Assessment report

for

Revatio

International Non-proprietary Name: sildenafil

Procedure No. EMEA/H/C/000638/II/0028

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Scientific discussion

1.1. Introduction

Sildenafil citrate is a potent and specific inhibitor of phosphodiesterase type 5 (PDE5). It was originally approved in 1998 for the treatment of male erectile dysfunction (MED), under the invented name Viagra, in both the United States (US) and the European Union (EU) (EMEA/H/C/202 authorised 14/09/1998). Sildenafil is approved in the EU since 2005 for pulmonary arterial hypertension (PAH) under the invented of Revatio (EU/1/05/318/001; 28-Oct-2005). The currently approved indication of Revatio (last revised 21/12/2009) is for: Treatment of patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. The approved dosage regimen for oral Revatio consists of one 20 mg tablet administered three times daily (TID).

Pulmonary arterial hypertension PAH is a rare, progressive and life threatening disease. Currently there are no approved therapies for PAH in children. Although the EU SmPC for the endothelin receptor antagonist bosentan has dosing information for children over 12 years, it has no formal paediatric indication. Extrapolation from adults to children in PAH is not straightforward for several reasons: 1) The prevalence of the subtypes of PAH is different among both populations (e.g the idiopathic form is more prevalent in adults, whilst PAH associated with congenital heart disease is more frequent in children); 2) the anticipated lifespan of children is longer; and 3) before the advent of long-term vasodilator/antiproliferative therapy, the natural history remained significantly worse for children compared to adult patients.

This Type II variation application is being submitted in accordance with Article 16 of Commission Regulation (EC) No. 1234/2008. This Type II variation is intended to extend the indication of Revatio (sildenafil citrate) in a new population, pulmonary arterial hypertension (PAH) in paediatric patients based on quality and clinical data.

The intended new indication is treatment of paediatric patients aged 1-17 with pulmonary arterial hypertension. The proposed posology is 10 mg TID for low weight patients (<20 kg) and 20 mg TID in patients whose weight is ≥20 kg.

The present clinical application is based on paediatric studies including clinical pharmacology data from studies A1481134 and A1481157 with intravenous sildenafil in PAH (supportive for clinical pharmacology and safety data) and a pivotal study A1481131 for PK/PD data with oral sildenafil, establishing population PK and PK-PD models, and driving the oral dose recommendation for the paediatric population. Interim clinical data from study A1481156, which is the long term extension of study A1481131 are also submitted.

Development of an age appropriate powder for oral suspension (POS) is currently underway, with submission anticipated in Q3 2011. Until the POS formulation is available, the MAH proposes an oral suspension formulation which is extemporaneously prepared from the 20 mg tablet using Ora-Sweet and Ora-Plus diluents (Paddock Laboratories) to reach a concentration of 10 mg/ml.

The spirit of the Paediatric Regulation encourages the industrial development, manufacture and control of specific age-appropriate formulations for paediatric use. However, in the interim period when such specific formulations are being developed, in exceptional cases it may be allowed to have an extemporaneous form for this purpose. Of course, this is intended as a temporary measure only, on the condition that the applicant has committed to the development of an industrially-prepared and validated product within a strict and agreed timeframe. Furthermore, for example the suitability, stability of the extemporaneous form must be demonstrated by appropriate studies. Since these conditions are met in the present case, an extemporaneous form may be allowed. This is further discussed in the report.

Consequently, the present application for the paediatric indication concerns the oral tablet formulation only and not the IV formulation.

The scope of the present application is the following:

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

Update of Summary of Product Characteristics, annex II, labelling and Package Leaflet to introduce a new indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.

This application is based on quality and clinical data based on 3 clinical studies A1481134, A1481157 and A1481131.

The above extension of indication applies to the oral tablet formulation only.

In addition, minor amendments are introduced in the product information for both tablets and IV formulation based on QRD comments received from the renewal application as agreed with the CHMP as FUM.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision number P33/2010 for the following condition:

- Pulmonary arterial hypertension

On the agreement of a paediatric investigation plan (PIP). The PIP is not yet completed.

Information related to orphan market exclusivity

Sildenafil was granted an orphan designation (EU/3/03/178) by the European Commission on 12 December 2003 for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considered Revatio not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to authorized orphan medicinal products for the same therapeutic indication.

Since then, an additional product volibris (ambrisentan) was granted orphan designation for pulmonary arterial hypertension.
Similarity was again assessed during the extension of indication for Revatio (variation II21) in class II PAH with the following conclusion. "Having considered the arguments presented by the MAH of Revatio on 10 December 2008, it is concluded that sildenafil does not share the same principal molecular structural features as ambrisentan and bosentan and the differences in molecular structure are not only minor. Sildenafil is regarded as structurally not similar to ambrisentan and bosentan. As defined in Art. 3 of Commission Regulation (EC) No 847/2000), Revatio is considered as non-similar to Volibris and Tracleer".
This conclusion remains valid in the present application for an extension of indication.

Similarity with authorised orphan medicinal products

The claimed indication of Revatio in paediatric patients aged one to 17 years old does not overlap with the indications granted to EU authorised orphan medicinal products; Tracleer (bosentan) and Ventavis (iloprost), Volibris (ambrisentan) and treprostinil (Remodulin).

There is currently no approved treatment for use in paediatric pulmonary arterial hypertension. The paediatric pharmaceutical formulation registered for Tracleer does not constitute a paediatric indication in PAH (refer to EPAR Tracleer). Paediatric pulmonary arterial hypertension remains an area of unmet medical need.

Having considered the arguments presented by the MAH of Revatio and with reference to Article 3 of Commission Regulation (EC) No 847/2000 on orphan medicinal products, The CHMP considers that

sildenafil is not a similar product to any orphan medicinal product approved in the EU for paediatric pulmonary hypertension. Sildenafil is the first orphan medicinal product approved in EU for paediatric pulmonary arterial hypertension.

With reference to article 8 of Regulation (EC) No. 141/2000, the granting of the extension of indication of Revatio in children aged one to 17 years old does not overlap with any existing marketing authorisation for any orphan medications authorised for PAH.

1.2. Chemical, pharmaceutical and biological aspects

1.2.1. Introduction

The medicinal product Revatio 20 mg film-coated tablets contains 20 mg of sildenafil (as citrate) as active substance and is presented as white, round, biconvex film-coated tablets. Other ingredients are summarised in section 6.1 of the SmPC for Revatio 20 mg film-coated tablets. Revatio 20 mg film-coated tablet was approved via the centralised procedure on 28th October 2005 (EU/1/05/318/001). The applicant applied for a Type II variation to extend the indication for Revatio 20 mg film-coated tablets in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.

In the absence of an industrially-prepared and controlled age-appropriate dosage form, it was exceptionally agreed to allow an extemporaneous form to be prepared from the current tablet for paediatric patients, i.e. the subset that cannot swallow the tablet, or who require a dose of less than 20 mg.

Development experience with sildenafil citrate indicated that formulation of an oral liquid would be difficult due to issues of palatability and stability and that the best oral liquid formulation would be a powder for oral suspension. As agreed with the Paediatric Committee (PDCO) an appropriate powder for oral suspension is currently being developed. Until the powder for oral suspension formulation is available, an extemporaneously prepared formulation is allowed for use in the interim period to ensure rapid access to Revatio for paediatric patients unable to swallow intact immediate release Revatio 20 mg film-coated tablets. The extemporaneously prepared formulation is an oral suspension with final concentration 10 mg/ml. For paediatric patients aged 1 year to 17 years old, the recommended dose in patients ≤ 20 kg is 10 mg (1 ml of compounded suspension) three times a day and for patients > 20 kg is 20 mg (2 ml of compounded suspension or 1 tablet) three times a day.

In support of this Type II variation the marketing authorisation holder submitted an updated Module 2.3 Quality Overall Summary and an addendum to Module 3.2.P.2 Pharmaceutical development.

- ***Extemporaneous Preparation***

The extemporaneously-prepared formulation (final concentration 10 mg/ml) requires that it be prepared from readily available components and be easily prepared by a compounding pharmacy. The proposed suspension is prepared by suspending crushed Revatio 20 mg tablets in a 75:25 mixture of commercially sweetening and suspending vehicles; Ora-Sweet and Ora- Plus. Ora-Sweet is a citrus-berry flavoured sweetening vehicle and contains sweeteners and preservatives. Ora-Plus is a suspending vehicle and contains suspending agents, preservatives and antifoaming agents. Both vehicles are buffered to a slightly acidic pH. For the quantitative composition of both vehicles reference is made to section 6.6 of the SmPC.

