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Evaluation of Medicines for Human Use

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ASSESSMENT REPORT
FOR
Thelin

International non-proprietary name/Common name:
sitaxentan sodium

EMEA/H/C/000679/II/0018

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

Thelin contains sitaxentan sodium, which is an endothelin receptor antagonist, with higher selectivity for the ETA receptor than the ETB receptor subtype. Endothelin-1 (ET-1) is a potent vascular paracrine and autocrine peptide in the lung, and can also promote fibrosis, cell proliferation, cardiac hypertrophy and remodeling, and is pro-inflammatory. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension (PAH), as well as other cardiovascular disorders and connective tissue diseases, including scleroderma, acute and chronic heart failure, myocardial ischaemia, systemic hypertension, and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In PAH and heart failure, in the absence of endothelin receptor antagonism, elevated ET-1 concentrations are strongly correlated with the severity and prognosis of these diseases. Additionally, PAH is also characterised by reduced nitric oxide activity. ET-1 actions are mediated through endothelin A receptors (ETA), present on smooth muscle cells, and endothelin B receptors (ETB), present on endothelial cells. Predominant actions of ET-1 binding to ETA are vasoconstriction and vascular remodelling, while binding to ETB results in ET-1 clearance, and vasodilatory/ antiproliferative effects due in part to nitric oxide and prostacyclin release.

Thelin was granted a marketing authorisation by the European Commission on 10 August 2006 and is indicated for the Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries, characterized by vascular proliferation and remodelling. It results in a progressive increase in pulmonary arterial resistance and, ultimately, right ventricular failure and death. The functional classification (FC) of PAH according to clinical parameters modified from the New York Heart Association (NYHA) classification of patients with cardiac disease, is as follows:

- Class I: PAH without a resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain, or near-syncope.
- Class II: PAH resulting in a slight limitation of physical activity. The patient is comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
- Class III: PAH resulting a marked limitation of physical activity. The patient is comfortable at rest, but less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.
- Class IV: PAH resulting in an inability to carry out any physical activity without symptoms. The patient has signs of right heart failure. Dyspnoea, fatigue, or both may be present even at rest, and discomfort is increased by any physical activity.

It has been shown that patients who improve from functional class III or class IV to functional class II after treatment have significantly improved survival. Therefore, it might be reasonable to expect that early treatment of WHO functional class II patients might provide an improvement in survival as progression to functional class III might be delayed. Furthermore, early treatment of functional class II patients is supported by the finding that not all patients respond to treatment and if treatment initiation is delayed until the patient progresses to functional class III or IV, a significant proportion will remain in functional class III or class IV.

Until recently, no therapeutic options were available in the EU for WHO/NYHA functional class II patients. In 2008, ambrisentan (Volibris) was approved as a new chemical entity for both functional class II and III patients, and bosentan (Tracleer) had its functional class III label extended to include benefit in functional class II patients. The basis to include WHO functional class II patients were on two grounds:

1. The functional class II subjects recruited into the trials were a demonstrably different population from the functional class III subjects;
2. Efficacy was demonstrated for both functional class II and class III subjects.

Sildenafil (Revatio) and tadalafil (Adcirca) have also received recent approvals in functional class II.

In this type II variation, the Marketing Authorisation Holder (MAH) applied to extend Section 4.1 of the Summary of Product Characteristics (SPC) with the statement "*Some improvements have also been shown in patients with pulmonary arterial hypertension (PAH) WHO functional class II (see section 5.1)*" and to amend Section 5.1 of the SPC with updated information by functional class (FC) and updated long term survival data.

Further to the assessment of the data submitted in the variation application and in the responses to the CHMP requests for supplementary information, the CHMP considered that efficacy data to support an extension of the indication in section 4.1 of the SPC to WHO FC II patients was insufficient. Results of the 6-minute walk test were not statistically significant, while data on the effect on clinical worsening were based from a post-hoc analysis which also failed to show statistical significance. Benefit seen on FC and haemodynamics are supportive, but insufficient. However, the CHMP considered acceptable to include relevant haemodynamic data in section 5.1 of the SPC as the information can be useful to the prescriber.

1.2. Clinical aspects

No new clinical studies were included to support this type II variation. The MAH re-evaluated data from two previously submitted pivotal studies: STRIDE 1 (FPH01) and STRIDE 2 (FPH02), to support the requested changes with regard to WHO FC II. The MAH believed that WHO FC II subjects have been adequately studied in these trials.
The MAH also referred to two other medicinal products, namely ambrisentan and bosentan, which are indicated for WHO FC II patients. The MAH was convinced that the considerations of ambrisentan and bosentan can now be similarly applied to the sitaxentan data.

1.2.1. Clinical efficacy

1.2.1.1. Main studies

Data from two pivotal studies, STRIDE 1 and STRIDE 2 with supporting safety information from the extension study STRIDE 2X (FPH02X) and long term survival data for subjects in STRIDE 2 were included in the submission.

Patients from study STRIDE 2X were eligible to enter a long-term open-label study STRIDE 3 (FPH03). Survival status in this study together with the survival status of patients who were included in studies STRIDE 2 and STRIDE 2X but did not enter study STRIDE 3 was also included.

At the request of the CHMP, the MAH also submitted the results of study STRIDE 4.

- **Methods and baseline**

STRIDE-1 included 3 groups (sitaxentan 100 mg, sitaxentan 300 mg, placebo dosed orally once daily) of approximately 60 subjects with FC II-IV per group, treated in a double-blind fashion for 12 weeks. The primary efficacy endpoint was the change from baseline to Week 12 in percent of predicted peak oxygen uptake (VO_2). According to the MAH, the primary endpoint was chosen at the time (early 2001) in order to address the concern that the standard use of the 450-meter upper limit for 6-minute walk distance (6-MWD) would exclude many of the functional class II from the study. At the time, cardiopulmonary exercise testing (CPET) was felt to be a more sensitive indicator of change in PAH patients; however, it remains a difficult endpoint in a multicenter trial due to technical difficulties in performing and standardizing the testing.
The secondary endpoints included the 6-minute walk test (6-MWT), WHO functional class, time to clinical worsening and haemodynamic measures. The inclusion/exclusion criteria did not include any constraint on distance walked in the 6-MWT.

STRIDE-2 included 4 arms of approximately 60 subjects with FC II-IV per arm: placebo, sitaxentan 50 mg, sitaxentan 100 mg, treated in a double-blind fashion for 18 weeks; in addition, a fourth arm of

open-label bosentan 62.5 mg for 1 month, followed by 125 mg for the duration of the study, consistent with the approved labelling for bosentan, was included. The 6-MWT was the primary endpoint, while WHO functional class, time to clinical deterioration, and Borg Dyspnoea Score were secondary endpoints. Subjects were included in STRIDE 2 if they could walk between 150 and 450 meters at baseline on the 6-MWT.

