Product name: **TRACLEER**
Procedure No. **EMEA/H/C/401/II/27**

SCIENTIFIC DISCUSSION

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

The MAH submitted an application for a type II variation to change the indication with subsequent changes in sections 4.4, 4.8 and 5.1. The Package Leaflet is updated accordingly.
In support of the variation to extend the indication to pulmonary arterial hypertension (PAH) as a whole indication, the applicant presents three new additional clinical studies:

. In PAH associated with congenital heart disease with shunts (PAH-CHD)
    . Placebo-controlled trial AC-052-405 (Breathe-5)
    . Non comparative trial AC-052-403 : open label study
. In PAH associated with HIV infection :
    . Non-comparative trial AC-052-362 (Breathe-4)

1.2 Clinical aspects

1.2.1. Introduction

Pulmonary arterial hypertension is a rare and life-threatening disease characterized by medium- and small-size pulmonary artery vasculopathy with cell proliferation and hypertrophy, *in situ* thrombosis and fibrosis. This process causes raised pulmonary arterial pressure and pulmonary vascular resistance against which the right ventricle must work. Patients with PAH commonly develop progressive cardiac hypertrophy and right ventricular dysfunction. The symptoms, which include dyspnoea, chest pain and fatigue, become progressively debilitating, and most patients ultimately succumb to right heart failure. The pathological and clinical presentations of PAH are essentially the same regardless of the underlying etiology. This was recognized by pulmonary hypertension experts in the 1990s, leading to the clinical classification of five groups of PAH established by the WHO. In accordance with this WHO classification system, PAH is a diagnostic term that describes a number of etiologies that share common features regarding vascular pathology, pathophysiology, clinical picture and response to therapeutic intervention. An important aspect of the WHO Clinical classification for PAH is that patients within a WHO Group are likely to respond similarly to a given therapeutic intervention irrespective of the specific underlying etiology. A consensus algorithm for the management has been established by an international panel of European and US experts (see below).

This WHO classification was revised during the Third World Symposium on Pulmonary Hypertension in 2003 including 5 groups of clinical pulmonary hypertension. The applicant is claiming for the extension of indication of Tracleer to the WHO group 1 of the revised Venice 2003 classification as Pulmonary Arterial Hypertension.

Table 1: Clinical classification of pulmonary hypertension (Venice 2003)

WHO Group	WHO Subgroup	Indication
1		**Pulmonary arterial hypertension (PAH)**
	1.1	Idiopathic (IPAH)
	1.2	Familial (FPAH)
	1.3	Associated with (APAH): Collagen vascular disease Congenital systemic-to-pulmonary shunts Portal hypertension HIV infection Drugs and toxins Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary haemorrhagic telangiectasia, haemoglobinopathies, myeloproliferative disorders, splenectomy)
	1.4	Associated with significant venous or capillary involvement Pulmonary veno-occlusive disease (PVOD Pulmonary capillary haemangiomatosis (PCH)
	1.5	Persistent pulmonary hypertension of the newborn
2		**Pulmonary hypertension with left heart disease**
	2.1	Left-sided atrial or ventricular heart disease
	2.2	Left-sided valvular heart disease
3		**Pulmonary hypertension associated with lung diseases and/or hypoxaemia**
	3.1	Chronic obstructive pulmonary disease
	3.2	Interstitial lung disease
	3.3	Sleep-disordered breathing
	3.4	Alveolar hypoventilation disorders
	3.5	Chronic exposure to high altitude
	3.6	Developmental abnormalities
4		**Pulmonary hypertension due to chronic thrombotic and/or embolic disease**
	4.1	Thromboembolic obstruction of proximal pulmonary arteries
	4.2	Thromboembolic obstruction of distal pulmonary arteries
	4.3	Non-thrombotic pulmonary embolism (tumour, parasites, foreign material)
5		**Miscellaneous** Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumour, fibrosing mediastinitis)

The two pivotal registration studies (AC-052-351 and BREATHE-1) included mainly patients in WHO Functional Class III with primary PAH (72%), or PAH secondary to systemic sclerosis or other connective tissue diseases (21%), or to autoimmune diseases (7%). Consequently, the currently approved indication emphasizes these patient demographics via a statement that efficacy has been demonstrated in primary PAH (now known as idiopathic PAH or 'IPAH' and familial PAH) and PAH secondary to scleroderma (systemic sclerosis, PAH-SSc), or in other words, patients in WHO subgroups 1.1, 1.2 and partially subgroup1.3.

1.2.2 clinical data in PAH associated with congenital heart diseases with shunts (PAH-CHD)- STUDY AC-052-405 (BREATHE-5)

a) Methodology - study design

This study AC-052-405 (BREATHE-5) was a multi-center, double blind, placebo controlled, parallel groups, randomized, 16-week trial to evaluate, as a primary safety end point, the effect of Tracleer (bosentan) on oxygen saturation in patients with pulmonary arterial hypertension related to Eisenmenger physiology.

The effects on cardiac hemodynamics (via cardiac catheterization), clinical efficacy on exercise capacity (using 6-minute walk test and Borg dyspnea index) and WHO functional class, general safety and tolerability, were assessed as secondary objectives.

To be eligible for this study, patients were to be with class III pulmonary arterial hypertension related to Eisenmenger physiology, in stable conditions for at least 3 months, echocardiographically established as atrial septal defect ≥ 2 cm effective diameter and/or ventricular septal defect ≥ 1 cm effective diameter, pulmonary hypertension was to be confirmed by cardiac catheterization at baseline: mean pulmonary arterial pressure (mPAP) > 25 mmHg, pulmonary capillary wedge pressure (PCWP) < 15 mmHg and pulmonary vascular resistance (PVR) > 3 mmHg/L/min. Patients had to have documented oxygen saturation ≤ 90% and > 70%, at rest with room air and a baseline walk test ≥ 150 m and ≤ 450 m.
Patients were excluded if they had left ventricular dysfunction (ejection fraction < 40%), restrictive lung disease (TLC < 70% predicted), obstructive lung disease (FEV1 < 70% predicted, with FEV1/FVC < 60%), systolic blood pressure < 85 mmHg, coronary arterial disease.

The 16-week treatment period consisted of an initial dosing phase (administration of bosentan 62.5 mg b.i.d. or matching placebo for 4 weeks), followed by a target dose treatment phase (bosentan 125 mg b.i.d. or matching placebo for 12 additional weeks). Patients who did not tolerate the 125 mg b.i.d. target dose could be down titrated to the starting dose (62.5 mg b.i.d.).

Patients who were not withdrawn from this study were to be enrolled in the extension study (AC 052-403) discussed later in this report.

b) Baseline characteristics
Fifty-four adult patients with Eisenmenger physiology secondary to congenital ventricular or atrial septal defects, or combination defects, were randomized 2:1 to bosentan (n = 37) or placebo (n = 17). Patients had symptomatic PAH, mainly in WHO Function Class III. Baseline characteristics, including mean arterial oxygen saturation (SpO_2), mean pulmonary vascular resistance (PVR), which, as expected was very high in this population, and 6 min walk test (6MWD), were comparable in both groups.

Table 2 BREATHE-5 baseline disease characteristics

	Placebo (n=17)	**Bosentan (n=37)**
Mean age (min, max)	44.2 (30, 56)	37.2 (15, 73)
Time to Eisenmenger diagnosis, years (SD)	20.5 (13.0)	23.7 (13.6)
Congenital cardiac defect	ASD: 5 (29%)	ASD: 8 (22%)
	VSD: 12 (71%)	VSD: 24 (65%)
	ASD + VSD: 0	ASD + VSD: 5 (13%)
Oxygen saturation, SpO_2 (SD)	83.6% (5.1)	82.4% (5.3)
Mean PVRi (dyn·sec·cm^{-5}) (SD)	2870.0 (1209.3)	3425.1 (1410.5)
Mean 6MWD (SD)	366.4 (67.5)	331.9 (82.8)

SD = standard deviation; ASD = atrial septal defect; VSD = ventricular septal defect; SE = standard error of the mean; PVRi = pulmonary vascular resistance indexed; 6MWD = 6-minute walk distance.

