21 June 2012
EMA/CHMP/394431/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Volibris

ambrisentan

Procedure No.: EMEA/H/C/000839/II/0026

Note

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

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxo Group Ltd. submitted to the European Medicines Agency on 7 February 2012 an application for a variation.

This application concerns the following medicinal product:

Orphan Medicinal product:	International non-proprietary name:	Presentations:
Volibris	ambrisentan	See Annex A

The following variation was requested:

Variation(s) requested		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH proposed the update of sections 4.4 and 5.1 of the SmPC after the assessment of the 7th PSUR, in order to add a warning about the use of ambrisentan in patients with Idiopathic Pulmonary Fibrosis (IPF). The Package Leaflet was proposed to be updated in accordance.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Concepcion Prieto Yerro

1.2. Steps taken for the assessment

Submission date:	7 February 2012
Start of procedure:	19 February 2012
Rapporteur's assessment report circulated on:	12 April 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 April 2012
MAH's responses submitted to the CHMP on:	21 May 2012
Rapporteur's assessment report on the MAH's responses circulated on:	18 June 2012
CHMP opinion:	21 June 2012

2. Scientific discussion

2.1. Introduction

Ambrisentan is an orally active, propanoic acid-class, endothelin receptor antagonist (ERA) selective for the endothelin type A (ET_A) receptor. Endothelin plays a significant role in the pathophysiology of pulmonary arterial hypertension (PAH). Ambrisentan blocks the ET_A receptor subtype, localized predominantly on vascular smooth muscle cells and cardiac myocytes. This prevents endothelin-

mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation. The selectivity of ambrisentan for the ET_A over the ET_B receptor is expected to retain ET_B receptor mediated production of the vasodilators nitric oxide and prostacyclin.

Ambrisentan is indicated for the treatment of patients with PAH classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease (PAH-CTD). It was approved in the EU through a centralised procedure under the trade name Volibris on 21st April 2008. Orphan designation had been granted by the EC on 11th April 2005. Ambrisentan is available as 5 mg and 10 mg film-coated tablets for oral administration.

Patients with IPF are known to express increased levels of endothelin 1 receptor (ET-1) in the lungs and ET-1 inhibition is being tested for the management of IPF. In the 7th PSUR (period covered: 15.12.10 - 14.06.11) the MAH reported that three studies in IPF had been discontinued. This type II variation application was submitted to provide the data from the ARTEMIS-IPF study [GS-US-231-0101] for which the final clinical study report (CSR) was available at the time. The combined clinical study report for the other two studies, ARTEMIS-PH [GS-US-300-0128], A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Centre, Parallel-Group Study to Evaluate the Efficacy and Safety of Ambrisentan in Subjects with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension, and the extension study [GS-US-300-0146], A Phase 3, Long-Term, Open-Label, Multi-centre, Safety Study of Ambrisentan in Subjects with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis, was not available at the time of the initial submission, but was submitted in the responses to the Request for Supplementary Information in May 2012.

2.2. Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

Study GS-US-231-0101 - ARTEMIS-IPF

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel-Group, Event-Driven Study to Evaluate the Efficacy and Safety of Ambrisentan in Subjects with Early Idiopathic Pulmonary Fibrosis (IPF)

Objectives:

The primary objective of this study was:

• To determine if ambrisentan was effective in delaying disease progression and death in subjects with IPF.

The secondary objectives of this study were:

• To evaluate the safety of ambrisentan

• To evaluate the effect of ambrisentan on development of pulmonary hypertension, quality of life (QOL), and dyspnoea symptoms in this subject population

Methodology: This was a randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy and safety of ambrisentan in subjects with IPF. The study consisted of 3 periods: screening, titration, and treatment. Screening occurred over a period of not more than 28 days. Following screening, all eligible subjects were stratified based on:

(1) the presence or absence of PH on right heart catheterization (RHC), defined per protocol as mean pulmonary artery pressure (mPAP) > 25 millimeters mercury (mmHg) with a normal (≤ 15 mmHg) pulmonary capillary wedge pressure (PCWP), and

(2) whether or not a surgical lung biopsy (SLB) by independent core pathologists confirmed a diagnosis of definite or probable usual interstitial pneumonia (UIP).

SLB was not a study procedure. Subjects were then randomized in a 2:1 ratio to receive either ambrisentan or placebo. During the titration period, subjects received 5 mg ambrisentan or placebo once daily for 14 days. Subjects then received 10 mg ambrisentan or placebo from the beginning of the treatment period through the remainder of the study. Two blinded dose reductions were permitted during the treatment period if the subject did not tolerate investigational new product (i.e., 10 mg to 5 mg). Study visits occurred every 84 days (± 6 days) from the first treatment visit.

Number of Subjects (Planned and Analysed): Planned: 660 subjects (440 subjects in the ambrisentan arm and 220 in the placebo arm); Analysed: 492 subjects treated (329 subjects in the ambrisentan arm and 163 in the placebo arm).

Diagnosis and Main Criteria for Inclusion:

1. Male or female from 40 to 80 years of age

2. Diagnosis of IPF based on the following criteria in accordance with American Thoracic

Society/European Respiratory Society (ATS-ERS) guidelines for diagnosing IPF:

- Definite or probable UIP confirmed on SLB by core pathologist, or
- In absence of SLB, high resolution computed tomography (HRCT) scan showing definite findings for IPF (bibasilar reticular abnormalities with minimal ground glass opacities) determined by core review and three of the following "minor criteria":
    - Age > 50 years
    - Insidious onset of otherwise unexplained dyspnoea on exertion
    - Duration of illness ≥ 3 months
    - Bibasilar, inspiratory crackles
    - Diagnosis confirmed by HRCT within 90 days of study enrolment

3. Honeycombing ≤ 5% as assessed on HRCT; HRCT results underwent a core review process to confirm diagnosis.

4. Willingness to undergo RHC at baseline and at 48 weeks (Visit 7) or end of study

5. Willingness and ability to comply with required monitoring of liver function every 28 days. Liver function tests (LFTs) included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl transferase (GGT), and total bilirubin concentrations

6. FVC > 50 to ≤ 95% of predicted with a ratio of forced expiratory volume in 1 second (FEV1) to FVC (FEV1/FVC) ≥ 0.7. Pulmonary function tests completed no more than 90 days before screening

7. Ability to perform a 6MWT at screening

Duration of Treatment: This was an event-driven study. The study was to be terminated after 278 subjects experienced an initial event meeting the primary endpoint (disease progression or death). It was anticipated that the accrual period would be 24 to 27 months with an 18-month follow-up

evaluation of the last subject enrolled. The study was terminated early for futility – the primary endpoint could not be met and there were more events of deaths, disease progression and respiratory hospitalisations in the ambrisentan group compared to the placebo group.