The key features of the two studies are summarized in Table 1.

Table 1 - Key study design features of STRIDE 1 and STRIDE 2

	STRIDE 1	**STRIDE 2**
Study type	Randomized, placebo controlled	Randomized, placebo controlled
Treatment groups	Placebo Sitaxentan 100 mg Sitaxentan 300 mg	Placebo Sitaxentan 50 mg Sitaxentan 100 mg Open-label (rater blinded) Bosentan (62.5mg, followed by 125mg) BID
Study duration	12 Weeks	18 Weeks
Subjects	Functional class II-IV	Functional class II-IV
Baseline 6MWD≤450m	Not set	Required
Efficacy endpoints		
Primary	Percent predicted peak oxygen uptake (VO_2)	6MWD
Secondary	6MWD WHO functional class Time to clinical worsening Hemodynamic measures	WHO functional class Time to clinical worsening Borg Dyspnea Score

STRIDE-4 was an 18-week multicentre, international study which randomised 98 patients with PAH (idiopathic or associated with connective tissue disease or congenital heart disease). Patients included were FCII, FCIII or FCIV, and had a 6MWD between 150 and 450 metres at baseline. The primary efficacy endpoint was the change from baseline in 6-MWD at Week 18. Secondary efficacy endpoints included: WHO FC change from baseline at each follow-up assessment; and time to clinical worsening through Week 18.

Baseline characteristics for STRIDE 1 and STRIDE II WHO functional class II and III patients are presented Table 2 and Table 3.

Table 2 - Baseline demographics and characteristics – STRIDE 1

Mean (±SD) or n (%)	Class WHO II			Class WHO III		
	Placebo N=22	**Sitax 100 mg N=16**	**Sitax 300 mg N=21**	**Placebo N=36**	**Sitax 100 mg N=39**	**Sitax 300 mg N=42**
Age (years)	50.2 (15.8)	43.7 (16.4)	41.0 (10.1)	46.8 (13.2)	45.3 (13.4)	45.6 (11.9)
Gender Male (%) Female (%)	 7 (32%) 15 (68%)	 3 (19%) 13 (81%)	 6 (29%) 15 (71%)	 6 (17%) 30 (83%)	 5 (13%) 34 (87%)	 10(24%) 32 (76%)
Aetiology IPAH (%) Secondary PAH (%)	 12 (55%) 10 (45%)	 11 (69%) 5 (31%)	 10 (48%) 11 (52%)	 23 (64%) 13 (36%)	 12 (31%) 27 (69%)	 24 (57%) 18 (43%)
Percent of Predicted VO_2 at AT	38.8 (10.5) (n=21)	33.5 (11.2) (n=14)	31.6 (11.3) (n=19)	34.7 (10.6) (n=34)	33.2 (9.2) (n=32)	32.7 (11.8) (n=38)
6MWD (m)	**460.1(102.7)**	**435.4 (106.4)**	**453.1 (75.9)**	**388.7 (99.3)**	**377.3 (114.2)**	**354.1 (110.7)**
Mean PAP (mmHg)	50.9 (21.8)	47.6 (16.3)	51.2 (13.2)	52.3 (11.8)	57.2 (16.3)	56.0 (13.7)
PCWP (mmHg)	9.1 (4.0)	9.1 (3.0)	9.1 (2.7)	8.7 (3.3)	8.1 (3.0)	9.6 (2.7)
PVR (dyne.s/cm^5)	872.7 (684.8)	777.9 (463.1)	783.6 (333.2)	908.1 (362.0)	1132.9 (752.5)	1027.7 (529.5)

VO_2: oxygen uptake; AT: anaerobic threshold; 6MWD: 6 minute walk distance; PAP: pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance

Table 3 - Baseline demographics and characteristics – STRIDE 2

Mean (±SD) or n (%)	Class WHO II				Class WHO III			
	Placebo N=23	**Sitax 50 mg N=21**	**Sitax 100 mg N=26**	**Bosentan N=23**	**Placebo N=35**	**Sitax 50 mg N=38**	**Sitax 100 mg N=34**	**Bosentan N=37**
Age (years)	51.1 (14.9)	54.6 (15.7)	56.6 (11.3)	49.3 (15.3)	55.1 (15.5)	56.6 (11.8)	54.4 (15.8)	48.7 (16.3)
Gender Male (%) Female (%)	 4 (17%) 19 (83%)	 2 (10%) 19 (90%)	 4 (15%) 22 (85%)	 6 (26%) 17 (74%)	 11 (31%) 24 (69%)	 6 (16%) 31 (84%)	 14 (40%) 21 (60%)	 6 (16%) 31 (84%)
Etiology Primary PH (%) Secondary PAH (%)	 14 (61%) 9 (39%)	 11 (52%) 10 (48%)	 17 (65%) 9 (35%)	 14 (61%) 9 (39%)	 22 (63%) 13 (37%)	 20 (54%) 17 (46%)	 23 (66%) 12 (34%)	 20 (54%) 17 (46%)
6MWD (m)	**349.8 (70.9)**	**375.2 (60.5)**	**376.4 (60.6)**	**378.9 (62.0)**	**316.2 (85.6)**	**308.6 (79.9)**	**349.4 (77.1)**	**315.9 (72.6)**
Mean PAP (mmHg)	45.6 (16.3)	48.5 (18.6)	41.1 (12.7)	47.0 (13.2)	51.3 (12.4)	48.0 (12.4)	47.0 (10.6)	52.3 (16.0)
PCWP (mmHg)	9.4 (4.0)	8.8 (3.8)	10.3 (4.5)	9.0 (3.4)	8.3 (3.8)	10.0 (3.9)	9.0 (3.6)	8.6 (3.2)
PVR (mmHg/L/min)	9.9 (9.5)	9.5 (7.2)	7.2 (3.6)	10.0 (4.1)	12.4 (6.6)	10.3 (6.6)	12.3 (7.7)	12.0 (5.5)

Representativeness of FC WHO II

At the time when sitaxentan was evaluated for approval, concerns were raised in relation to the representativeness of patients included in WHO functional class II and the magnitude of the effect achieved in the measurement of 6-MWT. As a result, only WHO functional class III labelling was considered for sitaxentan. The concerns regarding the representativeness of the WHO FC II population in the sitaxentan study population were based on a publication in 2000 by Miyamoto *et al*. in which patients with PAH WHO FC II should walk approximately 450 m in 6 minutes.
Later, Humbert, *et al*. published results from the French National PAH Registry in 2006, indicating that patients of WHO FC II, were expected to walk about 415 m (±86 m) in 6 minutes.