In addition, excerpts from table 3 below shows some more details regarding the cardiac abnormality and the shunt direction.

Table 3

SHUNT [n (%)]		
n	17	37
present	17 100%	37 100%
DIRECTION OF THE SHUNT (*) [n (%)]		
n	17	37
right to left	10 58.8%	6 16.2%
bi-directional	7 41.2%	31 83.8%
LEVEL OF THE SHUNT (*) [n (%)]		
n	17	37
atrial	5 29.4%	8 21.6%
ventricular	12 70.6%	24 64.9%
atrial + ventricular	-	5 13.5%

Antithrombotic agents and high-ceiling diuretics were the most frequently used treatments in both groups, respectively 67.6% and 27.0% in the bosentan group and 64.7% and 52.9% in the placebo group. Antiarrhythmics Class I and III were used by 21.6% and 17.6% of bosentan- and placebo treated patients, respectively. The treatment groups were well matched with regard to most treatment classes, but high-ceiling diuretics were less frequent in the bosentan than in the placebo group.

The first primary endpoint was the mean change from baseline comparing bosentan target dose 125mg *vs.* placebo in SpO_2 at rest at Week 16, assessed using a non-inferiority approach with a –5% delta. The second primary endpoint was the mean change from baseline *vs* placebo in pulmonary vascular resistance indexed (PVRi) at Week 16, assessed using a superiority design. Secondary endpoints included exercise capacity, Borg dyspnoea index, WHO functional class and changes from baseline to Week 16 in cardiopulmonary haemodynamics (mean pulmonary arterial pressure, mean right atrial pressure, pulmonary blood flow/systemic blood flow indexed, PVRi/systemic vascular resistance indexed).

c) Efficacy Results

The Week 16 oxygen saturation was missing for 2 patients on placebo that had been discontinued before study end because of an adverse event. These patients had no assessment at the time of withdrawal

Table 4 BREATHE-5 results

	Placebo n = 17				**Bosentan n = 37**				**Treatment effect (bosentan-placebo)**	
All-randomized set	Baseline		Week 16	Change from BL	Baseline		Week 16	Change from BL		
	N	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	**N**	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	**Mean (SE)**	**p-value t-test**
SpO_2 %*	17	83.6 (1.2)	84.0 (1.6)	0.4 (0.9)	35	82.4 (0.9)	83.8 (0.9)	1.5 (0.4)	1.0 (0.9)	Noninferiority shown 95% CI [−0.7, 2.8]
PVRi (room air) dyn·sec·cm^{-5}	17	2870.0 (293.3)	3025.1 (298.3)	155.1 (134.0)	36	3425.1 (235.1)	3108.2 (223.7)	−316.9 (138.3)	−472.0 (221.9)	0.0383 95% CI [−917.6, −26.5]
SVRi dyn·sec·cm^{-5}	15	3589.3 (348.4)	4036.1 (353.2)	446.8 (228.0)	34	3223.4 (244.2)	2846.7 (200.4)	-376.7 (228.6)	-823.4 (377.1)	0.0340 95% CI [-1582.0;-64.8]
6MWD m	17	366.4 (16.4)	356.7 (29.3)	−9.7 (22.3)	37	331.9 (13.6)	375.3 (15.5)	43.4 (8.1)	53.1 (19.2)	0.0079 95% CI [14.5, 91.7]

* Per protocol analysis for SpO_2;
BL = baseline; SE = standard error; SpO_2 = Oxygen saturation; PVRi = pulmonary vascular resistance indexed; SVRi = systemic vascular resistance indexed; 6MWD = 6-Minute Walk Distance.

SVRi had decreased from baseline in bosentan-treated patients (-376.7 ± 228.6 dyn·sec·cm-5) and increased in placebo-treated patients (+446.8 ± 228.0 dyn·sec·cm-5), resulting in a mean treatment effect of –823.4 ± 377.1 dyn·sec·cm-5 (p = 0.0340, Student's t-test).

After week 16, and despite a significant effect on systemic vascular resistance, the results of these studies concluded that bosentan did not relevantly worsen hypoxemia and improved pulmonary vascular resistance.
Non inferiority of bosentan as compared to placebo on the primary safety end point i.e. oxygen saturation at rest at room, can be recognised since the 95% two-sided confidence interval of the mean difference between placebo and bosentan did not include the predefined threshold difference of 5 units: CI95% [-0.7, 2.8] > -5 , based on Student's distribution.
At week 16, the mean oxygen saturation was not significantly different for patients on bosentan and for those on placebo, with a mean treatment effect of +1.0 ± 0.9% and a mean oxygen saturation increased in both group (placebo :+0.5 ; bosentan : +1.5). At week 16, no bosentan-treated patient had a decrease from baseline to Week 16 in oxygen saturation ≥ 10%. At the Week-16 assessment, PVRi had decreased from baseline in bosentan-treated patients (-316.9 ± 138.3 dyn·sec·cm-5) and increased in placebo-treated patients (+155.1 ± 134.0 dyn·sec·cm-5), resulting in a mean treatment effect of -472.0 ± 221.9 dyn·sec·cm-5 (p = 0.0383, Student's t-test

This study was designed to monitor an early temporary oxygen desaturation that may occur during the first one or two weeks of bosentan treatment, and with dosage up titration. Assessments of oxygen saturation were to be performed at W1, 4, 5, 8, 12. The results and analysis on oxygen saturation at these in- between dates and the analysis of the evolution on the oxygen saturation since the initiation of the treatment were requested during the assessment through a Request for Supplementary Information addressed to the MAH.

The MAH has provided exploratory analysis on SpO_2 at weeks 1, 4, 5, 8 and 12, showing no clinically relevant differences between placebo and bosentan. No substitution rules were applied in these analyses. Weeks 1 and 5 are of especial interest since these immediately follow initial dosing and up-titration, respectively. Each exploratory analysis carried out at each scheduled timepoint showed that the lower limit of the 95% two-sided CL of the difference in observed change from baseline remained greater than –5, meeting the predefined non-inferiority hypothesis for the primary endpoint analysis. Maximum decreases from baseline in both groups were similar. No decreases in SpO_2 were associated with adverse events or drug discontinuation.

It is noticed that the magnitude of the maximum decrease observed in SpO_2 at weeks 1, 4, 5, 8 and 12 (W1= -6.0; W4 = - 7.0; W5 = - 6.0; W8 = - 7.0; W12=- 5.0) were greater than at Week 16 =: -2. The maximal observed value in decrease of SpO_2 was similar in the bosentan and placebo groups at all time points except at W8 were the maximum decrease was – 7 in the bosentan group and – 4 in the placebo group. Nevertheless, at W8, the mean change from baseline remained positive and higher than placebo in the bosentan group.
In conclusion the CHMP considered that the mean change from baseline in SpO_2 was positive at all time points in the bosentan group. There is no signal of a specific risk of worsening of the shunt related to the use of bosentan especially at initiation of treatment (W1) and up titration (W5).

At the Week-16 assessment, the Borg dyspnea index had decreased from baseline for bosentan-treated patients (-0.6 ± 0.3) and increased for placebo-treated patients (+0.1 ± 0.6), resulting in a mean treatment effect of –0.7 ± 0.6 (p = 0.2481, Student's t-test).

At baseline, all bosentan- and placebo-treated patients were in Class III. At the Week-16 endpoint, 13 bosentan-treated patients (35.1%) and 2 placebo-treated patients (12.5%) had improved to Class II; 1 bosentan-treated patient (2.7%) and 1 placebo-treated patient (6.3%) had deteriorated to Class IV; all other patients remained in class III.

