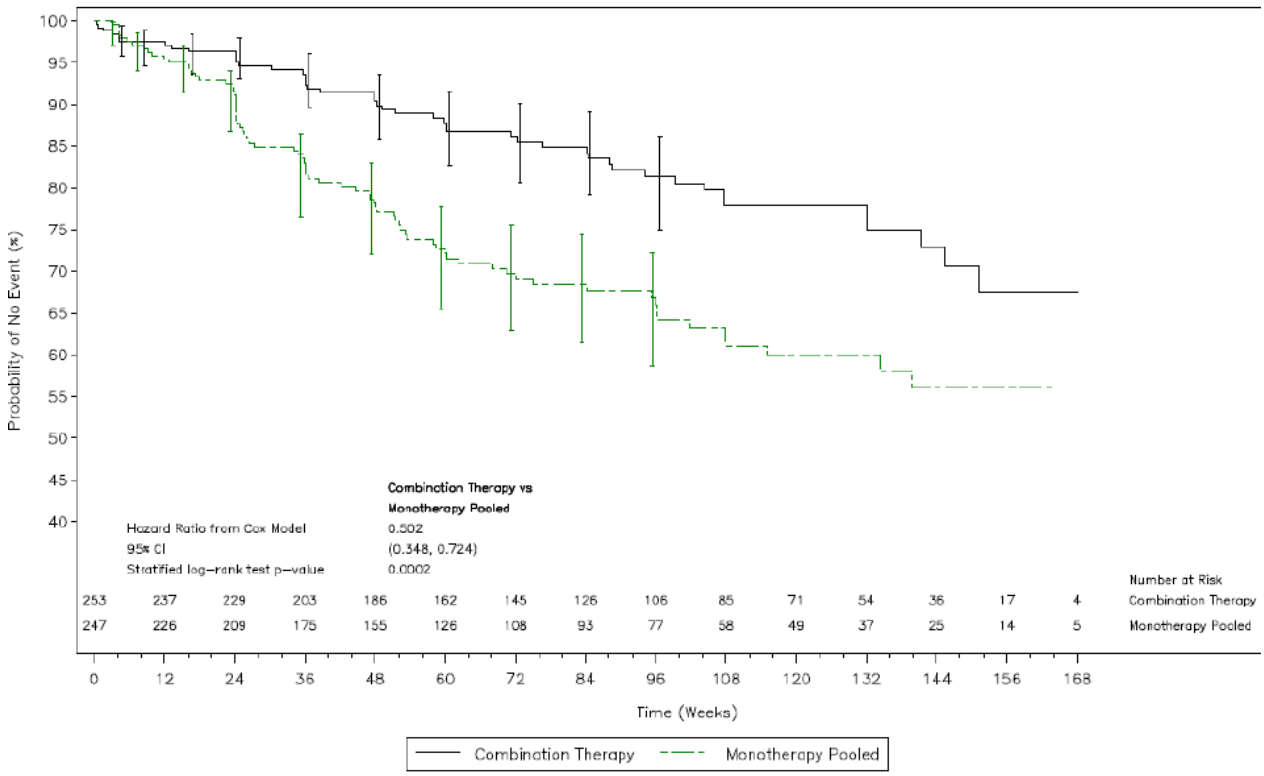
Subjects with Event	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		Total N=500	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hazard Ratio (Cox Model)			0.502		0.477		0.528			
95% CI			(0.348, 0.724)		(0.314, 0.723)		(0.338, 0.827)			
Stratified log-rank test p-value			**0.0002**		**0.0004**		**0.0045**			
Proportional Hazards assumption p-value			0.9489		0.7595		0.8951			

K-M = Kaplan-Meier

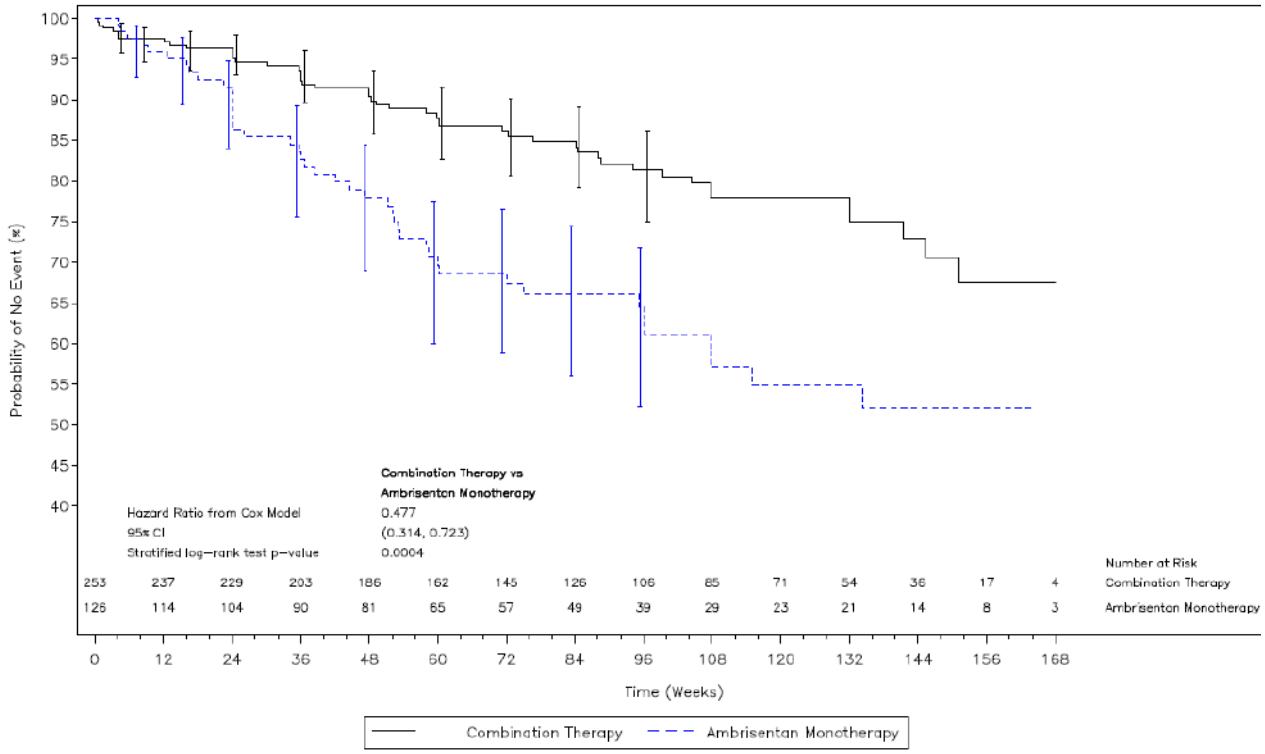
Table is based on a subject's first event. Hazard ratio from the Cox Proportional Hazards model and stratified log-rank p-value adjusted for Etiology of PAH (IPAH/HPAH vs Non-IPAH) and WHO Functional Class (II vs III). For censored subjects, time (days) is calculated as the number of days from randomization to final assessment visit. Comparisons are for combination therapy relative to monotherapy pooled, ambrisentan monotherapy or tadalafil monotherapy. The values in the Total column are calculated across all subjects from the combination therapy, ambrisentan monotherapy, and tadalafil monotherapy columns.

For all treatment group comparisons, Kaplan-Meier curves are shown in Figure 6. The probability of not having a first adjudicated clinical failure event from Baseline to FAV was statistically significantly greater for subjects in the combination therapy group compared with the pooled or individual monotherapy groups. Evidence of sustained efficacy was reflected in maintained divergence of the KM curves through FAV.

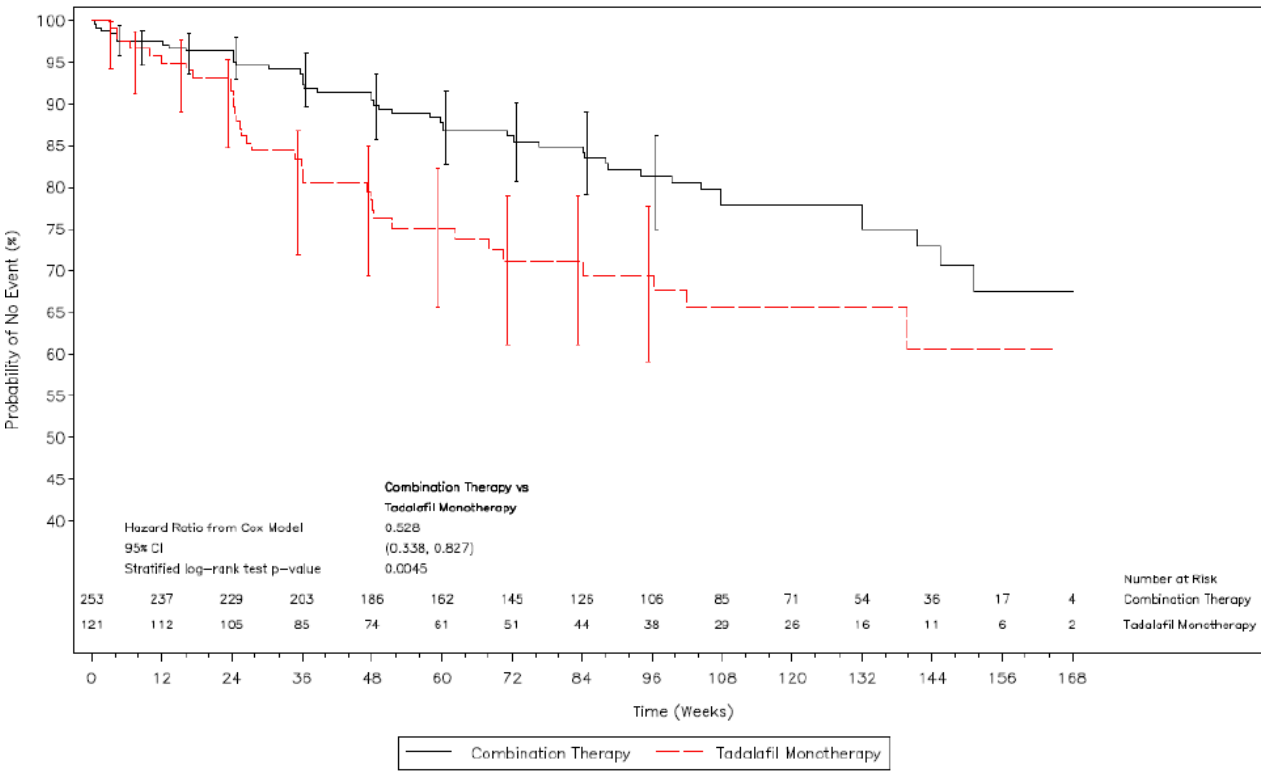
Figure 6 Kaplan-Meier Cumulative Curve for Time to First Adjudicated Clinical Failure (Baseline to FAV); mITT (Randomized Treatment) Population
a) Combination Therapy vs Monotherapy Pooled



b) Combination Therapy vs ambrisentan monotherapy



c) Combination Therapy vs tadalafil monotherapy



Primary endpoint in the ITT population:

The results in the ITT population were similar to those in the mITT population. The HR from the Cox model indicated that subjects in the ITT population treated with combination therapy had a lower risk of having a first adjudicated clinical failure event at any time from Baseline to FAV compared with those in the pooled monotherapy group. This risk reduction was 47% and was statistically significant (HR = 0.532, 95% CI: 0.385, 0.733, log-rank p-value < 0.0001). The comparisons of the combination therapy group with the

ambrisentan monotherapy group (HR = 0.507, 95% CI: 0.350, 0.734, log-rank p-value = 0.0002) and the tadalafil monotherapy group (HR = 0.551, 95% CI: 0.374, 0.813, log-rank p-value = 0.0023) were statistically significant. The risk reductions for the comparisons with the ambrisentan monotherapy group (49%) and tadalafil monotherapy group (45%) were similar to the reduction in risk observed for the comparison with the pooled monotherapy group. The 1-, 2-, and 3-year KM probabilities of a first adjudicated clinical failure event were lower with combination therapy compared with pooled monotherapy and with each individual monotherapy.

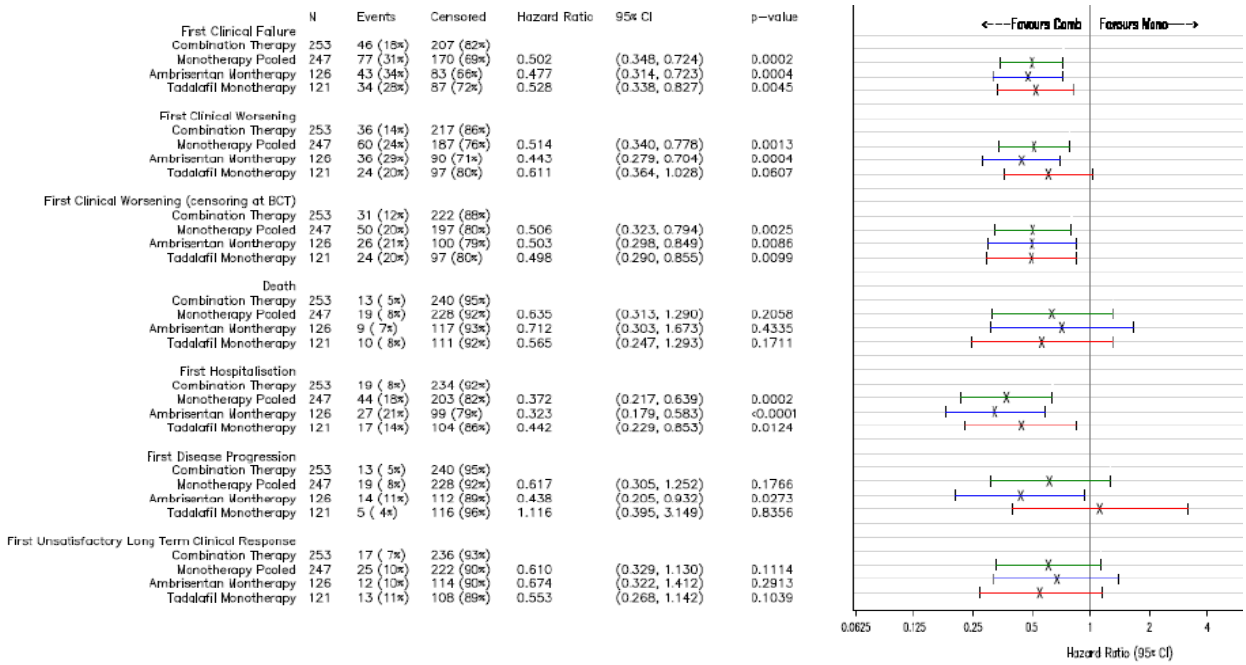
Non-mITT Population: In the non-mITT population, the direction of treatment effect was consistent (ie, in the same direction) with what was observed in the mITT and ITT populations. Numerically fewer subjects (29%) in the combination therapy group had a first adjudicated clinical failure event compared with subjects in the pooled monotherapy group (38%) and ambrisentan (38%) and tadalafil (37%) monotherapy groups (m5.3.5.1, AMB112565/GS-US-300-0140, Source Table 6.1).

Components of the primary endpoint:
Supportive analyses of time to each clinical failure component as well as time to first adjudicated clinical worsening event (death, hospitalization for worsening PAH, disease progression and first unsatisfactory long-term clinical response) were performed. Supportive analyses were also performed for **time to first adjudicated clinical worsening event** (composite of death, hospitalization for worsening PAH and disease progression) with and without censoring at the initiation of blinded combination therapy.

A Forest plot displaying the hazard ratios for the treatment group comparisons from the analysis of time to the first adjudicated clinical failure event from Baseline to FAV shows that the hazard ratio is <1 for all treatment group comparisons, and therefore favors combination therapy (Figure 7).The figure also displays results for additional adjudicated events. Note that each event included is the first event of that type; subjects may have more than one type of event. For the components of clinical failure, the hazard ratio was <1 for all treatment group comparisons with the exception of the combination vs. tadalafil monotherapy comparison for first adjudicated disease progression (HR=1.116).

Time to First Clinical Worsening Event (Adjudicated): In the mITT population, the HR from the Cox model indicated that subjects treated with combination therapy had a lower risk of having a first adjudicated clinical worsening event at any time from Baseline to FAV compared with those in the pooled monotherapy group. This risk reduction was 49% and was statistically significant (HR = 0.514, 95% CI: 0.340, 0.778, log-rank p-value = 0.0013). The comparison of the combination therapy group versus the ambrisentan monotherapy group was statistically significant (HR = 0.443, 95% CI: 0.279, 0.704, log-rank p-value = 0.0004). The comparison of the combination therapy group versus the tadalafil monotherapy group was not statistically significant (HR = 0.611, 95% CI: 0.364, 1.028, log-rank p-value = 0.0607).