Efficacy primary endpoint of this study was time to death or disease progression, defined as the first occurrence of any of the following:

- Either a relative decrease of ≥ 10% in FVC (L) and a relative decrease of ≥ 5% in Diffusing Capacity of Lung for Carbon Monoxide (DLCO) (mL/min/mmHg), or a relative decrease of ≥ 5% in FVC (L) and a relative decrease of ≥ 15% in DLCO (mL/min/mmHg); (deterioration in FVC and DLCO confirmed at the subsequent visit within 28 (± 14) days)
- Respiratory hospitalization as defined in the protocol. Events adjudicated by a blinded Endpoint Committee
- All-cause mortality

Secondary efficacy endpoints were change in pulmonary function tests (FVC and DLCO) at Visit 7; change in 6-minute walk test (6MWT) at Visit 7; change in QOL score at Visit 7 as assessed by SF-36 and SGRQ; change in dyspnoea as assessed by change in TDI score at Visit 7; among subjects without PH at baseline, the proportion who developed PH on-study (documented by RHC).

Safety: Safety evaluations included 12-lead electrocardiograms (ECGs), adverse event (AE) assessments, vital sign measurements, physical examinations, and clinical laboratory evaluations. Serum ALT, AST, alkaline phosphatase, GGT, and total bilirubin were monitored in all subjects every 28 (± 2) days at treatment and/or monitoring visits.

Statistical methods: Prior to randomization, eligible subjects were stratified by baseline presence of PH on RHC (defined per protocol as mPAP > 25 mmHg with a normal [≤ 15 mmHg] PCWP) and whether an SLB had been performed with definite or probable UIP, determined by a core pathologist to confirm diagnosis. Within the four strata, subjects were randomized in a 2:1 ratio to receive ambrisentan or placebo. The full analysis set included all subjects randomized to treatment who received at least one dose of investigational medicinal product (IMP), analysed according to randomized treatment group. The efficacy full analysis set (FAS) was the primary analysis set for the assessment of efficacy. The safety full analysis set also included all subjects randomized to treatment who received at least one dose of IMP.

Efficacy: The primary endpoint was the time to death or disease progression. The primary treatment comparison was made using a stratified log-rank test with a two-tailed significance level of 0.05. Subjects who prematurely discontinued study participation were censored at the time of their last clinic visit. The individual components of the primary endpoint (death, respiratory hospitalization, deterioration in pulmonary function) were summarized to investigate consistency of effect across all components. The proportions of subjects who developed PH on-study were compared between the 2 treatment groups using Fisher's Exact test. Changes from baseline in pulmonary function tests, QOL scores, UNOS LAS, and dyspnoea score were compared between treatment groups using the van Eleren stratified rank test. An independent Data Monitoring Committee (DMC) monitored the safety and welfare of the study subjects. The DMC met at designated intervals to review accumulated data and was empowered to make recommendations regarding early termination of the study or modification of the study design based on study results or relevant new findings in the medical literature. In addition, the DMC performed an unblinded formal statistical analysis of the primary endpoint after 116 events had been observed. Based on this analysis, the DMC could recommend early termination of the study for treatment benefit if $p < 0.0001$. In addition, the DMC could recommend early termination of the study for futility. In the case of a significant treatment benefit on the primary

endpoint, the DMC was to consider the totality of the efficacy data and the sufficiency of the safety database prior to conferring with the sponsor and steering committee to issue their recommendation. With 237 events for the primary analysis, there was at least 80% power to detect a 30% reduction in the risk of death or disease progression with ambrisentan compared with placebo, i.e., a hazard ratio of 0.7. To achieve 237 events, it is anticipated that 660 subjects would be enrolled over 24 to 27 months, with an 18-month follow-up of the last subject enrolled.

Safety: Safety data, including adverse events, 12-lead ECGs, vital signs and clinical laboratory results were summarized by treatment group. In particular, the incidence of elevated LFTs was summarized.

Study GS-US-300-0128 - ARTEMIS-PH

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Parallel-Group Study to Evaluate the Efficacy and Safety of Ambrisentan in Subjects with Idiopathic Pulmonary Fibrosis and Pulmonary Hypertension

Objectives:

To evaluate the effectiveness and safety of ambrisentan in patients with IPF.

The primary objective of this study was:

• To compare the change in 6-minute walk distance (6MWD) after initiating ambrisentan or placebo treatment in subjects with PH associated with IPF

The secondary objectives of this study were as follows:

• To evaluate changes in other clinical measures of PH and IPF after initiating ambrisentan or placebo treatment, including long-term survival, a composite morbidity/mortality endpoint, dyspnoea symptoms, World Health Organization (WHO) functional class, pulmonary function tests, quality of life, and serum N-terminal pro-B-type natriuretic peptide concentrations

• The safety and tolerability of ambrisentan treatment were compared to placebo treatment.

Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study, designed as a 60-week study in 3 periods: a screening period (up to 6 weeks duration), a placebo-controlled treatment period (48 weeks duration), and an ambrisentan treatment period (8 weeks duration). Eligible subjects were stratified based on the magnitude of their PH (mean pulmonary artery pressure [mPAP] ≤ 30 mm Hg or > 30 mm Hg). Subjects were randomized in a 2:1 ratio to ambrisentan or placebo. Subjects randomized to ambrisentan treatment received a dose of 5 mg once daily for the first 4 weeks and a dose of 10 mg once daily for the next 44 weeks. After the Week 4 visit, 1 blinded dose reduction was permitted if a subject was not tolerating study drug. After 48 weeks of blinded treatment, all subjects received ambrisentan, blinded to dose, for an additional 8 weeks. Subjects initially randomized to ambrisentan received their current dose. Subjects initially randomized to placebo received 5 mg once daily for 4 weeks followed by 10 mg once daily for 4 weeks.

Number of Subjects (Planned and Analysed):

Planned: 225 subjects; Analysed: 40 subjects (N = 25 in the ambrisentan group and N = 15 in the placebo group)

Diagnosis and Main Criteria for Inclusion: Subjects must have had a diagnosis of IPF based on modified American Thoracic Society and European Respiratory Society guidelines. Subjects must have had either a historical high-resolution computed tomography (HRCT) scan showing definite or consistent findings for IPF (bibasilar reticular abnormalities with minimal ground glass opacities) or, in the absence of definite or consistent findings for IPF by HRCT, definite or probable usual interstitial

pneumonia confirmed on historical surgical lung biopsy by a core pathologist. Subjects must have also had documented PH diagnosed by recent (≤ 24 weeks before screening or during the screening period) right heart catheterization with mPAP ≥ 25 mm Hg, pulmonary vascular resistance > 240 dynes·s/cm5, and pulmonary capillary wedge pressure or left ventricular end-diastolic pressure of ≤ 15 mm Hg. Subjects must have been able to walk a distance of at least 50 meters during 2 consecutive 6-minute walk tests performed during the screening period. These tests must have met each of the following criteria: (1) the distance walked in these 2 tests could not have varied by more than 15%, (2) subjects must have maintained a transcutaneous oxygen (O2) saturation ≥ 88% (with or without supplemental O2) during these 2 tests unless receiving at least 6 L/min of supplemental O2, and (3) the supplemental O2 flow rate must have been the same for these 2 tests (if applicable).

Duration of Treatment: 48 weeks blinded, placebo-controlled treatment followed by 8 weeks of dose-blinded treatment with ambrisentan. This study was terminated early in anticipation of futility in parallel with termination of the ARTEMIS IPF study.

Criteria for Evaluation of Efficacy: Efficacy endpoints include 6MWD, dyspnoea symptoms (via the transitional dyspnoea index), Kaplan-Meier estimates of survival, WHO functional class, and acute IPF exacerbations.

Criteria for Evaluation of Safety: Safety was evaluated by assessment of adverse events, clinical laboratory tests, vital signs, body weight, electrocardiograms, and concomitant medication use.

Statistical Methods:

Efficacy: Efficacy endpoints addressed in this abbreviated clinical study report include the primary endpoint of change from baseline to Week 16 in 6MWD, change from baseline in dyspnoea symptoms, and long-term survival (by Kaplan-Meier analysis).

Safety: Safety data were summarized using descriptive statistics. Treatment-emergent AEs were summarized, defined as events that began or worsened after administration of the first dose of study drug.

2.2.2. Results

Study GS-US-231-0101 - ARTEMIS-IPF

The disposition of subjects is summarized in Table 1. A total of 494 subjects were randomized, 330 subjects to ambrisentan and 164 subjects to placebo.

Table 1. Disposition of subjects

	Placebo	Ambrisentan	Total
Subject Disposition			
Randomized, N	164	330	494
	n (%)	n (%)	n (%)
Treated	163 [a] (99.4)	329 [b] (99.7)	492 [a, b] (99.6)
Completed Study	1 (0.6) [c]	1 (0.3) [c, d]	2 (0.4) [c, d]
Did Not Complete Study	162 (98.8)	327 (99.1)	489 (99.9)
Reasons for Not Completing Study			
Safety or Tolerability Reasons	2 (1.2)	9 (2.7)	11 (2.2)
Protocol Deviation	1 (0.6)	5 (1.5)	6 (1.2)
Withdrew Consent	7 (4.3)	13 (3.9)	20 (4.0)
Investigator's Discretion	3 (1.8)	2 (0.6)	5 (1.0)
Subject Never Dosed With Study Drug	0	1 (0.3)	1 (0.2)
Study Discontinued by Sponsor	140 (85.4)	271 (82.1)	411 (83.2)
Death	5 (3.0)	21 (6.4)	26 (5.3)
Other	3 (1.8)	5 (1.5)	8 (1.6)
Unknown	1 (0.6)	0	1 (0.2)

Denominator for percentages was the number of subjects in the full safety analysis set of the corresponding treatment.
Source: Section 11.1, Table 11
a Subject 0375 was randomized in error. Subject did not meet criteria for diagnosis of IPF (Inclusion crition 2) (Appendix 16.2, Listing 55).
b Subject 0802 was randomized in error. Subject did not exhibit honeycombing ≤ 5% (Inclusion criterion 3) IPF (Appendix 16.2, Listing 55).
c These subjects were not captured in the "discontinued study" data source.
d An additional subject was not included in this tally due to missing data.

Demographic characteristics are presented in Table 2.

Table 2. Demographic characteristics

Demographic Characteristic	Placebo (N = 163)	Ambrisentan (N = 329)	Total (N = 492)
Age (years)			
Mean (SD)	66.1 (7.1)	65.8 (7.4)	65.9 (7.3)
Median	67.0	66.0	67.0
Minimum, Maximum	45, 81	35, 82	35, 82
Sex (n, %)			
Female	52 (31.9)	85 (25.8)	137 (27.8)
Male	111 (68.1)	244 (74.2)	355 (72.2)
Race (n, %)			
Black or African Heritage	0	1 (0.3)	1 (0.2)
White	145 (89.0)	293 (89.1)	438 (89.0)
Asian	1 (0.6)	4 (1.2)	5 (1.0)
American Indian or Alaskan Native	1 (0.6)	1 (0.3)	2 (0.4)
Other	16 (9.8)	27 (8.2)	43 (8.7)
Not Permitted	0	3 (0.9)	3 (0.6)

Denominator for percentages was the number of subjects randomized and treated.
Unknown, not recorded, and missing categories were excluded from percentage calculation.
Source: Section 11.1, Table 4

Primary endpoint (time to death or disease progression): A total of 90 subjects (27.4%) treated with ambrisentan and 28 subjects (17.2%) treated with placebo experienced death or disease progression (HR: 1.74; 95%CI: 1.14 to 2.66; p = 0.010) at week 48 (Table 3).