The extemporaneously prepared suspension is designed to be prepared in a compounding pharmacy by a licensed pharmacist. Compounding instructions are provided in section 6.6 of the SmPC and in the package leaflet of Revatio 20 mg film-coated tablets. The compounding instructions are considered to be clear and provide sufficient detail. The pharmacist is recommended to deliver the extemporaneous oral suspension in amber glass or HDPE bottles and should consider dispensing the suspension with an appropriate graduated oral syringe for measuring the required volumes of suspension.

The development studies include tests for taste evaluation and palatability, formulation robustness, compatibility with packaging materials, and tests to define the storage conditions. A technical report detailing the development of the extemporaneously prepared is provided as an appendix to Module 3.2.P.2.

- ***Suitability Studies with the Extemporaneous Preparation***

The extemporaneous oral suspension has been tested for the following parameters: potency and purity (HPLC), content uniformity, dose delivery, evaluation of the active substance solid form (powder X-ray diffraction), microscopy, pH, viscosity, density and preservative efficacy (Ph.Eur.). These parameters were evaluated over time to ensure that both the 10 mg (1 ml) and 20 mg (2 ml) doses could be delivered accurately over the in-use period specified in section 6.3 of the SmPC. The commercially available sweetening and suspending vehicles that are to be used to formulate the extemporaneously prepared suspension, as described in the SmPC contain excipients which are compliant with the USP or NF specifications, or are food grade.

There is evidence that the *in vitro* dissolution of sildenafil from the suspension in acid, pH 4.5 and pH 6.8 is comparable to that from the tablet under the same conditions, in some cases faster, as expected. This finding is considered to be not clinically relevant. Furthermore, the relative bioavailability of the extemporaneously prepared oral suspension was compared to a crushed Revatio 20 mg film-coated tablet mixed with apple sauce and to an intact Revatio 20 mg film-coated tablet, in healthy volunteers under fasting conditions.

- ***Stability***

The compatibility of the extemporaneous oral suspension in various types of bottles was studied. The extemporaneous oral suspension was evaluated in HDPE, PETG and amber glass vials at 25°C and 40°C. No degradation products greater than 0.05% were formed during the study period in all packaging. Storage of the compounded extemporaneous oral suspension in HDPE or amber glass bottles is specified in the Revatio 20 mg film-coated tablets SmPC section 6.6. HDPE or amber glass bottles are considered readily availably materials in pharmacies.

Stability studies have been performed on samples of the extemporaneous oral suspension prepared following the compounding instructions and stored in conventional HDPE bottles and caps. The samples were stored at several conditions 5°C, 25°C, 30°C and 40°C up to six weeks without a significant loss of potency and without the formation of drug related degradation products greater than 0.05%. The extemporaneous oral suspension was also evaluated after three cycles of freezing and thawing, no changes were observed. When the extemporaneous oral suspension was stressed under light conditions a colour change was noted due to photodegradation of the sweetening and suspending vehicles, Ora-Sweet and Ora- Plus. Based on the stability data provided, the proposed in-use shelf-life and storage conditions after preparation (as defined in section 6.3 of the SmPC) are considered acceptable.

1.2.2. Overall conclusions on Quality

The extemporaneous oral suspension shows to have adequate palatability, chemical and physical stability, microbiological quality and accuracy of dose delivery. The commercially available vehicles which are to be used in the preparation of the extemporaneous oral suspension are appropriate and the compounding instructions are clear. The results indicate that the extemporaneous oral suspension, compounded following the detailed instructions provided, is appropriate for use with adequate stability and accurate dose delivery over the desired use period and in the proposed storage conditions. At the time of the CHMP opinion, there were no unresolved quality issues having an impact on the benefit/risk ratio of the product.

The present changes are affecting the oral tablets presentation only.

Furthermore, the proposed extemporaneous formulation is considered a temporary measure and the company has been requested to develop an age appropriate formulation which is reflected in the attached letter of undertaking. This age appropriate formulation is being developed as a powder for oral solution and is planned for regulatory submission in Q32011.

1.3. Non clinical aspects

No new non-clinical data have been submitted for this Type II variation application. All documentation concerning this new therapeutic indication, paediatric patients with pulmonary arterial hypertension (PAH) is supported by nonclinical data previously submitted (Revatio film-coated tablets and solution for injection, EMEA/H/C/638) and clinical data. In this way, an additional comparison between plasma

concentrations of sildenafil in animals (rats and dogs) and in paediatrics has been made to specifically support the Revatio paediatric submission EMEA/H/C/638.
An environmental risk assessment that has been conducted in accordance with Article 8 (ca) and (g) of Directive 2001/83/EC as amended has been provided.

1.3.1. Pharmacology

All of the pharmacology information contained within this section has been previously submitted in the either the oral Revatio EMEA/H/C/638 or Viagra EMEA/C/202 submissions. A combined summary is provided below based on these existing submissions.

- **Primary Pharmacodynamics**

UMechanism of Action

Sildenafil inhibits cyclic GMP phosphodiesterase type 5 (PDE5). PDE5 is found in human pulmonary arterial smooth muscle (PASM) (Rabe et al, 1994) and hydrolyses cGMP which is the mediator of nitric oxide (NO) and atrial natriuretic factor activity. The action of sildenafil results in an increase in cGMP within the PASM cell and a consequent relaxation in PASM tone leading to a decrease in pulmonary vascular resistance and, therefore, pulmonary artery pressure. PDE5 is found in other types of vascular smooth muscle, in corpus cavernosum smooth muscle of the penis and in platelets and visceral smooth muscle, but not in human heart.

Phosphodiesterase Selectivity

PDE5 is a member of the superfamily of cyclic nucleotide phosphodiesterases which contains 11 families (PDE1 to PDE11). Sildenafil, across species, consistently and potently inhibits PDE5 in human, rat, dog, and rabbit (IC50 range 3.5-10.9 nM). Sildenafil has selectivity for human PDE5 over other human PDEs.
The circulating metabolite, UK-103,320, was slightly weaker than parent sildenafil as an inhibitor of PDE5. UK-103,320 has a similar PDE selectivity profile to sildenafil parent.

In Vivo Pulmonary Vasodilator Effects of Sildenafil

Sildenafil, administered i.v. at 4 dose levels attenuated hypoxia-induced pulmonary vasoconstriction in anesthetized dogs producing only minor effects on systemic haemodynamic parameters.

- **Secondary Pharmacodynamics**

Relevant Functional Effect of PDE5 Inhibition

In vitro, sildenafil potentiated the relaxant actions of NO in rabbit and human isolated corpus cavernosal smooth muscle. In anesthetized dogs enhances the increase in intracavernosal pressure.

Sildenafil increased the levels of cGMP in canine isolated coronary artery sections with no effects on cyclic adenosine monophosphate (cAMP) levels and had no inotropic activity on dog isolated trabeculae. Sildenafil displayed arteriovenous dilator properties *in vivo* and at higher doses caused a modest fall on blood pressure in rat. In conscious dog, sildenafil produced modest, dose-related, falls in systemic vascular resistance and LV and diastolic pressure, which were accompanied by increases in cardiac contractility (LV dP/dt max) and heart rate. There was no evidence that sildenafil directly affected electrical conductance in the heart.

Sildenafil had no effect per se on agonist-induced aggregation of rabbit or human platelets although, as expected, it potentiated the platelet anti-aggregatory effects of the NO donor, SNP, *in vitro* and *ex vivo*.

Sildenafil was neither synergistic with heparin nor aspirin with respect to bleeding time in the rat, but its effect on this parameter was additive with that of heparin.

Higher concentrations of sildenafil caused smooth muscle relaxation in rat, mouse, guinea pig, and dog, and can slow intestinal transit in rodents, resulting in mortality associated with gastrointestinal dilation. It has been shown in a mouse carcinogenicity study. However, sildenafil has not been associated with any significant adverse gastrointestinal effects when used for the treatment of PAH apart from dyspepsia.

Sildenafil was demonstrated to be a selective pulmonary vasodilator in dogs. However, the absence of PDE5 in cardiac muscle, along with the lack of a direct effect on cardiac contractility supported the view that it would not have adverse cardiac effects in patients with pulmonary arterial hypertension.

Functional Effects of PDE6 Inhibition

Sildenafil inhibits PDE6 expressed in human, rat, and dog retina, resulting in a decrease in the cGMP concentration (Koutalos and Yau, 1996) and hyperpolarisation of the photoreceptor membrane. *In vitro* and *in vivo* studies in dogs showed that sildenafil affects retinal function, without causing structural changes to the retina. Sildenafil did not affect eye development in rat or rabbit and ophthalmological assessment in juvenile and young adult animals did not reveal any treatment-related findings. Visual effects have been observed in humans although were always transient, reversible and without significant alterations in visual function.

- **Safety Pharmacology**

The safety pharmacology studies are unremarkable except for a moderate affinity of sildenafil for adenosine A2a receptors, although this finding is unlikely to have any functional consequences.