Figure 7. Forest plot of fist adjudicated endpoints (Baseline to FAV); mITT (Randomized Treatment) Population

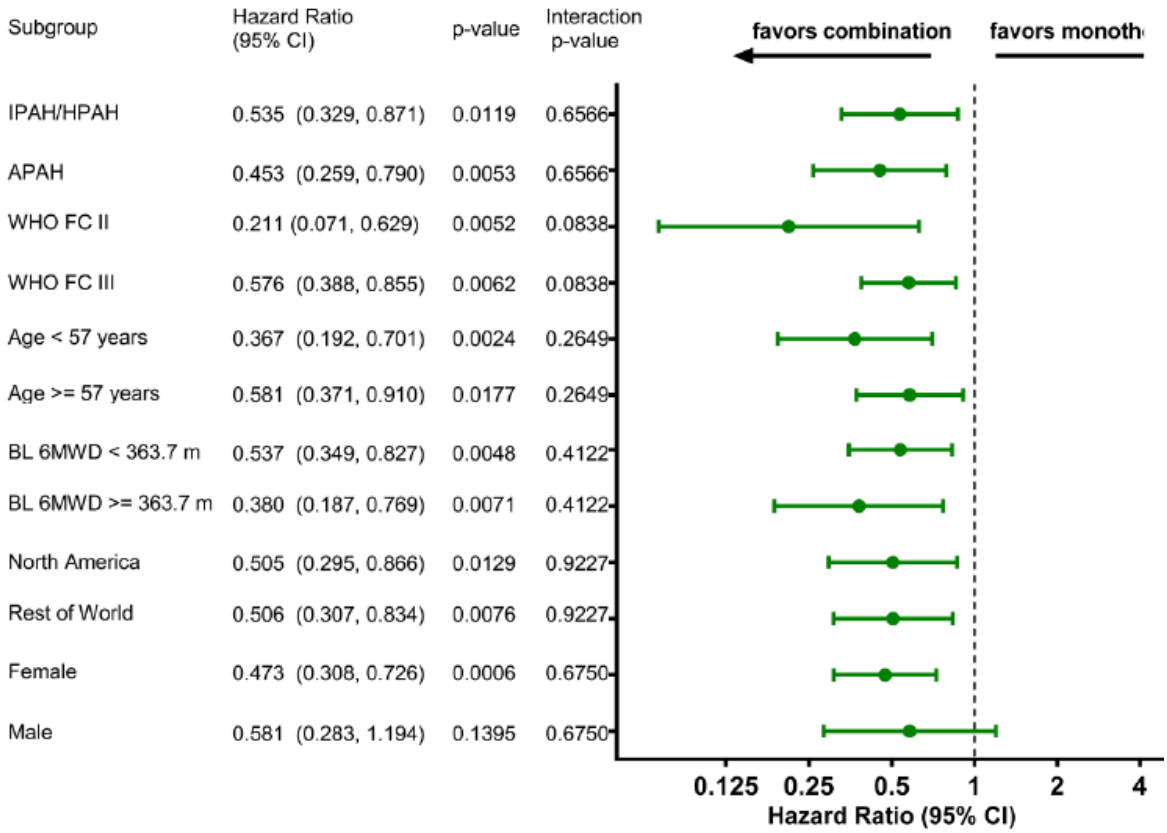


Note: Adjusted hazard ratio > 1 indicates a higher risk for Combination therapy compared with monotherapy group.
Hazard ratio from the Cox Proportional Hazards model and stratified log-rank p-value adjusted for Aetiology of PAH (IPAH/HPAH vs Non-IPAH) and WHO functional class (II vs III).

Subgroup analyses

Subgroup analyses for the primary efficacy endpoint of time to first adjudicated clinical failure event from Baseline to FAV were performed for subgroups of interest based on the following: etiology of PAH (IPAH/HPAH and non-IPAH), Baseline WHO FC (II, III), region (North America, rest of world (predominantly European subjects), Baseline age group (< 65, ≥ 65 years), Baseline age group above or below study median age, sex, and Baseline 6MWD above or below study median 6MWD. Note that "study median" refers to the median within each population. A Forest Plot displaying the comparisons of the combination therapy group versus the pooled monotherapy group for these subgroups of interest is presented in Figure below.

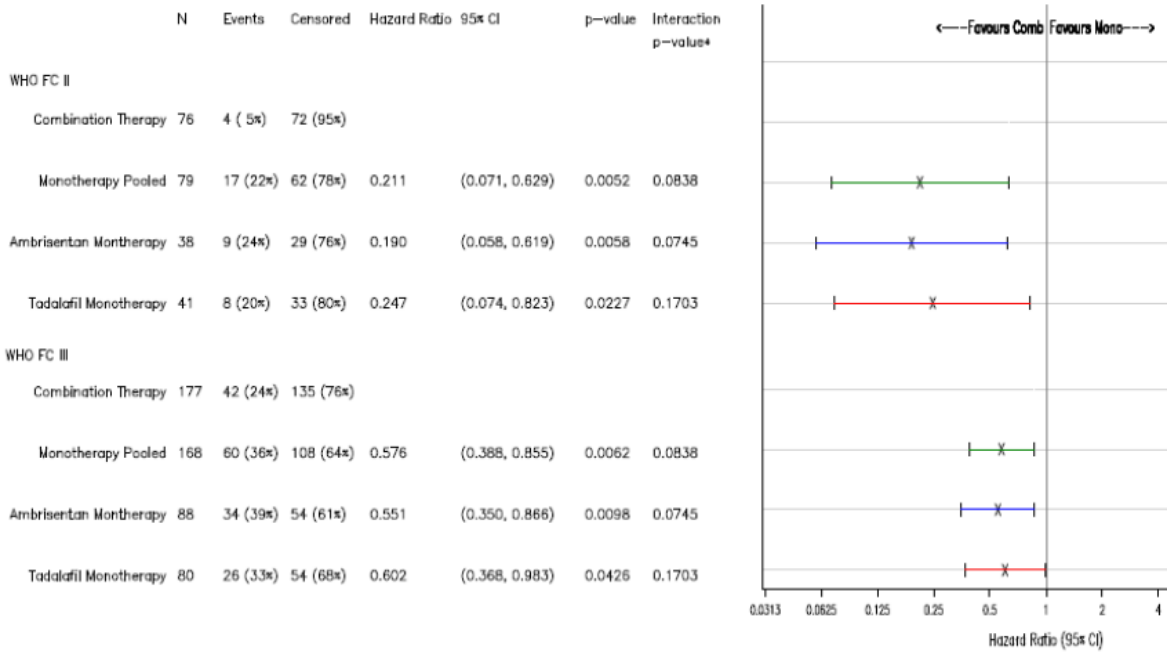
Figure 8. Subgroup Analyses of Time to First Clinical Failure Event (Primary Efficacy Endpoint – Combination Therapy vs. Monotherapy Pooled)



Source: m5.3.5.1, AMB112565/GS-US-300-0140, Source Table 4.33, Source Table 4.37, Source Table 4.39, Source Table 4.41,Source Table 404.29, and Source Table 404.31

The only subgroups in the mITT population for which a significant treatment by subgroup interaction ($p < 0.10$) was observed were the WHO FC subgroups. Overall, the treatment response for combination therapy appeared to be greater in the WHO FC II subgroup than in the WHO FC III subgroup; however, for both subgroups, a favorable treatment response for combination therapy relative to the pooled monotherapies and individual monotherapies was observed (Figure below).

Figure 9. Forest Plot of First Adjudicated Clinical Failure Endpoint by Baseline WHO Functional Class (eCRF Data) (Baseline to FAV); mITT (Randomized Treatment) Population



Source: Figure 14 of AMBITION CSR (AMB112565/GS-US-300-0140)

Sensitivity analyses of main efficacy endpoint and their components:

The key sensitivity analyses are described below. Overall, the results of sensitivity analyses generally support the conclusions from the primary efficacy endpoint analysis, but some comparisons for "time to first clinical worsening" are non-statistically significant (section c):

a) Clinical failure events in the ITT Population: The risk reduction in the primary endpoint of the combination versus pooled monotherapy was statistically significant in the ITT population (HR: 0.53; 95%CI: 0.39 to 0.70; log-rank p-value<0.0001). The comparisons with the ambrisentan monotherapy group (HR: 0.49, 95%CI: 0.35 to 0.68; log-rank p-value <0.0001) and the tadalafil monotherapy group (HR: 0.56, 95% CI: 0.39, 0.79; log-rank p-value= 0.0007) were also statistically significant.

b) Investigator-assessed clinical failure events: The weighted Cohen's Kappa Statistic for overall agreement between adjudicated and investigator-assessed events was 0.874 (95% CI: 0.838, 0.911), indicating a strong degree of agreement between adjudicated and investigator-assessed events in the mITT. Accordingly, the risk reduction in the investigator-assessed primary endpoint of the combination versus pooled monotherapy for first investigator-assessed clinical failure events (baseline to FAV) was statistically significant and consistent with the primary analysis (HR: 0.51; 95%CI: 0.36 to 0.70; log-rank p-value<0.0001). The comparisons with the ambrisentan monotherapy group (HR: 0.48, 95%CI: 0.33 to 0.69; log-rank p-value <0.0001) and the tadalafil monotherapy group (HR: 0.547; 95%CI: 0.36 to 0.80; log-rank p-value = 0.0020) were statistically significant.

c) *Sensitivity Analyses of Time to First Clinical Failure Event and Time to First Clinical Worsening from Baseline to FAV (Adjudicated), Including Events Adjudicated After First Database Freeze:*
Twenty-six events (21 in the mITT population and 5 in the non-mITT population) that occurred before or at FAV were positively adjudicated following the first database freeze, including 12 additional first clinical failure events in 8 subjects in the mITT population (5 subjects in the combination therapy group and 3 subjects in the ambrisentan monotherapy group) and 4 subjects in the non-mITT population (3 subjects in

the combination therapy group and 1 subject in the tadalafil monotherapy group). Sensitivity analyses of the time to first clinical failure and time to first clinical worsening (and their components) from Baseline to FAV that included these additional adjudicated events were performed for the mITT and ITT populations. The results of these sensitivity analyses in both populations are generally consistent with the conclusions from the primary analyses, but the comparison between the combination therapy and tadalafil monotherapy becomes non-statistically significant (HR: 0.69; 95%CI: 0.42 to 1.14) (Table below).

Table 12. Adjudicated First Clinical Worsening Event, Including Events Adjudicated After First DBF (Baseline to FAV); mITT (Randomized Treatment) Population

	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		Total N=500	
Subjects with Event	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
First Clinical Worsening Event	41	(16)	62	(25)	38	(30)	24	(20)	103	(21)
Death (all-cause)	14	(6)	9	(4)	3	(2)	6	(5)	23	(5)
Hospitalization for worsening PAH	16	(6)	36	(15)	22	(17)	14	(12)	52	(10)
Any hospitalization for worsening PAH	8	(3)	24	(10)	14	(11)	10	(8)	32	(6)
Initiation of parenteral prostanoid therapy	8	(3)	12	(5)	8	(6)	4	(3)	20	(4)
Lung or heart/lung transplant	0	-	0	-	0	-	0	-	0	-
Atrial septostomy	0	-	0	-	0	-	0	-	0	-
Disease progression	11	(4)	17	(7)	13	(10)	4	(3)	28	(6)
Analysis of time to first clinical worsening event										
Number of subjects censored	212	(84)	185	(75)	88	(70)	97	(80)		
Kaplan-Meier probability of event by 1 yr (%)	7.76		18.96		19.35		18.59			
95% CI	(4.95, 12.05)		(14.35, 24.82)		(13.16, 27.94)		(12.36, 27.44)			
Kaplan-Meier probability of event by 2 yrs (%)	18.10		27.97		31.03		24.57			
95% CI	(13.11, 24.70)		(22.05, 35.08)		(22.79, 41.35)		(16.85, 35.01)			
Kaplan-Meier probability of event by 3 yrs (%)	29.52		37.32		47.31		24.57			
95% CI	(20.50, 41.34)		(28.50, 47.83)		(33.99, 62.77)		(16.85, 35.01)			
Hazard Ratio from Cox Model			0.563		0.473		0.689			
95% CI			(0.379, 0.835)		(0.304, 0.737)		(0.415, 1.144)			
Stratified log-rank test p-value			0.0038		0.0007		0.1473			
Proportional Hazards assumption p-value			0.7672		0.7794		0.4298			

Source: Table 4004.8 and Table 4004.10

Notes: Table is based on a subject's first event. Hazard ratio from the Cox Proportional Hazards model and stratified log-rank p-value adjusted for Etiology of PAH (IPAH/HPAH vs Non-IPAH) and WHO Functional Class (II vs III). For censored subjects, time (days) is calculated as the number of days from randomization to final assessment visit. Comparisons are for combination therapy relative to monotherapy pooled, ambrisentan monotherapy or tadalafil monotherapy. This output was not included in the RAP and was identified post database freeze.

Deaths:

Vital status was evaluated at FAV (for the time period 26 Feb 2014 to16 Apr 2014) and at End of Study (for the time period 21 May 2014 to 21 Jul 2014; Table 13).

Table 13. Summary of Vital Status at FAV and End of Study; mITT and ITT (Randomized Treatment) Populations

mITT (Randomized Treatment) Population												
Subject Status	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		BCT Initiated N=83		Total N=500	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vital Status at FAV: 26FEB2014 to16APR2014:												
Alive	227	(90)	217	(88)	109	(87)	108	(89)	76	(86)	444	(89)
Dead	19	(8)	21	(9)	11	(9)	10	(8)	11	(13)	40	(8)
Unknown	7	(3)	9	(4)	6	(5)	3	(2)	1	(1)	16	(3)
Number (%) of subjects who died from study discontinuation to16APR2014 (subset of above deaths)												
Dead	12	(5)	6	(2)	5	(4)	1	(<1)	2	(2)	18	(4)
Vital Status at End of Study: 21MAY2014 to 21Jul2014												
Alive	222	(88)	207	(84)	103	(82)	104	(86)	70	(80)	429	(86)
Dead	21	(8)	27	(11)	14	(11)	13	(11)	16	(18)	48	(10)
Unknown	10	(4)	13	(5)	9	(7)	4	(3)	2	(2)	23	(5)
Number (%) of subjects who died from study discontinuation to 21Jul2014 (subset of above deaths)												
Dead	13	(5)	10	(4)	7	(6)	3	(2)	5	(6)	23	(5)

ITT (Randomized Treatment) Population												
Subject Status	Combination Therapy N=302		Monotherapy Pooled N=303		Ambrisentan Monotherapy N=152		Tadalafil Monotherapy N=151		BCT Initiated N=108		Total N=605	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vital Status at FAV: 26FEB2014 to16APR2014:												
Alive	264	(87)	256	(84)	128	(84)	128	(85)	93	(86)	520	(86)
Dead	27	(9)	32	(11)	15	(10)	17	(11)	14	(13)	59	(10)
Unknown	11	(4)	15	(5)	9	(6)	6	(4)	1	(<1)	26	(4)
Number (%) of subjects who died from study discontinuation to16APR2014 (subset of above deaths)												
Dead	19	(6)	10	(3)	6	(4)	4	(3)	3	(3)	29	(5)
Vital Status at End of Study: 21MAY2014 to 21Jul2014												
Alive	258	(85)	243	(80)	121	(80)	122	(81)	86	(80)	501	(83)
Dead	29	(10)	41	(14)	19	(13)	22	(15)	20	(19)	70	(12)
Unknown	15	(5)	19	(6)	12	(8)	7	(5)	2	(2)	34	(6)
Number (%) of subjects who died from study discontinuation to 21Jul2014 (subset of above deaths)												
Dead	20	(7)	15	(5)	8	(5)	7	(5)	6	(6)	35	(6)

Source: Table 1.29 and Table 2.29

Per protocol population:

The applicant was requested to provide with a PP analysis excluding the 81 patients with important protocol deviations). The main results are provided below:

Time to First Adjudicated Clinical Failure Event (Baseline to Final Assessment Visit) (by Randomized Treatment [mITT Population]) patients without important protocol deviations

Subjects with Event	Combination Therapy N=253		Monotherapy Pooled N=247		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of Subjects without important protocol deviations	208		211		114		97	
First Clinical Failure Event	35	17	62	29	39	34	23	24
Death (all-cause)	7	3	7	3	2	2	5	5
Hospitalization for worsening PAH	9	4	24	11	16	14	8	8
Disease progression	5	2	11	5	10	9	1	1
Unsatisfactory long-term clinical response	14	7	20	9	11	10	9	9
Analysis of time to first clinical failure event	35	17	62	29	39	34	23	24
Number of subjects censored	173	83	149	71	75	66	74	76
Hazard Ratio (Cox Model)			0.479		0.423		0.570	
95% CI			0.315 – 0.729		0.266 – 0.672		0.334 – 0.971	
Stratified log-rank test p-value			0.0004		0.0002		0.0360	
Source Tables 44.0101 and 44.0301								

The TTCF for combination vs pooled monotherapy analysis for the mITT population excluding the 81 patients with important deviations was consistent with the overall mITT population analyses, with statistically significant reductions with the CT in comparison with pooled monotherapies and each of the monotherapies separately.

Secondary endpoints:

A summary of results of each comparison for each of the secondary endpoints in the mITT population is shown below (Table 14).

Table 14. Summary of secondary efficacy results of hierarchical testing (randomized treatment, mITT population

Secondary Endpoint	Combination Therapy vs Pooled Monotherapy	Combination Therapy vs Ambrisentan Monotherapy	Combination Therapy vs Tadalafil Monotherapy
Change from Baseline at Week 24 in NT-pro-BNP Geometric Mean difference (ng/L) 95%CI p-value	-33.81 (-44.78, -20.66) P < 0.0001	-25.09 (-40.04, -6.40) P = 0.0111	-41.51 (-53.16, -26.97) P < 0.0001
% Subjects with Satisfactory Clinical Response at Week 24 OR (Logistic Regression Observed case with no imputation) 95%CI p-value	1.56 (1.05, 2.32) P =0.0264	1.42 (0.88, 2.31) P = 0.1518	1.72 (1.05, 2.83) P = 0.0321
Change from Baseline at Week 24 in 6MWD Median difference, m (Stratified Wilcoxon Rank sum test) 95%CI p-value	+22.75 (+12.00, +33.50) P < 0.0001	+24.75 (+11.00, +38.50) P = 0.0005	+20.85 (+8.00, +33.70) P = 0.0030
Change from Baseline at Week 24 in WHO Functional Class Median difference, m (Stratified Wilcoxon Rank sum test) 95%CI p-value	0 (0, 0) P = 0.2287	0 (0, 0) P = 0.3211[a]	0 (0, 0) P = 0.3259[a]
Change from Baseline at Week 24 in BDI Median difference (Stratified Wilcoxon Rank Sum test with imputation - LOCF/Worst Rank) 95%CI p-value	-0.38 (-0.75, 0.00) P = 0.0376[a]	-0.50 (-1.00, 0.00) P =0.0960[a]	-0.50 (-1.00, 0.00) P = 0.0855[a]

a- Not tested per hierarchical testing strategy, p-value provided for informational purposes only

The results on 6MWD are shown in more detail in the following table, as it has been the primary endpoint in initial pivotal studies.