Baseline 6-MWT and Functional Class

As shown in Table 4, WHO functional classes II and III were comparably differentiated, with respect to baseline walking distance, in STRIDE 1, STRIDE 2 (Sitaxentan studies), AMB-320, AMB-321 (Ambrisentan studies) and the EARLY Study (Bosentan study). The 6-MWT observed in STRIDE 1 and STRIDE 2 was also comparable with the expected 6-MWT according to the walking distance reported in the French registry.

Table 4 - Baseline 6-MWT by Functional Class for Sitaxentan, Ambrisentan, Bosentan and French Registry

	WHO FC	**N**	**Median baseline 6-MWT**	**minimum**	**maximum**
Sitaxentan					
STRIDE 1	II	59	447 m	247 m	657 m
	III	117	379 m	79 m	607 m
STRIDE 2	II	91	390 m	179 m	448 m
	III	148	335 m	152 m	450 m
Ambrisentan					
AMB-320	II	65	380 m	160 m	449 m
	III	117	354 m	192 m	442 m
AMB-321	II	86	398 m	190 m	449 m
	III	99	350 m	150 m	445 m
Bosentan					
EARLY	II bosentan	80	440 m	251 m	598 m
	II placebo	88	436 m	178 m	660 m
			Baseline 6MWD Mean +/- SD		
French Registry	I-II	134	415 +/- 86 m	N/A	N/A
	III	359	319 +/- 92 m	N/A	N/A

Baseline 6-MWT by Cut-off Point

In the ambrisentan application, 400m was used as a cut-off point for the 6-MWT to show that a substantial number of less severe patients (class II) could have been included in its two clinical trials. When both clinical studies are combined, nearly half of the patients (47%) with functional class II had a 6MWD>400m compared with 26.9% of patients with functional class III (when both clinical trials are combined). This data suggests that a substantial number of less severe patients (class II) could have been included in both clinical trials (Volibris EPAR).

In STRIDE 1, 75% of functional class II subjects walked > 400m at baseline; 42% of functional class III subjects walked >400m at baseline. In STRIDE 2, 38% of class II subjects walked > 400m at baseline; 17% of class III subjects walked >400m at baseline. The difference between STRIDE 1 and STRIDE 2 here is likely due to the difference in entrance criteria in these studies, i.e. while no upper limit was set for 6MWD in STRIDE 1; it was limited to 450m in STRIDE 2.

Haemodynamics

In STRIDE-1, there were differences between WHO functional classes II and III with respect to baseline Pulmonary Vascular Resistance (PVR), Mean Pulmonary Artery Pressure (mPAP), Heart Rate, Right Atrial Pressure (RAP), and Systemic Vascular Resistance (SVR) (Table 5). No significant differences for Wedge Pressure (PCWP), Cardiac Index (CI), Cardiac Output (CO), Mean Arterial Pressure (MAP) were detected.

Table 5 - Baseline Haemodynamic Parameters by Baseline Functional Class – STRIDE 1

	Mean (SD)			
Parameter	**Class II**	**Class III**	**Mean Difference (95% CI)**	**P-value**
Cardiac Index	2.48 (0.71)	2.35 (0.79)	0.13 (-0.11 to 0.37)	0.288
Cardiac Output	4.40 (1.09)	4.15 (1.45)	0.24 (-0.18 to 0.66)	0.219
Mean Pulmonary Arterial Pressure	50.1 (17.4)	55.3 (14.1)	-5.12 (-9.95 to -0.29)	0.038
Mean Pulmonary Capillary Wedge Pressure	9.08 (3.25)	8.84 (3.04)	0.25 (-0.73 to 1.23)	0.618
Pulmonary Vascular Resistance	815.3 (515.3)	1024 (572)	-209 (-384 to -33.7)	0.02
Pulmonary Vascular Resistance Index	1454 (876)	1797 (1019)	-344 (-652 to -35.9)	0.029
Heart Rate	73.9 (14.5)	81.6 (12.5)	-7.66 (-11.82 to -3.50)	<0.001
Mean Arterial Pressure	87.5 (16.4)	91.4 (14.0)	-3.93 (-8.62 to 0.77)	0.101
Mixed Venous Oxygen Saturation	66.7 (7.72)	63.4 (8.58)	3.31 (0.65 to 5.97)	0.015
Arterial Oxygen Saturation	95.3 (3.67)	92.1 (5.79)	3.23 (1.53 to 4.93)	<0.001
Diastolic Pulmonary Arterial Pressure	33.0 (13.9)	36.9 (11.9)	-3.94 (-7.91 to 0.03)	0.052
Systolic Pulmonary Arterial Pressure	80.1 (27.8)	88.9 (20.4)	-8.83 (-16.1 to -1.53)	0.033
Mean Right Atrial Pressure	6.85 (4.57)	8.62 (5.23)	-1.78 (-3.36 to -0.19)	0.028
Systemic Vascular Resistance	1539 (489)	1778 (690)	-239 (-440 to -39.1)	0.009

In STRIDE-2, haemodynamic parameters were only collected at the baseline visit and no post-treatment assessments were taken. Based on the key haemodynamic parameters in PAH, there is clear differentiation between subjects assessed as FCII and FC III at baseline with respect to baseline pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR) and cardiac index (CI), the key haemodynamic parameters for diagnosis of PAH (Table 6). As expected, no significant difference in pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) were evident.

Table 6 - Baseline Haemodynamic Parameters by Baseline Functional Class – STRIDE 2

Parameter	Mean (SD) FCII	FCIII	Mean Difference (95% CI)	P-value
Cardiac Index (L/min/m^2)	2.63 (0.69)	2.33 (0.84)	0.29 (0.08 to 0.51)	0.008
Mean Pulmonary Arterial Pressure (mmHg)	45.0 (14.9)	49.6 (13.3)	-4.62 (-8.38 to -0.86)	0.016
Pulmonary Capillary Wedge Pressure (mmHg)	9.43 (3.94)	9.20 (3.56)	0.22 (-0.78 to 1.23)	0.662
Pulmonary Vascular Resistance (mmHg/L/min)	8.99 (6.44)	11.6 (6.64)	-2.63 (-4.42 to -0.84)	0.004
Right Atrial Pressure (mmHg)	8.23 (10.13)	9.28 (6.34)	-1.05 (-3.27 to 1.18)	0.391

- **Efficacy Results**

The 6-MWT, haemodynamics, WHO FC and survival results presented below are based on the intent-to-treat population ITT defined as all randomized subjects who received any dose of study drug, and subjects were analyzed by the group to which they were randomized regardless of which treatment they received. One subject in STRIDE 1 and one in STRIDE 2 did not receive the treatment randomized: the subject in STRIDE 1 was randomized to placebo but received sitaxentan 100 mg; the subject in STRIDE 2 was randomized to sitaxentan 100 mg but received sitaxentan 50 mg. Only data for the approved dose sitaxentan 100 mg are presented in the following sections.