In animal safety pharmacology studies on the central and peripheral nervous systems and on cardiovascular, renal, gastrointestinal, and pulmonary function, sildenafil was well-tolerated in mice and rats. The only effects of sildenafil noted were consistent with its known vasodilator action.

1.3.2. Drug interactions

No relevant pharmacodynamic interaction studies were conducted in animals.

1.3.3. Pharmacokinetics

- **Absorption**

All of the nonclinical information contained within this section has been previously submitted (Revatio Oral and Solution for Injection EMEA/H/C/638). Some additional comparisons have been made to specifically support the Revatio paediatric submission EMEA/H/C/638.

Oral absorption of sildenafil is rapid and high in all species. Systemic bioavailability is attenuated by pre-systemic hepatic metabolism to an extent consistent with the plasma clearance value in each species. A species-specific gender difference in pharmacokinetics in the rat reflects the more rapid metabolism to UK-103,320 in males.

Plasma Concentrations in Toxicology Studies

Plasma concentrations of sildenafil and the metabolite UK-103,320, the major circulating active metabolites in humans, were assayed during toxicology studies as is shown in the table below.

Table 1: Unbound Plasma Exposure of Sildenafil and the Metabolite UK-103,320 during Toxicology Studies (at the NOAEL) and in Paediatric Subjects

		Sildenafil		UK-103,320	
Species and gender	Dose (mg/kg)	Unbound CRR_{max} (ng/ml)PP[a]	Unbound AUC (0-24) a (ng.h/ml)	Unbound C_{max} (ng/ml)[a]	Unbound AUC (0-24) a (ng.h/ml)[a]
Rat (M)b	60	18	30	363	2079
Rat (F)b	60	422	2705	102	1397
Dog (F+M)c	15	174	1890	28	462
Humand <20 kg B.W.		8.12	115	3.48	57.0
Humand >20 kg B.W.		17.2	278	6.90	120

NOAEL = No observable adverse effect level; Cmax = Maximum plasma concentration; AUC(0-24) = Area under the plasma concentration time curve from zero to 24 hours; M = Male; F = Female. **a.** Rat unbound fraction (fu) of sildenafil is 0.05 and UK-103,320 is 0.11. Dog fu of sildenafil is 0.14 and UK-103,320 is 0.14. Human fu of sildenafil is 0.04 and UK-103,320 is 0.05.
b. 6 month oral administration, study number: 91098. **c**. 6 month oral administration, study number: 91099.
d. Maximum arithmetic mean exposure at 20 mg TID for subjects <20 kg and 80 mg TID dose for subjects >20 kg (study A1481131) predicted from population PK/PD modelling (study report Supplemental_PK_Report_A1481131).

A gender difference in plasma exposure of both parent drug and metabolite was apparent in rat, but not in dog, for which data from both genders have been averaged. Relative to males, female rats showed in general a much higher plasma exposure of sildenafil and a somewhat lower plasma exposure of the metabolite UK-103,320. Plasma exposure of parent compound exceeded that of the metabolite in female rats, whereas the reverse was generally the case in males. This species-specific gender difference reflects the faster metabolism of sildenafil to UK-103,320 observed in vivo and in vitro in male rats.

The pharmacokinetics of sildenafil and UK-103,320 were determined following 16-week oral TID administration to paediatric subjects with PAH (the pivotal study A1481131). Each subject was allocated into one of three weight categories and received either placebo or low, medium or high doses of sildenafil. Due to sparse pharmacokinetic sampling in the paediatric study, the human Cmax and AUC values were predicted using the population pharmacokinetic/ pharmacodynamic (PK/PD) model described in study report: Supplemental_PK_Report_A1481131. The maximum modelled unbound exposure within each of the weight categories, that is, 20 mg TID for <20 kg subjects and 80 mg TID for >20 kg subjects from this clinical study are shown in Table III.2.1.

Comparison of Plasma Concentrations in Toxicology Studies and in Humans

For paediatric subjects two oral doses of sildenafil, 10 mg TID for subjects weighing less than 20 kg and 20 mg TID for subjects weighing greater than 20 kg have been proposed. A comparison of the maximum modelled unbound exposure of sildenafil and UK-103,320 to the exposures determined in the toxicology studies at the no observable adverse effect level (NOAEL), was made in A1481131 study, where subjects weighing <20 kg received 20 mg TID of sildenafil and subjects weighing >20 kg received 80 mg TID of sildenafil. Note this is higher than the actual proposed clinical doses resulting in a conservative estimate of the exposure multiples. The results of this exposure comparison are shown in the Table 2 below.

Table 2: Dose and Unbound Exposure Multiples for Sildenafil and UK-103,320 Based on NOAELs in Toxicology Species Compared with Modelled Human Paediatric Data

			Sildenafil				**UK-103,320**			
			Unbound Cmax Multiple a		Unbound AUC (0-24)		Unbound Cmax Multiple a		Unbound AUC (0-24)	
Species (gender)	**NOAEL (mg/kg)**	**Dose Multiple a**	**<20 kg**	**>20 kg**	**<20 kg**	**>20 kg**	**<20 kg**	**>20 kg**	**<20 kg**	**>20 kg**
Rat (M)	60	>48	2.22	1.05	0.261	0.108	104	52.6	36.5	17.3
Rat (F)	60	>48	52.0	24.5	23.5	9.73	29.3	14.8	24.5	11.7
Dog	15	>12	21.4	10.1	16.4	6.80	8.05	4.06	8.11	3.85

NOAEL: No observable adverse effect level; M = Male; F = Female, Cmax = Maximum plasma concentration; AUC (0-24) = Area under the plasma concentration time curve from zero to 24 hours.

a. Dose multiple based on 10 mg dose for paediatrics weighing 8 kg.

The low exposure multiple for sildenafil in the male rat at the NOAEL is a consequence of a species-specific sex difference which results in higher concentrations of the metabolite in the male (previously presented in Revatio EMEA/H/C/638). Consequently, in the male rat, an appreciable exposure multiple does exist for UK-103,320. In female rat and dog, exposure in terms of both Cmax and AUC of sildenafil is greater than that observed in paediatrics in both weight categories. Thus, overall, when data for both parent compound and UK-103,320 are considered, the exposure multiples indicate a clear separation between clinical exposure in paediatrics and the exposure associated with NOAELs in rat and dog up to the expected maximum clinical doses.

- **Distribution**

Volume of distribution is similar in rodents and humans but is higher in dog. The pattern of tissue distribution of drug is widespread, including an affinity for melanin which is believed to have no toxicological significance.

- **Metabolism**

In all species studied, clearance of sildenafil is via five principal pathways of oxidative metabolism. Metabolism in man is mediated by CYP3A4, present at similar levels from two years to adults, and CYP2C9. Sildenafil also can be substrate of CYP3A7 presents in the foetus and newborn infants. Based on these metabolism data, it is expected that sildenafil metabolic pathways will be similar in both paediatrics and adults. Circulating metabolites are present, but only one (UK-103,320) would be expected to make a contribution to therapeutic activity.

- **Excretion**

The majority of the dose of sildenafil is excreted in the faeces over 48 hours.

1.3.4. Toxicology

All of the toxicity information contained within this section was generated for the Viagra EMEA/C/202 submission and was re-submitted in full for the Revatio EMEA/H/C/638 marketing authorization for the treatment of PAH. Consequently, only a brief summary is provided below.

The toxicology of sildenafil has been investigated by the oral and i.v. route. The minimal lethal dose of sildenafil was 500-1000 mg/kg in mice and 300-500 mg/kg in rats by the oral route. No signs of toxicity or mortality were reported in single dose i.v. administration, and the NOEL was 20 mg/kg in mice and 10 mg/kg in rats. In oral repeated-dose toxicity studies, the top dose levels were limited by isolated deaths at 200 mg/kg in rats and by gastric intolerance in dogs at 80 mg/kg. The main effect was hepatic centrilobular hypertrophy in rats and heart rate increased without changes in blood

pressure in dogs. In oral studies, the NOAELs were 60 mg/kg in rats and 15 mg/kg in dogs and are the basis of the margins presented in comparison of plasma concentrations in toxicology studies and in humans. Treatment-related mortality noted on repeat studies in mice was due to the pharmacological activity of sildenafil on the intestinal musculature. This effect was not noted in rats, dogs and clinically. No treatment-induced local irritation was noted in an intra-arterial tolerance study in rabbits.

Sildenafil did not adversely affect fertility in rats and was not teratogenic in rats and rabbits. Treatment at the high dose caused a decrease in viable litter size at birth, decreased pup survival from postnatal Days 1-4 and a reduced birth weight. NOAEL for developmental toxicity was established at 30 mg/kg. Although exposure was not monitored in this study, the minimal effects on postnatal development at 60 mg/kg equates to an unbound Cmax of approximately 24 and 50 times the paediatric exposure for an oral dose of 10 mg or 20 mg TID, respectively, and thus provide a sufficient margin of safety for paediatric investigations.