Change in 6MWD:

The primary statistical analysis (WRS with LOCF/worst rank imputation) showed a statistically significant difference between the combination therapy group and the pooled monotherapy in median change from Baseline at Week 24 in 6MWD (median difference=22.75 meters, 95% CI: 12.00, 33.50, p<0.0001). There was also a statistically significant greater median change from Baseline at Week 24 in 6MWD in the combination therapy group compared with the ambrisentan monotherapy group (27.00 meters, 95% CI: 12.50, 38.00) (median difference=24.75 meters, 95% CI: 11.00, 38.50, p=0.0005) and compared with the tadalafil monotherapy group (median difference=20.85 meters, 95% CI: 8.00, 33.70, p=0.0030).

Table 15. 6 Minute Walk Distance Results (Meters) at Week 24 (Change from Baseline); mITT (Randomized Treatment) Population

Visit	Combination Therapy N=253	Monotherapy Pooled N=247	Ambrisentan Monotherapy N=126	Tadalafil Monotherapy N=121
Baseline (observed), n	253	247	126	121
Mean (SD)	353.50 (87.888)	351.72 (91.827)	354.19 (92.317)	349.15 (91.626)
Median	357.00	365.50	368.50	363.30
Min – Max	127.0 – 498.5	115.5 – 517.5	115.5 – 517.5	126.0 – 502.5
Week 24 (observed), n	229	216	108	108
Mean (SD)	408.17 (98.898)	387.24 (106.706)	385.73 (113.511)	388.75 (99.947)
Median	414.00	400.05	407.00	392.00
Min – Max	0 – 619.0	0.0 – 590.0	0.0 – 590.0	121.9 – 586.0
Primary Statistical Methodology				
Primary Analysis				
Stratified Wilcoxon Rank Sum Test, n (Imputed Data - LOCF/Worst Rank)[1]	248	244	124	120
Median (95% Confidence Interval)	48.98 (39.00, 57.50)	23.80 (19.00, 33.50)	27.00 (12.50, 38.00)	22.70 (16.50, 35.50)
Median Difference (95% Confidence Interval)		22.75 (12.00, 33.50)	24.75 (11.00, 38.50)	20.85 (8.00, 33.70)
p-value		<0.0001	0.0005	0.0030
Sensitivity Analyses				
Analysis of Covariance, n (Imputed Data - LOCF/Worst Case)[2]	248	244	124	120
Mean (Mean Difference)	45.81	16.81 (29.00)	11.83 (33.98)	21.79 (24.01)
95% Confidence Interval		(14.37, 43.62)	(16.14, 51.82)	(5.97, 42.05)
p-value		0.0001	0.0002	0.0092
Mixed Model Repeated Measures, n (No Imputation)[3]	229	216	108	108
Mean (Mean Difference)	51.74	27.26 (24.49)	21.21 (30.53)	33.30 (18.44)
95% Confidence Interval		(12.85, 36.13)	(16.27, 44.80)	(4.12, 32.76)
p-value		<0.0001	<0.0001	0.0117

Exploratory endpoints:

Health Outcomes/Quality of Life Results: Scores for all the CAMPHOR components examined in all 3 randomized treatment groups showed a decrease (improvement) at Week 24 compared with Baseline. However, no statistically significant differences between the combination therapy group and the pooled monotherapy group were observed. Scores for all the SF-36 domains and components in all 3 randomized treatment groups showed an upward trend (improvement) at Week 24 compared with Baseline. No statistically significant differences between the combination therapy group and the pooled monotherapy group were observed.

Treatment Effect on 6MWD at Peak and Trough Plasma Concentrations: In the combination therapy group, the ratio of the tadalafil-corrected mean change from Baseline through 6MWD at Week 16 to the tadalafil-corrected mean change from Baseline peak 6MWD at Week 16 was greater than 1, with the increase in 6MWD greater in the trough group (19.34 meters) than in the peak group (6.22 meters).

Uptitration and treatment compliance:

More than 90% of subjects had uptitrated both ambrisentan and tadalafil at or before Week 8, indicating that the titration scheme used in the AMBITION study was well tolerated. In the mITT population, overall mean compliance was high (≥93%) and generally similar across the randomized treatment groups.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present variation application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16. Summary of efficacy for trial AMB112565 / GS-US-300-0140 (AMBITION)

Title: AMBITION: A Randomized, Multicenter Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension			
Study identifier	GSK Study AMB112565 /Gilead Study Number GS-US-300-0140		
Design	This was a Phase III/IV, randomized, double-blind, event-driven study. Enrollment and study duration were dependent on the study event rate. All eligible subjects were to receive a minimum of 24 weeks of therapy. After screening and randomization assessments, subjects were assessed for efficacy and safety at Weeks 4, 8, 16, 24, and every 12 weeks thereafter. In between clinic visits, subjects had monthly laboratory safety assessments.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		18 Oct 2010 (first subject first visit [FSFV]) to 31 Jul 2014 (last subject last visit [LSLV]) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Combination therapy (ambrisentan + tadalafil)		ambrisentan 10mg OD + tadalafil 40mg OD, ≥ 24 weeks (N=306)
	Pooled monotherapy		ambrisentan 10mg OD or tadalafil 40mg OD, ≥ 24 weeks (N=304)
	Ambrisentan monotherapy		ambrisentan 10mg OD, ≥ 24 weeks (N=152)
	Tadalafil monotherapy		tadalafil 40mg OD, ≥ 24 weeks (N=152)
Endpoints and definitions	Primary endpoint	Time to the first clinical Failure (TtCF) event	Defined as the time from randomization to the first occurrence of: 1) Death (*all-cause*) 2) Hospitalization for worsening PAH (*adjudicated*): a) Any hospitalization for worsening PAH; b) Lung or heart/lung transplant; c) Atrial septostomy; d) Initiation of parenteral prostanoid therapy; 3) Disease progression (*adjudicated*): >15% decrease from Baseline in 6MWD combined with WHO class III or IV symptoms (*at 2 consecutive post-Baseline clinic visits separated by ≥14 days*) 4) Unsatisfactory long-term clinical response (*adjudicated*, all criteria required): a) Receiving at least 1 dose of randomized treatment and being in the study for at least 6 months; b) A decrease from Baseline in 6MWD at 2 consecutive post-Baseline clinic visits separated by ≥14 days; c) WHO class III symptoms assessed at 2 clinic visits separated by ≥ 6 months

	Secondary endpoint	NT-pro-BNP	Change from Baseline measured at Week 24 in N-terminal pro-B-type natriuretic peptide (NTpro-BNP)
	Secondary endpoint	% Subjects with satisfactory clinical response measured at Week 24	- 10% improvement in 6MWD compared with Baseline and - Improvement to or maintenance of WHO class I or II symptoms and - No events of clinical worsening1 prior to or at the Week 24 visit
	Secondary endpoint	6MWD	Change from Baseline in 6 minute walk distance (6MWD) measured at Week 24
	Secondary endpoint	WHO functional class	Change from Baseline measured at Week 24 in WHO Functional Class
	Secondary endpoint	Borg Dyspnea Index (BDI)	Change from baseline measured at Week 24 in BDI immediately following exercise
Database lock	Initial database lock on 20-May-2014 (after the last randomized subject had the opportunity to receive at least 24 weeks of therapy and the 105th adjudicated first primary efficacy endpoint was projected to have occurred in the mITT population. A safety follow-up by phone was performed 30 days after the subject's last dose of IP, after which the data were cleaned (prior to final database lock). Final database lock: exact date not provided.		

Results and Analysis

Analysis description*	**Primary Analysis, primary endpoint**				
Analysis population and time point description	**mITT population:** All randomized subjects who met the PAH diagnosis and inclusion/exclusion criteria and who also received at least one dose of IP. **Time point:** from randomization to the final assessment visit (FAV) (in the first database freeze).				
Descriptive statistics and estimate variability	Treatment group	Combination therapy	Monotherapy pooled	Ambrisentan monotherapy	Tadalafil monotherapy
	Number of subject	N=253	N=247	N=126	N=121
	First clinical failure event, n (%)	46 (18%)	77 (31%)	43 (34%)	34 (28%)
	K-M probability of event by 1 yr, % (95%CI)	11% (8-16%)	24% (19-31%)	24% (17-33%)	25% (18-34%)
	K-M probability of event by 2 yrs, % (95%CI)	20% (15-27%)	37% (30-44%)	39% (30-50%)	34% (25-46%)
	K-M probability of event by 3 yrs, % (95%CI)	32% (23-44%)	44% (36-53%)	48% (37-60%)	39% (28-54%)

Effect estimate per comparison*	**Primary endpoint (time to first adjudicated clinical failure event)**	Combination therapy vs. monotherapy pooled	
		HR (Cox model)	0.50
		95%CI	0.39 to 0.72
		P-value (stratified log-rank test)	**0.0002**
		Combination therapy vs. ambrisentan monotherapy	
		HR (Cox model)	0.48
		95%CI	0.31 to 0.72
		P-value (stratified log-rank test)	**0.0004**
		Combination therapy vs. tadalafil monotherapy	
		HR (Cox model)	0.53

		95%CI	0.34 to 0.83
		P-value (stratified log-rank test)	**0.0045**
Analysis description	**Primary analysis, secondary endpoints**		
Effect estimate per comparison	**Change in NT-pro-BNP from baseline to week 24**	Combination therapy vs. monotherapy pooled	
		Geometric Mean difference (ng/L)	-33.81
		95%CI	-44.78 to -20.66
		P-value	**<0.0001**
		Combination therapy vs. ambrisentan monotherapy	
		Geometric Mean difference (ng/L)	-25.09
		95%CI	-40.04 to -6.40
		P-value	**0.0111**
		Combination therapy vs. tadalafil monotherapy	
		Geometric Mean difference (ng/L)	-41.51
		95%CI	-53.16 to -26.97
		P-value	**<0.0001**
Effect estimate per comparison	**Satisfactory clinical response at week 24**	Combination therapy vs. monotherapy pooled	
		OR (Logistic Regression Observed case with no imputation)	1.56
		95%CI	1.05 to 2.32
		P-value	**0.0264**
		Combination therapy vs. ambrisentan monotherapy	
		OR (Logistic Regression Observed case with no imputation)	1.42
		95%CI	0.88 to 2.31
		P-value	0.1518
		Combination therapy vs. tadalafil monotherapy	
		OR (Logistic Regression Observed case with no imputation)	1.72
		95%CI	1.05 to 2.83
		P-value	**0.0321**
Effect estimate per comparison	**Change in 6MWD from baseline to week 24**	Combination therapy vs. monotherapy pooled	
		Median difference, m (Stratified Wilcoxon Rank sum test)	+22.75
		95%CI	+12.00 to +33.50
		P-value	**<0.0001**
		Combination therapy vs. ambrisentan monotherapy	
		Median difference, m (Stratified Wilcoxon Rank sum test)	+24.75
		95%CI	+11.00 to +38.50
		P-value	**0.0005**
		Combination therapy vs. tadalafil monotherapy	
		Median difference, m (Stratified Wilcoxon Rank sum test)	+20.85
		95%CI	+8.00 to +33.70
		P-value	**0.0030**
Effect estimate per comparison	**Change in WHO FC from baseline to week 24**	Combination therapy vs. monotherapy pooled	
		Median difference (Stratified Wilcoxon Rank sum test)	0
		95%CI	0 to 0

		P-value	0.2287
		Combination therapy vs. ambrisentan monotherapy	
		Median difference (Stratified Wilcoxon Rank sum test)	0
		95%CI	0 to 0
		P-value	0.3211[a]
		Combination therapy vs. tadalafil monotherapy	
		Median difference (Stratified Wilcoxon Rank sum test)	0
		95%CI	0 to 0
		P-value	0.3259[a]
Effect estimate per comparison	**Change in BDI score from baseline to week 24**	Combination therapy vs. monotherapy pooled	
		Median difference (Stratified Wilcoxon Rank Sum test with imputation - LOCF/Worst Rank)	-0.38
		95%CI	-0.75 to 0.00
		P-value	0.0376[a]
		Combination therapy vs. ambrisentan monotherapy	
		Median difference (Stratified Wilcoxon Rank Sum test with imputation - LOCF/Worst Rank)	-0.50
		95%CI	-1.00 to 0.00
		P-value	0.0960[a]
		Combination therapy vs. tadalafil monotherapy	
		Median difference (Stratified Wilcoxon Rank Sum test with imputation - LOCF/Worst Rank)	-0.50
		95%CI	-1.00 to 0.00
		P-value	0.0855[a]

*Notes: Based on a subject's first event. Hazard ratio (HR) from the Cox Proportional Hazards model and stratified log-rank p-value adjusted for Etiology of PAH (IPAH/HPAH vs. Non-IPAH) and WHO Functional Class (II vs III). Comparisons are for combination therapy relative to monotherapy pooled, ambrisentan monotherapy or tadalafil monotherapy.
[a] Analysis not formally tested as per the hierarchical testing strategy, p-value provided for informational purposes only.

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

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

No complete reports of supportive studies have been submitted. The following additional studies are mentioned but information is limited to publications or abstracts to Congresses. The results of these studies are consistent with a benefit of dual ambrisentan+PDE5i therapy versus monotherapy with ambrisentan or PDF5i:

1) ATHENA-1 [Oudiz et al. Chest. 2011;140(meeting abstract): 905A]: The efficacy and safety of ambrisentan added to background PDE-5i therapy in subjects with WHO FC III PAH who had a suboptimal response to the PDE-5i were determined in a Phase 4 open-label study. Eligible subjects were enrolled to receive ambrisentan in addition to preexisting background PDE-5i therapy (sildenafil or tadalafil) that must

have been administered for ≥ 12 weeks and have been in a stable regimen for at least 8 weeks before enrollment. Subjects received 5-mg ambrisentan once daily for the initial 4 weeks, then 10-mg ambrisentan once daily for an additional 44 weeks. The primary endpoint was the change from Baseline in PVR at Week 24. Additional endpoints included other hemodynamic measures such as mean pulmonary artery pressure (mPAP), mean right atrial pressure, and cardiac index; 6-minute walk distance (6MWD); dyspnea index; and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP). Of the 38 subjects enrolled, 31 subjects received concomitant sildenafil and 7 subjects received concomitant tadalafil. The addition of ambrisentan to suboptimal PDE-5i monotherapy resulted in statistically significant improvements in PVR, cardiac index, and other supportive cardiopulmonary hemodynamic parameters. Treatment benefits also were observed in several secondary efficacy endpoints, including 6MWD, dyspnea index, WHO FC, and NT-pro-BNP. Ambrisentan was generally well tolerated in this population when co-administered with a PDE-5i.

2) Zhuang et al, (Hypertension Research. 2014;37:507-12): A recently published, prospective, double-blind, randomized, controlled clinical study investigated the efficacy and safety of tadalafil in subjects who were receiving background ambrisentan therapy [Zhuang, 2014]. A total of 124 adult subjects with symptomatic PAH were enrolled and randomized to receive either tadalafil (40 mg once daily) or placebo in addition to existing therapy with ambrisentan (10 mg once daily). The study evaluated exercise capacity (as measured using 6MWD), symptom improvements, and hemodynamic parameters. A statistically significant improvement was observed in the 6MWD at Week 16 in the tadalafil plus ambrisentan combination group compared with the ambrisentan alone group. A statistically significant reduction in clinical worsening events also was observed in the combination group. Although not statistically significant, differences between the treatment groups were observed in cardiopulmonary hemodynamic parameters, with improvements in PVR, mean PAP, and cardiac output being greater in the combination group than in the ambrisentan alone group. The lack of statistical significance may have been due to the relatively small sample size. The safety results suggested that tadalafil was well tolerated when added to background ambrisentan therapy.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The AMBITION study (n=605 patients) is the single pivotal study that provides clinical data in support of the claim for combination therapy for ambrisentan. This study was a Phase 3/4, randomized, double-blind, event-driven study designed to compare the safety and efficacy of initiating pharmacotherapy with a combination of ambrisentan and tadalafil to initiating pharmacotherapy with ambrisentan or tadalafil monotherapy at the same doses. Events were blindly adjudicated by a study specific Clinical Endpoints Committee (CEC). In an EMA advice, the CHMP did not endorse the Company's strategy to base a claim on the combination of ambrisentan and tadalafil in comparison to the pooled monotherapy arms. In order to show a benefit of both components, two comparisons, one against each monotherapy arm, were considered needed. The company then included secondary comparisons of the combination therapy with the individual monotherapy arms. These comparisons were only performed if the comparison of the combination arm vs. pooled monotherapy arms was significant (5% significance level, 2-sided) (Hierachical procedure). The same procedure was applied for secondary outcomes, which is acceptable.

The AMBITION study was aimed to answer a relevant question: Whether starting treatment with PAH with a combination of an ERA and a PDE5 inhibitor would be better than starting on a single specific therapy (ERA or PDE5 inhibitor alone) in relationship with clinical outcome. PAH is a progressive disease. The longer you have PAH, the more fibrosis and the more negative effects on ventricular function and the earlier the impact on PAH deterioration and hospitalisations. "The earlier the better" could theoretically apply for starting PAH treatment with a combination therapy of drugs of different pharmacological class and complementary

mechanisms of action (i.e.: endothelin receptor antagonism and PDE5 inhibition). Therefore, the study design allowed to collect information on the ambrisentan/tadalafil combination therapy in PAH that could be potentially relevant for standard practice. The global design and objectives are endorsed.

Inclusion criteria were implemented to recruit patients in whom a diagnosis of Group 1 PAH (IPAH/HPAH or PAH associated with connective tissue disease, drugs or toxins, human immunodeficiency virus (HIV) infection, or congenital heart defects repaired) > 1 year prior to screening; current diagnosis of WHO FC II or III symptoms; and several haemodynamic criteria to reduce the likelihood of enrolling subjects with PH due to potential covert left ventricular diastolic dysfunction (WHO Group 2 PH) (non-mITT population).

Patients recruited into the study were purely naive. Some additional PAH medications, like nitrates, and specific PAH medications, like other ERAs, PDE5is and inhaled nitric oxide were not allowed.

Exclusion criteria were quite more extensive than the contraindications already included in the SmPCs of Volibris and Adcirca, as patients with risk factors for developing adverse reactions to ambrisentan were excluded (e.g.: anemia, fluid retention, retinal problems and baseline values of ALT and/or AST>2xULN).