6-Minute Walk Test

- 6-MWT by Functional Class

Table 7 reports the comparisons in change from baseline in 6-MWT at Week 12 relative to placebo for the 100 mg sitaxentan dose by baseline FC (II, III) in studies STRIDE-1 and STRIDE-2. No statistically significant difference was found in placebo comparisons of change from baseline in 6-MWT after 12 weeks of sitaxentan 100 mg treatment in patients with WHO FC II.

Table 7 - Placebo comparisons of change from Baseline in 6-MWT at Week 12 in Sitaxentan 100 mg Group by Baseline Functional Class (Non Parametric Analysis) - STRIDE 1 and STRIDE 2

Baseline Functional Class	Placebo comparisons of change from Baseline in 6MWT at		
	Week 12 (missing data at week 12 are excluded)	Week 12 (LOCF)	Week 12 (missing data set to 0)
STRIDE 1 (6-MWT measured as a secondary endpoint)			
II	20m (p=0.143) N = 16 (sitax) N = 22 (pbo)	20m (p=0.143) N = 16 (sitax) N = 22 (pbo))	20m (p=0.143) N = 16 (sitax) N = 22 (pbo)
III	37m (p=0.018) N = 38(sitax) N = 33 (pbo)	41m (p=0.006) N = 39(sitax) N = 36 (pbo)	44m (p=0.009) N = 39(sitax) N = 36 (pbo)
STRIDE 2 (6-MWT measured as the primary endpoint)			
II	3m (p=0.717) N = 26 (sitax) N = 22 (pbo)	6m (p=0.582) N = 26 (sitax) N = 23 (pbo)	7m (p=0.541) N = 26 (sitax) N = 23 (pbo)
III	31m (p=0.039) N = 32 (sitax) N = 28 (pbo)	37m (p=0.008) N = 35 (sitax) N = 35 (pbo)	43m (p=0.016) N = 35 (sitax) N = 35 (pbo)

Sitax: sitaxentan; pbo: placebo; N: number of subjects

Differences between treatments for each functional class were assessed by the Wilcoxon rank-sum test and Hodges-Lehmann estimates of treatment effect.

In STRIDE 4, there was no significant different in the 6-MWT in the whole cohort, or those with FC II at baseline (Table 8). The MAH attributed this to the higher variability in the placebo group in STRIDE 4 compared to that in the other 2 studies.

Table 8 - Change from baseline in 6MWD (LOCF) at Week 18 STRIDE-4

6-Minute Walk Distance	Placebo	100 mg	FC II		FC III	
STRIDE 4	**(N=34)**	**(N=32)**	**Placebo N=19**	**Sitaxentan N=18**	**Placebo N=14**	**Sitaxentan N=14**
Baseline	341.6	342.8	346.6	378.8	346	299
Mean (SD) change to Wk 18	33.76 (88.51)	58.04 (63.65)	54.8 (84.6)	53.8 (56.3)	-5.2 (77.9)	63.5 (73.9)
Estimate of treatment difference	24.28		-3.0		62.5	
P-value	0.2078		0.9978		0.0196	

- 6-MWT by Cut-off Point

Table 9 below reports the comparisons in change from baseline in 6-MWT at Week 12 relative to placebo for the 100 mg sitaxentan dose in STRIDE-1 by Baseline 6-MWT with cut off 400m and 415m, respectively.

Table 9 - Placebo comparisons of change from Baseline in 6-MWT by Baseline 6-MWT in Sitaxentan 100 mg Group (Non Parametric Analysis) – STRIDE 1

Baseline Walk Distance	**Placebo comparisons of change from Baseline in 6MWD at**		
	Week 12 (missing data at week 12 are excluded)	**Week 12 (LOCF)**	**Week 12 (missing data set to 0)**
<= 400m	**41.9m (p=0.031)** N = 24 (sitax) N = 21 (pbo)	**48.8m (p=0.009)** N = 25 (sitax) N = 24 (pbo)	**53.3m (p=0.016)** N = 25 (sitax) N = 24 (pbo)
> 400m	23.1m (p=0.102) N = 30 (sitax) N = 34 (pbo)	23.1m (p=0.102) N = 30 (sitax) N = 34 (pbo)	23.1m (p=0.102) N = 30 (sitax) N = 34 (pbo)
<= 415m	**38.6m (p=0.025)** N = 30 (sitax) N = 24 (pbo)	**43.0m (p=0.007)** N = 31 (sitax) N = 27 (pbo)	**47.2m (p=0.012)** N = 31 (sitax) N = 27 (pbo)
> 415m	22.6m (p=0.169) N = 24 (sitax) N = 31 (pbo)	22.6m (p=0.169) N = 24 (sitax) N = 31 (pbo)	22.6m (p=0.169) N = 24 (sitax) N = 31 (pbo)

Sitax: sitaxentan; pbo: placebo; N; number of subjects
Differences between treatments for each functional class were assessed by the Wilcoxon rank-sum test and Hodges-Lehmann estimates of treatment effect.

Statistically significant improvement in 6MWT was observed in the more severe PAH patients after sitaxentan 100 mg treatment by both cut-off points. However, no statistically significant improvement or clinically relevant improvements were seen after sitaxentan 100 mg treatment in WHO FC II subjects.

Due to the small number of placebo subjects with baseline 6MWD >400m in the STRIDE 2 study, STRIDE 2 results were not analyzed for this endpoint. Presenting the 6-MWT results of STRIDE-4 with baseline cut-off values of above and below 400 m, did not reveal any significant difference for either group.

Haemodynamic Results

Table 10 summarises change from baseline to Week 12 in PVR, PVRI, and CI parameters in STRIDE 1. After 12 weeks of sitaxentan 100 mg treatment, PVR, PVRI and CI were significantly different in both functional class II and functional class III patients compared with placebo.