Table 3: Summary of Primary Efficacy Endpoint and Components at Week 48

	Placebo (N = 163)	Ambrisentan (N = 329)	p-valuea	Hazard Ratio (95% CI)
Primary Endpoint: Time to Death or Disease Progression				
Number of Primary Endpoint Eventsa	28 (17.18%)	90 (27.36%)		
Median Time to Event Estimateb, (95% CI)	-- (71.286, --)	84.143 (60.000, --)	0.010	1.739 (1.137, 2.660)
Primary Endpoint Components				
Deaths				
Number of Events[c]	6 (3.7%)	26 (7.9%)		
Median Time to Event Estimate[b], (95% CI)	-- (--, --)	-- (--, --)	0.100	2.078 (0.750, 5.757)
Decrease in FVC/DLCO				
Number of Events[c]	19 (11.7%)	55 (16.7%)		
Median Time to Event Estimate[b], (95% CI)	-- (71.29, --)	-- (84.14, --)	0.109	1.527 (0.840, 2.776)
Respiratory Hospitalizations				
Number of Events[c]	9 (5.5%)	44 (13.4%)		
Median Time to Event Estimate[b], (95% CI)	-- (--, --)	-- (--, --)	0.007	2.593 (1.141, 5.893)

-- = Not estimable

a A subject was only counted once based on the time of the first event (decrease of ≥ 10% in FVC [L] and a decrease of ≥ 5% in DLCO [mL/min/mmHg] or a decrease of ≥ 10% in FVC [L] and a decrease of ≥ 5% in DLCO [mL/min/mmHg] confirmed at a subsequent visit 28 [14 – 56 days], respiratory hospitalization, or death).

b Based on KM estimates of pooling over strata.

Deaths: Twenty-six subjects (7.9%) treated with ambrisentan and 6 subjects (3.7%) treated with placebo died (Table 3). Among the deaths in this study, 16% were due to acute exacerbation of IPF (placebo: 0, ambrisentan: 5), 13% were due to disease progression (placebo: 0, ambrisentan: 4), 9% were due to pneumonia (placebo: 1, ambrisentan: 2), 19% were due to non-respiratory events (placebo: 1, ambrisentan: 5), 3% were due to indeterminate causes (placebo: 0, ambrisentan: 1), and 41% were due to other causes (placebo: 4, ambrisentan: 9). In a secondary analysis through a Cox model adjusted for baseline IPF severity (CPI and St. George Respiratory Questionnaire [SGRQ]), the risk of ambrisentan-treated subjects meeting the primary endpoint was reduced to 1.42 (95% CI 0.85 - 2.05) and no longer statistically significant (p=0.108).

Disease progression: Fifty-five subjects (16.7%) treated with ambrisentan and 19 subjects (11.7%) treated with placebo experienced disease progression (Table 3).

Respiratory hospitalizations: Forty-four subjects (13.4%) treated with ambrisentan and 9 subjects (5.5%) treated with placebo experienced respiratory hospitalizations (Table 3). The time to respiratory hospitalization was significantly shorter for subjects treated with ambrisentan compared to subjects treated with placebo (p=0.007). Among respiratory hospitalizations, 21% were due to acute exacerbation of IPF (placebo: 1, ambrisentan: 10), 25% were due to disease progression (placebo: 1, ambrisentan: 12), 19% were due to pneumonia (placebo: 1, ambrisentan: 9), 17% were due to bronchitis (placebo: 3, ambrisentan: 6), 6% were due to left heart failure (placebo: 0, ambrisentan: 3), and 13% were due to other causes, which included haemoptysis and coronary artery disease (placebo: 0, ambrisentan: 1), pleurisy (placebo: 0, ambrisentan: 1), diffuse alveolar haemorrhage (placebo: 0, ambrisentan: 1), right heart failure/cor pulmonale (placebo: 0, ambrisentan: 1), and uncharacterizable (placebo: 3, ambrisentan: 0). Acute exacerbations, disease progression, pneumonia, and bronchitis together accounted for 84% of the respiratory hospitalizations among subjects who received ambrisentan, and 67% among subjects who received placebo.

Similar trends were noted in terms of death and disease progression and the number of respiratory hospitalisations remained significantly higher in the ambrisentan treated group. The presence of

pulmonary hypertension (PH) was associated with more severe IPF and lower exercise capacity. There remained a higher risk for disease progression and respiratory hospitalization among subjects with PH at baseline. There was no statistically significant difference between treatment groups in the proportion of subjects who developed PH during the study.

No statistically significant differences were noted in the secondary endpoints of change from baseline in FVC and mean change in DLCO predicted at week 48, 6 minute walk distance, QOL and in all domains of SGRQ.

Secondary Efficacy Endpoints: There were no significant differences between treatment groups in mean change from baseline at Week 48 in FVC percent predicted, DLCO percent predicted, 6MWT, SF-36 scales, SGRQ scores, and TDI.

Pulmonary Hypertension Analysis: Ambrisentan treatment was associated with an increase in risk for disease progression among subjects without PH at baseline (HR 1.64, 95% CI 1.04 - 2.60, p = 0.034, Table 4). There was also a trend toward higher risk for disease progression among subjects with PH at baseline (HR 2.42, 95% CI 0.79 - 7.38, p = 0.121). In patients with PH at baseline mortality rates were 13% with ambrisentan and 0% with placebo (Table 4). Among subjects without baseline PH, ambrisentan treatment was associated with a significant increase in risk for respiratory hospitalization (HR 2.72, 95% CI 1.21 - 6.10, p = 0.015, Table 4). There was also a trend toward higher risk for respiratory hospitalization among subjects with PH at baseline (HR 2.21, 95% CI 0.45 - 10.69, p = 0.326).