Sildenafil was negative in a battery of genotoxicity tests and had no antigenic potential. There was no carcinogenic effect in mice. The Mortality in this study was associated with gastrointestinal dilation since mice are particularly sensitive to effects of sildenafil on the gastrointestinal tract. Sildenafil has no carcinogenic potential for humans.

Sildenafil has effects in retina which were reversible and proportional to plasma sildenafil concentrations. These are higher than those active on the pulmonary vasculature. (Isaacs, 1997; 1998a; 1998b; 1998c). The arteritis in the vessels of the optic nerve was considered a manifestation of a stress-related and dog-specific condition known as Beagle Pain Syndrome (Hayes et al, 1989; Snyder et al, 1995).

Studies in Juvenile Animals

An extensive range of nonclinical studies has already been conducted in support of the clinical development of sildenafil, which adequately addressed the potential risks for the paediatric populations.

Clinical trials in paediatric patients with PAH did not identify any new safety signals that had not been identified already in the adult PAH population. Consequently, juvenile toxicity studies were not conducted to support the paediatric submission.

- **Other Toxicity Studies**

Phototoxicity

No studies have been conducted. No phototoxicity/phototoxic reactions associated with the use of sildenafil have been found in a search of the medical literature and in the post-marketing experience during more than 10 years of commercial use in over 37 million patients worldwide.

Immunotoxicity

There were no findings in the repeat-dose studies or in an antigenicity study in guinea pigs to indicate immunotoxicity and therefore no specific immunotoxicity studies were conducted.

1.3.5. Environmental Risk Assessment

An environmental risk assessment that has been conducted in accordance with Article 8 (ca) and (g) of Directive 2001/83/EC as amended, has been provided by the Applicant.

$$PEC_{\text{SURFACE WATER}} = \frac{DOSEai \cdot Fpen}{WASTEWinhab \cdot DILUTION}$$

*DOSE*ai =	60	(mg patient^{-1} d^{-1})
F_{pen} =	0.0001	(refined; patient inh^{-1})
*WASTEW*inhab =	200	(L inh^{-1} d^{-1})
DILUTION =	10	(–)

The $PEC_{surface\ water}$ is calculated using the default F_{pen} of 0.01.

This ERA includes a Phase I Environmental Exposure Assessment. No environmentally related labels are proposed for orphan medicinal product Revatio based on the outcome of the Phase I exposure assessment (PECsurfacewater=0.003 µg/L, below action limit of 0.01 µg/L, according to the Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447). It is agreed that based on the published prevalence data, the addition of the pediatric population to the indication will not lead to a prevalence of higher than 1 in 10,000 assuming that all patients covered by the prevalence will use the product 365 days per year, leads to an F_{pen} equal to the prevalence, i.e. 1 in 10,000 or 0.0001. Therefore, in this Type II variation application, the PEC surfacewater is derived using a refined Fpen of 0.0001.

This worst-case F_{pen} leads to a $PEC_{surface\ water}$ of 3 ng L^{-1}, which is below the action limit. A Phase II assessment is not deemed necessary.

1.3.6. Discussion on non clinical aspects

No new non-clinical data have been submitted for this Type II variation application.
The Applicant has provided a comparison of AUC and Cmax data for sildenafil in the blood samples of rats, dogs and paediatric subjects (study A1481131). According to these data, there is no safety margin between blood samples of male rats and paediatric subjects and this margin is less than the safety margin reported for adult patients. Although this finding is a consequence of a species-specific sex difference which results in higher concentrations of the metabolite in the male rats, the applicant provided clarification on the clinical relevance of this finding.
Clinical data indicate that exposure is not higher, and possibly even lower, in young children compared to older children or adults. This indicates that exposure multiples from data presently in the dossier will suffice for the paediatric indication, except for the male rat. However, in the male rat, the exposure to the metabolite is high, indicating that sildenafil was quickly metabolised into N-desmethyl metabolite UK-103,320 which represents 50% of the potency of sildenafil as a PDE5 inhibitor. Therefore, male rats were also at least partly exposed to the pharmacologic action of the compound. In summary, up to now there are no signals that an extra risk is expected in paediatric patients and no additional data are necessary.

1.3.7. Conclusion on non clinical aspects

Based on present non-clinical data, no additional risks on top of those already identified are expected for paediatric patients. However, there is some concern regarding the youngest patients, since the pulmonary system is still in development up to 2 years and the cardiovascular system up to 5 years. This is further addressed in the safety section of the clinical part.

1.4. Clinical aspects

Four studies involved use of sildenafil in paediatric patients. These studies are listed in Table below.

Table 3: List of studies utilising sildenafil citrate in paediatric patients

Study Title and Design	Dose	Endpoints
A1481134: Phase 2, randomised, double-blind, placebo-controlled, multicentre study to assess IV sildenafil citrate as treatment of PH post-corrected heart surgery for CHD (18 patients; terminated prematurely due to lack of recruitment)	Target Plasma Concentration of 40, 120, 360 ng/mL. Loading Dose followed by 24-72 hr Infusion (Concentration 1 mg/mL)	Receipt of Additional Therapy, Time to Extubation, Safety and PK
A1481157: (Part 1) Multicentre, randomised, placebo-controlled, dose-ranging study, IV sildenafil citrate for PPHN (36 patients; terminated prematurely due to lack of recruitment)	Target Plasma Concentration up to 150 ng/mL. Loading Dose followed by Infusion for up to 7 Days.	PK and Safety
A1481131: Phase 3 randomised, double-blind, multi-centre, placebo controlled parallel group, dose ranging study. Subject's aged 1 to 17 years with body weight ≥8 kg, and with primary pulmonary hypertension (PH), PAH secondary to congenital heart disease (PAH associated with congenital systemic-to-pulmonary shunts, d-transposition of the great arteries and PAH in subjects who had undergone surgical repair of other congenital heart lesions ≥6 months prior to screening), or collagen vascular disease.	10, 20, 40, or 80 mg TID depending upon bodyweight to achieve steady state concentrations of 47, 140, and 373 ng/mL at the low, medium, and high doses, respectively.	Efficacy, safety, tolerability, and PK.
A1481156: Long-term extension to Study A1481131	10, 20, 40, or 80 mg TID	Safety, tolerability, and long-term efficacy.

CHD – Congenital heart disease; PH- Pulmonary Hypertension; PPHN – Paediatric Pulmonary Hypertension of the Newborn; PD – Pharmacodynamics; PK- Pharmacokinetics.

The 3 paediatric studies including clinical pharmacology data pertinent to this submission are Studies A1481134 and A1481157 with intravenous sildenafil in PAH (supportive for clinical pharmacology and safety data) and pivotal study A1481131 for PK/PD data with oral sildenafil, establishing population PK and PK-PD models, and driving the oral dose recommendation for the paediatric population. Neither data from Study A1481134 nor Study A1481157 have been used to derive the dose recommendation or have been directly used for the corresponding population PK model building and will not be discussed here.

1.4.1. Clinical pharmacology

Study A1481131: A randomised, double-blind, placebo controlled, dose ranging, parallel group study of oral sildenafil in the treatment of children, aged 1-17 years, with pulmonary arterial hypertension.

Primary Objective: to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in paediatric subjects aged 1 to 17 years, with PAH.

Secondary Objectives: to assess safety, tolerability, and pharmacokinetics of 16 weeks of chronic treatment with oral sildenafil in paediatric subjects, aged 1 to 17 years with PAH, and to assess the survival status of subjects who did not enter Study A1481156.

Study Design: A randomised, double-blind, multi-centre, placebo controlled parallel group, dose ranging study. The study included subjects, aged 1 to 17 years with body weight ≥8 kg, and with primary PAH or PAH secondary to congenital heart disease.

Pharmacokinetic Evaluations: Blood samples for pharmacokinetic evaluations were collected pre-dose at baseline, and at Weeks 4, 8 and 16, and additionally after the first dose of the day at Week 16 during the following sampling windows: 15 minutes to 3 hours, 3 to 6 hours and >6 to 8 hours.

Study medications: Subjects were randomised to receive either 1 of 3 sildenafil doses (low, medium or high, also depending on body weight ranges) TID (see Table 2), or placebo.

Preparation of study medications: For subjects able to swallow tablets, sildenafil or placebo were dosed TID with water, at least 2 hours after food intake, and 2 hours prior to next food intake. For subjects unable to swallow tablets, caregivers were provided with a tablet crusher and written instructions on

how to prepare and administer the powder obtained (see the full description of the study methods in the "Clinical Efficacy" section of current AR).