Ambrisentan was uptitrated from 5 mg OD (initial dose) to 10 mg OD (target dose) after 8 weeks, and tadalafil was uptitrated from 20 mg OD (initial dose) to 40 mg OD after 4 weeks if the therapy was well tolerated. If the subject did not tolerate IP, the following algorithms for changes were to be followed by the investigator: 1) Separation of dosing of ambrisentan and tadalafil to occur in the morning and evening, respectively; 2) Request blinded down-titration of ambrisentan or tadalafil to the initial dose.

The applicant based the justification of 10 mg use on incidence of fluid retention (which increase was observed in ARIES studies along with higher efficacy of 10 mg dose in patients with class III symptoms) after up titration from 5 mg to 10 mg, continued decrease of NT-pro-BNP from week 8 to 16 in ambrisentan monotherapy arm and continued improvement in 6MWD from week 8 to 16. The Company showed that the incidence of fluid retention AE did not increase after up titration. It was also shown that there is positive trend in both efficacy variables after up titration to 10 mg for all patients; therefore applicant's approach regarding the use of the 10 mg was accepted.

The main composite endpoint was "clinical failure", defined as time to first event of "all-cause death", "hospitalisation", "disease progression" and/or "unsatisfactory long-term clinical response". In an EMA advice (, the first three components of the proposed composite (all-cause death, hospitalization for PAH worsening, disease progression) were considered adequate and in line with applicable guidance to represent clinical worsening. However, the additional fourth component "unsatisfactory long-term clinical response" as proposed by the Company was not supported.

The definition of "clinical failure" was not entirely consistent with the EMA definition of "clinical worsening" included in the PAH guideline (EMEA/CHMP/EWP/356954/2008). Although the inclusion of "all-cause death" and "PAH hospitalization" are consistent in both definitions, there were differences in the third and fourth component ("disease progression" and "unsatisfactory long-term clinical response" used in AMBITION versus "time to PAH-related deterioration" included in the PAH guideline).

Secondary endpoints included the change from baseline to week 24 in N-Terminal pro-B-type natriuretic peptide (NT-pro-BNP), satisfactory clinical response (week 24), 6-minute walk distance (6MWD), WHO functional class and Borg Dyspnea index (BDI). Exploratory endpoints included Quality of life and peak-trough assessment of 6MWD.

Acceptable methods were used for randomisation, sample size calculation and maintaining of blinding/masking. However, given the possibility of unblinding due to the different safety profiles of ambrisentan and tadalafil, the applicant was requested to show the main efficacy outcome separately for patients with and without adverse events related to study medication by the investigators. The same

analysis was requested for patients who tolerated the full investigational doses versus those who did not tolerate uptitration to the full investigational doses. These ancillary analyses reasonably ruled out a potential influence of unblinding in the main study results.

The primary comparison was between the hazard rates of time to clinical failure in the combination therapy arm (ambrisentan and tadalafil) and the pooled monotherapy arm (ambrisentan and placebo plus tadalafil and placebo) following the final assessment visit for each subject. The mITT population was utilized for this comparison. The comparison was made at a 5% significance level (2-sided). Secondary comparisons were of the combination therapy with the individual monotherapy arms. These comparisons were only performed if the comparison of the combination arm vs. pooled monotherapy arms was significant (5% significance level, 2-sided) (Hierarchical procedure). The same procedure was applied for secondary outcomes. Differences between the Kaplan-Meier event-free curves of time to clinical failure from randomization to individual subject's FAV were tested for significance by the stratified log-rank statistic test (stratified by the etiology of PAH and WHO functional class). The hazard ratio was used to characterize the treatment effect, and 95% confidence intervals (CIs) were calculated using a Cox proportional hazards regression model.

Time for censoring: a) any subject who was withdrawn or lost to follow-up was censored on the date of their last clinical worsening event assessment prior to their being lost from the study; b) at first adjudicated event; c) at FAV in those without adjudicated events at FAV or whose first adjudicated event occurred after their FAV.

Several supportive analyses of time to first clinical worsening (TtCW) event (death, hospitalization for PAH, and disease progression) and time to each of the components of the primary endpoint up to FAV (first database freeze) were also performed. Sensitivity analyses for TtCF, TtCW and the individual components were performed up to EoS. Additionally, time to death was analysed up to the final contact. For the analysis of time to death, any subject who was withdrawn or lost to follow-up was censored at the date last known alive. Additional analyses were performed on investigator assessed events. Sensitivity analyses for time to clinical worsening up to FAV and EoS, respectively, were performed that censored subjects (with or without a clinical worsening event) at the time of initiation of blinded combination therapy.

Efficacy data and additional analyses

AMBITION included a population (mainly females) with idiopathic PAH and PAH associated to connective tissue disease in FC II-III (mainly III) without left ventricular diastolic dysfunction (WHO Group 2 PH).

Primary endpoint

The reduction in risk of a first adjudicated clinical failure event (mITT; FAV) was 50% for subjects in the combination therapy group (HR = 0.50 [95% CI: 0.39, 0.72]). With respect to the primary endpoint clinical failure, the differences between the combination therapy group and each of the individual monotherapy were statistically significant for the ambrisentan monotherapy group (HR = 0.48 [95% CI: 0.31, 0.72] and for the tadalafil monotherapy group (HR = 0.53; 95%CI: 0.34, 0.83). The 1-, 2-, and 3-year KM probabilities of having a first adjudicated clinical failure event were lower with combination therapy compared with pooled monotherapy and with each monotherapy.

Several sensitivity analyses showed consistency in the primary endpoint, including the analysis in the ITT population and in the investigator-assessed clinical failure events. The effect on the primary endpoint was also consistent in most subgroups, but more pronounced in FCII than in FCIII in relative terms. However, the absolute differences between CT and pooled MT in time to first event were 16% in FC II and 12% in FCIII. Therefore, clinical relevance of starting PAH specific treatment with ambrisentan+tadalafil combination therapy is of similar relevance in both FC II and FCIII naive patients.

"PAH-related hospitalisation" was the key component driving the difference in the main efficacy endpoint. The analysis of first events of PAH hospitalisation showed a 63% decrease in risk with the CT versus MT (HR: 0.37; 95%CI: 0.22 to 0.64).There was no difference seen in hospitalizations between Europe and rest of world (mostly North America) and benefit in reduction of hospitalizations was consistent between regions.The numbers of censorings prior to FAV was significant [25 (12%) vs 33 (19%)]. However, the rates are similar to those reported in the review of the SERAPHIN study, in which there were 93 (12.5%) subjects who did not have any primary events and were censored before the end of the study (double blind period) without any further data collection after the end of the study. Theoretically, this issue might have led to an even greater observed benefit for combination therapy (i.e. censoring could favor the monotherapy arms), but this assumption cannot be demonstrated, as these patients represent "lost to follow-up". Therefore the concern was adequately addressed.

The applicant also analysed the time to first clinical worsening (CW) event (defined as the composite of "death", "hospitalization for worsening PAH" and "disease progression"; i.e.: excluding "unsatisfactory long-term clinical response" from the main endpoint). This analysis yielded statistically significant results for the CT versus pooled MT (HR = 0.51; 95% CI: 0.34 to 0.78) and versus ambrisentan monotherapy (HR = 0.44; 95%CI: 0.28 to 0.70) but not versus tadalafil monotherapy (HR = 0.61; 95%CI: 0.36 to 1.03). Anyway, the trend in the secondary endpoint of CW was positive in favour of the CT versus tadalafil monotherapy and similar to that obtained for the primary endpoint. These results are likely to be attributed to insufficient statistical power, but not because the effect on CW could be considered different to that obtained in the primary endpoint of "clinical failure ", which is considered clinically relevant.

A sensitivity analysis including Events Adjudicated After First Database Freeze did show the same non-significant trend in time to CW between combined therapy and tadalafil monotherapy (HR: 0.69; 95%CI: 0.42 to 1.14). Consistently, the effect of the CT versus MT on satisfactory clinical response was more pronounced on the comparison with ambrisentan MT than with tadalafil MT, also suggesting a less relevant contribution of ambrisentan than that of tadalafil in this parameter.

Another previous meta-analysis including only 6 RCT and 729 patients [Fox et al. Am J Cardiol. 2011; 108(8): 1177-82] was unable to show statistical differences between CT and MT in CW (defined as the combined endpoint of mortality, admission for worsening PAH, lung transplantation, or escalation of PAH therapy) (RR 0.42, 95% CI 0.17 to 1.04), probably due to insufficient power. However, the point estimate (0.42) was broadly similar to that of the more recent meta-analysis by Manes et al 2014 and to the point estimate of the HR (0.51) as defined in AMBITION, for clinical worsening. The meta-analysis by Fox et al showed an increase in the 6-minute walk distance at the end of follow-up in favor of CT versus MT (Mean difference = +25.2 m; 95%CI: 13.3 to 37.2 m), which is broadly consistent with the +22.75m improvement in 6MWD seen in AMBITION with CT versus MT. Incidence of study-drug discontinuation in the meta-analysis was similar between the CT and MT groups (RR: 0.89; 95% CI 0.53 to 1.48), which is again consistent with the trend towards less study-drug discontinuations observed in AMBITION with the CT versus MT (22% vs. 29%).

The reduction in all-cause mortality (CT vs. MT) was not significant in AMBITION (HR: 0.64; 95%CI: 0.31 to 1.29; mITT; FAV). Mortality ranged from 40 cases (8%) in the mITT-FAV (3% in the combination therapy compared to 2% in ambrisentan MT and 7% in tadalafil MT) to 70 cases (12%) in the ITT-End-of-Study (10% in the combination therapy compared to 13% in ambrisentan MT and 15% in tadalafil MT), which is also consistent with that reported in the more recent meta-analysis of CT versus MT (OR 0.84; 95% CI 0.52–1.35; p=0.47) [Manes et al. Eur Heart J. 2014; 35 (Suppl.1):11 (abstract 68)]. The incidence of mortality in RCTs with PAH medications is relatively low and to achieve statistical significance a sample size of several thousands of patients may be required. In contemporary trials, including AMBITION, the main component driving the difference are the PAH hospitalisations, while the effect on mortality in relative and absolute terms remains modest.

Regarding the quality of the data, vital status was not available for 26 patients (4%) at FAV and for 34 (6%) patients at end of study (ITT population). The applicant showed that these figures were similar to those observed in contemporary studies.

Secondary endpoints

Secondary endpoints included the change from baseline to week 24 in N-Terminal pro-B-type natriuretic peptide (NT-pro-BNP), satisfactory clinical response (week 24), 6-minute walk distance (6MWD), WHO functional class and Borg Dyspnea index (BDI). Exploratory endpoints included Quality of life and peak-trough assessment of 6MWD. The results are described below:
Change in NT-pro-BNP (mean difference: -33.81 ng/L; 95%CI: -44.78 to -20.66), satisfactory clinical response (OR: 1.56; 95%CI: 1.05 to 2.32), change in 6MWH (Median difference: -22.75; 95%CI: -12.00 to +33.50), and no significant difference in mortality, change in WHO FC, change in BDI score or QoL scores.

The effect of the combination therapy versus monotherapy on decrease in NT-pro-BNP was more pronounced on the comparison with tadalafil monotherapy than with ambrisentan monotherapy, suggesting a more relevant contribution of ambrisentan than that of tadalafil in this parameter. On the contrary, the effect of the combination therapy versus monotherapy on satisfactory clinical response was more pronounced on the comparison with ambrisentan monotherapy than with tadalafil monotherapy, suggesting a more relevant contribution of tadalafil than that of ambrisentan in this parameter. NI-proBNP is more likely a disease marker than a PD marker.

The proBNP marker correlates with prognosis in patients with acute and chronic HF [Savarese et al. JACC Heart Fail. 2014;2:148-58] and the result is consistent with the reduced rate of PAH hospitalisations in AMBITION, mainly related to heart failure, which is the main component driving the superiority in the main endpoint of clinical failure. However, NI-proBNP is more likely a disease marker than a PD marker. The applicant was requested to investigate the correlation (at the population and individual level) between the effect in NT-proBNP (reduction/no reduction) and several clinical efficacy endpoints (e.g.: no clinical failure/clinical failure, no clinical worsening/clinical worsening, and response/no response in 6MWD) before accepting the inclusion of this information in section 5.1 of the SmPC as requested by the MAH .

No statistically significant differences were found in change from Baseline at Week 24 in median WHO FC in the combination therapy group compared with the pooled monotherapy group, and change from Baseline at Week 24 in BDI was not tested per the hierarchical testing strategy.

Scores for all the CAMPHOR components and the SF-36 domains and components examined in all 3 randomized treatment groups showed an improvement (decrease in CAMPHOR and increase in SF-36 components) at Week 24 compared with Baseline, but no statistically significant differences between the combination therapy group and the pooled monotherapy group were observed.

Wording of the indication / posology

The wording of the indication proposed as the general statement *"...or in combination*" was debated during all the procedure.

The company is suggesting deletion of Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease". However the patient population studied do not change current approved wording. Therefore, this statement should be maintained in the indication.

The CHMP considered that the proposed wording reference to "improved outcomes" should be deleted, in line with indication approved for other products eg Opsumit.
Upon request, the applicant provided further data supporting the use in combination with other agents than tadalafil.

Data in combination with sildenafil:

There are clinical data, although scarce, supporting the use of ambrisentan in combination with sildenafil from subgroup analyses of the ATHENA-1 study (n of the subgroup with concomitant sildenafil = 31) [Shapiro et al. 2012; 31(4Suppl): S28-S29 (abstract)] and ARIES-3 study (in of the subgroup with concomitant sildenafil = 58) [McGoon et al. Am J Respir Crit Care Med. 2010; 181:A3351 (abstract)]. Although with the limitations of subgroup analyses, the studies showed a beneficial effect of the ambrisentan/sildenafil combination in haemodynamic parameters (ATHENA-1) and 6MWD (ARIES-3) that were comparable to those reported with ambisentan-tadalafil in the AMBITION study and generally expected for a ERA+PDE5i combination, as shown by recent meta-analyses of combination therapy [Fox et al. Am J Cardiol. 2011; 108(8): 1177-82] . In addition, there are safety data from a number of subjects (n=383) in the VOLT study where ambrisentan was added onto background therapy (predominately sildenafil) or in whom additional therapy was added during the study period. The AE profile when ambrisentan was added to existing sildenafil treatment was similar to that when ambrisentan was added to existing tadalafil treatment and the most common AE was oedema.

However, there are very limited data regarding the titration process of the combination of ambrisentan with other PDE5i, as it has only been studied in AMBITION. In the AMBITION study, patients received 5 mg ambrisentan daily for the first 8 weeks before up titrating to 10 mg, dependent on tolerability. When used in combination with tadalafil, patients were initiated with 5 mg ambrisentan and 20 mg tadalafil. Dependent on tolerability the dose of tadalafil was increased to 40 mg after 4 weeks and the dose of ambrisentan was increased to 10 mg after 8 weeks. This information is lacking for the combination of ambrisentan with other PDE5i and is therefore not reflected in the SmPC.

Data in combination with prostanoids:

There were 97 patients who initiated prostanoid therapy during the AMBITION study: 31 (10%) combination therapy patients and 46 (15%) (26 (17%) ambrisentan and 20 (13%) tadalafil) pooled monotherapy. Safety data provided do not raise any major concern. However, no efficacy data are available.

There are safety data from 97 patients who initiated prostanoid therapy during the AMBITION study, but no prospective randomised data in combination with prostanoids is currently available. Finally, there are no data for the combination of ambrisentan with other targeted PAH therapies such as soluble guanylate cyclase stimulators.

In view of the limited dara in combination with other targeted PAH therapies apart from tadalafil, the company proposed a new wording :"including use in initial combination with tadalafil" . However the CHMP considered that the new proposal was not appropriate as this wording creates ambiguity about the scope of the approved indication, and it may imply that ambrisentan cannot be used with other therapies than tadalafil.

It is recognized that he use of combination treatment is becoming the standard of care in the treatment of PAH, in view of a number of studies showing the benefit of combination treatment. This is reflected in the recently updated ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension, which recommends the initiation of combination treatment in patients with mild, intermediate and severe PAH [Galie 2015a].

SERAPHIN and AMBITION were both long term outcome studies, however, AMBITION had active treatment control, and there was a similar extent of combination use in both studies with phosphodiesterase 5 inhibitors (PDE-5i) or prostacyclines (Table 1).

Table 1. Combination use with macitentan and ambrisentan in studies with efficacy

	Macitentan		Ambrisentan			
	SERAPHIN		AMBITION		ATHENA 1	ARIES 3
	upfront	Sequential	upfront	Sequential*	Sequential	Sequential
Sildenafil	0	140	0	0	31	57
Tadalafil	0	2	302	70	7	0
Prostacycline	0	15	0	57	0	22

*Added to any treatment arm containing ambrisentan, or ambrisentan added to tadalafil
Source Data: Pulido 2013, Table 2000.26, CSR Tables 14 and 65; Badesch 2012; GSK response to Volibris AMBITION CHMP request for supplementary information: EMEA/H/C/000839/II/0041 (D2015-3165) p3. Submitted to the EMA, 22 May 2015, FDA NDA 204410 Opsimit (macitentan) PM Overview.

The table below shows the available sources of combination data for ambrisentan.

Table 2. Sources of combination data with ambrisentan

	AMBITION	VOLT	ATHENA 1	ARIES 3	Zhuang	Total
Upfront combination with Tadalafil	302					302
Sildenafil added to ambrisentan		128				128
Ambrisentan added to sildenafil		383	31	57		471
Tadalafil added to ambrisentan	44	52			124	220
Ambrisentan added to tadalafil	26	12	7			45
Prostacycline added to ambrisentan	57	79				136
Ambrisentan added to prostacycline		96		22		118

Source Data: CSR Tables 14, CSR table 65, Table 2000.26, VOLT Tables 55.0101, 55.0102, 55.0201, 55.0202, 55.0103 and 55.0203, Badesch 2012, Zhuang 2014, GSK response to Volibris AMBITION CHMP request for supplementary information: EMEA/H/C/000839/II/0041 (D2015-3165) p3. Submitted to the EMA, 22 May 2015.