A beneficial effect of bosentan can be recognised at week 16 on exercise capacity and WHO functional class in this study. At the Week-16 assessment, the 6-minute walk distance had increased from baseline for the bosentan-treated patients (+43.4 ± 8.1 m ; from 331.9 meters at baseline to 375.3 meters at week 16) resulting in a mean treatment effect as compared to placebo of +53.1 ± 19.2 m ; CI95% : [+14.5, + 91.7] (p = 0.0079, Student's t-test).
These results are in the same extent as those observed in the initial other studies performed in primary pulmonary arterial hypertension and associated to sclerodermia (AC6052-351, BREATHE-1).

All enrolled patients had either a predominantly right to left bidirectional shunt or an exclusively right to left shunt, as well as hypoxemia and clinically significant cyanosis. Patients were defined as having a bidirectional shunt if they presented any level of residual left to right blood flow through the defect, identified during Doppler echocardiography, primarily during the diastole. This residual diastolic left to right flow was negligible and did not influence the severity of systemic oxygen saturation (SpO_2), which was assessed independent of echocardiographic shunt. No patient had a net left to right shunt. Hence, no clinically meaningful differences were expected between these subgroups.

As requested by the CHMP, the applicant has conducted a sensitivity analysis first looking at differences in treatment effects between the subgroup of patients with bidirectional shunts and those with right to left shunt. In addition to analysis of baseline demographics by shunt, the treatment effects analyzed were change from baseline to Week 16 in SpO_2 (for non-inferiority), pulmonary vascular resistance indexed (PVRi) and six-minute walk distance (6MWD) (for superiority) (see tables on following pages). The adjusted treatment effect on SpO_2, PVRi and 6MWD with its two-sided 95% confidence limits was also evaluated using the general linear model with treatment and shunt direction as fixed effects.

Demographics and baseline characteristics of the subgroups were similar. Overall, the results of the subgroup analyses on SpO_2, PVRi and 6MWD suggest that there were no clinically meaningful differences in the evaluated efficacy or safety parameters between the echocardiography-defined shunt direction subgroups.

The magnitude of reduction of PVRi was greater in the bidirectional group; the treatment effect was –451.73 (dyn*sec*cm-5) [CI: -949.83, 46.38] when adjusted with shunt direction as a covariate.

The applicant was asked to compare the results for the right-to-left shunt patients (n=6) in BREATHE-5 with the results of the open label part AC-095-405

Six bosentan treated patients were included in the right to left shunt echocardiography subgroup of placebo-controlled, randomized, double-blind international study AC-052-405, whereas 11 patients were included in the open, uncontrolled Canadian pilot study AC-052-403.

SpO_2 was measured with finger pulse oximetry in both studies. In study AC-052-403, measurements were made at rest and following exercise (6MWD), whereas only at rest measurements were conducted in study AC-052-405. A comparison between SpO_2 at rest at baseline and week 16 identifies very similar trends between the two studies.

	Mean (SE) for Baseline	Week 16	Change
AC-052-403 (n = 11)	82.0 (1.8)	83.2 (1.7)	1.2 (1.5)
AC-052-405 (n = 5)	80.2 (3.9)	80.8 (4.5)	0.6 (0.9)

No comparison between the two studies can be made for PVRi, since no right heart catheterization was performed during study AC-052-403.

Six-minute walk distance was conducted with the same standard requirements in both studies. Comparison between 6MWD at baseline and week 16 identifies similar trends between the two

studies. Although the change from baseline is greater in AC-052-405, the clinical importance of this difference is again difficult to interpret due to the small sample size.

	Mean (SE) for Baseline	Week 16	Change
AC-052-403 (n = 11)	298.4 (23.2)	323.9 (22.97)	25.5 (24.8)
AC-052-405 (n = 6)	291.0 (36.2)	385.6 (51.0)	94.6 (21.9)

The applicant provides the sub-groups by shunt analysis of the treatment effect on change from baseline to week 16 in SpO_2 (at rest in room air), pulmonary vascular resistance indexed (PVRi) and 6 minute walked distance (6MWD).
At week 16, the treatment effect on SpO_2 was in favour of bosentan in the subgroup of patients with bidirectional shunt: mean treatment effect as compared to placebo was : + 3.3 ; [95% CL of mean : + 0.8 ; + 5.9]. The mean change from baseline in SpO_2 as measured at W16 was + 1.6 (Min: - 3.0; Max :+9.0) in the bosentan group (placebo : - 1.7 ; Min: - 9.0; Max : + 5.0).
In the subgroup of patients with a shunt direction exclusively right to left, although the lower limit of the 95% CL of the difference in observed change from baseline to week 16 SpO_2 remained greater than – 5 (which was the limit set to test non inferiority primary hypothesis), the mean value of the treatment effect as compared to placebo was in favour of the placebo : - 1.3 ; [95% CL of mean : - 4.0 ; + 1.4]. However, in this subgroup of patients with an exclusively right to left shunt direction, the maximum decrease in SpO_2 observed at week 16 in the bosentan group was minor : – 2.0 (similar value in the placebo group : - 2.0). In this subgroup, the average change from baseline remained positive in patients treated with bosentan : + 0.6 .
Thus, the controlled study AC-052-405 (BREATH-5) provides sufficiently reliable data allowing to conclude that there is no meaningful signal of worsening of the shunt related to the vasodilatory effect of bosentan when it is used in patients with intracardiac shunt and Eisenmenger's syndrome.

d) Discussion

The findings from this study show that the effects of bosentan on exercise capacity are of similar magnitude as those observed in patients with idiopathic/familial PAH and PAH associated with systemic sclerosis. The MAH regards the patients studied in BREATH-5 as belonging to WHO Group 1.3 "pulmonary hypertension associated with congenital systemic-to-pulmonary shunts", and the Sponsor has with this study covered an additional group of patients with PAH.

Patients were selected with atrial and/or ventricular septal defect associated with a right to left or bi-directional shunt. To maintain homogeneity in the compared group, Eisenmenger related to other type of shunts or associated to extracardiac abnormalities were not included. It can be recognised with the applicant that this selection of patients represents the majority of defects leading to the Eisenmenger physiology, and would permit for generalization of the results of the study to the main population of patients with PAH related to Eisenmenger physiology.
However, the two groups were well matched at baseline except for the direction of the shunt. Indeed, only 6/37= 16.2% patients in the bosentan group showed a right to left shunt direction (that in general reflect a more severe Eisenmenger physiology) while the shunt was bidirectional in 83.8% patients in this group. The proportion of patients with right to left shunt was higher in the placebo group 10 /17= 58.8%). A right-to-left shunt is a sign of more severe pulmonary hypertension and therefore the MAH was asked to discuss if and how the results might be affected by this difference between the groups.

Regarding efficacy parameters assessed in the placebo controlled study AC-052-405 (BREATH-5), the mean effect of bosentan on PVRi as compared to placebo was lower in the subgroup of patients with exclusively right to left shunt (Mean treatment effect as compared to placebo = -94; 95%CL : – 947.1, 758.9 ; p= 0.95) than in the bidirectional shunt group (Mean treatment effect as compared to placebo = – 688.0 ; 95% CL : - 1330.0 ; -45.7; p=0.04] , but the 6MW distance remains in favour of bosentan in both subgroups by shunt.

Thus, in summary, although the compared treatment groups were imbalanced in the placebo controlled AC-052-405 with regards to the direction of the shunt at baseline, as identified by Doppler echocardiography, it can be accepted to recognise that this study provide reliable data that allow to conclude that a benefit of bosentan has been demonstrated in patients with Eisenmenger. There is no specific signal regarding a potential worsening of the existing intracardiac shunt relating to a systemic vasodilatory effect when using bosentan in Eisenmenger patients with grade III functional status.

In conclusion, the BREATHE-5 study provides evidence that bosentan does not cause a deterioration in the SpO_2 in patients suffering from PAH and Eisenmenger's syndrome. The results regarding the pulmonary vascular resistance and the 6 min walking test improved significantly, especially the difference in 6 min walk test of about 53 m is considered clinically relevant.