Results and Conclusions: A population PK analysis was completed for Study A1481131. A one compartment model with first order absorption and a lag-time, with weight and dose as covariates was developed for sildenafil.
This model is different from the population PK model developed in PPHN (A1481157 study), as this is a model describing the oral dosing in children (1 year to 17 years), where the former model describes the IV dosing in neonates. A similar model was also developed for the metabolite UK-103,320.
The following PK parameters for sildenafil and UK-103,320 were calculated for each subject using either the observed concentration time data or predicted from the population PK model: apparent clearance, apparent volume of distribution, absorption rate constant, maximum observed concentration at steady state, maximum predicted concentration at steady state, time for Cmax, minimum predicted concentration at steady state, area under plasma concentration-time profile within the dosing interval, and elimination half-life. The details of establishing population PK and PK-PD models, and deriving the dose recommendation for the paediatric population can be found in the subsection below.

Population PK and PK/PD analysis of sildenafil in children

An analysis of the PK and PK/PD from Study A1481131 was conducted in order to assess the PK and efficacy of sildenafil in relation to plasma exposure and to establish the recommended dose in paediatric PAH patients. The analysis utilised a nonlinear mixed effect modelling approach on the population PK and PD endpoint data (peak volume of oxygen consumed [pVO2]) obtained from Study A1481131.
Based on the results from previous adult PAH patients (Study A1481140) with the oral formulation, body weight (range 41 – 122 kg) and age did not affect apparent oral plasma clearance (CL/F). In contrast, after administering the IV formulation in neonate patients (Study A1481157) plasma clearance (CL) showed a rapid, 3 fold increase within 7 days after birth and the CL showed a high correlation with body weight. Results from Study A1481131 suggested that the children over 1 year already show a relatively high CL/F and a shallow increase would be expected with further body weight increase. In addition, the increase would reach a constant value at some body weight.

The analysis was conducted in 2 parts:

- The first part focused on the population PK data from Study A1481131 in conjunction with data gathered in the adult PAH population (Study A1481140). Both datasets were analysed simultaneously as the weight range observed in Study A1481140 overlapped with that observed in Study A1481131.
- In Study A1481131, the 6 minute walk distance (6MWD) was not considered a feasible endpoint and the pVO2 assessed during a cycle ergometry in cardiopulmonary exercise (CPX) test was used as the primary endpoint. However, only 115 out of 234 subjects were developmentally able to perform the test. Thus, the second part of the PK/PD analysis focused on these 115 subjects.

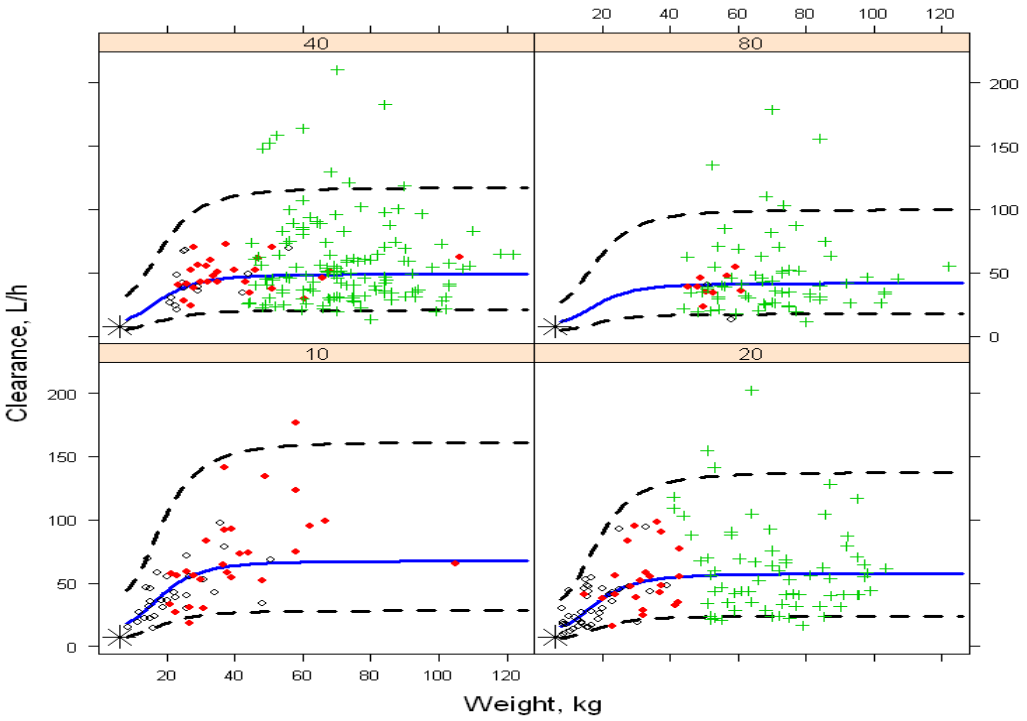
The objectives of the PK analysis were:
- To investigate the PK of sildenafil in children with PAH after TID dosing.
- To develop a population PK model which can be used to describe PK data in both paediatric and the adult PAH populations.
- To predict the range of mean steady-state concentrations (Cav,ss) throughout the observed weight range.
- To provide typical values (TV) and Bayesian estimates (EBE) of Cav,ss as an exposure measure for each patient to be utilised in the subsequent PK/PD analysis.

Methods: The population PK analysis was performed using the combined data from both adult (Study A1481140) and paediatric (Study A1481131) patients in order to develop a model which describes the relationship between weight and PK parameters such as CL/F and V/F. A one compartment, first order absorption model with a lag time was applied as the structural PK model. The dependency of CL/F with body weight increase was expressed by a sigmoid model with an intercept. The CL/F is expected to be already relatively high at an age of 1 year, which, as mentioned earlier, reflects the early maturation of metabolic processes in the postnatal period. Applying this model the CL/F increases with body weight and reaches a plateau at some value of weight. In the combined analysis of A1481131 and A1481140 data, body weight is a convenient explanatory factor which integrates both datasets.

Data: Pharmacokinetic data from 380 patients (A1481131: 173, A1481140: 207) were collected (placebo group was not counted). A total of 1931 concentrations were included in the population pharmacokinetic analysis. Between 3 and 6 serum samples per subject were collected. In Study A1481131, Visit 1 (Week 0), Visit 2 (Week 4) and Visit 3 (Week 8) included 1 sample and Visit 4 (Week 16) included 4 samples, at 1-2, 3-5, and 6-8 hours after dose. In Study A1481140, Visit 1 (Week 0) included 3 samples, Visit 3 (Week 8) 2 samples and Visit 4 (Week 12) 5 samples.

Results: The PK model described above showed a good fit with the observed plasma concentrations. The typical estimates (± SE) of maximum CL/F, the intercept of CL/F, the body weight at half of max CL/F and the Hill coefficient were estimated at 57.8 (±2.67) L/h, 13.9 (±1.98) L/h, 21.3 (±1.76) kg and 3.7 (±0.87), respectively (See Module 5.3.4.2 for the detailed PK analysis results).Using the estimated CL/F it is possible to estimate the average plasma concentration during one day at steady state (Cav,ss) for each dosage. The typical values of decay half-life from model prediction were 4.2 hours for 10 kg and 4.4 hours for 70 kg of body weight, showing no weight-related relevant difference. Maximum plasma concentration (Cmax) after 20 mg sildenafil PO was estimated at 49, 104 and 165 ng/mL for 70, 20 and 10 kg patients, respectively. The time of peak concentration (Tmax) was calculated to be approximately 1 hour and was almost independent of body weight (Cmax in adults is 113 ng/ml and half-life is 3-5 h at steady state).

Figure 1: Relationship Between Body Weight and CL/F for Each Dose Group



Lines represent population mean and 90% PI, Symbols represent individual Bayesian estimates [●:A1481131 (developmentally); ○:A1481131(not developmentally); +: A1481140; The * at 3 kg represents the clearance estimate from Study A1481157, adjusted for oral bioavailability.]

The CL/F in heavier children (≥30 kg) is similar to adults. In lighter children, the change in CL/F was less than proportional to changes in body weight. Thus to achieve the same exposure as given by Cav,ss, in the lighter children, the dose would need to be halved.

PK/PD profile in children

The analysis focuses on the relationship between the Cav,ss and the change in peak VO2 (pVO2) only. The objectives of the PK/PD analysis were:

- To investigate the PK/PD relationship between Cav,ss and pVO2 increase.
- To estimate the placebo and maximum response in pVO2 at Week 16 compared to change from baseline.
- To estimate the threshold Cav,ss at which pVO2 reaches 90% response (EC90).
- To evaluate the efficiency of various dosing regimens utilising success criteria as defined as an improvement in pVO2 over a certain percentage compared to placebo.

Methods: Peak VO2 values at baseline and at week 16 were included in the PK/PD modelling exercise. EBE and TV predictions of Cav,ss were derived from the population PK model. TVs are based on the covariates (dose and weight) only. A sigmoid Emax model was used as the structural PK/PD model. The data from the placebo group was included.