For a general recommendation in section 4.1 of use in combination, there is a need to provide compelling data with different specific PAH medications (Doc. Ref. EMEA/CHMP/EWP/356954/2008). In this respect, the applicant was requested to show data available with ambrisentan in combination with PAH agents other than tadalafil (i.e.: sildenafil, vardenafil, or prostanoids).
Ambrisentan was first approved in 2007 and there are a number of additional studies that contain data on combination use with ambrisentan, which means there is a greater totality of use and data in combination use with ambrisentan (Table 2). The extent of combination data with ambrisentan includes 560 patients in combination with tadalafil, 600 patients in combination with sildenafil and 232 patients in combination with prostacyclines from 5 clinical studies.

It was accepted that these data provide comparable evidence with existing data with macitentan, for which a general recommendation of use as monotherapy or in combination was granted. Additionally, the indication statement for Adempas (riociguat) for the treatment of PAH supports combination use with endothelin receptor antagonists including ambrisentan ("*as monotherapy or in combination with endothelin receptor antagonists"*).

The company provided a new proposal for the indication as follows:
"*Volibris is indicated for* ***initiation and maintenance in the long-term*** *treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III,* ***including use in combination treatment*** *(see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease*."

In view of the above, the general mention to "... *including use in combination treatment*" was considered consistent with the indications granted for Opsumit and Adempas, does not deny patient access to treatment options and physician choice of treatment (e.g.: not viewed as limited to combination with tadalafil), and was deemed acceptable by the CHMP.
However the CHMP did not accept to modify the current wording of the indication from "*treatment " into "initiation and maintenance in the long term",* as there is no scientific or regulatory justification supporting the modification.
Overall the CHMP considered that the ambition data together with the additional supportive justification provided support the inclusion of the use in combination treatment in the indication.

Finally, with respect to posology stated in the SmPC, the CHMP considered that the posology should accurately reflect the up titration (from 5 mg to 10 mg) and down titration (when needed) process included in AMBITION.
Ambrisentan was up titrated from 5 mg OD (initial dose) to 10 mg OD (target dose) after 8 weeks, and tadalafil was up titrated from 20 mg OD (initial dose) to 40 mg OD after 4 weeks if the therapy was well tolerated. If the subject did not tolerate the treatment, down titration was initiated. Patients recruited into the study were purely naive. Some additional PAH medications, like nitrates, and specific PAH medications, like other ERAs, PDE5is and inhaled nitric oxide were not allowed.

2.4.3. Conclusions on the clinical efficacy

The pivotal study supporting current variation is the AMBITION study (n=605 patients), which was a well designed and acceptably executed RCT in PAH. The results of this study show superiority of ambrisentan+tadalafil versus the pooled monotherapy and versus the two monotherapies with each of the compounds separately on the main endpoint of clinical failure, as well as superiority over the pooled monotherapy and versus the two monotherapies with each of the compounds separately for the supportive/secondary endpoints of Change in NT-pro-BNP and change in 6MWD.

Additional justifications provided to the CHMP concerns were considered acceptable and the main point described below, in relation to the claimed extension of indication related to combination therapy.

However, the definition of "clinical failure" used as primary endpoint was further explored and clarified with additional analysis.. Several sensitivity analyses showed consistency in the primary endpoint, including the analysis in the ITT population and in the investigator-assessed clinical failure events. The effect on the primary endpoint was also consistent in most subgroups (FC).

The applicant analysed the time to first clinical worsening (CW) event (defined as the composite of "death", "hospitalization for worsening PAH" and "disease progression"; i.e.: excluding "unsatisfactory long-term clinical response" from the main endpoint). This analysis yielded statistically significant results for the CT

versus pooled MT (HR = 0.51; 95% CI: 0.34 to 0.78) and versus ambrisentan monotherapy (HR = 0.44; 95%CI: 0.28 to 0.70) but not versus tadalafil monotherapy (HR = 0.61; 95%CI: 0.36 to 1.03). Anyway, the trend in the secondary endpoint of CW was positive in favor of the CT versus tadalafil monotherapy and similar to that obtained for the primary endpoint. These results are likely to be attributed to insufficient statistical power, but not because the effect on CW could be considered different to that obtained in the primary endpoint of "clinical failure ", which is considered clinically relevant. No significant differences between treatment were found in mortality, change in WHO FC, BDI score or QoL scores.

Sequential CT is the most widely utilized strategy both in clinical trials and in clinical practice. From monotherapy there is addition of a second and then third drug in cases of inadequate clinical results or in cases of deterioration [Galie et al. J Am Coll Cardiol. 2013;62:D60–72]. The AMBITION study has added further evidence on CT by showing that, in naive FC II-III patients with PAH, starting with ambrisentan-tadalafil combination therapy may be more effective than starting with monotherapy. The improvement (less clinical failures) was clinically relevant, particularly in patients with FC II, which is reassuring.

The appropriateness of the claim of combination therapy in the indication was debated during the procedure. The efficacy data from the AMBITION study in combination with tadalafil together with the additional evidence from other studies provided are acceptable to support an extension of indication. In response to the 3rd RSI, the applicant proposal below was consistent with the indications granted for Opsumit and Adempas, does not deny patient access to treatment options and physician choice of treatment (e.g.: not viewed as limited to combination with tadalafil), thus considered acceptable.

However the CHMP did not accept to modify the current wording of the indication from "*treatment " into initiation and maintenance in the long term",* as there is no scientific or regulatory justification supporting the modification.
Overall the CHMP considered that the ambition data together with the additional supportive justification provided support for the inclusion of the use in combination treatment in the indication as follows :
Volibris, is indicated for the treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, ***including use in combination treatment*** ~~*to improve exercice capacity*~~ *(see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.*

2.5. Clinical safety

2.5.1. Introduction

Current application is based on the AMBITION pivotal study, which was conducted at 120 investigational centers in 14 countries. A total of 764 subjects were screened, 610 subjects were randomized to IP, and 605 subjects received IP. All 605 subjects who received IP were included in the ITT population, 500 were included in the mITT population, and 105 were included in the non-mITT population. Data for the mITT population is primarily presented in this report.

The AMBITION study is the pivotal trial within this application. A total of 764 subjects were screened, 610 subjects were randomized to IP, and 605 subjects received IP.

3 analysis populations were evaluated for safety:

a) ITT: randomized subjects who received ≥ 1 dose of investigational product);

b) mITT: Subjects in the ITT population who met the Protocol Amendment No. 2 (without potential diastolic dysfunction or thromboembolic PAH.

c) non-mITT population: population with potential PAH due to covert diastolic dysfunction being enrolled (WHO Group 2) or associated thromboembolic PAH.

Time period for assessing safety depending on medication received:

a) Through FAV (from baseline to final assessment visit): Patients without clinical failure. The target doses for subjects in the AMBITION study were 10 mg of ambrisentan once daily and 40 mg of tadalafil once daily.

b) From BCT initiation: following the declaration of a clinical failure event by the investigator (the investigator did not need to wait for a decision from the Clinical Endpoints Committee), the investigator could request that the subject receive post-clinical failure blinded combination therapy (BCT) (to ensure the subject received combination therapy regardless of randomized treatment) and/or add non-parenteral prostanoids (inhaled) to the current therapy, if deemed appropriate.

2.5.1.1. Patient exposure

Overall subject exposure to IP (on randomized treatment) through FAV in the mITT population was generally similar across treatment groups: mean of 550.0 days each for ambrisentan and tadalafil in the combination therapy group and 466.5 and 501.2 days in the ambrisentan and tadalafil monotherapy groups, respectively.

In the mITT population, 83 subjects received BCT blinded combination therapy and 6 subjects who had not fully uptitrated received BCT monotherapy. Exposure to IP during BCT was longer during BCT blinded combination therapy (mean of 356.8 days each for ambrisentan and tadalafil) than during BCT monotherapy (55.6 and 14 days in the ambrisentan and tadalafil BCT monotherapy groups, respectively). Exposure data during randomized treatment for subjects in the non-mITT population are similar to those in the mITT population (Table 17).

Table 17. Summary of Overall Exposure to IP through FAV (mITT Population and non-mITT Population separately)

mITT population Exposure on Randomized Treatment mean (SD)	On Randomized Treatment			
	Combination Therapy		Monotherapy	
	Ambrisentan N=253	Tadalafil N=253	Ambrisentan N=126	Tadalafil N=121
Daily Dose (mg)	8.6 (1.80)	36.2 (6.15)	8.6 (1.58)	37.0 (4.19)
Cumulative Dose (mg)	5025.3 (3351.35)	20937.0 (13291.98)	4336.9 (3412.17)	19324.8 (13083.97)
Days on IP	550.0 (340.79)	550.0 (340.79)	466.5 (341.35)	501.2 (328.68)
Exposure During Blinded Combination Therapy mean (SD)	From BCT Initiation			
	Blinded Combination Therapy		BCT Monotherapy	
	Ambrisentan N=83	Tadalafil N=83	Ambrisentan N=5	Tadalafil N=1
Daily Dose (mg)	9.6 (1.22)	37.6 (5.27)	10.0 (0)	20.0 (-)
Cumulative Dose (mg)	3393.4 (2801.32)	13540.2 (11228.81)	556.0 (475.58)	280.0 (-)
Days on IP	356.8 (289.95)	356.8 (289.96)	55.6 (47.56)	14.0 (-)
Non-mITT population Exposure on Randomized Treatment, mean (SD)	On Randomized Treatment			
	Combination Therapy		Monotherapy	
	Ambrisentan N=49	Tadalafil N=49	Ambrisentan N=26	Tadalafil N=30
Daily Dose (mg)	8.5 (1.98)	34.8 (7.67)	8.3 (1.96)	34.8 (6.95)
Cumulative Dose (mg)	5238.9 (4130.90)	21498.0 (16756.41)	4496.7 (3511.87)	18080.7 (15797.04)
Days on IP	557.3 (419.92)	557.3 (419.92)	505.2 (370.79)	466.1 (395.43)
Exposure During Blinded Combination Therapy, mean (SD	From BCT Initiation			
	Blinded Combination Therapy		BCT Monotherapy	
	Ambrisentan N=19	Tadalafil N=19	Ambrisentan N=0	Tadalafil N=0
Daily Dose (mg)	9.9 (0.46)	35.0 (8.46)	-	-
Cumulative Dose (mg)	5023.9 (2893.21)	17865.3 (10986.51)	-	-
Days on IP	506.4 (286.89)	506.4 (286.89)	-	-

Cumulative Dose = Sum of all doses over the study.
Days on IP = (stop date of IP − start date of IP) + 1.
Daily Dose = Cumulative Dose / Days on IP.
Source: m5.3.5.1, AMB112565/GS-US-300-0140, Source Table 19.1

2.5.1.2. Adverse events

Safety data were collected for the entire study from Baseline to last contact. However, the main period of interest for the safety analyses was Baseline to FAV because treatment assignments were blinded during this time period and this was the period assessed in the primary efficacy evaluation.

Most Commonly Reported Adverse Events

The most commonly reported AEs by system organ class (SOC) from Baseline to FAV are summarized in Table 19. Overall, there were no meaningful differences between treatment groups or populations in regard to the types of SOCs in which AEs were commonly reported in the study.

Table 19. Most Commonly Reported (≥ 5% Subject Incidence in Any Randomized Treatment Group) Adverse Events (Baseline to FAV) by System Organ Class; mITT and Non-mITT (on Randomized Treatment) Populations

	On Randomized Treatment											
	mITT						Non-mITT					
	Combination Therapy N=253		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		Combination Therapy N=49		Ambrisentan Monotherapy N=26		Tadalafil Monotherapy N=30	
System Organ Class	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any AE	247	(98)	120	(95)	114	(94)	49	(100)	26	(100)	28	(93)
General disorders and administration site conditions	168	(66)	75	(60)	63	(52)	34	(69)	21	(81)	17	(57)

	On Randomized Treatment											
	mITT						Non-mITT					
	Combination Therapy N=253		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		Combination Therapy N=49		Ambrisentan Monotherapy N=26		Tadalafil Monotherapy N=30	
System Organ Class	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Infections and infestations	165	(65)	75	(60)	66	(55)	34	(69)	17	(65)	18	(60)
Nervous system disorders	158	(62)	69	(55)	56	(46)	30	(61)	18	(69)	19	(63)
Respiratory, thoracic, and mediastinal disorders	149	(59)	72	(57)	67	(55)	29	(59)	19	(73)	16	(53)
Gastrointestinal disorders	147	(58)	64	(51)	68	(56)	28	(57)	12	(46)	16	(53)
Musculoskeletal and connective tissue disorders	125	(49)	54	(43)	60	(50)	28	(57)	10	(38)	16	(53)
Vascular disorders	76	(30)	35	(28)	27	(22)	15	(31)	5	(19)	8	(27)
Skin and subcutaneous tissue disorders	66	(26)	31	(25)	27	(22)	11	(22)	6	(23)	12	(40)
Eye disorders	61	(24)	16	(13)	22	(18)	15	(31)	4	(15)	8	(27)
Metabolism and nutrition disorders	58	(23)	28	(22)	28	(23)	19	(39)	13	(50)	7	(23)
Investigations	57	(23)	19	(15)	25	(21)	14	(29)	7	(27)	6	(20)
Blood and lymphatic system disorders	53	(21)	12	(10)	20	(17)	10	(20)	6	(23)	4	(13)
Cardiac disorders	50	(20)	37	(29)	43	(36)	20	(41)	11	(42)	9	(30)
Psychiatric disorders	41	(16)	16	(13)	19	(16)	7	(14)	2	(8)	2	(7)
Injury, poisoning, and procedural complications	39	(15)	18	(14)	26	(21)	14	(29)	6	(23)	5	(17)

	On Randomized Treatment											
	mITT						Non-mITT					
	Combination Therapy N=253		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121		Combination Therapy N=49		Ambrisentan Monotherapy N=26		Tadalafil Monotherapy N=30	
System Organ Class	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Ear and labyrinth disorders	31	(12)	13	(10)	9	(7)	5	(10)	3	(12)	4	(13)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	18	(7)	5	(4)	7	(6)	2	(4)	3	(12)	1	(3)
Reproductive system and breast disorders	18	(7)	12	(10)	14	(12)	3	(6)	3	(12)	2	(7)
Renal and urinary disorders	13	(5)	10	(8)	9	(7)	8	(16)	2	(8)	0	-
Immune system disorders	10	(4)	3	(2)	3	(2)	2	(4)	2	(8)	1	(3)

Note: Only AEs with an onset between the first dose of IP and the last dose of IP + 30 days through FAV are tabulated.
Source: m5.3.5.1, AMB112565/GS-US-300-0140, Source Table 17.6 and Table 19.6

Adverse Events by severity

In the mITT population, most of the AEs reported across all 3 treatment groups from Baseline to FAV were mild or moderate in severity (Table 21). The percentage of subjects with severe AEs was generally similar in the combination therapy, ambrisentan monotherapy, and tadalafil monotherapy groups (39%, 33%, and 40%, respectively).

In the non-mITT population, most of the AEs reported across all 3 treatment groups from Baseline to FAV were severe. The percentage of subjects with severe AEs was higher in the combination therapy and ambrisentan monotherapy groups (57% and 65%, respectively) than in the tadalafil monotherapy group (33%).

In the ITT population, like the mITT population, most of the AEs reported across all 3 treatment groups from Baseline to FAV were mild or moderate in severity. The percentage of subjects with severe AEs was generally similar in the combination therapy, ambrisentan monotherapy, and tadalafil monotherapy groups (42%, 38%, and 38%, respectively).

Adverse Events related to study medication

In the mITT population, the percentage of subjects with any AE considered by the investigator to be related to IP in the Baseline to FAV time period was higher in the combination therapy group (75%) than in either the ambrisentan (60%) or tadalafil (56%) monotherapy groups). In this population, the most common types of IP-related AEs (≥ 5% subject incidence in any randomized treatment group) were generally similar across treatment groups (Table 22). The 3 most common IP-related AEs in each treatment group were as follows:

- Combination therapy group: headache (38%), peripheral edema (30%), and nasal congestion (16%)
- Ambrisentan monotherapy group: peripheral edema (27%), headache (25%), and flushing (12%)
- Tadalafil monotherapy group: headache (22%), peripheral edema (13%), and myalgia (8%)
-

In the non-mITT population, the percentages of subjects with IP-related AEs in the Baseline to FAV time period were slightly higher in the combination therapy and ambrisentan monotherapy groups (71% and 69%, respectively) than in the tadalafil monotherapy group (63%). In this population, the most common IP-related AEs (≥ 5% subject incidence in any randomized treatment group) were generally similar across treatment groups (Table 23). The 3 most common IP-related AEs in each treatment group were as follows:

- Combination therapy group: headache (29%), peripheral edema (22%), and myalgia (10%)
- Ambrisentan monotherapy group: headache (35%), peripheral edema (31%), and nasal congestion (15%)
- Tadalafil monotherapy group: headache (27%), peripheral edema (17%), and dyspnea (13%)

In the ITT population, like the mITT population, the percentage of subjects with IP-related AEs in the Baseline to FAV time period was higher in the combination therapy group (75%) than in either the ambrisentan (62%) or tadalafil (58%) monotherapy groups. The 3 most common IP-related AEs in each treatment group in the ITT population were similar to those in the mITT population, including peripheral edema and headache in each treatment group, plus nasal congestion in the combination therapy and ambrisentan monotherapy groups, and myalgia and gastroesophageal reflux disease in the tadalafil monotherapy group. The most common events related to IP for the EU subjects did not differ from the group as a whole.