Table 4. GS-US-231-0101: Analyses of Disease Progression and Respiratory Hospitalizations by Baseline PH

	Placebo n/N (%)	Ambrisentan n/N (%)	Hazard Ratio (95% CI)	P-value
Disease Progression				
Baseline PH = yes	4/16 (25)	14/32 (44)	2.42 (0.79, 7.38)	0.121
Baseline PH = no	24/145 (17)	76/295 (26)	1.64 (1.04, 2.60)	0.034
Respiratory Hospitalization				
Baseline PH = yes	2/16 (13)	7/32 (22)	2.21 (0.45, 10.69)	0.326
Baseline PH = no	7/145 (5)	37/295 (13)	2.72 (1.21, 6.10)	0.015
Death				
Baseline PH = yes	0	4/32 (13)	Unestimable	0.996
Baseline PH = no	6/145 (4)	22/295 (7)	1.81 (0.74, 4.47)	0.196
Decrease in FVC/DLCO				
Baseline PH = yes	2/16 (13)	8/32 (25)	2.45 (0.52, 11.61)	0.257
Baseline PH = no	17/145 (12)	47/295 (16)	1.39 (0.80, 2.43)	0.242

n = number of events, N = number of subjects
Hazard ratio is based on Cox regression model.
Source: Section 15.1, Table 5109-3

Efficacy Analysis of Subgroups: A lower percentage of subjects treated with ambrisentan (6%) versus placebo (9%) in Latin America experienced respiratory hospitalizations. A lower percentage of females ≥ 67 years of age treated with ambrisentan versus placebo showed disease progression (16% versus 35%) and respiratory hospitalizations (12% versus 17%).

Follow-up: 40 patients with IPF and PH were recruited into GS-US-300-0128 [ARTEMIS-PH] and two patients with IPF continued into the extension study (GS-US-300-0146). Both studies were prematurely discontinued based on the findings in the ARTEMIS-IPF study (GS-US-231-0101).

Study GS-US-300-0128 - ARTEMIS-PH:

Subject Disposition and Demographics: A total of 40 subjects were enrolled and randomized to ambrisentan or placebo treatment. More than half of the subjects in both treatment groups were discontinued prematurely when the sponsor terminated the study. Three subjects in the ambrisentan group (12%) and 1 subject in the placebo group (7%) completed the study. Subjects were predominantly white (98%) and male (75%); the majority was enrolled at sites in the US (58%). No female subject was of childbearing potential. For all subjects, the mean age was 68 years and the mean body mass index was 31.2 kg/m2.

Efficacy Results: For 6MWD, transitional dyspnoea index, and survival time, ambrisentan and placebo distributions were similar and did not differ significantly.

As part of the responses to the RSI the MAH provided a combined analysis of deaths in the 3 IPF studies, with a thorough description and analysis of the causes of death for the overall population and the population with PH. This analysis showed that in the ARTEMIS-IPF study, the overall death rate was 8% with ambrisentan (26 of 329) and 4% with placebo (6 of 163). Most deaths were related to respiratory insufficiency. This was accompanied by a significant increase in disease progression and respiratory hospitalizations. Approximately 10% of patients had a baseline diagnosis of PH with normal wedge pressure (ambrisentan: 32; placebo: 16). Overall, 12.5% (4 of 32 subjects) on ambrisentan and 0% (0 of 16 subjects) on placebo who had baseline PH experienced a fatal outcome (table 4, above)

In the ARTEMIS-PH study, all patients had the combination of PH and idiopathic fibrosis. Deaths occurred in 4 of 25 patients with ambrisentan (16%) and 2 of 15 patients on placebo (13%). Most deaths were related to respiratory insufficiency. This was accompanied by a significant increase in SAEs, mainly related to worsening IPF (48% vs. 20%).

The analysis of causes of death is consistent with a deleterious effect of ambrisentan in patients with IPF. The presence of IPF and concomitant pulmonary hypertension in patients on ambrisentan was associated to a higher mortality compared with IPF patients without PH (approximately 16% in study ARTEMIS-PH and 12.5% in ARTEMIS-IPF with PH versus 7% in ARTEMIS-IPF without PH). The inclusion of the contraindication in patients with IPF, with or without PH is therefore considered necessary.

2.2.3. Discussion

Study GS-US-231-0101 (ARTEMIS-IPF) was a phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group, event-driven study to determine if ambrisentan was effective in delaying disease progression and death in subjects with IPF. In addition the study also evaluated the effect of ambrisentan on development of PH, QOL and dyspnoea symptoms as well as safety of ambrisentan in this patient population. During the titration period subjects received 5 mg of ambrisentan or placebo for 14 days followed by 10 mg once daily orally afterwards. This event driven study was expected to run for approximately 24-27 months with an 18 month follow up evaluation of the last enrolled subject. The primary efficacy endpoint (time to death or disease progression which is defined as a decrease of ≥ 10% in FVC and ≥ 5% in DLCO or a decrease of ≥ 5% in FVC and ≥ 15% in DLCO and respiratory hospitalisations) and their components were analysed using a Cox model adjusting for baseline presence or absence of pulmonary hypertension as determined by mean pulmonary arterial pressure >25 mmHg on RHC and whether or not SLB (Surgical Lung Biopsy) has been performed to confirm diagnosis. All hospitalizations and deaths were evaluated in a blinded manner by an Endpoint Adjudications Committee of IPF expert clinicians.

The study was to be terminated after 278 subjects experienced an initial event meeting the primary endpoint (disease progression or death).