E) Safety results

36/37 patients (97.3%) had received at least 12 weeks bosentan treatment and 30 received at least 16 weeks of bosentan treatment (81.1%).
The total number of adverse events, excluding unrelated ones, was 22 in the bosentan group (n = 37) and 5 in the placebo group (n = 17).

Adverse events that occurred in a greater proportion of patients on bosentan than on placebo included peripheral oedema (18.9% vs. 5.9%), headache (13.5% vs. 11.8%), palpitations (10.8% vs. 0%), dizziness (8.1% vs. 5.9%) and chest pain (8.1% vs. 0%). Few adverse events were of severe intensity (8.1% in the bosentan group vs 17.6% in the placebo group). A similar proportion of patients in the bosentan and placebo groups experienced an SAE during the study (13.5% vs. 17.6%, respectively).
Bosentan-treated patients had a decrease in mean systolic and diastolic artery pressure (-5.2 and -4.5 mmHg, respectively) compared with placebo (+0.7 and - 2.3 mmHg, respectively); one case of hypotension was reported in the placebo group, and one case of vasovagal crisis was reported in the bosentan group. Only small changes from baseline were measured on ECG, and no clinically relevant differences were observed between treatment groups.

Two bosentan-treated patients (5.4%) had an increase in liver aminotransferases over 3 x ULN. For one patient, the increase was over 5 x ULN and led to discontinuation; for the other, the increase was due to biliary colic with transient liver enzyme elevation (>8xULN) which resolved without sequelae.
No patient had a marked decrease in hemoglobin concentration.
During the study, 4 patients, 2 on bosentan and 2 on placebo, were prematurely discontinued from study treatment because of an adverse event. Adverse events leading to discontinuation in the bosentan group were angina pectoris and abnormal liver function tests.
No patient died during the study. One bosentan-treated patient died from right heart failure following non-protocol-related closure of the shunt-related ASD with a device; death occurred 60 days after discontinuation of bosentan.
In conclusion, the CHMP noticed that no new safety concerns were raised from this study regarding the safety profile of bosentan.

1.2.3 Study AC-052-403: Open label Study to Investigate the Safety of Tracleer (bosentan) in Adult Patients with Pulmonary Arterial Hypertension Related to Eisenmenger

a) Methodology- study design

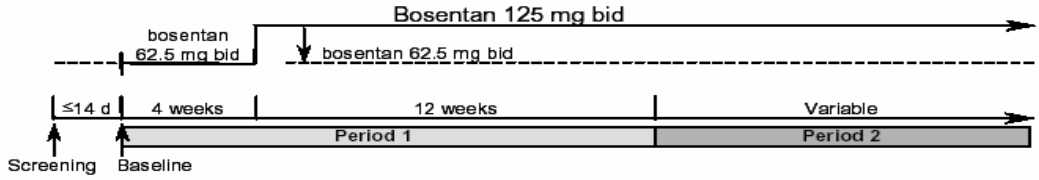
This was a multicenter, open-label, single-arm study of 16 weeks oral bosentan in adult patients with PAH related to Eisenmenger physiology.

This study was designed to primarily assess the safety of bosentan in patients with PAH related to Eisenmenger, particularly with regards to oxygen saturation, laboratory tests, and tolerability.
Change at week 16 from baseline on exercise capacity (as assessed by 6-minute walk test, Borg index), WHO functional class, 12-lead electrocardiogram (ECG), doppler-echocardiography

measurements and quality-of life questionnaire (using the Medical Outcomes Study 36-item Short-form Health Survey [SF-36]) were also assessed.

After screening, eligible patients were enrolled and treated (initial dose of 62.5 mg b.i.d. for 4 weeks followed by the target dose of 125 mg b.i.d.) for a minimum of 12 weeks. Patients progressed to Period 2 (variable duration) without interruption, and end-of-study visits were scheduled for all patients when the last enrolled patient completed Period 1.
Patients who continued their participation until the end of the study were eligible to continue treatment in a long-term extension study (AC-052-408).

Figure 1 Overall study design



A total of 11 patients with WHO functional class III or IV PAH related to Eisenmenger physiology (right-to-left or bi-directional shunt confirmed by echocardiography), documented oxygen saturation <90% (at rest, room air) and >70% (at rest, with or without oxygen), with a 6 min walk distance of 150 to 450 were enrolled in the study. One patient withdrew from the study at the end of Period 1 and one patient was withdrawn prematurely due to an adverse event during Period 2.
Patients were predominantly female (63.6%) and Caucasian (90.9%), with one black patient. Median age was 31 years (range of 19 to 55 years), median weight was 64 kg, and median height was 157 cm.

The nine remaining patients completed the study and entered the following open-label extension study (AC-052-408).
Further to the RSI adopted by the CHMP, the applicant committed to provide as a follow up measure the results of the open label study AC-052-408 soon after the study has completed.

b) Efficacy Results
All 11 patients received bosentan 62.5 mg b.i.d. for the first 4 weeks followed by bosentan 125 mg b.i.d. for the remainder of the study. All treated for at least 16 weeks and up to 48 weeks. The change in mean oxygen saturation from baseline to Week 16 at rest was 1.3% (95% CI −1.3; 3.8) (p = 0.292; t-test) and 1.3% after the 6MWT (−7.2; 9.8) (p = 0.746; t-test). There was a mean 25.5-meter increase in walk distance, a decrease in mean dyspnoea index, and a WHO functional class improvement from III to II in 45% of patients, with none deteriorating. No patient had an increase in PAH medication.

A decrease in oxygen saturation was observed in some patients, particularly following exercise. Maximal observed decrease after 16 weeks (from baseline) was –11%, at end of treatment: – 17%. The applicant was asked to further analyze these situations and discuss on the unfavorable results on oxygen saturation that were observed after exercise tests.

It is also important to consider the method of assessing systemic oxygen saturation after exercise testing. Post-exercise oxygen saturation levels obtained in this study were a one-point measurement via finger pulse oximetry taken immediately after the exercise session. Typically, oxygen saturation is at its lowest point right after exercise and then increases to the patient's habitual level over the next several minutes. Post-exercise oxygen saturation is highly variable in this patient population since it is affected by not only the patient's disease status, but by the intensity of the exercise itself. This can partially explain the inter-patient variability observed in post-exercise oxygen saturation between the baseline values and the week 16 or end of treatment values.

The levels of oxygen saturation observed in this study most likely reflect the minimum value and are likely to be more variable than measuring mean oxygen saturation over a specified time frame of several minutes.

To ensure that these decreases (–11% and –17%) were not reflective of an increase in disease symptoms or a reaction to the study medication, a further review of these data confirmed that the decreases were not associated with any adverse events and were observed in conjunction with an improvement of symptoms as assessed by the WHO Functional Class and an improved exercise capacity as assessed by the 6-Minute Walk Test (6MWT). Although SpO_2 decreased -11% for two patients from baseline to Week 16, their 6MWT increased by +39 m and +78 m. At end of study assessments beyond Week 16, these two patients also had improved 6MWT, +28m and +48m. The patient who experienced an SpO_2 decrease of -17%, the maximum decrease observed, at end of study had an improvement in 6MWT of +33m.

Depending on the specific health component tested, between 27% and 64% of patients reported an improved quality of life, with eight patients showing improvement in at least one component.
Improvement was also observed in mean health transition item (-0.6, 95% CL of -1.6 and 0.4), with five patients (45.5%) reporting an improvement in their quality of life, and one patient (9.1%, Patient 2/201) reporting a worsening. In this analysis, four other patients (36.4%) remained the same, and one patient had no assessment.
A number of reports of uncontrolled, published studies are available. They all describe efficacy findings in line with those made in the well-controlled trial BREATHE-5.

c) Safety results
The mean treatment duration during this study was 35.8 weeks with a range of 17.4 to 48.4 weeks. Patients were treated for variable durations during Period 2.
One patient (Patient 1/101) withdrew after 17.4 weeks of treatment, and all other patients (90.9%) received at least 28 weeks of study treatment.