Table 10 - Summary Statistics of PVR, PVRI and CI at Each Visit (mean (SD) by Functional Class – STRIDE 1

Functional Class	Treatment	N	Baseline	Week 12	Change from Baseline
PVR (dyne*sec/cm^5)					
II	Placebo	21	890.6 (696.5)	868.9 (636.1)	-21.7 (168.4)
	Sitax 100 mg	16	777.9 (463.1)	577.9 (285.5)	-200.0 (322.8)
III	Placebo	33	910.7 (344.7)	1021.3 (470.3)	110.6 (285.1)
	Sitax 100 mg	36	1070.2 (657.8)	833.7 (451.9)	-236.4 (494.1)
PVRI (dyne*sec/(cm^5/m^2))					
II	Placebo	21	1542.9 (1074.6)	1502.7 (983.4)	-40.2 (289.2)
	Sitax 100 mg	15	1434.2 (881.6)	1075.8 (542.7)	-358.4 (592.1)
III	Placebo	33	1572.2 (574.1)	1766.1 (797.4)	193.9 (481.9)
	Sitax 100 mg	35	1825.6 (1166.3)	1372.9 (724.3)	-452.7 (851.2)
CI (L/min/m^2)					
II	Placebo	22	2.43 (0.80)	2.47 (0.92)	0.04 (0.47
	Sitax 100 mg	15	2.38 (0.59)	2.85 (0.42)	0.47 (0.58)
III	Placebo	33	2.41 (0.84)	2.34 (0.91)	-0.07 (0.53)
	Sitax 100 mg	37	2.41 (0.86)	2.61 (0.93)	0.20 (0.56)

Only subjects who have been randomised to placebo or sitaxentan 100 mg and for whom both baseline and Week 12 data are available are included. PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CI: cardiac index Sitax: sitaxentan; N: number of subjects. PVRI has been derived as PVR*BSA.

Only baseline haemodynamics were collected in STRIDE-2 and -4.

Functional Class Changes

WHO functional class data from STRIDE-1, -2 and -4 over 12 weeks and 18 weeks of treatment with sitaxentan 100 mg compared to placebo are presented in Table 11.

Table 11 - Change from Baseline to End of Treatment (EOT) using LOCF in WHO Functional Class – STRIDE-1, STRIDE-2 and STRIDE-4

STRIDE-1	Week 12 Improved N (%)	Week 12 No Change N (%)	Week 12 Worsened N (%)
Baseline FCII			
Placebo	2 (9.1)	18 (81.8)	2 (9.1)
Sitaxentan 100 mg	1 (6.3)	15 (93.8)	0
Baseline FCIII			
Placebo	6 (16.7)	28 (77.8)	2 (5.6)
Sitaxentan 100 mg	15 (38.5)	24 (61.5)	0
STRIDE- 2	**Week 18** Improved N (%)	**Week 18** No Change N (%)	**Week 18** Worsened N (%)
Baseline FCII			
Placebo	0	18 (78.3)	5 (21.7)
Sitaxentan 100 mg	3 (11.5)	22 (84.6)	1 (3.8)
Baseline FCIII			
Placebo	5 (14.3)	26 (74.3)	4 (11.4)
Sitaxentan 100 mg	5 (14.3)	30 (85.7)	0
STRIDE- 4	**Week 18** Improved N (%)	**Week 18** No Change N (%)	**Week 18** Worsened N (%)
Baseline FCII			
Placebo	4 (21.1)	13 (68.4)	2 (10.5)
Sitaxentan 100 mg	7 (38.9)	11 (61.1)	0
Baseline FCIII			
Placebo	4 (28.6)	8 (57.1)	2 (14.3)
Sitaxentan 100 mg	8 (57.1)	6 (42.9)	0

The number of patients who showed a worsening of FC was lower in the sitaxentan sodium 100 mg treatment group compared to placebo. This benefit was observed across all studies and was independent of baseline FC severity.

There was a statistically significant improvement in FC following sitaxentan sodium 100mg treatment for baseline FCIII patients in STRIDE-1 and baseline FCII patients in STRIDE-2 (Table 12).

Table 12 - Logistic Regression of FC at EOT by Study and Baseline FC – STRIDE-1, -2 and -4

Study	Population	Odds Ratio[1]	95% CI	p-value
STRIDE-1	FCII	1.64	0.24, 11.34	0.6153
	FCIII	3.52	1.20, 10.27	0.0216
STRIDE-2	FCII	10.05	1.15, 87.63	0.0368
	FCIII	1.86	0.56, 6.19	0.3112
STRIDE-4	FCII	2.96	0.72, 12.13	0.1324
	FCIII	4.20	0.90, 19.55	0.0672
[1] Sitaxentan sodium 100mg/Placebo				

Pooling data from the three studies, it appears that FCII patients treated with sitaxentan sodium 100 mg were 3.26 (p=0.0140) times more likely to show improvements in FC than those on placebo. This is similar to data for FCIII patients, in which the odds ratio estimate was 2.78 (p=0.0037) for improvements in FC (Table 13).

Table 13 – Combined Logistic Regression of FC at EOT – STRIDE-1, -2 and -4 Combined

Population	Odds Ratio[1]	95% CI	p-value
FCII	3.26	1.27, 8.37	0.0140
FCIII	2.78	1.39, 5.56	0.0037
[1] Sitaxentan sodium 100mg/Placebo			

Given the known association of survival with FC in PAH, the long-term survival of the 145 patients treated with sitaxentan sodium 100mg was further analysed for its association with FC in STRIDE-2X. The results indicate that the long term survival was associated with FC at baseline (Hazard ratio 2.12; p=0.0246). However, an improvement in FC did not appear to improve survival. This suggests that an improvement in FCIII to FCII does not afford the same survival benefit as maintaining patients in FCII.

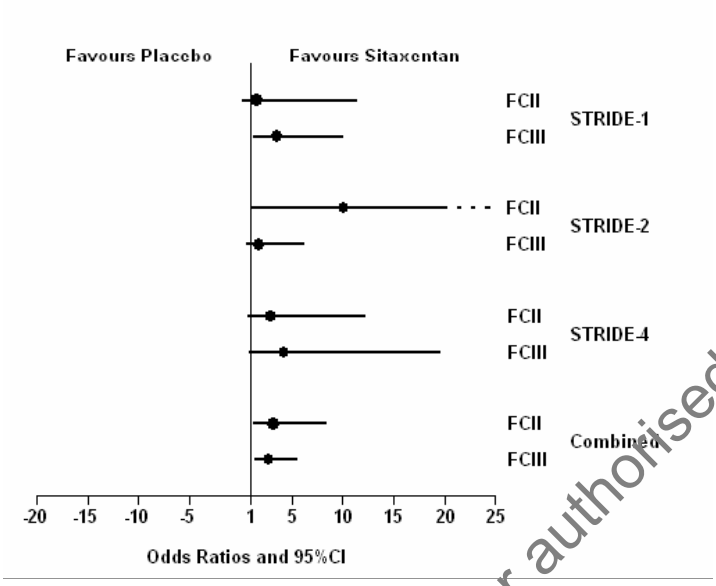

Figure 1 - Improvements in Functional Class with sitaxentan sodium 100 mg

Time to clinical worsening

At the request of the CHMP, the MAH presented results on time to clinical worsening. The MAH conducted an analysis using a consistent definition of time to clinical worsening (TTCW) from the *Draft CHMP Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension* (EMEA/CHMP/EWP/356954/2008), which is the first occurrence of 1) death; 2) hospitalisation due to worsening of PAH; 3) a 15% reduction from baseline in 6MWD in two consecutive visits; and 4) worsening in FC from baseline in two consecutive visits. TTCW was assessed in pooled analysis of data from all three randomised, controlled clinical trials comparing sitaxentan sodium 100mg vs placebo in the treatment of PAH (STRIDE-1, - 2 and -4). Additionally, TTCW in patients treated with sitaxentan sodium 100mg was compared to bosentan-treated patients enrolled in STRIDE-3/2X.