The results from GS-US-231-0101 (ARTEMIS-IPF) show a deleterious effect (rather than a lack of efficacy) of ambrisentan in patients with IPF as shown by an increase in the composite of death and/or disease progression at 48 weeks (HR: 1.74; 95%CI: 1.14 to 2.66; p = 0.010). The presence of PH was associated with a trend towards more severe outcome (Primary outcome HR: 2.42; 95% CI 0.79-7.38). In patients with PH at baseline mortality rates were 13% with ambrisentan and 0% with placebo (Table 4). The combined safety data from the extension study (GS-US-300-0146) and the ARTEMIS-PH study (GS-US-300-0128) are consistent with those of the ARTEMIS-IPF study. The data confirms that IPF, with or without secondary pulmonary hypertension, should be included among contraindications to the use of ambrisentan.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

Study GS-US-231-0101 - ARTEMIS-IPF

Extent of Exposure

Mean duration of exposure was similar between the 2 treatment groups

Table 7-1. GS-US-231-0101: Duration of Exposure to Study Medication (Safety Full Analysis Set)

	Placebo (N = 163)	Ambrisentan (N = 329)
Total Exposure to Study Medication (weeks)		
N	163	329
Mean (SD)	35.62 (21.56)	34.21 (21.67)
Min, Max	0.1, 88.1	0.3, 100.1
	n (%)	n (%)
Number of subjects exposed to study drug < 12 weeks	24 (14.7)	57 (17.3)
Number of subjects exposed to study drug ≥ 12 weeks	139 (85.3)	272 (82.7)
Cumulative exposure for the remaining 4-week categories:		
≥ 24 weeks	107 (65.6)	208 (63.2)
≥ 36 weeks	76 (46.6)	148 (45.0)
≥ 48 weeks	48 (29.4)	91 (27.7)
≥ 60 weeks	23 (14.1)	40 (12.2)
≥ 72 weeks	10 (6.1)	19 (5.8)
≥ 84 weeks	2 (1.2)	4 (1.2)
≥ 96 weeks	0 (0.0)	2 (0.6)

Exposure to study drug is the number of weeks between the first dose and last dose of study medication.
Date of last dose may be estimated by date of last PFT, vital signs, or laboratory tests.

2.3.2. Results

Study GS-US-231-0101 - ARTEMIS-IPF

Adverse events

The percentage of subjects experiencing treatment-emergent AEs was similar between the 2 treatment groups: 278 subjects (84.5%) treated with ambrisentan and 136 subjects (83.4%) treated with placebo

Study drug-related AEs were experienced by 125 subjects (38.0%) treated with ambrisentan and 39 subjects (23.9%) treated with placebo. Thirty-two subjects (9.7%) treated with ambrisentan and 9 subjects (5.5%) treated with placebo discontinued due to AEs.

Treatment-emergent serious adverse events (SAEs) were experienced by 73 subjects (22.2%) treated with ambrisentan and 25 subjects (15.3%) treated with placebo. Study drug-related SAEs were experienced by 6 subjects (1.8%) treated with ambrisentan and 6 subjects (3.7%) treated with placebo.

Twenty-six subjects (7.9%) receiving ambrisentan and 6 subjects (3.7%) receiving placebo died on study.

Frequent adverse events

Peripheral oedema was the most frequently experienced AE. Peripheral oedema was reported by significantly more subjects treated with ambrisentan (73 subjects [22.2%]) than treated with placebo (14 subjects [8.6%]) ($p < 0.001$). Upper respiratory tract infection and headache were the next most frequently reported AEs. Among AEs experienced by at least 5% of the subjects in either treatment group, significantly more subjects treated with ambrisentan compared to placebo reported the following: dyspnoea ($p = 0.027$), IPF ($p = 0.009$), and dizziness ($p = 0.018$). Significantly more subjects treated with placebo compared to ambrisentan reported respiratory tract infection ($p = 0.043$).

Serious adverse events

The most frequently reported SAE was IPF, reported by 20 subjects (6.1%) treated with ambrisentan and 4 subjects (2.5%) treated with placebo. Dyspnoea and pneumonia were the next most frequently reported SAEs.

The most frequently reported drug-related SAE was peripheral oedema, experienced by 3 subjects (0.9%) treated with ambrisentan and 1 subject (0.6%) treated with placebo. Dyspnoea, increased ALT, nasal congestion, and constipation were the next most frequently reported drug-related SAEs.

Treatment-Emergent AEs leading to study drug discontinuation

The most frequently reported treatment-emergent AE leading to study drug discontinuation was IPF, experienced by 8 subjects (2.4%) treated with ambrisentan and 1 subject (0.6%) treated with placebo. Dyspnoea and pneumonia were the next most frequently reported treatment-emergent AEs leading to discontinuation of study drug.

Clinical laboratory evaluations

Similar percentages of subjects in both treatment groups experienced ≤ 1x ULN changes at Week 48 in ALT, AST, alkaline phosphatase, GGT, and total bilirubin, ranging from 83.2% to 100.0%. In the ambrisentan treatment group 1 subject (1.1%) had a value for GGT at Week 48 that was > 8x ULN.

Deaths

A total of 32 subjects (6.5%) died on study, 6 of 163 subjects (3.7%) treated with placebo and 26 of 329 subjects (7.9%) treated with ambrisentan. Three subjects receiving ambrisentan and 1 subject receiving placebo had drug-related AEs ongoing at the time of death. An additional 3 enrolled, unrandomized subjects died prior to receiving study drug.

Immediate cause of death in the 26 fatal cases of ambrisentan group were respiratory failure (8), IPF (6), respiratory arrest (2), pneumonia (2), cardiopulmonary arrest (1), septic shock (1), respiratory failure postoperative complication (1), acute myocardial infarctation (2), unknown (1), fatal car accident (1) and unknown (1).

Immediate causes of death of the 6 fatal cases in placebo group were respiratory failure (2), lung collapse (1), multiorganic failure (1), pulmonary embolus (1) and pneumonia (1).