Simulations and inferences: Stochastic simulations were performed to assess the performance of various dosing regimens given the estimated population PK and PK/PD models. Success on an individual level within the simulations is defined as a 10% improvement on pVO2.

Results: The sigmoid Emax model could successfully be applied to the pVO2 data. The representation of the sigmoid Emax model results are shown in Figure 2. The results from the model fits obtained for both EBE and TV Cav,ss are listed in Table 4. In all subsequent simulations, the TV Css,av have been used because the TV model had a 2 points lower objective function value compared to the EBE model. For both models, E0 (placebo effect) was not significant from zero. Under the null hypothesis (Emax=0) a delta (increase) in the -2LL of 15.803 points was obtained, i.e. Emax was significant ($p<0.001$, df=3). The typical value Emax was estimated to be around 8-9%. EC50 and EC90 were estimated at around 25-30 and 30-40 (95%CI: 20-55) ng/mL, respectively (Table 3).

Table 4. Population PK/PD Estimates Exercise Bayesian Estimation (EBE): OF=802.264

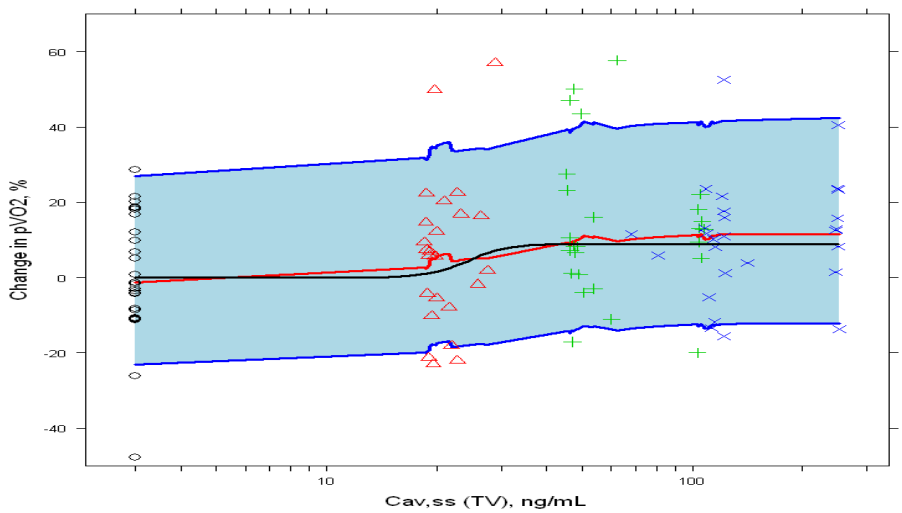
	Mean	SEM	CV	SD (%)	95% CI	
					Lower	Upper
Baseline-pVO2	17.60	0.433	2.46	23.7	16.7	18.45
Emax, %	8.41	2.31	27.47		3.88	12.94
EC50, ng/ml	31.00	5.81	18.74		19.6	42.39
HILL	8.00					
Res-error%	12.00					
EC90, ng/ml	40.8	7.65	18.75		25.8	55.79

Typical Value (TV): OF=800.124

	Mean	SEM	CV†	SD (%)	95% CI	
					Lower	Upper
Baseline-pVO2	17.60	0.417	2.37	23.60	16.78	18.42
Emax, %	9.09	2.21	24.31		4.76	13.42
EC50, ng/ml	23.7	3.59	15.15		16.66	30.74
HILL	8.00					
Res-error%	11.90					
EC90, ng/ml	31.19	4.73	15.16		21.93	40.46

†CV calculated as SEM/Meanx100; SD (%) calculated as square root of interindividual variance

Figure 2: Relationship of pVO2 as Change from Baseline (%) to Cav,ss



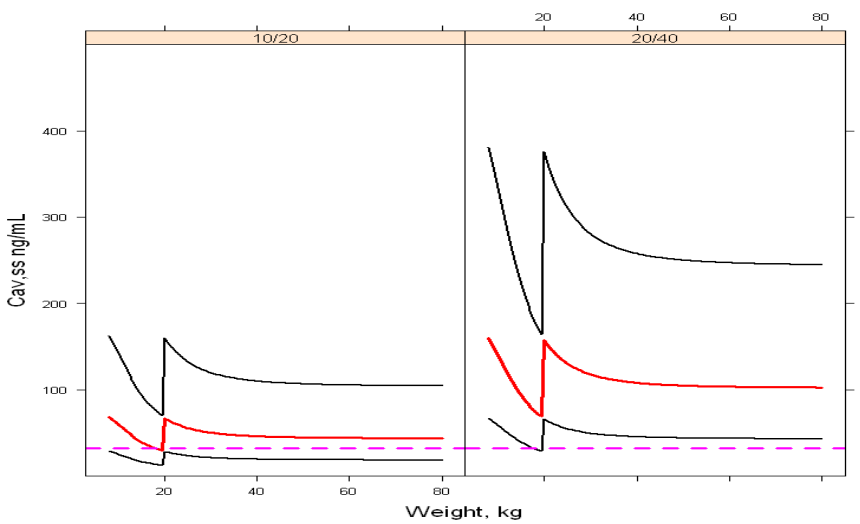
Mean (black line) and 90% PI (blue shaded area, median: red line) as obtained from a simulation of the final PK/PD model. The symbols reflect the observed change from baseline. The colour represents the randomised dose groups (Δ: low, +: mid, ×: high) and the placebo group (☐). The latter is set for convenience at 3 ng/mL.

Simulations: The prediction interval for 2 dose regimens is included in Figure 3: 1) 10 mg TID up to a weight of 20 kg, and 20 mg TID for a weight of 20 kg and above, 2) 20 mg TID up to a weight of 20 kg, and 40 mg TID for a weight of 20 kg and above. Under the low dose regimen (10/20 mg TID), a small fraction would not exceed the threshold based on the EC90 derived from the PK/PD model, while under high dose regimen (20/40 mg TID) nearly all subjects would exceed the target concentration.

Dosing Recommendation Based on Clinical Pharmacology Data

A population PK and PK/PD analysis was applied to the data from Study A1481131 (and A1481140 for PK). The maximum CL/F estimated in this combined analysis of 57.8 L/h is consistent with the previously reported value of 50.9 L/h obtained in adults (A1481140 population PK report).

Figure 3: Relation Between Body weight and Cav,ss for Each Dose Strategy

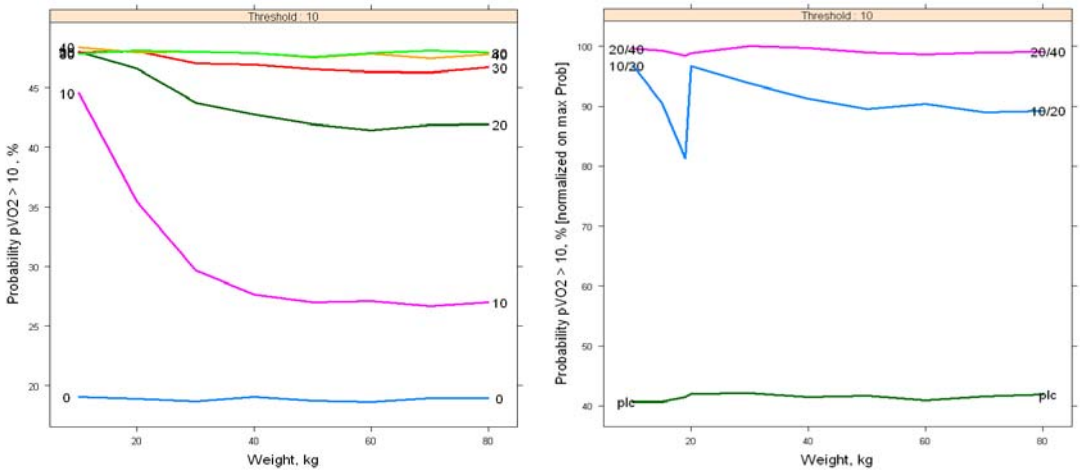


Black line shows 90%PI and the red line shows the population mean. The pink dotted line expresses the expected EC90 (point estimation without uncertainty) as derived in the section of PK/PD analysis.

Using a dose of 10 mg TID for children up to 20 kg and 20 mg TID above 20 kg, a 90% PI of Cav,ss would result as depicted on the left panel of Figure 3. With this strategy almost 90% of patients would achieve Cav,ss equivalent to EC90. However, as depicted by the right panel, when a dose of 20 mg TID up to 20 kg and 40 mg TID above 20 kg is used the 90% PI of Cav,ss would result. With this dosing regimen almost all patients would achieve an exposure over EC90.