Two patients (18.2%) were prematurely discontinued from the study (Table 3). Patient 1/101 had Down's syndrome, and withdrew consent after 122 days (17.4 weeks) of treatment because it was too inconvenient to continue with study visits. Patient 2/201 was withdrawn during Period 2 (Day 197) due to a worsening condition (leg edema).

No deaths occurred during or up to 28 days after the end of study treatment.

Two patients (18.2%) experienced a serious adverse event (SAE) during study treatment. One patient experienced severe hypoglycemia, which was resolved with intravenous glucose administration. One patient experienced moderate leg edema on two occasions, which resulted in permanent discontinuation of study treatment. No additional SAEs were reported up to 28 days after the end of study treatment.

Headache (5 patients) was the most frequently reported event, followed by leg edema (3 patients), abdominal pain, dizziness, and flushing (2 patients each).
Events considered to be related to study treatment included headache, flushing, leg edema, and abnormal hair growth (increase). Events were generally mild or moderate in intensity; only one severe event was reported (hypoglycemia).

A 1.0-g/dL mean decrease in hemoglobin concentration was observed consistent with that observed with bosentan therapy in other studies.
No marked increases in ALT or AST were observed in this study. A marked increase in bilirubin was observed (Patient 1/103) followed a high bilirubin and alkaline phosphatase at baseline, but ALT and AST were $< 2 \times$ the ULN at all times.

No clinically relevant changes from baseline in vital signs or body weight were observed at the end of study treatment. A small mean decrease in systolic blood pressure (BP) (-4.5 ± 13.0 mmHg; ± standard deviation) was observed with no change in diastolic blood pressure (0.0 ± 10.2 mmHg). In many patients, blood pressure decreased following the first dose of study medication and tended to return towards baseline with continued bosentan treatment. Hypotension was not reported for any patient.

Table 23 Oxygen saturation: Summary of changes from baseline to Week 16 and to the end of study treatment, safety population

Mean O_2 saturation (%) (95% CL)	At rest	After the 6-min walk test
Baseline	82.0 (78.0, 86.0)	69.1 (59.4, 78.8)
Week 16	83.3 (80.3, 86.3)	70.4 (63.4, 77.4)
Change to Week 16	1.3 (–1.3, 3.8)	1.3 (–7.2, 9.8)
p-value (paired t-test)	0.2923	0.7461
p-value (paired signed-rank test)	0.3652	0.7910
End of study treatment	83.2 (79.3, 87.1)	68.3 (60.3, 76.2)
Change to end of treatment	1.2 (–2.2, 4.6)	–0.8 (–9.6, 8.0)
p-value (paired t-test)	0.4544	0.8404
p-value (paired signed-rank test)	0.4414	0.9395

Note: Exploratory statistical tests were performed on the change from baseline to Week 16 and to the end of study treatment.
Abstracted from Table 36 and Table 37, Section 15.3.
CL = confidence limits.

The mean changes in oxygen saturation at rest from baseline to Week 16 were not significant.
A decrease in oxygen saturation was observed in some patients, particularly following exercise. Maximal observed decrease after 16 weeks (from baseline) was –11%, at end of treatment: - 17% (table 36,37 of study report).

Since there was no control group, conclusions are difficult to draw from this study regarding the claimed indication of PAH associated to cardiac shunt. The decrease in oxygen saturation in some patients when measured after exercise is difficult to interpret without any control group. **N**o new safety concern has emerged from this study.

I.3.2. PAH ASSOCIATED WITH HIV INFECTION

Study AC-052-362: Open- label, non comparative study assessing safety and efficacy of bosentan in pulmonary arterial hypertension associated with HIV infection - BREATHE 4

A) Methodology – Study design

This was a multi-center, open-label, non-comparative study assessing safety and efficacy of bosentan in pulmonary arterial hypertension associated with HIV infection.

Patients characteristics were patients with PAH of World Health Organization (WHO) functional class III to IV associated with HIV infection despite optimal therapy for at least 1 month prior to screening, and a Baseline 6-min walk distance of < 450 m. Patients were to be on stable antiviral therapy for ≥3 months prior to screening, and CD4 count > 100 cells/mm3 (changed from >200 cells/mm3 with amendment1)

Portal hypertension, cirrhosis, moderate to severe liver impairment, or liver enzymes greater than three times the upper limit of normal (ULN) were considered as exclusion criteria.

The study was primarily a safety study, assessing liver function test and efficacy on antiretroviral therapy (as evaluated by CD4 cell count and plasma HIV-1 RNA), and trough plasma levels of protease inhibitors and NNRTIs among several endpoints.

Efficacy endpoints such as Change from baseline to Week 16 in 6 -minute walk distance, Borg dyspnea index, WHO functional class, Hemodynamic variables (right heart catheterization), Echocardiographic variables, Quality of life assessments (Medical Outcomes Study SF-36 health questionnaire and Euro Quality of Life- 5D questionnaire), incidence of clinical worsening at the end of 16 weeks of treatment, increase in therapy for PAH during 16 weeks of treatment were used to fulfill the secondary objective of the study

Three Protocol amendments were made during the study, one of them to reduce the number of enrolled patients from 30 to 18. This is particularly unfortunate as regards the reliability of the efficacy/safety data to be derived from this study.

All patients completed the 16-week treatment period. As regards the populations analyzed, the all-treated (all patients who receive at least one dose of bosentan) and safety populations (at least one assessment of safety) were identical.

b) Baseline characteristics
Overall, the patient population was male with a median age of 36.5 y (only one patient >60y).
The median CD4 cell count was of 333/mm3 and 6 patients had viral load >400 copies/ml (including 2 patients with more than 4 log copies/ml and 1 patient with more than 5 log copies/ml), the remainder having an undetectable viral load (LOQ 400 copies/ml). At screening, all but one patient was on concomitant HAART. All 15 patients were administered a nucleoside reverse transcriptase inhibitor (primarily lamivudine), and nine were also receiving a protease inhibitor (primarily ritonavir).
At baseline, all patients were in WHO PAH Class III except one patient who was in Class IV. The Mean 6-minute walked distance at baseline was 332.6 meters (range 150- 426 meters).
The mean time since diagnosis of PAH was 1.7 years, and that of HIV was 8.8 years. For four (25%) patients, the time since diagnosis of HIV had been more than 15 years. 50% of patients were CDC stage C.
Eight patients had at least one positive indicator of hepatitis B, and three patients had a positive indicator of hepatitis C.

c) Efficacy results

In the BREATHE-4 study the mean improvement in 6-minute walk distance at 16 weeks was +91 m ± 60m from 333 ± 79 m at baseline to 424 ± 57 m at week 16 ($p < 0.001$) (see table 6). This compares well with +44m (95%CI 21.4, 67; $p = 0.0002$) at 16 weeks in the pivotal study BREATHE-1 ($n = 213$) and +76m (95%CI 12.5, 139.2; $p = 0.02$) in the pivotal study AC-052-351 ($n = 33$).

After 16 weeks of treatment, patient-rated dyspnoea immediately following the walk test decreased by a mean of 1.9 on the Borg index compared with baseline values ($p = 0.013$).

Table 6 BREATHE-4 efficacy results

Parameter	Baseline (mean ± SE)	Week 16 (mean ± SE)	Mean change (95% CL)
6MWD (m)	333 ± 19.7	424 ± 14.1	+91 (59.7, 123.2)
Borg Dyspnea Index (0-10)	3.4 ± 0.6	1.5 ± 0.4	-1.9 (-3.3, -0.5)

Only one patient met the criteria for clinical worsening (i.e., death, hospitalization due to PAH, use of epoprostenol, lung transplantation, or septostomy). Patient 3/41 was hospitalized on Day 46 for fluid retention and right-sided heart failure related to PAH. There was no death, epoprostenol use, lung transplantation, or septostomy during the study.