Table 5.6 describes data of analysis of time to death:

Table 5-6. GS-US-231-0101: Kaplan-Meier Analysis of Time to Death (Efficacy Full Analysis Set)

	Placebo (N = 163)			Ambrisentan (N = 329)		
	n[a]	Events[b]	% Survival[c]	n[a]	Events[b]	% Survival[c]
Day 0/ Week 0	163	0	100	329	0	100
Day 84/ Week 12	145	2	99	287	5	98
Day 168/ Week 24	115	4	97	228	13	95
Day 252/ Week 36	85	6	95	168	19	92
Day 336/ Week 48	56	6	95	110	23	90
Day 420/ Week 60	31	6	95	58	24	89
Day 504/ Week 72	11	6	95	23	25	85
Day 588/ Week 84	5	6	95	10	26	79
Day 672/ Week 96	---	---	---	4	26	79

a Number of subjects remaining at risk at each time point.
b Cumulative number of endpoint events which occurred on or before each time point.
c Estimated percentage of subjects surviving at each time point based on the KM estimator.
Source: Section 11.1, Figure 11

Study GS-US-300-0128 - ARTEMIS-PH:

Duration of exposure to study drugs was not significantly different between the 2 treatment groups: mean duration of exposure was 27.4 weeks in the ambrisentan group and 27.6 weeks in the placebo group. During this study, 88% of subjects in the ambrisentan group and 80% of subjects in the placebo group experienced at least 1 AE. More subjects in the ambrisentan than the placebo group discontinued due to AEs (20% versus 13%). Frequent AEs (> 10%) experienced by subjects in the ambrisentan group included dyspnoea (32%), nasal congestion (24%), peripheral oedema (20%), headache (20%), constipation (16%), upper respiratory tract infection (16%), hypoxia (16%), IPF (16%), pneumonia (12%), and cough (12%). Frequent AEs (> 10%) experienced by subjects in the placebo group included dyspnoea (33%), fatigue (27%), peripheral oedema (20%), urinary tract infection (20%), back pain (20%), headache (20%), diarrhoea (13%), nausea (13%), respiratory tract infection (13%), diverticulitis (13%), lower respiratory tract infection (13%), dizziness (13%), cough (13%), and flushing (13%). Adverse events considered related to study drug by the investigator that were reported in at least 10% of subjects in the ambrisentan group included nasal congestion and dyspnoea (4 subjects [16%] and 3 subjects [12%], respectively). No treatment-related AEs in the placebo group were reported in ‡ 10% of subjects.

A total of 6 subjects died, 4 (16%) in the ambrisentan group and 2 (13%) in the placebo group. A greater percentage of subjects in the ambrisentan group had at least 1 SAE compared to the placebo

group (48% versus 20%). SAEs reported in more than 1 subject included IPF (3 subjects), and dyspnoea, hypoxia, and pneumonia (each in 2 subjects). All deaths and the remaining other SAEs were considered unrelated to study treatment. Adverse events led to study drug or study discontinuation in 5 subjects (20%) in the ambrisentan group and in 2 subjects (13%) in the placebo group. In all but 1 subject, the AEs leading to discontinuation were SAEs. No subject in the ambrisentan group developed elevations in liver function tests > 3 × the upper limit of the normal range (ULN). One subject in the placebo group had a value for gamma glutamyl transpeptidase (GGT) that was > 3 × ULN but < 5 × ULN. In the ambrisentan group, treatment-emergent laboratory abnormalities that occurred in > 1 subject and at multiple time points were noted as follows: emergent low cholesterol at all time points; emergent low haemoglobin at Weeks 4 through 16 and 24; emergent low haematocrit at Weeks 8, 16, and 20; and emergent high GGT at Weeks 8, 12, and 20. Other emergent abnormalities were noted in single subjects at isolated time points in both treatment groups. Differences between ambrisentan and placebo treatment groups in mean values and mean changes from baseline in heart rate, blood pressures, and respiratory rate were small in magnitude and not clinically meaningful. There were no pregnancies; no female subject was of childbearing potential.

Safety results from extension study GS-US-300-0146:

Two subjects from Study GS-US-300-0128 were subsequently enrolled in Study GS-US-300-0146, an open-label study designed to assess the long-term safety of ambrisentan in subjects who had completed GS-US-300-0128 or GS-US-231-0101. Study GS-US-300-0146 was stopped early due to early termination of the 2 prerequisite studies. In the long-term study, all subjects were to begin treatment with ambrisentan 5 mg once daily and titrate up to 10 mg once daily after 4 weeks. Because only 2 subjects were enrolled into the long-term safety study at the time of termination, an electronic database was not created.

One subject received ambrisentan (5 mg once daily) for approximately 5 weeks. This subject reported 4 AEs that were considered related to treatment (increase in shortness of breath, lower extremity oedema, fatigue, change in WHO functional class to IV) and 5 AEs that were considered unrelated to treatment (vomiting, nausea [2 occurrences], left wrist pain, and cough). The second subject received ambrisentan (5 mg once daily) for approximately 2 months. This subject had 3 SAEs: dyspnoea, hypoxemia, and cardiopulmonary arrest leading to death, none of which was considered related to treatment.

For 6MWD, transitional dyspnoea index, and survival time, ambrisentan and placebo distributions were similar and did not differ significantly. These data do not support the efficacy of ambrisentan in subjects with IPF and PH.

2.3.3. Discussion

Most of the AEs reported in ambrisentan group in the Study ARTEMIS –IPF submitted are listed in the current SmPC of Volibris or are monitored in postmarketing surveillance. No new relevant AEs for ambrisentan have been identified during this study.

As commented in clinical efficacy section, the study Artemis-IPF has shown a higher mortality rate in ambrisentan group (at week 48, HR, 2.078, 95% CI 0.750, 5.757). At week 84 the estimated percentage of subjects surviving (KM analysis) was 95% in placebo group whereas in ambrisentan group was 79%. Only 10% of patients had PH, but in this subgroup of patients the same trend was observed being mortality rates 13% (4/32) in ambrisentan group and 0 in placebo group.

In view of these data the CHMP concluded that idiopathic pulmonary fibrosis (IPF) with or without secondary pulmonary hypertension should be included in the SmPC as a contraindication in section 4.3. This change has also been in the package leaflet in section 2.