Figure 4 shows the responder rate for an increase in pVO2 of over 10%. Over 43% would be responders at 20 mg TID and over 48% at 40 mg TID and above. The right panel shows the probabilities normalised on maximum responder fraction for each dose strategy. The responder ratio with 10/20 mg TID reaches 87% of the maximum ratio, which is achieved with 20/40 mg TID.

Figure 4: Success rate across dose & weight assuming an individual response at an improvement in pVO2 of more than 10% for each dose group (left panel) and dose strategy (right panel, normalised on maximum responder fraction)



The fraction of responders above the 10% threshold is given for all dose groups across the weight range of 10 to 80 kg on the left panel of Figure 4. Normalising the probabilities for the 2 dose regimens (10/20 mg or 20/40 mg TID) on the maximally achievable responder fraction is shown on the right panel. In summary at 20/40 mg TID, a close to maximum responder ratio is achieved, while 87% of the maximum responder ratio is achieved on 10/20 mg TID.

With 10/20 mg TID dosage, the upper limit of 90% PI for Cav,ss is less than 4 fold greater than the efficacious exposure (EC90). However, with 20/40 mg TID, the upper limit is more than 8 fold greater than EC90 and 5% of patients are expected to achieve Cav,ss of more than 8 times the EC90, although no significant exposure-safety relationship has been found so far.

Therefore, based on the PK/PD analysis, the recommended dosing regimen in children is 10 mg TID for children weighing less than 20 kg and 20 mg TID for children weighing 20 kg or more.

1.4.2. Discussion and conclusion on clinical pharmacology

From the analysis of the PK profile of sildenafil in patients involved in the paediatric clinical trial A1481131, body weight was shown to be a good predictor of drug exposure in children. Sildenafil plasma concentration half-life values were estimated to range from 4.2 to 4.4 hours for a range of 10 to 70 kg of body weight. Cmax after a single 20 mg sildenafil dose administered PO was estimated at 49, 104 and 165 ng/ml for 70, 20 and 10 kg patients, respectively. Cmax after a single 10 mg sildenafil dose administered PO was estimated at 24, 53 and 85 ng/ml for 70, 20 and 10 kg patients, respectively. Tmax was estimated at approximately 1 hour and was almost independent from body weight. The values for Tmax and half-life obtained in children are similar to those in adults (in adults, Tmax is 60 minutes and half-life is 3-5 h at steady state).

In children above 45 kg, a 10 mg TID dose was considered a "low-dose", but it is probably a "medium" dose; a dose of 40 mg TID dose (medium) is probably a high dose (2-fold dose compared to the 20 mg TID dose used in adults) and the high dose (80 mg TID) is probably a very high dose (3-fold dose compared to adults). This may have been resulted in an overexposure in children treated with sildenafil.

The Applicant considered that a dose of 10 mg TID should be administered to children weighing less than 20 kg and that 20 mg TID should be administered to children weighing 20 kg or more. However the rationale for dose recommendation in children should be ultimately based on efficacy and safety data from study A1481131 and is further discussed in the report (low, intermediate and high sildenafil dose) in the efficacy and safety section.

The oral bioavailability of the 20 mg tablets is approximately 41%. In study A1481131, children unable to swallow the tablets received a powder obtained with a tablet crusher, mixed with 5 mL spoonful of soft food for immediate use. The "formulation" intended for authorisation is an oral suspension formulation which is extemporaneously prepared by a pharmacist from the 20 mg tablet using Ora-Sweet and Ora-Plus diluents to reach a concentration of 10 mg/ml.
The applicant has shown that there are minor differences in relative bioavailability among the 10 mg tablet strength and the other strengths that are likely due to nonlinearity of PK of sildenafil. In any case, these differences are not considered to be of clinical significance.

It is important to highlight that the suspension for extemporaneous formulation is an interim measure temporally accepted. The MAH has committed to develop a suitable age appropriate formulation in a form of a powder for oral suspension (POS) which is currently under development.

1.5. Clinical efficacy

The pivotal study supporting the efficacy and safety of oral sildenafil in children with PAH is the study **A1481131,** which has a long-term extension (study A1481156). There are two additional supportive studies (A1481134 and A1481157) with intravenous sildenafil that were already included in the intravenous Revatio submission and previously assessed, therefore not further described here.

1.5.1. Main study – Study A1481131

1.5.1.1. Methodology

This was a randomised, double-blind, multi-center, placebo controlled parallel group, dose ranging study in paediatric patients with PAH aged 1 to 17 years with body weight ≥ 8 kg. The study lasted from 2003-2008.

Recruited patients included primary PAH and secondary PAH associated with congenital systemic-to-pulmonary shunts with a baseline resting room air oxygen saturation (SaO2) ≥88 or with d-transposition of the great arteries repaired within the first 30 days of life; patients who had undergone surgical repair of other congenital heart lesions ≥6 months prior to screening and did not have clinically significant residual left-sided heart disease consistent with the exclusion criteria, aged from 1 to 17 years (subject to country specific protocols) and weighing ≥8 kg who had symptomatic PAH were also included.

The inclusion criteria did not specify limitations regarding exercise capacity or WHO functional class, the main requisite being symptomatic PAH. The doses used are based on in vitro PDE inhibition. The medium dose treatment groups were calculated to achieve target sildenafil steady-state maximum concentrations of 140 ng/mL. This is the most comparable to the 113 ng/ml achieved in adults patients administered the approved Revatio dose of 20 mg TID (Revatio SPC). Based on the PK/PD analysis (see before) this was later also decided to be the recommended dose.

Subjects were excluded from the study if they had PH secondary to other diseases, left-sided heart disease and other similar heart-related diseases, or had treatment with off-label sildenafil, an endothelin-A receptor antagonists or prostacyclin/prostacyclin analogue within 30 days prior to randomization, or who were taking medications such as parenteral inotropic medication, parenteral vasodilators within 3 months prior to screening, alpha-blockers or cytochrome P450 (CYP) 3A4 inhibitors.

Outcomes/endpoints

The primary objective of study A1481131 was to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in paediatric PAH patients, aged 1 to 17 years.
Secondary objectives included assessment of the safety, tolerability, and pharmacokinetics (PK/PD analysis), in addition to survival status of subjects who did not enter the long term extension study.

The choice of the efficacy endpoint cardiopulmonary exercise CPX testing resulted in prolongation of the recruitment period to 5 years. During this period, many developments occurred in the field of PAH although still no drugs are approved for paediatrics. The use of a placebo-controlled design in drug naive paediatrics is accordingly justified.

The primary efficacy endpoint was percent change in peak VO2 (normalised to body weight) from baseline at Week 16 assessed by cardiopulmonary exercise CPX testing by bicycle ergometry, evaluated in those subjects who were developmentally able to perform the CPX test.

The primary efficacy parameter (peak VO2) and all CPX test parameters were analysed for all subjects developmentally able to perform the CPX test (approximately >7 years). Subjects were assumed to be developmentally able if they had an adequate CPX test at any visit during the study.

For the purposes of this study, the applicant considered that peak VO2, as determined by CPX, was deemed a more objective method for accurate assessment of exercise capacity in children as it was reasoned that children would be unable to perform the 6MWD consistently and reproducibly, and that their cooperation and motivation may vary.

CPX testing is a comprehensive exercise test that measures cardiopulmonary performance at rest and during exercise. The reduction in peak VO2 reflects the blunting of increases in cardiac output and perfusion of the pulmonary vascular bed during exercise, which is a key manifestation of the disease. As such these measures can be used to track the physiological responses to treatment of the disease and small open label studies have demonstrated improvements in CPX following treatment with sildenafil (Hoeper et al, 2004; Oudiz et al., 2007). CPX testing was standardised across centers with the provision of standard equipment and training to the technicians. The cycle ergometry protocol imposed a progressively increasing workload on the subject until the limit of their tolerance was reached. Data were collected and sent to a core laboratory for interpretation. If the test was deemed inadequate by the core laboratory (eg, endpoint could not be determined), the subject was asked to repeat the test on the same day, no less than 4 hours apart.

Secondary efficacy endpoints included invasive haemodynamic measurements for all the patients, WHO functional class and Child Health Questionnaire.

Doses administered:

Subjects were randomised to receive either 1 of 3 sildenafil doses (low, medium or high) TID, or placebo. The randomisation was stratified according to weight group and developmental ability to perform cardiopulmonary exercise testing (table 5). Target plasma concentrations of sildenafil were selected based on in vitro PDE5 inhibition data. Sildenafil dose levels were then selected based on body weight such that target plasma concentrations would be achieved at steady state:

- Patients in the low weight stratum (≥8-20 kg) were randomised in a 1:2:1 ratio to receive sildenafil medium or high doses, or placebo. Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects (ie, subjects would receive the same dose because of the available tablet strengths); consequently there was no low dose for this weight strata.