Table 22. Most Common (≥ 5% Subject Incidence in Any Randomized Treatment Group) Adverse Events Related to IP by Preferred Term (Baseline to FAV); mITT (on Randomized Treatment) Population

	On Randomized Treatment					
	Combination Therapy N=253		Ambrisentan Monotherapy N=126		Tadalafil Monotherapy N=121	
Preferred Term	n	(%)	n	(%)	n	(%)
Headache	96	(38)	32	(25)	27	(22)
Oedema peripheral	75	(30)	34	(27)	16	(13)
Nasal congestion	40	(16)	12	(10)	7	(6)
Flushing	38	(15)	15	(12)	6	(5)
Nausea	21	(8)	9	(7)	6	(5)
Dyspepsia	19	(8)	2	(2)	6	(5)
Diarrhoea	18	(7)	9	(7)	7	(6)
Dizziness	18	(7)	9	(7)	8	(7)
Gastrooesophageal reflux disease	16	(6)	6	(5)	7	(6)
Anaemia	14	(6)	2	(2)	4	(3)
Hypotension	14	(6)	3	(2)	4	(3)
Myalgia	12	(5)	5	(4)	10	(8)
Sinus congestion	12	(5)	6	(5)	2	(2)
Arthralgia	4	(2)	4	(3)	6	(5)

Note: Only AEs with an onset between the first dose of IP and the last dose of IP + 30 days through FAV are tabulated. Common AEs are those with ≥ 5% (with rounding) incidence for randomized treatment. Where relationship was unknown, for the purpose of this table, the relationship was assumed to be related. IVRS unblinding may have occurred before the EoS clinic visit, so there was potential for bias in the assessment of AE severity.

Analysis of Adverse Events by Organ System or Syndrome

The assessment of AEs by organ system or syndrome was confined to a categorical evaluation of AESIs. These categories included AEs related to fluid retention, hypotension, anemia, hypersensitivity, and liver events. The AESI categories were identified based on the known side effect profiles of ambrisentan and tadalafil as well as any potential for additive or synergistic adverse reactions.

CHMP comments :
Compared to monotherapy, patients on CT had: a) more total AEs, severe adverse events, related AEs, AEs leading to permanent discontinuation of study medication: b) similar total SAEs and AE leading to withdrawal from the study: c) less fatal SAEs (ITT population).

Similar results were found in the mITT and non-mITT populations.

By system-organ class, most commonly reported AEs where "general disorders and administration site conditions" (66% in the CT versus 52-60% in the MT groups), "infections and infestations" (65% in the CT group versus 55-60% in the MT groups) and "nervous system disorders" (62% in the CT group versus 46-55% in the MT groups) (mITT). Other AEs that were more frequent in the CT group than in the MT groups where "eye disorders" (24% vs. 13-18%) and "ear and labyrinth disorders" (12% vs. 7-10%) (mITT).

The most commonly reported AEs in the CT that in addition were found with >5% difference in subject incidence versus MT) (mITT population) were: **Fluid retention** (55% combination, 40% ambrisentan, 36% tadalafil); **Peripheral oedema** (45% combination, 33% ambrisentan, and 28% tadalafil), **Headache** (42%

combination, 33% ambrisentan, and 35% tadalafil) and **nasal congestion** (21% combination, 15% ambrisentan, and 12% tadalafil). Other AEs that were more frequent in the CT than in the MT groups were**:** **Dizziness** (20% combination, 19% ambrisentan, and 12% tadalafil); **Anemia** (20% combination, 10% ambrisentan, and 13% tadalafil); **Flushing** (15% combination, 14% ambrisentan, and 9% tadalafil); **Dyspepsia** (11% combination, 4% ambrisentan, and 12% tadalafil); **Bronchitis** (11% combination, 4% ambrisentan, and 8% tadalafil)

The 6 most common drug-related AEs in the CT group (that in addition where more frequent in the CT than in the MT groups) were: **headache** (38% combination, 25% ambrisentan, 22% tadalafil); **peripheral edema** (30% combination; 27% ambrisentan; 13% tadalafil); **nasal congestion** (16% combination; 10% ambrisentan, 6% tadalafil); **flushing** (15% combination, 12% ambrisentan, 5% tadalafil); **nausea** (8% combination, 7% ambrisentan, 5% tadalafil); and **dyspepsia** (8% combination, 2% ambrisentan, 5% tadalafil).

Exclusion criteria in AMBITION pivotal study were quite more extensive than the contraindications already included in the SmPCs of Volibris (ambrisentan) and Adcirca (tadalafil), thus limiting the external validity of the study and probably resulting in underestimation of adverse event and adverse reaction rates. In this respect:

a) It should be added in Section 4.8 that the expected frequencies of adverse reactions with the combination therapy is based on a selected patient population, as patients with some risk factor for developing adverse reactions to ambrisentan were excluded (e.g.: anemia, fluid retention, retinal problems, baseline values of ALT and/or AST>2xULN, when contraindication to Volibris is for >3xULN).

b) A warning should be included in section 4.4 indicating that, when ambrisentan is given concomitantly with tadalafil, the occurrence of peripheral edema and anemia is significantly increased, particularly during the first month of treatment. Additionally an increase in frequency for the following ADR is noted; anemia, headache, nasal congestion, dizziness, flushing, dyspepsia and bronchitis
The SmPC wording suggested "slightly increase in anemia" should be amended, as a two-fold increase in anemia (from 10% to 20%) cannot be considered as "slight".

c) The imbalance in adverse events of anemia (CT 20% vs ambrisentan 10%, mITT, FAV) is of concern, as anemia is a marker of poor prognosis in the long-term in patients with PAH (Krasuski et al. Int J Cardiol. 2011;150:291-5; Hampole et al. Am J Cardiol. 2009; 104:868-72) and was further clarified.
The mean change from baseline in haemoglobin and haematocrit are quite insensitive about significant variations in individual patients.The incidence of anemia reported as adverse event on combination treatment is 10% higher than ambrisentan treatment and 7% higher than tadalafil treatment.

Looking at patients with transfusions (CT: 12; ambrisentan MT: 5; tadalafil: 10), it seems that tadalafil is the main responsible for anemia in the CT, which is consistent with the higher rate of AEs of anemia in the tadalafil MT group than in the ambrisentan MT group (13% vs 10).

With respect to the analysis of the main endpoint in patients with anemia AEs, there is a discrepancy between the mITT (efficacy population) analysis (fewer clinical failure events with the CT: 20% vs ambrisentan MT 29% and tadalafil MT 40%), and the ITT (safety population) analysis (patients experiencing a clinical failure event following the onset of anemia was approximately the same: CT 25% vs ambrisentan MT 24% vs. tadalafil MT 27%). In both cases, it seems that the worse results in both analyses are for patients on tadalafil MT, which is consistent with a more relevant decrease in efficacy with tadalafil MT than with the other options in patients who develop anemia.

Finally, with respect to all-cause mortality, the numerical trend was against the CT in patients with anemia in the mITT (CT 2 cases vs ambrisentan MT 0 cases vs tadalafil MT 2 cases) and the ITT (CT 5 cases vs. ambrisentan MT 0 cases vs tadalafil MT 2 cases), although events numbers were very low.

Therefore, data provided suggest that in patients having an AE of anemia, there is a less robust benefit in efficacy with the CT versus pooled MT than in patients without anemia, mainly attributable to the tadalafil component. However, no definitive conclusions can be reached, due to the limitations of subgroup analyses and low event rates.

d) It was further explored whether the lack of benefit in QoL despite lower rate of hospitalisations with CT could be due to the significant increase in some adverse events with the CT compared to monotherapy (e.g.: fluid retention, peripheral oedema, headache, anemia). Subgroup analyses of QoL in patients with and without these adverse events could be of interest.
The applicant stated that that there is an improvement in QoL for all study arms and no statistical difference between them. This is endorsed, but the requested analyses were not provided by the MAH. The increased rate of AEs is probably the cause for not finding benefits in QoL with the CT, despite a significantly better efficacy. Anyway, this issue will not change the Benefit risk and no further information was pursued.

Hypersensitivity reactions were more common in the CT group than in the ambrisentan or tadalafil monotherapy groups (13% vs. 10% vs. 7%). The most commonly reported hypersensitivity AE was rash (CT group 7%, ambrisentan monotherapy 5%, taladafil monotherapy 2%). Most cases were mild and only 2 of them (in the ambrisentan monotherapy group) required discontinuation of IP or withdrawal from study. The SmPC already includes that rash is a "very common" adverse reaction observed at a higher frequency category when ambrisentan was administered long term (>12 weeks duration) in combination with tadalafil, which is acceptable.

Statistical analysis of safety data: The applicant, upon request, submitted additional statistical analysis of the safety data to show whether there is a statistically significant difference in the safety profile of the combination group in comparison with the monotherapy groups. Of greatest interest would be the analysis of SAEs (fatal included) and AESI (anemia, fluid retention). The Applicant stated that due to the fact the study was not powered on adverse events and given the multiple events discussed only descriptive statistics were presented. This is acknowledged by the CHMP and not pursued further.

2.5.1.3. Serious adverse event/deaths/other significant events

Deaths

For the safety summaries, treatment-emergent fatal AEs were reported between 1st dose of study drug and last dose + 30 days (on randomized treatment and from BCT initiation). For the efficacy analyses, outcomes of death were reported to last contact as part of the vital status follow up and thus include subject deaths which occurred >30 days after discontinuation of IP. Outcomes of death reported >30 days after discontinuation of IP were not reported as fatal AEs for safety purposes. Table 28 summarizes fatal AEs by population for the time periods Baseline to FAV and overall (on randomized treatment), as well as subject deaths from the efficacy analysis for the time periods Baseline to last contact (and from BCT initiation).

Table 28. Summary of Subjects with Fatal AEs from Safety Summaries and Deaths from Efficacy Analyses; by Population

	Randomized Treatment Groups					
	Combination Therapy		Ambrisentan Monotherapy		Tadalafil Monotherapy	
	n/N	(%)	n/N	(%)	n/N	(%)
Fatal AEs (from safety summaries, on randomized treatment)						
mITT (Baseline to FAV)	7/253	(3)	3/126	(2)	8/121	(7)
mITT (Overall)	8/253	(3)	3/126	(2)	9/121	(7)
Deaths (from efficacy analyses; includes subject deaths on BCT and deaths from vital status follow-up)						
mITT (Baseline to Last Contact)	21/253	(8)	14/126	(11)	13/121	(11)
Fatal AEs (from safety summaries, on randomized treatment)						
Non-mITT (Baseline to FAV)	1/49	(2)	3/26	(12)	2/30	(7)
Non-mITT (Overall)	2/49	(4)	3/26	(12)	2/30	(7)
Deaths (from efficacy analyses; includes subject deaths on BCT and deaths from vital status follow-up)						
Non-mITT (Baseline to Last Contact)	8/49	(16)	5/26	(19)	9/30	(30)
Fatal AEs (from safety summaries, on randomized treatment)						
ITT (Baseline to FAV)	8/302	(3)	6/152	(4)	10/151	(7)
ITT (Overall)	10/302	(3)	6/152	(4)	11/151	(7)
Deaths (from efficacy analyses; includes subject deaths on BCT and deaths from vital status follow-up)						
ITT (Baseline to Last Contact)	29/302	(10)	19/152	(13)	22/151	(15)

With respect to all-cause death, as commented in the efficacy section:

Mortality was relatively low for a severe disease like PAH and for an mean exposure to study drugs about 1,5 years (mean exposure between 467 to 550 days). All-cause mortality ranged from 18 cases in the mITT-FAV (3% in the combination therapy compared to 2% in ambrisentan monotherapy and 7% in tadalafil monotherapy) to 70 cases in the ITT-End-of-Study (10% in the combination therapy compared to 13% in ambrisentan monotherapy and 15% in tadalafil monotherapy).

In addition, numbers of deaths shown in the tables correspond to the baseline to FAV (24 deaths in the ITT population, FAV), which is an underestimation of total deaths (those occurring after FAV were not included). Total deaths in AMBITION were 70 cases (ITT population, baseline to last contact). The applicant is requested to provide with a summary table including "all" 70 deaths reported in AMBITION study in the ITT population (by intended treatment group) (baseline to FAV; FAV to end of study; and end of study to last contact). The 70 deaths should be reported by group and SOC.

With respect to the causes of death in the ITT population (FAV), the trend towards a lower number of deaths in the CT group versus pooled MT was related to deaths due to heart failure or cardiac arrest (1 in the CT group vs. 5 deaths in the pooled MT group) and worsening of PAH (2 in CT group vs. 3 deaths in the pooled MT group), which is consistent with the results of the primary endpoint favouring CT versus pooled MT.

Some discrepancies have been identified in the submitted data for SAE (Deaths) and were further clarified by the applicant.

2.5.1.4. Other SAEs

In the mITT population (Table 32), generally similar percentages of subjects across treatment groups from Baseline to FAV had a serious adverse event (SAE; 36% of subjects each in the combination therapy and

ambrisentan monotherapy groups and 41% of subjects in the tadalafil monotherapy group). The 3 most common SAEs in each treatment group were as follows:

- Combination therapy group: pulmonary hypertension (4%), pneumonia (4%), and dyspnea and syncope (3% each)
- Ambrisentan monotherapy group: pulmonary hypertension (9%), pneumonia (6%), and cardiac failure and syncope (3% each)
- Tadalafil monotherapy group: pulmonary hypertension (7%) and syncope and anemia (4% each)

No SAEs were reported more commonly (> 5% difference in subject incidence) in the combination therapy group than in either monotherapy group in the mITT population from Baseline to FAV.

In the non-mITT population (Table 33), the percentages of subjects from Baseline to FAV with an SAE in the combination therapy group (57%) and ambrisentan monotherapy group (58%) were higher than that in the tadalafil monotherapy group (43%). The most common SAEs in each treatment group were as follows:

- Combination therapy group: pneumonia and anemia (8% each), which were the only SAEs reported for > 2 subjects in this group
- Ambrisentan monotherapy group: pulmonary hypertension (19%), right ventricular failure (15%), and pneumonia (12%), which were the only SAEs reported for > 2 subjects in this group)
- Tadalafil monotherapy group: no SAEs were reported for > 2 subjects in this group

The only SAE reported more commonly (> 5% difference in subject incidence) in the combination therapy group than in either monotherapy group in the non-mITT population from Baseline to FAV was anemia, which was reported for 8% of subjects in the combination therapy and ambrisentan monotherapy groups and no subjects in the tadalafil monotherapy group.

SAEs in the ITT Population (Baseline to FAV)

The percentage of subjects with any SAE was 40% in the combination therapy group, 39% in the ambrisentan monotherapy group, and 42% in the tadalafil monotherapy group (Table 34). The 3 most frequently reported SAEs in the combination therapy group were pneumonia, pulmonary hypertension, dyspnea, anemia, and syncope. In the ambrisentan monotherapy group the 3 most frequently reported SAEs were pulmonary hypertension, pneumonia, and right ventricular failure. In the tadalafil monotherapy group the 3 most frequently reported SAEs were pulmonary hypertension, pneumonia, and syncope. No SAEs were reported more commonly (> 5% difference in subject incidence) in the combination therapy group than in either monotherapy group in the ITT population from Baseline to FAV.

Table 34. Serious Adverse Events on Randomized Treatment (Baseline to FAV) Reported in >=2 Subjects in Any Treatment Group; ITT Population

SOC (bolded) Preferred Term	On Randomized Treatment					
	Combination Therapy N=302		Ambrisentan Monotherapy N=152		Tadalafil Monotherapy N=151	
	n	(%)	n	(%)	n	(%)
Any SAE	120	(40)	60	(39)	63	(42)
Respiratory, thoracic and mediastinal disorders	**42**	**(14)**	**25**	**(16)**	**22**	**(15)**
Pulmonary hypertension	11	(4)	16	(11)	10	(7)
Dyspnoea	9	(3)	2	(1)	4	(3)
Pleural effusion	4	(1)	0	-	2	(1)
Pulmonary oedema	4	(1)	1	(<1)	0	-
Respiratory failure	4	(1)	2	(1)	1	(<1)
Acute respiratory failure	3	(<1)	1	(<1)	0	-
Pulmonary embolism	3	(<1)	0	-	2	(1)
Atelectasis	2	(<1)	1	(<1)	0	-
Pulmonary arterial hypertension	2	(<1)	0	-	1	(<1)
Haemoptysis	0	-	2	(1)	0	-
Infections and infestations	**38**	**(13)**	**21**	**(14)**	**21**	**(14)**
Pneumonia	15	(5)	10	(7)	6	(4)
Respiratory tract infection	4	(1)	1	(<1)	1	(<1)
Cellulitis	2	(<1)	4	(3)	3	(2)
Gastroenteritis	2	(<1)	0	-	0	-
Lung infection	2	(<1)	1	(<1)	1	(<1)
Sepsis	2	(<1)	1	(<1)	3	(2)
Urinary tract infection	2	(<1)	1	(<1)	0	-
Bronchitis	1	(<1)	0	-	3	(2)
Upper respiratory tract infection	1	(<1)	0	-	2	(1)
Cardiac disorders	**24**	**(8)**	**14**	**(9)**	**15**	**(10)**
Right ventricular failure	5	(2)	6	(4)	3	(2)
Cardiac failure	4	(1)	5	(3)	3	(2)
Cardiac failure congestive	3	(<1)	2	(1)	1	(<1)
Angina pectoris	2	(<1)	2	(1)	0	-
Atrial flutter	2	(<1)	1	(<1)	0	-
Cardiac arrest	2	(<1)	0	-	1	(<1)
Coronary artery stenosis	2	(<1)	0	-	0	-
Supraventricular tachyarrhythmia	2	(<1)	0	-	0	-
Atrial fibrillation	1	(<1)	1	(<1)	3	(2)
Supraventricular tachycardia	0	-	0	-	2	(1)
General disorders and administration site conditions	**15**	**(5)**	**4**	**(3)**	**8**	**(5)**
Non-cardiac chest pain	6	(2)	0	-	0	-
Oedema peripheral	5	(2)	1	(<1)	0	-
Pyrexia	1	(<1)	1	(<1)	2	(1)
Chest pain	0	-	0	-	2	(1)
Gastrointestinal disorders	**13**	**(4)**	**2**	**(1)**	**9**	**(6)**
Gastrointestinal haemorrhage	3	(<1)	1	(<1)	1	(<1)
Gastritis	2	(<1)	0	-	0	-
Gastrooesophageal reflux disease	1	(<1)	0	-	2	(1)
Blood and lymphatic system disorders	**12**	**(4)**	**3**	**(2)**	**7**	**(5)**
Anaemia	9	(3)	3	(2)	5	(3)
Iron deficiency anaemia	2	(<1)	0	-	0	-
Nervous system disorders	**12**	**(4)**	**9**	**(6)**	**11**	**(7)**
Syncope	9	(3)	5	(3)	**6**	**(4)**
Presyncope	1	(<1)	2	(1)	1	(<1)
Musculoskeletal and connective tissue disorders	**11**	**(4)**	**6**	**(4)**	**2**	**(1)**
Osteonecrosis	2	(<1)	1	(<1)	0	-
Metabolism and nutrition disorders	**10**	**(3)**	**6**	**(4)**	**5**	**(3)**
Fluid overload	5	(2)	1	(<1)	3	(2)
Fluid retention	3	(<1)	0	-	0	-
Dehydration	1	(<1)	2	(1)	1	(<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps	**9**	**(3)**	**4**	**(3)**	**3**	**(2)**
Colon cancer	2	(<1)	0	-	0	-
Basal cell carcinoma	0	-	2	(1)	0	-
Investigations	**5**	**(2)**	**1**	**(<1)**	**0**	**-**
Transaminases increased	2	(<1)	0	-	0	-
Renal and urinary disorders	**5**	**(2)**	**4**	**(3)**	**2**	**(1)**
Renal failure acute	3	(<1)	0	-	1	(<1)
Renal failure	2	(<1)	2	(1)	0	-
Vascular disorders	**5**	**(2)**	**3**	**(2)**	**4**	**(3)**
Hypotension	3	(<1)	2	(1)	2	(1)
Hepatobiliary disorders	**4**	**(1)**	**2**	**(1)**	**1**	**(<1)**
Cholelithiasis	2	(<1)	1	(<1)	0	-
Ear and labyrinth disorders	**3**	**(<1)**	**0**	**-**	**0**	**-**
Sudden hearing loss	2	(<1)	0	-	0	-
Reproductive system and breast disorders	**2**	**(<1)**	**1**	**(<1)**	**1**	**(<1)**
Vaginal haemorrhage	2	(<1)	0	-	0	-

Source: Table 18.35

Note: Only adverse events with onset between 1st dose of study drug and last dose + 30 days through FAV are tabulated.