The Kaplan-Meier rates of clinical worsening events are presented for individual studies in Table 14 and Table 15 and a pooled analysis of STRIDE-1, -2 and -4 in Table 16.

A relatively low number of clinical worsening events would be expected, given this observation period, and a disproportionately greater number of events would be anticipated in FCIII patients compared to FCII. A numerical benefit in the time to clinical worsening was observed in STRIDE-2 and STRIDE-4 (non-significant). There was no difference observed in the event rate in the 12-week STRIDE-1 study. This could be due to a combination of few FCII patients and short study duration.

Table 14 – Kaplan-Meier Estimate of TTCW in STRIDE-1, -2 and -4 (Safety Population)

	STRIDE-1		STRIDE-2		STRIDE-4	
FCII	Placebo	Sitax 100mg	Placebo	Sitax 100mg	Placebo	Sitax 100mg
# of Patients	21	17	23	26	19	18
Patients with Events	1	1	3	1	2	0
Patients censored (%)	20 (95.2)	16 (94.1)	20 (87.0)	25 (96.2)	17 (89.5)	18 (100.0)
Kaplan-Meier Rate of Clinical Worsening	4.8%	5.9%	13.0%	3.8%	10.5%	0%
Log Rank Test	p=0.8640		p=0.2431		p=0.1751	
	STRIDE-1		STRIDE-2		STRIDE-4	
FCIII	Placebo	Sitax 100mg	Placebo	Sitax 100mg	Placebo	Sitax 100mg
# of Patients	36	39	35	34	14	14
Patients with Events	6	0	6	0	3	2
Patients censored (%)	30 (83.3)	39 (100.0)	29 (82.9)	34 (100.0)	11 (78.6)	12 (85.7)
Kaplan-Meier Rate of Clinical Worsening	17.2%	0%	19.2%	0%	22.1%	14.3%
Log Rank Test	p=0.0071		p=0.0106		p=0.6393	
Note: In the case of tied first occurrences for Clinical Worsening, causation was allocated in the following order: (1) Death; (2) Hospitalisation for worsening PAH; (3) Worsening of Functional Class on two occasions; (4) 15% reduction in 6MWD on two occasions						

The pooled analysis (Table 15) shows that for FC II, the Kaplan-Meyer estimate for clinical worsening was 3.3% and 9.8% for sitaxentan and placebo respectively (p=0.163).

Table 15 – Pooled analysis of Kaplan-Meier estimate of TTCW in STRIDE-1, STRIDE- 2 and STRIDE-4 (Safety Population)

	FCII		FCIII		FCII and FCIII Combined	
	Placebo	Sitax 100mg	Placebo	Sitax 100mg	Placebo	Sitax 100mg
# of Patients	63	61	85	87	148	148
Patients with Events	6	2	15	2	21	4
Patients censored (%)	57 (90.5)	59 (96.7)	70 (82.4)	85 (97.7)	127 (85.8)	144 (97.3)
Kaplan-Meier Rate of Clinical Worsening	9.8%	3.3%	21.7%	2.3%	16.2%	2.7%
Log Rank Test	p=0.1630		p=0.0006		p=0.0003	

Table 16 depicts the first clinical worsening event in STRIDE-1,-2 and -4 combined.

Table 16 – First Occurrence of Clinical Worsening in STRIDE-1, -2 and -4 Combined (Safety Population)

		Reason for Clinical Worsening - number of patients (%)			
	Treatment	Death	Hospitalization	Functional Class	6MWD
FCII	Placebo	0	0	5 (83.3%)	1 (16.7%)
	Sitaxentan	0	0	1 (50.0%)	1 (50.0%)
FCIII	Placebo	0	5 (33.3%)	1 (6.7%)	9 (60.0%)
	Sitaxentan	0	0	0	2 (100%)
Note: In the case of tied first occurrences for Clinical Worsening, causation was allocated in the following order: (1) Death; (2) Hospitalisation for worsening PAH; (3) Worsening of Functional Class on two occasions; (4) 15% reduction in 6MWD on two occasions					

There were no statistically significant differences in the rates of clinical worsening between the bosentan and Sitaxentan sodium treatment arms for both FCII and FCIII patients (Table 17).

Table 17 – Kaplan-Meier Estimate of TTCW including Follow-up to 1 Year in STRIDE-2/STRIDE-2X (Safety Population)

	FCII		FCIII		All Patients	
	Bosentan	Sitax 100mg	Bosentan	Sitax 100mg	Bosentan	Sitax 100mg
# of Patients	34	56	45	82	84	145
Patients with Events	5	12	12	17	18	32
Patients censored (%)	29 (85.3)	44 (78.6)	33 (73.3)	65 (79.3)	66 (78.6)	113 (77.9)
Kaplan-Meier Rate of Clinical Worsening	18.0%	22.9%	30.4%	22.7%	25.0%	24.0%
Log Rank Test	p=0.5698		p=0.1961		p=0.7029	

In patients classified as FCII at baseline the majority of clinical worsening events were due to deterioration in FC in both the sitaxentan sodium 100mg (92%) and bosentan (60%) treatment groups. There was one death and one case of hospitalization due to worsening of PAH in the bosentan arm and one case of hospitalisation in the sitaxentan sodium 100mg arm. In FCIII patients the proportion of patients who were hospitalised was 50% and 35% in the bosentan and sitaxentan sodium 100mg treatment groups, respectively.

1.2.1.2 Discussion on clinical efficacy

No new clinical studies were submitted to support this application.

Ambrisentan and Bosentan (both endothelin receptor antagonists) are currently registered for PAH FC II based on the results of studies ARIES-1/ARIES-2 and the EARLY study, respectively. The ARIES studies were 12 week double-blind placebo-controlled multicenter studies in 394 PAH patients (both FC II and III) with as primary endpoint: 6-MWT. The EARLY study was a 6 month double-blind placebo-controlled study in 168 PAH WHO FC II patients with as primary endpoints: pulmonary vascular resistance (% from baseline), 6-MWT (% from baseline). One of the secondary endpoints was time to clinical worsening.