Furthermore, the improvements seen in WHO functional class in the BREATHE-4 study were also interesting according to the MAH. At baseline, 15 of the 16 patients were in functional class III, and one patient was in class IV (Table 7). After only 4 weeks of treatment, 9 (56.3%) patients showed improvement in functional class, including the class-IV patient. By Week 16, 14 (87.5%) patients had improved as regards functional class, including three patients who improved from class III at baseline to class I. None of the patients deteriorated in functional class.

Table 7 WHO functional class: change from baseline to Week 16 (all-treated / safety population)

Protocol: AC-052-362 (Table whoss, 01JUL04 - Data 01JUL04)

				Endpoint							
	n	Baseline WHO class	n	I		II		III		IV	
				No.	%	No.	%	No.	%	No.	%
Change to Week 4	16	III	15	-		8	50.0%	7	43.8%	-	
		IV	1	-		-		1	6.3%	-	
Change to Week 8	16	III	15	1	6.3%	7	43.8%	7	43.8%	-	
		IV	1	-		-		1	6.3%	-	
Change to Week 16	16	III	15	3	18.8%	10	62.5%	2	12.5%	-	
		IV	1	-		-		1	6.3%	-	

WHO = World Health Organization.

The above clinical endpoints are supported by and consistent with the objective haemodynamic parameters also studied. The haemodynamic findings in the BREATHE-4 study provide substantial reassurance on the consistency of efficacy findings (see table 5). All patients improved as compared with baseline; after 16 weeks of bosentan treatment, patients achieved a mean increase in cardiac index and mean decreases in mean PAP and PVR compared with baseline values. Exploratory testing found these improvements to be highly significant in both parametric and non-parametric analyses.

Table 8 Haemodynamic variables: change from baseline to Week 16 all-treated/safety population

Variable	Mean (95% CL) (N = 16)	Median (N = 16)	p value paired t test	p value paired signed rank test
Cardiac index (L/min/m^2)				
Baseline	2.55 (2.18, 2.93)	2.47		
Week 16	3.43 (2.98, 3.89)	3.59		
Change from BL	0.88 (0.49, 1.26)	1.01	**< 0.001**	**< 0.001**
Mean PAP(mmHg)				
Baseline	51.7 (44.5, 58.8)	49.5		
Week 16	40.6 (33.0, 48.2)	37.0		
Change from BL	–11.0 (–17.4, –4.7)	–13.8	**0.002**	**0.002**
PVR (dyn·sec·cm^{-5})*				
Baseline	781 (642, 919)	749		
Week 16	442 (305, 578)	329		
Change from BL	–339 (–454, –223)	–297	**< 0.001**	**< 0.001**

* N = 15
CL = confidence limits, PAP = pulmonary arterial pressure, PVR = pulmonary vascular resistance,

D) Discussion

The CHMP considered that only exploratory data are expected to be driven from this small study performed in 16 HIV infected patients with no statistical hypotheses tested and whose primary objective pertains to safety.

The study in patients with HIV was conducted without a control group. Since placebo effects tend to differ remarkably between different studies in patients with pulmonary hypertension the efficacy data cannot be regarded as conclusive. Considering that the overall study population was only 16 patients, that safety in patients receiving multiple drug is a prominent issue of concern, and that there are major uncertainties regarding possible interactions especially with antiretroviral drugs, an indication in this group of patients cannot be granted based on the submitted data only. The applicant therefore was requested to provide additional information to the CHMP.

According to the Applicant, the 6-minute walk distance (6MWD) progressively and consistently worsens over time in placebo-treated PAH patients, at least in patients in WHO functional class III and worse, where the clinical condition progressively and often rapidly deteriorates. This was demonstrated in the two pivotal registration studies submitted in support of the original Tracleer submission, which showed a consistent reduction in 6MWD over the study period in patients receiving placebo.
Thus, it has been repeatedly demonstrated that PAH, WHO functional class III and worse is associated with rapid deterioration of exercise capacity, measured as 6MWD, also over shorter trial durations than the 16 weeks assessed in trial BREATHE-4. The mean and, consistently positive individual responses in 6MWD seen in trial BREATHE-4 are considered incompatible with a placebo effect are believed to represent a true response to treatment with bosentan.

The MAH argued that PAH associated with HIV infection is a very rare condition within an already Orphan therapy area with an incidence currently estimated to be 0.5% of the HIV positive population. Given its rarity and the ethical issues surrounding the use of placebo-controlled studies in HIV patients, the applicant argued that it is extremely difficult to foresee sufficiently large, prospective and placebo-controlled studies in this population. However, the CHMP pointed out that the orphan drug status cannot support by itself the grant of a marketing authorisation or a specific indication when strong doubts on benefit/risk ratio are remaining.
The applicant considered that the beneficial clinical findings from BREATHE-4 must be seen from the perspective of the rare Orphan disease of PAH, and in the context of findings from other studies performed in this therapy area.

Notwithstanding the above, the applicant agreed with the CHMP that the interpretability of the findings from study AC-052-362 (BREATHE-4) are complicated by the small patient numbers and uncontrolled nature of the study. Prognosis is particularly poor in HIV patients who develop PAH, with an estimated survival rate of 32–46% at 2 years, making the development of PAH a specific rate-limiting event for survival of patients with HIV. This survival rate is substantially worse than that of HIV patients without PAH, making it even more important to provide a treatment option for patients with this condition.

The applicant acknowledged that it is difficult to draw full conclusions regarding the safety of Tracleer in the PAH-HIV population from the BREATHE-4 study alone. However, the safety data obtained in the 102 PAH-HIV patients entered into the Tracleer PMS database, and discussed in the submission to this variation application, provides a degree of reassurance regarding the safety of Tracleer in this patient population.

It is recognised that there is a theoretical concern for increased hepatotoxicity of bosentan in PAH-HIV patients due to the multiplicity of concomitant medications as well as the high prevalence of hepatitis B/C co-infection. From the Tracleer PMS database, when compared with the idiopathic PAH (IPAH) population, the incidence of reported elevated aminotransferases in the 102 patients with PAH associated with HIV was 8.8% versus 8.4% in the IPAH group after a median exposure to bosentan of 33.4 weeks. Approximately 28.4% of patients with PAH associated with HIV reported at least one potential safety signal, compared with 36.7% in the IPAH population. Thus, it does not appear that the theoretical concern of increased hepatotoxic potential of Tracleer in patients with PAH-HIV materialises in the clinical setting, although close monitoring is warranted. The Applicant is of the opinion that the current risk-management programme, involving at least monthly monitoring of LFTs, together with the education programme for new prescribers, is sufficient to manage the hepatotoxicity concern in this group. Furthermore, as there is a theoretical concern for greater potential for hepatic and haematological toxicity in this population, the Applicant has committed to specifically assess the safety of the co-administration of bosentan and antiretroviral medicinal products in this specific population within the forthcoming PSURs.

The data provided by the applicant in the Request for Supplementary Information were considered not sufficient to support the approval of the indication in patients with PAH associated to HIV.
However, since prescribers will probably attempt the use of bosentan in patients with PAH associated to HIV infection and since there are still strong doubts on a potential increase of the risk of hepatotoxicity and haematological toxicity, and on a decrease of the antiretroviral drugs efficacy to control retroviral replication, special warnings are warranted in the SPC. Moreover, the limited available data from Breathe 4 have been included in section 5.1 (see section on the SPC).
The CHMP also noted that there are major uncertainties regarding possible interactions with bosentan especially with antiretroviral medicinal products.

Potential for pharmacokinetic interactions between bosentan and antiretroviral drugs
Bosentan is extensively metabolised in the liver by the cytochrome P-450 (CYP) isoenzymes CYP3A4 and CYP2C9, with biliary excretion of three identified metabolites as the main route of elimination. Upon multiple dosing, plasma concentrations of bosentan decrease gradually to 50–65% of those seen after single-dose administration, probably the effect of auto-induction of the metabolising liver enzymes. Steady-state conditions are reached within 3–5 days. Importantly, bosentan is an inducer of CYP3A4 and CYP2C9 and possibly CYP2C19 and thus, the exposure to drugs, which are substrates for one of these isoenzymes may be decreased when administered concomitantly with bosentan. Conversely, a drug, which acts as an inducer or inhibitor of CYP3A4 and/or CYP2C9 activity could alter the exposure to bosentan when administered concomitantly.