Furthermore, taking into account the potential off-label use of ambrisentan in this population, the CHMP requested that a Direct Healthcare Professional Communication (DHPC) be implemented in order to inform the physicians about the results of this study (see section 2.6. Direct Healthcare Professional Communication).

2.4. Risk management plan

The current version of RMP for ambrisentan already addresses the potential risk of off- label use for ambrisentan in the IPF population. The CHMP considers this, together with the update of the PI to add a contraindication in this population, and the dissemination of a DHPC, to be sufficient in terms of the necessary risk minimisation activities. These changes however will be taken into account in the next scheduled update of the RMP due in August 2012.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Summary of Product characteristics

4.3 Contraindications

• Hypersensitivity to the active substance, to soya, or to any of the excipients (see sections 4.4 and 6.1).

• Pregnancy (see section 4.6).

• Women of child-bearing potential who are not using reliable contraception (see sections 4.4 and 4.6).

• Lactation (see section 4.6).

• Severe hepatic impairment (with or without cirrhosis) (see section 4.2).

• Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT))>3xULN (see sections 4.2 and 4.4).

• Idiopathic pulmonary fibrosis (IPF), with or without secondary pulmonary hypertension (see section 5.1).

5.1 Pharmacodynamic properties
[...]

Idiopathic Pulmonary Fibrosis:

A study of 492 patients (ambrisentan N=329, placebo N=163) with idiopathic pulmonary fibrosis (IPF), 11% of which had secondary pulmonary hypertension (WHO group 3), has been conducted, but was terminated early when it was determined that the primary efficacy endpoint could not be met (ARTEMIS-IPF study). Ninety events (27%) of IPF progression (including respiratory hospitalizations) or death were observed in the ambrisentan group compared to 28 events (17%) in the placebo group. Ambrisentan is therefore contraindicated for patients with IPF with or without secondary pulmonary hypertension (see section 4.3).

Package Leaflet

2. BEFORE YOU TAKE VOLIBRIS

Don't take Volibris:

- if you are **allergic** (hypersensitive) to ambrisentan, soya, or any of the other ingredients of Volibris (listed in Section 6).
- **if you are pregnant,** if you are **planning to become pregnant,** or if you **could become pregnant** because you are not using reliable birth control (contraception). Please read the information under 'Pregnancy and Breast feeding'.
- if you are **breast feeding**.
- if you **have liver disease**. Talk to your doctor, who will decide whether Volibris is suitable for you.
- if you **are under 18 years old**
- if you have **scarring of the lungs**, of unknown cause (idiopathic pulmonary fibrosis).

2.6. Direct Healthcare Professional Communication

The CHMP considered that a Direct Healthcare Professional Communication was needed to communicate on the fact that:

- Ambrisentan must not be used in patients with idiopathic pulmonary fibrosis,
- A clinical study in patients with IPF has shown higher rates of respiratory hospitalizations, mortality events, and decreases in respiratory function in the ambrisentan group versus placebo,
- Patients with IPF who may have already been on treatment with ambrisentan should be assessed carefully and alternative therapies should be considered.

The target audience for the DHPC are the following: chest physicians, cardiologists, rheumatologists internal Medicine Physicians and hospital pharmacists.

The final version of this DHPC agreed by the CHMP is provided in Attachment 5 together with the Communication Plan.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent once the CHMP opinion has been adopted.

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

Ambrisentan, a selective ETA receptor antagonist, has shown to be effective in idiopathic PAH and in PAH associated with connective tissue disease.

Patients with Idiopathic Pulmonary Fibrosis (IPF) are known to express increased levels of ET receptors in the lungs. The applicant has tested ambrisentan in patients with IPF in 3 studies: GS-US-231-0101 (ARTEMIS-IPF), GS-US-300-0128 study (ARTEMIS-PH) and extension study GS-US-300-0146.

ARTEMIS-IPF was a phase 3, randomized, double-blind, placebo-controlled, multi-centre, parallel-group, event-driven study to determine if ambrisentan was effective in delaying disease progression and death in subjects with IPF. The study was to be terminated after 278 subjects experienced an initial event meeting the primary endpoint (disease progression or death), showing a deleterious effect (rather than a lack of efficacy) of ambrisentan in patients with IPF as shown by an increase in the composite of death and/or disease progression at 48 weeks (HR: 1.74; 95%CI: 1.14 to 2.66; p =

0.010). The presence of PH was associated with a trend towards more severe outcome (Primary outcome HR: 2.42; 95% CI 0.79-7.38). In IPF patients with PH at baseline, the mortality was 13% with ambrisentan and 0% with placebo.

In the ARTEMIS-PH study, all patients had the combination of PH and IPF. Deaths occurred in 4 of 25 patients with ambrisentan (16%) and 2 of 15 patients on placebo (13%). This was accompanied by a significant increase in SAEs, mainly related to worsening IPF (48% vs. 20%).

Most deaths in both studies were related to respiratory insufficiency and IPF progression. The presence of IPF and concomitant pulmonary hypertension in patients on ambrisentan was associated to a higher mortality compared with IPF patients without PH (approximately 16% in study ARTEMIS-PH and 12.5% in ARTEMIS-IPF with PH versus 7% in ARTEMIS-IPF).

The combined safety data from the extension study (GS-US-300-0146) and the ARTEMIS-PH study (GS-US-300-0128) are consistent with those of the ARTEMIS-IPF study. The clinical data provided confirms that ambrisentan has a deleterious effect on IPF. In this regard, the CHMP has concluded that IPF, with or without secondary pulmonary hypertension, has to be included among contraindications to the use of ambrisentan, and that a DHCP is needed to inform physicians about this issue.

4. Recommendations

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

Variation(s) accepted		**Type**
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Update of sections 4.3 and 5.1 of the SmPC after the assessment of the 7th PSUR, in order to add a contraindication in idiopathic pulmonary fibrosis (IPF) with or without secondary pulmonary hypertension, and to add information about a clinical study in patients with IPF. The package leaflet has been updated accordingly.

The variation proposed amendments to the SmPC and Package Leaflet.