The rationale for extending the indication to WHO FC II for both bosentan and Ambrisentan is presented above. Extrapolating efficacy from one endothelin receptor antagonist to the other is not possible.

With the publishing of the French Registry of PAH patients (Humbert et al., 2006) based on data from 674 patients, lower 6-MWT values were assigned for FC II than those previously reported in the article by Miyamoto et al., 2000: 415m vs 450 m respectively. The values reported in the French Registry are currently the accepted ones. Accordingly, re-evaluating data shown above from STRIDE-1 and STRIDE-2 provides evidence that PAH FC II and III subjects were clinically distinguishable populations regarding the 6-MWT, comparable to those recruited in the Ambrisentan and Bosentan studies. The use of concomitant medications in FCIII was more than in FC II, which further supports the differentiation of these functional classes at baseline in STRIDE-1 and STRIDE-2 studies. The submitted data support that recruited PAH patients in STRIDE-1 and STRIDE-2 had statistically different haemodynamic values for WHO FC II and III.

In both sitaxentan studies, the placebo-corrected changes in the 6-MWT at week 12 for WHO FC II were not statistically significant, which constitutes a major objection to the extension of the indication to this FC. STRIDE-1 and STRIDE-2 recruited 16 and 35 patients in FC II respectively. The results of the 6-MWT presented at EOT (+20 m and +11.3 for STRIDE-1 and STRIDE-2 respectively) compare better than the results at week 12 for both studies (+20m and +6m respectively). Still the results are not reassuring considering that STRIDE-2 was the larger study. The results of the sitaxentan arm in general (inclusive FC II and III) and specifically for WHO FC III as shown in Table 7 on the other hand are statistically and clinically significant, which is the basis for the registration of sitaxentan for the corresponding class.

Analysis of the 6-MWT using different cut-offs support the previous results. There is a statistically and clinically relevant improvement in the 6-MWT test in patients in the more severe PAH patients after 12 weeks in the sitaxentan treatment group, but not in the patients with milder disease. This again supports the previous conclusion. On the other hand, the administration of Ambrisentan consistently resulted in significant improvements whatever the cut-off used.

In STRIDE-1, sitaxentan administration resulted in statistically significant haemodynamic changes in WHO FC II, though obviously less than those achieved for WHO FC III. Haemodynamic measurements are not generally accepted as primary endpoints in PAH clinical studies and their role are mainly in Phase II studies to investigate the mechanism of action or the dose response relationship.

In PAH patients with FC II at baseline, improvements in FC were only significant in STRIDE-2; sitaxentan did not show significant improvements in FC in STRIDE-1 and -4. However, pooling of the

3 studies improve the results, leading to significant improvement in FC. The robustness of such pooling/results is questioned specially in light of the opposite direction of the results of the 6-MWT. The results are generally supportive as the improvement of WHO FC is not considered as a robust primary endpoint. In addition, no formal statistical analysis was conducted.

TTCW was assessed in STRIDE-1,-2 and -4 as a secondary endpoint, though with different definitions in each study. For the sake of consistency, the MAH conducted an analysis using a single definition in line with that defined in the draft CHMP guideline for PAH. The results generally show significant benefit in the whole cohort studied, but this was primarily due to a benefit in FC III. For FC II, no statistical significance can be shown using any method of analysis (individual studies or pooled data). This could have been expected considering the relatively short duration of the studies (STRIDE-1,-2 and -4) which varied between 12 and 18 weeks. The numerical benefit that was noted in FC II compared to placebo (overall 6 vs. 2 events) are mainly driven by less worsening of FC as other endpoints (death, hospitalisation) did not occur. No robust conclusions can be drawn on such data considering the post-hoc analysis.

1.2.2 Clinical safety

Safety database for WHO FC II patients is based on patients recruited in STRIDE 1 and STRIDE 2/STRIDE 2X studies. The use of sitaxentan in these patients was well tolerated. Generally, sitaxentan 100 mg was better tolerated in WHO FC II subjects compared with the overall populations in these studies. There were no deaths and no treatment-related SAEs among WHO FC II patients who had received sitaxentan 100 mg. There were no discontinuations due to AE or laboratory test abnormalities among WHO FC II patients in STRIDE 1 or STRIDE 2. In the 1-year extension study STRIDE 2X, few subjects (<4%) in the sitaxentan 100 mg group discontinued from study due to treatment-related adverse events compared with 11-12% of subjects in the bosentan group. In STRIDE 2X, there were no discontinuations due to laboratory test abnormalities among functional class II patients treated with sitaxentan, and there was one subject with transaminases elevation >8x ULN requiring discontinuation of bosentan treatment.

- **<u>Long Term Survival Data</u>**

Patients completing STRIDE 2 were eligible to enrol in STRIDE 2X, an open-label extension study of sitaxentan 100 mg and bosentan. Subjects randomized to sitaxentan 50 mg or 100 mg in STRIDE 2 received sitaxentan 100 mg in STRIDE 2X. Subjects randomized to bosentan in STRIDE 2 continued their bosentan treatment in STRIDE 2X. Subjects randomized to placebo in STRIDE 2 were randomly assigned in a 1:1 ratio (in blocks of 2) to receive 1 of the 2 study treatments in STRIDE 2X (sitaxentan 100mg or bosentan). STRIDE 2X ended when the last subject had completed one year in the study. Day 1 for the survival analysis was the first day of sitaxentan treatment, i.e., Day 1 in STRIDE 2 for subjects randomized to sitaxentan 100 mg or sitaxentan 50 mg and Day 1 of STRIDE 2X for subjects who had been randomized to placebo in STRIDE 2. The Kaplan-Meier method was used for the survival analysis.

After 1 year, the 145 patients treated with sitaxentan 100 mg in STRIDE 2 or STRIDE 2X were either entered into a long-term open label study (STRIDE 3) or followed up, and survival information was collected through 3 years. For the 145 subjects who received sitaxentan 100 mg in STRIDE 2 or STRIDE 2X, the Kaplan-Meier survival rate was 95.9%, 84.7%, and 77.5% at 1 year, 2 years, and 3 years, respectively (Table 18), compared to the expected historical survival rate of 68%, and 48% of untreated PPH patients at 1 year and 2 years, respectively.

Table 18 - Survival Analysis for Sitaxentan 100 mg – All Subjects

	Year 1 Cutoff	Year 2 Cutoff	Year 3 Cutoff
Number of subjects	145	145	145
Subjects died	6	21	30
Subjects censored before cutoff, N (%)	0	17 (11.7)	18 (12.4)
Number of subjects at risk	139	107	97
K-M rate (95% CI) (%)	95.9 (92.6, 99.1)	84.7 (78.6, 90.7)	77.5 (70.4, 84.6)

Day 1 for the survival analysis was the first day of sitaxentan treatment.
Efforts were made to assess survival status; subjects were censored when lost to followed up.