Based on the above, a pharmacokinetic interaction between bosentan and antiretroviral drugs is likely. Bosentan may lower the concentrations of the latter, possibly resulting in reduced efficacy. Interaction studies performed with a number of compounds have shown that bosentan may reduce the exposure to other drugs by up to 60% although for most compounds a decrease of around 30-40% was observed.
The MAH considered that the antiretroviral drugs may increase or decrease bosentan concentrations or have no effect depending on the antiretroviral drug at issue. When bosentan would be combined with a

single antiretroviral, the direction of the effect of the antiretroviral on the exposure to bosentan (i.e., decrease or increase) can be predicted although the magnitude of the effect would need to be investigated. However, in clinical practice monotherapy is not the standard of care as, typically, antiretroviral therapy consists of at least 3 drugs. A large number of drug combinations is being used. To predict the direction of the pharmacokinetic interaction when bosentan is combined with a combination of antiretroviral drugs is practically impossible and will depend on the combination used.
When ketoconazole, a strong inhibitor of CYP3A4, was given concomitantly with bosentan, the exposure to bosentan doubled. In the presence of the strong enzyme inducer, rifampicin, the exposure to bosentan decreased by 58%. Based on these results the applicant considered it unlikely that any combination of antiretroviral drugs will more than double the exposure to bosentan or reduce it by more than half.

From the above, it is concluded by the applicant that bosentan will likely lower the exposure to antiretrovirals whereas the effect of antiretrovirals on bosentan exposure cannot be predicted and will depend on the combination of drugs tested. It should be noted that an interaction study performed between bosentan and an antiretroviral therapy (mono, dual or tri therapy) will give a result that is only valid for the particular combination tested.
Since bosentan will be inevitably associated with antiretroviral drugs, the assessment of the magnitude of the interaction between bosentan and antiretroviral drugs which are metabolized by CYP450 is of major importance to document the benefit/risk ratio of bosentan in the specific context of PAH associated to HIV.

Well-conducted studies assessing the drug-drug interaction at steady state both on bosentan concentrations and on antiretroviral drugs concentrations are needed within a short delay. The CHMP considered the need to perform, specific interaction studies with the gold standard, lopinavir/ritonavir, and with the boosted PI commonly used in salvage therapy tipranavir/ritonavir; in addition a study with a NNRTI representative (efavirenz) will also deserve to be explored] to provide clear recommendations to the prescribers as regards the co-administration of bosentan with PIs and NNRTIs.

Moreover, it is emphasized that tri therapy (HAART) will most often include 2 NRTI, which are not substrates for CYP450, plus 1 PI (or boosted PI) or 1 NNRTI. Thus, the sense and magnitude of the interaction will mainly be driven by the PI or the NNRTI used in the multitherapy. The drug-drug interaction studies that will assess the proper magnitude of the interactions of bosentan with PI and NNRTI will then be fully informative to establish the level of interaction in usual practice and therefore are warranted to document the benefit/risk ratio of bosentan in the context of HIV infection.

It must be reminded that there is a high risk of a decrease of the plasmatic concentration of antiretroviral drugs PI and NNRTI when bosentan, as a CYP3A4 and CYP2C9 (and possibly CYP2C19) inducer, is used concomitantly. A decrease in plasmatic concentration of antiretroviral drug would lead to suboptimal systemic exposure of antiretroviral drugs with a subsequent risk of reducing the control of retroviral replication and possibly the emergence of resistance to PI. It is emphasized that in this study AC-052-362, five patients had an increase in viral load. The consequences on the progress of the HIV infection is of major importance to establish the benefit/risk ratio of bosentan in the context of HIV infected patients. Moreover, the control of retroviral replication may be of high interest to control the progress of PAH itself associated to HIV infection.

Therefore, the CHMP requested the MAH to perform a drug drug interaction study with antiretrovirals. (see conclusion)

c) safety results

HIV-1 RNA titers were little changed after 8 weeks of bosentan therapy (mean change +0.45 log10 copies/ml, p = 0.122, paired t test) in the 13 patients who had both baseline and Week-8 assessments. This was also true among the seven patients who had < 400 copies/ml at baseline (mean change +0.62 log10 copies/ml, p = 0.196, paired t test). Overall, one patient improved during the study (> 400 copies/ml at baseline and < 400 copies/ml at Week 8, Patient 3/41). (Patients 1/1, 1/7, 1/13, 1/14, and 3/42; which included the two patients who were considered to have worsened (< 400 copies/ml at baseline and > 400 copies/ml at Week 8, Patients 1/14 and 3/42; Viral load in the two patients who worsened increased from < 400 copies/ml at baseline to 441 and 600 copies/ml, respectively, with no concomitant decrease in CD4 counts.
Since there was no effect on indices of HIV progression (CD4 cell count and HIV-1 RNA titers), no summary evaluation of plasma concentrations of protease inhibitors or NNRTIs was deemed necessary.
Concentrations in each patient were carefully monitored using published algorithms for comparison. Trough concentrations did decrease in some patients but remained unchanged for others for any given agent. The observed changes were likely the result of the heterogeneity of drug regimens, non standardized timing of sample collection, and intra- and inter-individual variability and did not appear to adversely impact the control of HIV infection."

Hemoglobin concentration decreased from 14.8 g/dl at baseline to 11.9 g/dl on Day 28 and reached marked levels (10.6 g/dl) on the last day of the study (Day 119). ALT, AST, and alkaline phosphatase were markedly increased on Day 56 from normal values at baseline and decreased thereafter without a change in study treatment. The mean decrease in hemoglobin concentration (-1.3 g/dl) was consistent with that observed in other studies. A mean decrease in neutrophils (-0.43 × 109 cells/L) was observed.

Eight patients had a marked abnormality in at least one laboratory variable. The most common abnormality was a marked decrease in neutrophil count, which occurred in five patients (31.3%).
The marked decreases in hemoglobin concentration and hematocrit and the marked increases in ALT, AST, and alkaline phosphatase all occurred in a single patient (1/14).
In addition to Patient 1/14, one other patient (3/42) had an increase in AST to > 3 × ULN.
However, the increase in AST to 76 U/l on Day 27 was from a baseline value of 66 U/l, and thus, it was not a marked increase. This patient was coinfected with the hepatitis C virus.

No deaths occurred during the 16-week treatment period. One patient died for unknown reasons approximately 16 days after completing the study while participating in the compassionate supply program. *(The investigator assessed the event as not related to bosentan)*

Given the limited number of patients exposed to bosentan no formal conclusion could be drawn on the safety profile of the drug in HIV infected patients, especially when considering that given the similar toxicity targets of bosentan and antiretroviral agents (hematologic and hepatotoxic) a potentialisation could not be excluded and is of particular concern.
Therefore, the CHMP asked the applicant to commit to specifically assess the safety of the co-administration in this specific population within the forthcoming PSURs

Conclusion

In conclusion, the BREATHE-5 study provides evidence that bosentan does not cause a deterioration in the SpO_2 in patients suffering from PAH and Eisenmenger's syndrome. The results regarding the pulmonary vascular resistance and the 6 min walking test improved significantly, especially the difference in 6 min walk test of about 53 m is considered clinically relevant. Therefore, the benefit/risk is considered positive and an amendment of the section 4.1 is considered acceptable by the CHMP.