2.5.1.5. Laboratory findings

Clinical laboratory evaluations included hematology, serum chemistry, and urinalysis.

Hematology: In the ITT population, for the period from Baseline to FAV, 18% of subjects in the combination therapy group had a hemoglobin value of clinical concern (<10 g/dl) compared with 10% in the ambrisentan monotherapy group and 14% in the tadalafil monotherapy group. This is consistent with the results of adverse events of "anemia" reported by the investigators.

Liver function tests: 9 subjects in the ITT population (5 in the combination treatment group, 2 in the ambrisentan group and 2 in the tadalafil monotherapy group) had significant liver chemistry results (aminotransferase elevations > 3 x ULN) which met the stopping criteria defined in the protocol. These results are within expected but should be interpreted with caution, as patients with aminotransferase 2-3xULN and/or bilirubin >1.5xULN at the Screening Visit were excluded from the study.

Potential Hy's Law cases (ALT >3xULN + bilirubin >2xULN): 2 subjects met biochemical criteria in Hy's Law (ITT, FAV). These 2 cases were not designated as Hy's Law cases because in each case the elevated liver enzyme levels could be attributed to other causes (lung carcinoma and cardiogenic shock).

Other parameters: no other remarkable disturbances were found in biochemistry, vital signs or ECG.

2.5.1.6. Safety in special populations

For the AMBITION study, summaries of AEs and SAEs by subgroups of sex, baseline 6-minute walk distance above or below median baseline 6-minute walk distance, baseline age group (< 65, ≥ 65 years), baseline age above or below median baseline age, etiology of PAH (idiopathic PAH/heritable PAH and nonidiopathic PAH), and baseline WHO FC (II or III) for the mITT and ITT populations showed that the AE profile and tolerability in the subgroups were consistent with the known AE profiles of ambrisentan and tadalafil.

Elderly:
There is no clinically relevant difference in the overall numbers of AEs by age, as nearly all patients had at least one AE during study regarless of age. However, in patients above 65 years, there is a trend towards a higher incidence of SAEs with CT (46%) than with monotherapy (41% in both monotherapy arms.
The data provided from AMBITION suggest no increased incidence of oedema peripheral in older subjects randomised to combination therapy as compared with monotherapy. There was no apparent age-related effect on serious oedema peripheral, serious fluid retention or serious anemia, but event rates were too low to draw any meaningful conclusion.

Children: The AMBITION study excluded subjects < 18 years of age. Therefore, no clinical data on the use of ambrisentan plus tadalafil in pediatric subjects are available.

Hepatic impairment: Subjects with severe hepatic impairment (Child-Pugh class C with or without cirrhosis), subjects with severe renal impairment (creatinine clearance < 30 mL/min), and subjects with serum ALT or AST values > 2 × ULN or serum bilirubin values > 1.5 × ULN were excluded from the AMBITION study. Therefore, no clinical data on the use of ambrisentan plus tadalafil in subjects with severe renal impairment or subjects with severe hepatic impairment are available.

Pregnancies: Three subject pregnancies were reported during the course of the study. Two pregnancies (1 CT group and 1 tadalafil monotherapy group) were terminated without further complications. The third patient (CT group) died while hospitalized for elective abortion, 9 days after the last dose of study medication.

2.5.1.7. Safety related to drug-drug interactions and other interactions

No clinically relevant PK interactions are expected between ambrisentan and tadalafil. However, both compounds are vasodilators. Therefore, a PD interaction resulting in vasodilatory (adverse) effects is likely to occur.

Hypotension was more common in the CT group than in the ambrisentan or tadalafil monotherapy groups (32% vs. 27% vs. 27%). The most commonly reported hypotensive adverse event was "dizziness" (CT group 20%, ambrisentan monotherapy 19%, taladafil monotherapy 12%). Most cases were mild and only 2 of them (in the CT group) required discontinuation of IP or withdrawal from study. The SmPC already includes that dizziness is a "very common" adverse reaction observed at a higher frequency category when ambrisentan was administered long term (>12 weeks duration) in combination with tadalafil, which is acceptable.

2.5.1.8. Discontinuation due to adverse events

AEs leading to discontinuation of IP (ITT population): similar percentages were found in the 3 groups (CT group 16%, ambrisentan group 14%, tadalafil group 13%). The 3 most frequently reported AEs leading to discontinuation of IP in the combination therapy group were dyspnea, peripheral edema and headache.

AEs leading to study withdrawal (ITT population): the percentage of subjects with these events was 11% in all 3 randomized treatment groups. The 3 most frequently TEAE reported as leading to withdrawal from the study in the combination therapy group were dyspnea, peripheral edema, and headache. In the ambrisentan monotherapy group the only TEAE leading to withdrawal from the study reported by more than 2 subjects was pulmonary hypertension. In the tadalafil monotherapy group no TEAE leading to withdrawal from the study was reported by more than 2 subjects.

The analysis of discontinuations due to AEs with CT therapy does not raise any particular concern in comparison to monotherapy with either ambrisentan or tadalafil.

2.5.1.9. Post marketing experience

Cumulative worldwide postmarketing exposure to ambrisentan and tadalafil based on sales data are estimated to be 56,600 patient-years and 53,400 patient-years, respectively.

2.5.2. Discussion on clinical safety

A total of 764 subjects were screened, 610 subjects were randomized to IP, and 605 subjects received IP. Exposure to IP (on randomized treatment) through FAV in the mITT population was generally similar across treatment groups: mean range from 467 to 550 days. Exposure to IP during BCT was longer during BCT blinded combination therapy (mean of 357 daysl) than during BCT monotherapy (56 and 14 days in the ambrisentan and tadalafil BCT monotherapy groups, respectively). This was expected as BCT was administered in stages and BCT monotherapy was administered only during the first stage for subjects randomized to monotherapy who had not uptitrated to the target dose. Exposure data during randomized treatment for subjects in the non-mITT population are similar to those in the mITT population. Exclusion criteria in AMBITION pivotal study were quite more extensive than the contraindications already included in the SmPCs of Volibris (ambrisentan) and Adcirca (tadalafil), thus limiting the external validity of the study and probably resulting in underestimation of adverse event and adverse reaction rates.

The AMBITION study excluded subjects < 18 years of age. Therefore, no clinical data on the use of ambrisentan plus tadalafil in pediatric subjects are available.

Total adverse events: compared to monotherapy, patients on CT had: a) more total AEs, severe adverse events and related AEs: b) similar total SAEs and AE leading to discontinuation or withdrawal from the study; c) less fatal SAEs (ITT population). Similar results were found in the mITT and non-mITT populations.

AEs by system-organ class: most commonly reported AEs where "general disorders and administration site conditions" (66% in the CT versus 52-60% in the MT groups), "infections and infestations" (65% in the CT group versus 55-60% in the MT groups) and "nervous system disorders" (62% in the CT group versus 46-55% in the MT groups) (mITT). Other AEs that were more frequent in the CT group than in the MT groups where "eye disorders" (24% vs. 13-18%) and "ear and labyrinth disorders" (12% vs. 7-10%) (mITT).

Most commonly reported AEs in the CT group that in addition were found with >5% difference in subject incidence versus MT (mITT population) were: Fluid retention (55% combination, 40% ambrisentan, 36% tadalafil); Peripheral edema (45% combination, 33% ambrisentan, and 28% tadalafil), Headache (42% combination, 33% ambrisentan, and 35% tadalafil) and nasal congestion (21% combination, 15% ambrisentan, and 12% tadalafil).

Other AEs that were more frequent in the CT than in the MT groups were: Hypotension (32% combination vs. 27% ambrisentan vs. 27% tadalafil), being Dizziness the more frequent manifestation (20% combination, 19% ambrisentan, and 12% tadalafil); Most cases were mild and only 2 of them (in the CT group) required discontinuation of IP or withdrawal from study. The SmPC already includes that dizziness is a "very common" adverse reaction observed at a higher frequency category when ambrisentan was administered long term (>12 weeks duration) in combination with tadalafil, which is acceptable. Anemia (20% combination, 10% ambrisentan, and 13% tadalafil); Flushing (15% combination, 14% ambrisentan, and 9% tadalafil); Dyspepsia (11% combination, 4% ambrisentan, and 12% tadalafil); Bronchitis (11% combination, 4% ambrisentan, and 8% tadalafil)

Most common drug-related AEs in the CT group, that in addition where more frequent in the CT than in the MT groups, were: headache (38% combination, 25% ambrisentan, 22% tadalafil); peripheral oedema (30% combination; 27% ambrisentan; 13% tadalafil); nasal congestion (16% combination; 10% ambrisentan, 6% tadalafil); flushing (15% combination, 12% ambrisentan, 5% tadalafil); nausea (8% combination, 7% ambrisentan, 5% tadalafil); and dyspepsia (8% combination, 2% ambrisentan, 5% tadalafil).

In conclusion, although total AEs are increased with the combination therapy as compared to monotherapy, the increase is mainly at expenses of non-serious AEs, while SAEs were similar across treatment groups and fatal SAEs were numerically lower in the CT group than in the MT groups. Therefore, there are no major safety concerns. However, some increases in labelled adverse events (anemia, fluid retention, peripheral oedema), and unlabelled events (osteonecrosis, non-cardiac chest pain and sudden hearing loss) and the potential underestimation of risk due to exclusion criteria in AMBITION study were further addressed by the applicant. Overall findings on the entire Volibris safety database (clinical trials, registries, spontaneous reports) indicate that osteonecrosis and non-cardiac chest pain do not warrant inclusion in section 4.8.

However, there were 5 cases of hearing loss/deafness (0.20%) with the CT reported by the investigators as related (all of them) and serious (3 of them). The applicant proposes to include sudden or other hearing loss for CT in the combination table of the SmPC section 4.8 which was endorsed.

Based on the above data, a warning was included in section 4.4 indicating that, when ambrisentan is given concomitantly with tadalafil, peripheral oedema and anemia was significantly increased.

The percentage of subjects with any SAE was similar in the 3 groups (CT 40%, ambrisentan 39%, tadalafil 42%) (ITT, baseline to FAV). The most frequently reported SAEs in the combination therapy group were pneumonia (15), pulmonary hypertension (11), dyspnea (9), anemia (9), and syncope (9).).

Hypersensitivity reactions were more common in the CT group than in the ambrisentan or tadalafil monotherapy groups (13% vs. 10% vs. 7%). The most commonly reported hypersensitivity AE was rash (CT group 7%, ambrisentan monotherapy 5%, taladafil monotherapy 2%). Most cases were mild and only 2 of them (in the ambrisentan monotherapy group) required discontinuation of IP or withdrawal from study. The SmPC already includes that rash is a "very common" adverse reaction observed at a higher frequency category when ambrisentan was administered long term (>12 weeks duration) in combination with tadalafil, which was acceptable.

2.5.3. Conclusions on clinical safety

The AMBITION study provides clinical safety data from 605 patients treated for 467 to 550 days (mean range) with ambrisentan in combination with tadalafil versus monotherapy with either of these compounds. Exclusion criteria in AMBITION pivotal study were quite more extensive than the contraindications already included in the SmPCs of Volibris (ambrisentan) and Adcirca (tadalafil), as some patients without contraindications to ambrisentan therapy, but at risk of developing adverse reactions with ambrisentan, were excluded (e.g.: pre-existing anemia, fluid retention, retinal problems, baseline values of ALT and/or AST>2xULN,.

Compared to monotherapy, patients on CT had: a) more total AEs, severe adverse events, related AEs, AEs leading to permanent discontinuation of study medication: b) similar total SAEs and AE leading to withdrawal from the study: c) less fatal SAEs (ITT population). Similar results were found in the mITT and non-mITT populations. Particularly, adverse events of anemia were increased with the CT (20% combination, 10% ambrisentan, and 13% tadalafil). However, ancillary analyses did not show a poorer prognosis in patients who experienced anemia with the CT. Other most commonly reported AEs in the CT group that in addition were found with >5% difference in subject incidence versus MT (mITT population) were: Fluid retention, Peripheral edema, Headache and nasal congestion). Other AEs that were more frequent in the CT than in the MT groups were: Hypotension, dizziness, flushing, dyspepsia and bronchitis. A warning was included in section 4.4 indicating the increase in anemia and peripheral oedema when ambrisentan is given concomitantly with tadalafil. Additionally the new ADR observed with the combination therapy is included (sudden or other hearing loss) in section 4.8.

Mortality was relatively low for a severe disease like PAH and for an mean exposure to study drugs about 1,5 years (mean exposure between 467 to 550 days). Regarding the quality of the data, vital status was not available for 26 patients (4%) at FAV and for 34 (6%) patients at end of study (ITT population), which is a poor figure for a population that is usually followed-up in specialised centers.

The percentage of subjects with any SAE was similar in the 3 groups (CT 40%, ambrisentan 39%, tadalafil 42%) (ITT, baseline to FAV).

Hypersensitivity reactions were more common in the CT group than in the ambrisentan or tadalafil monotherapy groups (13% vs. 10% vs. 7%), being "rash" the more commonly reported term. No major findings were evident regarding liver function tests, testicular function tests or special populations. Additional data provided by the applicant showed a higher rate of adverse reactions in patients above 65 years old compared with those below 65 years old, but with similar relative risks of adverse reactions of the CT vs. MT groups regardless of age.

In conclusion, although total AEs are increased with the combination therapy as compared to monotherapy, the increase was mainly at expenses of non-serious AEs, while SAEs were similar across treatment groups

and fatal SAEs were numerically lower in the CT group than in the MT groups. Therefore, there are no major safety concerns. SmPC amendments were made in relationship with anemia, fluid retention and hearing loss.

2.5.4. PSUR cycle

N/A

2.6. Risk management plan

The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report was endorsed by PRAC on 8 October 2015. (See Annex)

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

The PRAC considered that the risk management plan version 7.4 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 7.4 with the following content:

Safety concerns

Summary of safety concerns

Important identified risks	• Teratogenicity • Decreased haemoglobin, haematocrit, anaemia including anaemia requiring transfusion • Fluid retention (peripheral oedema, oedema) and heart failure associated with fluid retention • Hypersensitivity • Worsening dyspnoea of unclear aetiology occurring shortly after starting ambrisentan • Drug-drug interaction with cyclosporine A • Hepatotoxicity • Disease progression or death in patients with idiopathic pulmonary fibrosis
Important potential risks	• Autoimmune hepatitis • Testicular tubular atrophy/ Male infertility • Symptomatic hypotension
Important missing information	• Paediatrics • Severe renal impairment • Severe hepatic impairment • Lactation

Pharmacovigilance plan

On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan (Categories 1-3)

None

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks:		
Teratogenicity	Text within Sections 4.2, 4.3, 4.4 and 4.6 of the EU SPC	1. Pregnancy Prevention Program 2. Limited package supply
Decreased haemoglobin/haematocrit/ anaemia, including anaemia requiring transfusion	Text within Sections 4.4 and 4.8 of the EU SPC	No additional risk minimisation measures.
Fluid retention (peripheral oedema, oedema) and heart failure associated with fluid retention	Text within Sections 4.2, 4.4 and 4.8 of the EU SPC	No additional risk minimisation measures.
Hypersensitivity	Text within Sections 4.3, 4.4 and 4.8 of the EU SPC	No additional risk minimisation measures.
Worsening dyspnoea of unclear aetiology occurring shortly after starting ambrisentan	Text within Section 4.8 of the EU SPC	No additional risk minimisation measures.
Drug-drug interaction with cyclosporine A	Text within Sections 4.2, 4.5 and 5 of the EU SPC	No additional risk minimisation measures.
Hepatotoxicity	Text within Sections 4.2, 4.3, 4.4, 4.8, and 5.1 of the EU SPC	1. Prescriber/Pharmacist/Patient education materials 2. Limited package supply
Disease progression or death in patients with idiopathic pulmonary fibrosis	Text within Section 4.3 of the EU SPC	No additional risk minimisation measures.
Important Identified Potential Risks:		
Autoimmune Hepatitis	Text within Sections 4.4 and 4.8 of the EU SPC	No additional risk minimisation measures.
Testicular tubular atrophy/Male infertility	Text within Sections 4.6 and 5.3 of the EU SPC	No additional risk minimisation measures.
Symptomatic hypotension	Text within Sections 4.9 and 5.3 of	No additional risk minimisation

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the EU SPC	measures.
Missing Information:		
Paediatric use	Text within Section 4.2 of the EU SPC	No additional risk minimisation measures.
Use in patients with severe renal impairment	Text within Sections 4.2 and 5.2 of the EU SPC	No additional risk minimisation measures.
Use in patients with severe hepatic impairment	Text within Sections 4.2, 4.3 and 5.2 of the EU SPC	No additional risk minimisation measures.
Lactation	Text within Sections 4.3, 4.6 and 5 of the EU SPC	No additional risk minimisation measures.