For the subgroup of patients with PAH associated with connective tissue disease (CTD), the Kaplan-Meier survival rates were similar to the overall population (98%, 78%, and 67% at 1 year, 2 years, and 3 years, respectively).

A sensitivity analysis was conducted in which survival data were analyzed by treatment group in STRIDE 2; the Kaplan-Meier survival rate for the sitaxentan 100 mg group was 96.7%, 87.5%, and 78.0% at 1 year, 2 years and 3 years, respectively, similar to rates observed for all subjects who had received sitaxentan in STRIDE 2 or STRIDE 2X.

- **Survival Analysis by Baseline Functional Class**

Long term survival for WHO functional class II subjects was considerably better than for functional class III subjects. The Kaplan-Meier survival estimate for functional class II patients was 100%, 94.4%, and 82.8% at 1 year, 2 and 3 years, respectively, and for WHO functional class III patients, it was 93.8%, 79.1%, and 74.9% at 1 year, 2 years, and 3 years, respectively (Table 19).

Table 19 - Survival Analysis for Sitaxentan 100 mg by Functional Class

	Year 1 Cutoff	Year 2 Cutoff	Year 3 Cutoff
Functional class II			
Number of subjects	59	59	59
Subjects died	0	3	9
Subjects censored before cutoff, N (%)*	0	7 (11.9)	7 (11.9)
Number of subjects at risk	59	49	43
K-M rate (95% CI) (%)	100 (100, 100)	94.4 (88.2, 100)	82.8 (72.6, 93.0)
Functional class III			
Number of subjects	80	80	80
Subjects died	5	16	19
Subjects censored before cutoff, N (%)*	0	7 (8.8)	8 (10.0)
Number of subjects at risk	75	57	53
K-M rate (95% CI) (%)	93.8 (88.4, 99.1)	79.1 (70.0, 88.3)	74.9 (65.0, 84.7)

Day 1 for the survival analysis was the first day of sitaxentan treatment.

When analyzed by original treatment group in STRIDE 2 for sensitivity analysis, the Kaplan-Meier survival rate for sitaxentan 100 mg group was 100%, 100%, and 87.0% at 1 year, 2 years and 3 years, respectively, for the functional class II patients and 94.1%, 77.8%, and 71.0% at 1 year, 2 years and 3 years, respectively, for the functional class III patients

- **Functional Class and Long Term Survival**

Given the known association of survival with WHO functional class in PAH, the long term survival of the 145 subjects treated with sitaxentan 100 mg was further analysed for its association with functional class in STRIDE 2. The results indicate that the long term survival was associated with functional class at baseline (Hazard ratio 2.12; p=0.0246). However, an improvement in WHO functional class did not appear to improve survival. This implies that an improvement in WHO functional class III to functional class II does not afford the same survival benefit as maintaining patients in WHO functional class II. Therefore patients should be offered efficacious therapy whilst still in functional class II before they deteriorate to WHO functional class III.

This evidence suggests that administration of sitaxentan 100 mg to functional class II subjects delays disease progression and subsequent deterioration to class III, and survival is improved.

- **Discussion on clinical safety**

The presented safety data do not indicate a safety signal when sitaxentan is used in WHO FC II, however the numbers are too low to draw robust conclusions.

1.3. Benefit/Risk Assessment and Recommendation

PAH is a rare and devastating disease. Owing to the difficulties associated with the diagnosis, many patients will have progressed to WHO FC III or even IV before treatment is offered. Nevertheless, about 25% of PAH patients seen in the clinic are classified as WHO FC II or less at the time of diagnosis. Recently, it has been recognized that PAH patients in WHO FC II may benefit from specialized PAH therapy. Ambrisentan, bosentan, sildenafil and tadalafil have been recently approved for this indication (ref. respective EPARs).

The MAH did not submit new clinical data. Clinical data from previously submitted studies were re-evaluated. This data showed that patients with WHO FC II were adequately distinguished from WHO FC III in the STRIDE-1 and STRIDE-2 studies, mainly based on the baseline values of the 6-MWT and haemodynamic measurements. The recruited WHO FC II patients appeared comparable to those recruited in the corresponding ambrisentan and bosentan trials and the French Registry.

The benefit in FC II was re-assessed based on the STRIDE-1, -2 and -4 studies, in addition to STRIDE-2x. The 6-MWT was the primary endpoint in most of these studies; time to clinical worsening, improvement in functional class and haemodynamic data were assessed in some studies as secondary endpoints.

Both the 6-MWT and TTCW are considered relevant primary endpoints in PAH trials. Sitaxentan administration did not result in a significant improvement in 6 MWT in patients with FC II in any of the STRIDE studies. Only a trend was observed in STRIDE-1 (+20 m) and STRIDE-2 (+11.3 m) and no difference in STRIDE-4. Regarding TTCW, events were very low, differences with placebo not significant and primarily related to less worsening in FC. Sitaxentan resulted in significant improvement of functional class in FC II in only one study (STRIDE-2) or when all data were pooled. Haemodynamic data were positive in the one study in which it was investigated (STRIDE 1), and event-free survival was shown to be better than bosentan based on exploratory data. No safety issues were identified with long term use of sitaxentan in PAH patients in WHO FC II. However, the numbers are too low to draw robust conclusions.

In summary, the totality of the data with respect to FC II did not support a positive assessment, considering that the main efficacy endpoints were not significantly improved and only some improvement in FC did occur. This was further complicated by the inconsistency of the results across studies precluding any robust conclusions on efficacy. It should be noted that for the other endothelin-receptor antagonists registered for FC II, the indication was approved on the basis of a significant improvement in the 6 minute walking distance (ambrisentan) or a positive trend in this test, together with improvement in haemodynamic data and time to clinical worsening (bosentan).

In conclusion, the extension of indication in section 4.1 to include FC II was not acceptable. Based on the above post-hoc analysis, the results for TTCW were shown to be significant for FC III and the MAH proposed to include such data in section 5.1 of the SPC. This was not considered acceptable. Data in section 5.1 of the SPC should be balanced and based on sound statistical methods, which was not the case as neither pooling nor hierarchical analysis of secondary endpoints were pre-specified. The presented data are considered descriptive but not robust enough to be included in section 5.1 of the SPC.

However, the CHMP considered acceptable to include in section 5.1 of the SPC of the results of STRIDE 4 study, relevant haemodynamic data, effect on functional class and updated long-term survival data as the information can be useful to the prescriber.