The benefit/risk ratio in patients with HIV infection is not established since the safety concerns and major uncertainties, especially regarding the consequences and magnitude of drug-drug interactions with antiretroviral drugs that are substrates of CYP450 have not been solved. The provided open label,

non comparative study has included a very small group of only 16 patients. Given that there have been studies with remarkable positive placebo effects on the 6-minutes walk test in the past, the efficacy results from this uncontrolled designed and limited study are difficult to interpret. Further data, including drug-drug interactions with antiretroviral drugs PI (lopinavir/ritonavir), boosted PI tipranavir/ritonavir commonly used in salvage therapy (since tipranavir have shown to have a very high potential for interaction), and with a NNRTI representative (efavirenz) are requested before any indication in patients with HIV can be considered. Bosentan has an inducing effect on CYP450 but the magnitude of any potential interaction (reducing antiretroviral activity and variation of bosentan systemic concentration) of antiretroviral medicinal products, which are substrates for CYP450, has not been documented. It is noticed that there are some indications pointing to the fact that one of the causes of PAH in patients with HIV infection could be the presence of virus particles in blood. Also, some data suggests that the control of retroviral replication may be of high interest to control PAH associated to HIV infection. The limited current clinical development without controlled data and the lack of essential data in the specific population of patients with HIV infection with remaining strong doubts on the benefit/risk ratio preclude the approval of this indication in section 4.1 of the SPC.

Since prescribers will however certainly attempt the use of bosentan in patients with PAH associated to HIV infection and since there are concerns on an increased risk of hepatotoxicity and haematological toxicity, and on the decrease of the antiretroviral drugs efficacy to control retroviral replication, special warnings are warranted in section 4.4. of the SPC. The state of the art in the field of HIV infection from BREATHE-4 can be accepted as an information to be included in section 5.1. of the SPC. Individual paragraph on adverse effects in Eisenmenger's syndrome population and HIV infected patients have been included in section 4.8 and 5.1.

The MAH has committed in writing to conduct a pharmacokinetic drug-drug interaction study between bosentan and lopinavir/ritonavir (Kaletra) in healthy volunteers. A protocol will be forwarded to the rapporteur/CHMP for review before the end of 2006, to complete the study and submit a final study report to the CHMP by Q42007.
In addition, further drug-drug interactions, one with boosted PI tipranavir/ritonavir commonly used in salvage therapy (since tipranavir have shown to have a very high potential for interaction), and the other with a NNRTI representative (efavirenz) will be considered by the CHMP pending the interpretability of the results of the lopinavir/ritonavir results and their perceived usefulness to the prescriber.

I.3.3. Other clinical diseases included in Group 1 i.e. PAH of Venice 2003 classification:

The applicant has not provided new data regarding the other indications that are suggested in addition to the one already approved and the ones that have been assessed above.
Only casual experiences from limited cases are reported
It should also be noted that Tracleer cannot be recognized as the treatment for some items included in the Venice classification under the designation "pulmonary arterial hypertension": i.e. : association to significant venous or capillary involvement, persistent pulmonary hypertension of the newborn.

II OVERALL RECOMMENDATION FOR THE LABELLING

Based on the review of the data on safety and efficacy, the variation application EMEA/H/C/401/II/27 for Tracleer 62.5 mg and 125 mg, film coated tablets (bosentan) to change the extend of the indication to cardiac shunt associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome is acceptable.
The extension of the indication to PAH associated to HIV infection claimed by the MAH is not approvable. Therefore, the CHMP recommended wording in section 4.1 should read:
"*Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in:*

- *Primary (idiopathic and familial) PAH*
- *PAH secondary to scleroderma without significant interstitial pulmonary disease*

- *PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.*

The revised SPC includes also amendments to the sections 4.4, 4.8 and 5.1 derived from the data provided in this variation described below:

Section 4.4 Special warning and precaution for use :

"The benefit/risk balance of bosentan has not been established in patients with WHO class I or II functional status of pulmonary arterial hypertension. ~~No studies have been performed in secondary pulmonary hypertension other than related to connective tissue disease (primarily scleroderma)~~".

The additional paragraph in section 4.4 was slightly modified by the CHMP during the review process:

"Pulmonary arterial hypertension associated with HIV infection

There is limited clinical trial experience with the use of Tracleer in patients with PAH associated with HIV infection, treated with antiretroviral medicinal products (see section 5.1). No specific interaction studies between bosentan and antiretroviral medicinal products have been performed. Due to the potential for such interactions especially related to the inducing effect of bosentan on CYP450 (see section 4.5), which could affect the efficacy of antiretroviral therapy, these patients should be monitored carefully regarding control of their HIV infection. An increased risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products."

Section 4.8 Undesirable effects

Addition of the following wording further discussion with the applicant during the RSI assessment:

"Placebo-controlled trial in PAH associated with congenital heart disease (BREATHE-5)

The safety profile of Tracleer in this population was similar to that observed in the pivotal trials in patients with PAH. Adverse events that occurred in a greater proportion of patients on Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily (n = 37) than on placebo (n = 17) included peripheral oedema (18.9% vs. 5.9%), headache (13.5% vs. 11.8%), palpitations (10.8% vs. 0%), dizziness (8.1% vs. 5.9%) and chest pain (8.1% vs. 0%). Four patients discontinued due to adverse events, two (5.4%) in the bosentan group and two (11.8%) in the placebo group.

"Uncontrolled trial in patients with PAH associated with HIV infection (BREATHE-4)

The safety profile in this population (n = 16) when treated with Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily was similar to that observed in the pivotal trials in patients with PAH. The most frequent adverse events were peripheral oedema (31%), headache (19%), abnormal liver function (13%), muscle cramps (13%), fluid retention (13%) and vomiting (13%). Haematological abnormalities (anaemia and decrease in neutrophil count) were observed in some patients (see section 4.4)."

Section 5.1 Pharmacodynamic properties:

The paragraph describing study in patients with Eisenmenger's syndrome is added :

"In a prospective, multi-centre, randomized, double-blind, placebo-controlled study (BREATHE-5), patients with pulmonary arterial hypertension WHO functional Class III and Eisenmenger physiology associated with congenital heart disease received Tracleer 62.5 mg bid for 4 weeks, then 125 mg b.i.d. for a further 12 weeks (n = 37), or placebo (n = 17). The primary objective was to show that Tracleer did not worsen hypoxaemia. After 16 weeks, the mean oxygen saturation was increased in the bosentan group by 1.0% (95% CI –0.7; 2.8%) as compared to the placebo group, showing that bosentan did not worsen hypoxemia. The mean pulmonary vascular resistance was significantly reduced in the bosentan group, (with a predominant effect observed in the subgroup of patients with bidirectional intracardiac shunt). After 16 weeks, the mean placebo-corrected increase in 6-minute walk distance was 53 meters (p = 0.0079) reflecting improvement of exercise capacity."

The paragraph regarding PAH in HIV infected patients was amended following the RSI and further discussion with applicant taking into account the following remarks from the CHMP:

It should be made clear for the prescribers that only exploratory data are derived from study AC-O52-362 and no data are available to appreciate the effect in HIV infected patients beyond 16 weeks
The paragraph below was finally agreed.

*An open label, non-comparative study (AC-052-362**;** BREATHE-4) was performed in 16 patients with WHO Class III PAH associated with HIV infection. Patients were treated with Tracleer 62.5 mg bid for 4 weeks followed by 125 mg bid for a further 12 weeks. After 16 weeks treatment, there were significant improvements from baseline in exercise capacity: mean increase in 6-minute walk test: +91.4 meters from 332.6 meters on average at baseline (p < 0.001). As part of the safety assessment, the effect of bosentan on the antiretroviral therapy (i.e. reduced systemic concentrations of the co-administered antiretroviral agents with a potential negative impact on the efficacy of the antiretroviral therapy) was assessed through CD4 cell counts and HIV-1 RNA titers. Given the limitations of the study (small number of patients, non-standardized pharmacokinetic investigation of antiretroviral drugs, heterogeneity of drug regimens), no formal conclusion can be drawn regarding the effects of bosentan on antiretroviral drug efficacy. An increase in HIV viral load was observed in 5 patients (See also Section 4.4). No clinical data are available after 16 weeks from this study.*

III. CONCLUSION

- On 21 September 2006, the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.