2.7. Update of the product information

The MAH proposed to update sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and corresponding Package leaflet in order to include an expanded therapeutic indication for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1). In addition, the MAH took the opportunity to update Annex II to reflect a change in the PSUR cycle.

The main aspects related to amendments introduced in the SmPC sections, 4.1, 4.2 , 4.4 and 4.8 have been discussed earlier in the report. The key results of the ambition study are introduced in section 5.1.

2.7.1. User consultation

The submitted variation type II for expanded therapeutic indication for the treatment of pulmonary arterial hypertension, does not involve significant changes in the PIL. Therefore, the company´s justification to not undertake further consultation with target patient groups is considered acceptable.

3. Benefit-risk balance

3.1. Benefits

The AMBITION study (n=605 patients) is the single pivotal study that provides clinical data in support of the claim of combination therapy for ambrisentan. This study was a Phase 3/4, randomized, double-blind, event-driven study designed to compare the safety and efficacy of initiating pharmacotherapy with a combination of ambrisentan and tadalafil to initiating pharmacotherapy with ambrisentan or tadalafil monotherapy at the same doses. Events were blindly adjudicated by a study specific Clinical Endpoints Committee (CEC).

AMBITION included a population (mainly females) with idiopatic PAH and PAH associated to connective tissue disease in functional class II-III (mainly III) without left ventricular diastolic dysfunction (WHO Group 2).

Patients recruited into the study were purely naive. Some additional PAH medications, like nitrates, and specific PAH medications, like other ERAs, PDE5is and inhaled nitric oxide were not allowed. Ambrisentan was uptitrated from 5 mg OD (initial dose) to 10 mg OD (target dose) after 8 weeks, and tadalafil was uptitrated from 20 mg OD (initial dose) to 40 mg OD after 4 weeks if the therapy was well tolerated. If the subject did not tolerate, down-titration was initiated.

The results of the AMBITION showed superiority of ambrisentan+tadalafil combination therapy versus the pooled monotherapy with each of the compounds on the main endpoint of clinical failure [46 first events (18%) vs. 77 first events (31%); HR: 0.50; 95%CI: 0.39 to 0.72], Change in NT-pro-BNP (mean difference: -33.81 ng/L; 95%CI: -44.78 to -20.66), satisfactory clinical response (OR: 1.56; 95%CI: 1.05 to 2.32), change in 6MWH (Median difference: -22.75; 95%CI: -12.00 to +33.50), and no significant difference in mortality, change in WHO functional class, change in BDI score or Quality of Life scores.

With respect to the primary endpoint "clinical failure", the differences between the combination therapy and each of the individual monotherapy were also statistically significant for the ambrisentan monotherapy group (HR = 0.48 [95% CI: 0.31, 0.72] and for the tadalafil MT group (HR = 0.53; 95%CI: 0.34, 0.83). The 1-, 2-, and 3-year KM probabilities of having a first adjudicated clinical failure event were lower with combination therapy compared with pooled monotherapy and with each monotherapy. Several sensitivity analyses showed consistency in the primary endpoint, including the analysis in the ITT population and in the investigator-assessed clinical failure events. The effect on the primary endpoint was also consistent in most subgroups, but more pronounced in functional class II than in functional class III in relative terms. However, in absolute terms, the benefit was similar in both functional class I as absolute event rate of primary events has to be higher in functional class III than in less sick functional class II and III.PAH-related hospitalisation" was the key component driving the difference in the main efficacy endpoint. The analysis of first events of PAH hospitalisation showed a 63% decrease in risk with the combination therapy versus monotherapy (HR: 0.37; 95%CI: 0.22 to 0.64).
The applicant also analysed the time to first clinical worsening event (defined as the composite of "death", "hospitalization for worsening PAH" and "disease progression"; i.e.: excluding "unsatisfactory long-term clinical response" from the main endpoint). This analysis yielded statistically significant results for the combination therapy versus pooled monotherapy (HR = 0.51; 95% CI: 0.34 to 0.78).

3.2. Uncertainty in the knowledge about the beneficial effects

The Company's strategy to base a claim on the combination of ambrisentan and tadalafil in comparison to the pooled monotherapy arms was not endorsed in a previous EMA scientific advice. In order to show a benefit of both components, two comparisons, one against each monotherapy arm, were requested. The company then included secondary comparisons of the combination therapy with the individual monotherapy arms. These comparisons were only performed if the comparison of the combination arm vs. pooled monotherapy arms was significant (5% significance level, 2-sided) (Hierachical procedure). The same procedure was applied for secondary outcomes.

The main composite endpoint in AMBITION study was "clinical failure", defined as time to first event of "all-cause death", "hospitalisation", "disease progression" and/or "unsatisfactory long-term clinical response". Although the inclusion of "all-cause death" and "PAH hospitalization" are consistent in both definitions, there are differences in the third and fourth component ("disease progression" and "unsatisfactory long-term clinical response" used in AMBITION versus "time to PAH-related deterioration" included in the PAH guideline) (EMEA/CHMP/EWP/356954/2008).

CT reduced the risk of "Clinical Worsening" (applicant's definition) versus ambrisentan monotherapy (HR = 0.44; 95%CI: 0.28 to 0.70) but not versus tadalafil monotherapy (HR = 0.61; 95%CI: 0.36 to 1.03), thus suggesting that the contribution of ambrisentan to the combination in terms of clinical worsening could be less relevant than that of tadalafil. A sensitivity analysis including Events Adjudicated After First Database Freeze did show the same non-significant trend in time to clinical worsening between combination therapy and tadalafil monotherapy (HR: 0.69; 95%CI: 0.42 to 1.14). Consistently, the effect of the combination therapy versus monotherapy on satisfactory clinical response was more pronounced on the comparison with ambrisentan MT than with tadalafil MT, also suggesting a less relevant contribution of ambrisentan than that of tadalafil in this parameter. However, the effect was always in favour of the CT and the lack of statistical significance in these ancillary analyses is likely to be due to lack of statistical power.

The reduction in all-cause mortality (CT vs. MT) was not significant in AMBITION (HR: 0.64; 95%CI: 0.31 to 1.29; mITT; FAV) but showed the same positive trend as the main analysis..

Risks

Unfavourable effects

The AMBITION study provides clinical safety data from 605 patients treated for 467 to 550 days (mean range) with ambrisentan in combination with tadalafil versus monotherapy with either of these compounds

Compared to monotherapy, patients on CT had: a) more total AEs, severe adverse events, related AEs, AEs leading to permanent discontinuation of study medication: b) similar total SAEs and AE leading to withdrawal from the study: c) less fatal SAEs (ITT population). Similar results were found in the mITT and non-mITT populations. Particularly, adverse events of "anemia" were increased with the CT (20% combination, 10% ambrisentan, and 13% tadalafil). However, ancillary analyses did not show a poorer prognosis in patients who experienced anemia with the CT. Other most commonly reported AEs in the CT group that in addition were found with >5% difference in subject incidence versus MT (mITT population) were: Fluid retention, Peripheral edema, Headache and nasal congestion). Other AEs that were more frequent in the CT than in the MT groups were: Hypotension, dizziness, flushing, dyspepsia and bronchitis. A warning was included in section 4.4 indicating the increase in anemia and peripheral oedema when ambrisentan is given concomitantly with tadalafil. Additionally the new ADR observed with the combination therapy is included (sudden or other hearing loss) in section 4.8.

Mortality was relatively low for a severe disease like PAH and for an mean exposure to study drugs about 1,5 years (mean exposure between 467 to 550 days). Regarding the quality of the data, vital status was not available for 26 patients (4%) at FAV and for 34 (6%) patients at end of study (ITT population), which is a poor figure for a population that is usually followed-up in specialised centers.

The percentage of subjects with any SAE was similar in the 3 groups (CT 40%, ambrisentan 39%, tadalafil 42%) (ITT, baseline to FAV).

Hypersensitivity reactions were more common in the CT group than in the ambrisentan or tadalafil monotherapy groups (13% vs. 10% vs. 7%), being "rash" the more commonly reported term. No major findings were evident regarding liver function tests, testicular function tests or special populations. Additional data provided by the applicant showed a higher rate of adverse reactions in patients above 65 years old compared with those below 65 years old, but with similar relative risks of adverse reactions of the CT vs. MT groups regardless of age.

In conclusion, although total AEs are increased with the combination therapy as compared to monotherapy, the increase was mainly at expenses of non-serious AEs, while SAEs were similar across treatment groups

and fatal SAEs were numerically lower in the CT group than in the MT groups. SmPC amendments were made in relationship with anemia, fluid retention and hearing loss.

3.3. Uncertainty in the knowledge about the unfavourable effects

AMBITION study mainly included patients with idiopathic PAH (IPAH) and in PAH associated with connective tissue disease. Other types of PAH group 1 were not adequately represented. The patient population included mainly female patients.

Exclusion criteria in AMBITION pivotal study were more extensive than the contraindications already included in the SmPCs of Volibris (ambrisentan) and Adcirca (tadalafil), as some patients without contraindications to ambrisentan therapy, but at risk of developing adverse reactions with ambrisentan, were excluded (e.g.: pre-existing anemia, fluid retention, retinal problems, baseline values of ALT and/or AST>2xULN).

No clinical data on the use of ambrisentan plus tadalafil in pediatric subjects are available.

No clinical data on the use of ambrisentan plus tadalafil in subjects with severe renal impairment or subjects with severe hepatic impairment are available.

Benefit-risk balance

Importance of favourable and unfavourable effects

AMBITION study provides support of starting PAH combination therapy with ambrisentan and tadalafil versus monotherapy with each of the monocomponents for the aim of reducing "clinical failure". Although the definition of "clinical failure" used by the applicant in the study was not endorsed and could be open to criticism this was not the case for PAH-related hospitalisation. The analysis of first events of PAH hospitalisation showed a statistically significant 63% decrease in risk with the CT versus MT. Hospitalization is an important outcome in PAH, shown previously to correlate with rehospitalisations and long-term survival [Burger et al, 2014; Campo et al, 2011; Haddat et al, 2011; Sztrymf et al, 2010]. Hospitalisation therefore, represents a substantial burden both for patients with PAH and for the health-care system [Blecker et al, 2013].

Although total AEs were increased with the combination therapy as compared to monotherapy, the increase was mainly at expenses of non-serious AEs (anemia, fluid retention, peripheral oedema), while SAEs were similar across treatment groups and fatal SAEs were numerically lower in the CT group than in the MT groups.

In general, the favorable effects in reduction of PAH-related hospitalizations with CT versus MT are considered more important than the increase in unfavorable (mainly non-serious) adverse effects observed with CT versus MT.

3.4. Benefit-risk balance

3.4.1. Discussion on the benefit-risk balance

The pivotal study supporting current application is the AMBITION study (n=605 patients), which was a well-designed and acceptably executed RCT in PAH. The study was aimed to answer a relevant question: Whether starting treatment with PAH with a combination of an ERA and a PDE5 inhibitor would be better than starting on a single specific therapy (ERA or PDE5 inhibitor alone) in relationship with clinical outcome.

Therefore, the study design allowed to collect information on the ambrisentan/tadalafil combination therapy in PAH that could be potentially relevant for standard practice.

The results of this study suggest superiority of ambrisentan+tadalafil versus the pooled monotherapy and versus the two monotherapies with each of the compounds separately on the main endpoint of clinical failure, as well as superiority over the pooled monotherapy and versus the two monotherapies with each of the compounds separately for the supportive/secondary endpoints of Change in NT-pro-BNP and change in 6MWD.

Sequential CT is the most widely utilized strategy both in clinical trials and in clinical practice. From monotherapy there is addition of a second and then third drug in cases of inadequate clinical results or in cases of deterioration [Galie et al. J Am Coll Cardiol. 2013;62:D60–72]. The AMBITION study has added further evidence on CT by showing that, in naive FC II-III patients with PAH, starting with ambrisentan-tadalafil combination therapy may be more effective than starting with monotherapy. The improvement (less clinical failures) was clinically relevant, particularly in patients with FC II, which is reassuring.

The definition of "clinical failure" used as primary endpoint was further explored and clarified with additional analysis. Several sensitivity analyses showed consistency in the primary endpoint, including the analysis in the ITT population and in the investigator-assessed clinical failure events. The effect on the primary endpoint was also consistent in most subgroups (FC).

The applicant also analysed the time to first clinical worsening (CW) event (defined as the composite of "death", "hospitalization for worsening PAH" and "disease progression"; i.e.: excluding "unsatisfactory long-term clinical response" from the main endpoint). This analysis yielded statistically significant results for the CT versus pooled MT (HR = 0.51; 95% CI: 0.34 to 0.78) and versus ambrisentan monotherapy (HR = 0.44; 95%CI: 0.28 to 0.70) but not versus tadalafil monotherapy (HR = 0.61; 95%CI: 0.36 to 1.03). The trend in the secondary endpoint of CW was positive in favor of the CT versus tadalafil monotherapy and similar to that obtained for the primary endpoint. These results are likely to be attributed to insufficient statistical power. The results on CW (as defined by the applicant) in AMBITION (49% relative risk reduction of CT versus MT) are consistent with those results reported in a recent meta-analysis of 10 randomized clinical trials (RCTs) with CT including 2890 patients [Manes et al. Eur Heart J. 2014; 35 (Suppl.1):11 (abstract 68)]. That meta-analysis showed that, compared with the control group, CT reduced the risk of CW by 51% (RR: 0.49; 95% confidence interval: 0.34 to 0.71; p = 0.0001). No significant differences between treatment were found in mortality, change in WHO FC, BDI score or QoL scores.

The reduction in all-cause mortality (CT vs. MT) was not significant in AMBITION (HR: 0.64; 95%CI: 0.31 to 1.29; mITT; FAV). This is also consistent with the non-significant difference in mortality reported in the more recent meta-analysis of CT versus MT (OR: 0.84; 95% CI 0.52–1.35; p=0.47) [Manes et al. Eur Heart J. 2014; 35 (Suppl.1):11 (abstract 68)]. In contemporary trials, including AMBITION, the main component driving the difference are the PAH hospitalisations, while the effect on mortality in relative and absolute terms remains modest.

The AMBITION study provides clinical safety data from 605 patients treated for 467 to 550 days (mean range) with ambrisentan in combination with tadalafil versus monotherapy with either of these compounds.

Although total AEs are increased with the combination therapy as compared to monotherapy, the increase is mainly at expenses of non-serious AEs, while SAEs were similar across treatment groups and fatal SAEs were numerically lower in the CT group than in the MT groups.

A warning was included in section 4.4 indicating that, when ambrisentan is given concomitantly with tadalafil, peripheral oedema and anemia was significantly increased. Additionally the increase in frequency of ADRs (fluid retention, anemia) is included for the combination therapy in section 4.8. Additionally the new ADR observed with the combination therapy is included (sudden or other hearing loss) in section 4.8.

The appropriateness of the claim of combination therapy in the indication was debated during the procedure. The efficacy data from the AMBITION study in combination with tadalafil together with the additional evidence from other studies provided are acceptable to support an extension of indication. In response to the 3rd RSI, the applicant proposal below was consistent with the indications granted for Opsumit and Adempas, does not deny patient access to treatment options and physician choice of treatment (e.g.: not viewed as limited to combination with tadalafil), thus considered acceptable.

Volibris, is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, ***including use in combination treatment*** *(see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.*

Finally, with respect to posology, section 4.2 of the SmPC was amended to accurately reflect the uptitration (from 5 mg to 10 mg) and downtitration (when needed) process included in AMBITION.

4. Recommendations

Outcome

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 accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication for the treatment of pulmonary arterial hypertension (PAH), in adult patients of WHO Functional Class (FC) II to III including use in combination treatment; as a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. A warning related to the increase in peripheral oedema and anemia with the combination therapy is introduced in section 4.4. Section 4.8 is updated accordingly to include updated frequencies of ADRs observed in the AMBITION study and with a new ADR introduced (sudden hearing loss) in case of use in combination therapy. The Package Leaflet is updated in accordance. In addition, the annex II is updated with a minor change in the key messages to healthcare professionals and also in line with the latest version of the QRD template. A change to the list of local representatives is also introduced in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, labelling and Package Leaflet and to the Risk Management Plan (RMP).

This recommendation is subject to the following revised condition:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Additional risk minimisation measures**

Health care Professional information

The healthcare professional information regarding Volibris should contain the following key elements:

[…]

That hypersensitivity reactions (e.g. angioedema, rash), although uncommon in short term clinical trials and common in longer term trials and in combination with tadalafil, have been reported with Volibris.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP EMEA-000434-PIP01-08-M03) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication for the treatment of pulmonary arterial hypertension (PAH), in adult patients of WHO Functional Class (FC) II to III including use in combination treatment; as a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC are updated. A warning related to the increase in peripheral oedema and anemia with the combination therapy is introduced in section 4.4. Section 4.8 is updated accordingly to include updated frequencies of ADRs observed in the AMBITION study and with a new ADR introduced (sudden hearing loss) in case of use in combination therapy. The Package Leaflet is updated in accordance. In addition, the annex II is updated with a minor change in the key messages to healthcare professionals and also in line with the latest version of the QRD template. A change to the list of local representatives is also introduced in the Package Leaflet.

Summary

Please refer to Scientific Discussion Volibris-H-C-839-II-0041