- Patients in the medium (>20-45 kg) and high (>45 kg) weight strata were randomised in a 1:1:1:1 ratio to receive sildenafil low, medium or high doses, or placebo.
For subjects able to swallow tablets, 1 tablet of sildenafil (10, 20, 40 or 80 mg) or placebo was administered. For subjects unable to swallow tablets, tablets were crushed and mixed with a small (5 mL) spoonful of soft food, and the entire food portion was consumed immediately.

Table 5: Sildenafil Doses (TID) to Achieve Target Sildenafil Steady-State Maximum Concentrations of 47, 140 and 373 ng/mL at the Low, Medium and High Doses, Respectively

Body Weight (kg)	Dose (mg)		
	Low Dose Treatment Group	Medium Dose Treatment Group	High Dose Treatment Group
≥8-20	NAa	10a	20
>20-45	10	20	40
>45	10	40	80

TID=3 times daily; NA=not applicable
a Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects (ie, subjects would receive the same dose because of the available tablet strengths); consequently there was no low dose for this weight group.

Sample size:

There was only minimal guidance available from the literature to assist in sample size determination. Several assumptions were made and sample size estimation was revised several times. Originally, the following assumptions were made:
- Subjects in the placebo group would have a 5% worsening in their exercise capacity as measured by the percent change from baseline in peak VO2;
- Subjects in the highest sildenafil dose group would have a 15% improvement in exercise capacity as measured by the percent change from baseline in peak VO2;
-The common standard deviation was assumed to be 27%.

Due to the limited data on the variability of the primary endpoint, an interim sample size re-estimation was planned in the protocol. It was decided during the study that the primary analysis would compare the combined sildenafil dose groups to placebo (though the ratio of sildenafil to placebo subjects would remain 3:1); subjects in the sildenafil combined group would have a 10% improvement in exercise capacity as measured by the percent change from baseline in peak VO2. Three further re-estimations were performed throughout the study to adjust for the large discrepancy between the assumed and the observed variability (17.4%; 20.2% and 18.8% instead of 27%). Ultimately the sample size of 104 evaluable patients was calculated to be sufficient to yield the power specified in the protocol.

Statistical methods:

The primary endpoint was evaluated using analysis of covariance (ANCOVA) in which the response (defined as the percent change from baseline in peak VO2 at Week 16) in the 3 sildenafil treatment groups (low, medium and high dose) was contrasted to that in the placebo group (with contrast coefficients 1/3, 1/3, 1/3 and -1). Comparisons of the individual dose groups to the placebo group were also made. The ANCOVA model included terms for treatment, baseline peak VO2, aetiology and weight group. Center was not included as a covariate due to the small number of subjects anticipated at each center (in accordance with ICH E9). Statistical hypothesis testing was performed at the 2-sided 5% significance level. The above analysis was performed for all subjects in the ITT population with a Week 16/End of treatment (EOT) measurement.

1.5.1.2. Study results

Of the 324 subjects screened, 235 subjects were randomised to 1 of 4 treatment groups (Table 6) and 234 subjects were treated (and hence included in the ITT population). Of the 234 subjects, a total of 115 were developmentally able to perform CTX. A total of 228 subjects completed the study, of which 220 subjects entered the long-term extension Study A1481156.

Table 6: Subject Disposition in Study A1481131

	Sildenafil				
Treatment Group	Low	Medium	High	Combined	Placebo
Number (%) of subjects:					
Randomised	42	56	77	175	60
Treated	42	55[a]	77	174[a]	60
Completed	40 (95.2)	55 (98.2)	75 (98.7)	170 (97.1)	58 (96.7)
Entered Study A1481156	38 (90.5)	53 (94.6)	74 (96.1)	165 (94.3)	55 (91.7)
Had follow-up visit and did not enter Study A1481156	1 (2.4)	1 (1.8)	1 (1.3)	3 (1.7)	3 (5.0)
Did not have follow-up visit and did not enter Study A1481156	1 (2.4)	1 (1.8)	0	2 (1.1)	0
Discontinued prior to treatment	0	1 (1.8)[a]	0	1 (0.6)	0
Discontinued	2 (4.8)	0	2 (2.60)	4 (2.3)	2 (3.3)
Analyzed for efficacy					
ITT[b]	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Per Protocol	23 (54.8)	23 (41.1)	27 (35.1)	73 (41.7)	24 (40.0)
Aged ≥5 years	42 (100)	46 (82.1)	58 (75.3)	146 (83.4)	53 (88.3)
CHQ-PF28[c]	37 (88.1)	34 (60.7)	48 (62.3)	119 (68.0)	46 (76.7)
Developmentally able	28 (66.7)	28 (50.0)	29 (37.7)	85 (48.6)	30 (50.0)

The proportion of subjects in each age and ability subgroup was uneven over the treatment groups (table 7). This imbalance was predominantly due to the fact that the majority of subjects <7 years weighed between 8 and 20 kg and no subjects with weight ≤20 kg were randomised to the sildenafil low dose group and proportionally more of these subjects were randomised to the sildenafil high treatment group than to the other treatment groups.

Table 7: Allocation to Treatment Groups by Weight in Study A1481131

	Sildenafil							
Treatment Group	**Low**		**Medium**		**High**		**Placebo**	
Body weight, kg	**N (n)**	**Dose**	**N (n)**	**Dose**	**N (n)**	**Dose**	**N (n)**	**Dose**
≥8-20	NA	NA	15 (0)	10 mg	35 (2)	20 mg	18 (1)	NA
>20-45	31 (19)	10 mg	30 (19)	20 mg	31 (18)	40 mg	32 (21)	NA
>45	11 (9)	10 mg	10 (9)[a]	40 mg	11 (9)	80 mg	10 (8)	NA

N=total number of subjects in treatment group; n=number of developmentally able subjects in treatment group; NA=not applicable

[a] one Patient (medium dose) was misallocated to high weight and should have received sildenafil dose appropriate for medium weight (actual weight 44.6 kg)

Table 8: Patient Demography – Study A1481131

	Sildenafil				
Treatment Group	Low	Medium	High	Combined	Placebo
Number of subjects	42	55	77	174	60
Male, n (%)	17 (40.5)	24 (43.6)	26 (33.8)	67 (38.5)	22 (36.7)
Female, n (%)	25 (59.5)	31 (56.4)	51 (66.2)	107 (61.5)	38 (63.3)
Age (years), n (%):					
1-4	0	9 (16.4)	19 (24.7)	28 (16.1)	7 (11.7)
5-12	25 (59.5)	28 (50.9)	36 (46.8)	89 (51.1)	37 (61.7)
13-17	17 (40.5)	18 (32.7)	22 (28.6)	57 (32.8)	16 (26.7)
Race, number (%) of subjects					
White	19 (45.2)	26 (47.3)	28 (36.4)	73 (42.0)	24 (40.0)
Black	1 (2.4)	1 (1.8)	1 (1.3)	3 (1.7)	2 (3.3)
Asian	6 (14.3)	13 (23.6)	15 (19.5)	34 (19.5)	7 (11.7)
Other	16 (38.1)	15 (27.3)	33 (42.9)	64 (36.8)	27 (45.0)
Mean weight (range), kg	38.2 (20.0-105.0)	32.1 (8.6-106.0)	25.8 (8.2-61.0)	30.8 (8.2-106.0)	29.3 (9.1-60.0)
Mean BMI (SD), kg/m^2	18.2 (4.8)	17.6 (3.9)	16.3 (3.4)	17.2 (4.0)	16.9 (3.6)

Primary diagnoses were similar for all treatment groups with approximately a third of subjects having primary PAH (Table 9). The mean durations since first diagnosis for subjects with secondary PAH (5.1 to 7.5 years) were generally greater than those for subjects with primary PAH (1.1 to 2.2 years). Only 1 subject (in the placebo group) had duration since first diagnosis of primary PAH longer than 10 years.

Table 9: Summary of Subjects in Each Subgroup Analysed in Study A1481131

	Sildenafil Dose				
Number (%) of subjects:	Low	Medium	High	Combined	Placebo
Randomised	42	56	77	175	60
ITT[1]	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Aetiology					
a. Primary PAH b. Surgical repair c. Congenital systemic-to-pulmonary	12 (28.6) 14 (33.3) 16 (38.1)	19 (34.5) 16 (29.1) 20 (36.4)	26 (33.8) 25 (32.5) 26 (33.8)	57 (32.8) 55 (31.6) 62 (35.6)	21 (35.0) 16 (26.7) 23 (38.3)
Age and developmental ability					
a. < 7 year b. ≥ 7 year NDA c. ≥ 7 year DA	2 (4.8) 12 (28.6) 28 (66.7)	17 (30.9) 10 (18.2) 28 (50.9)	28 (36.4) 20 (26.0) 29 (37.7)	47 (27.0) 42 (24.1) 85 (48.9)	16 (26.7) 14 (23.3) 30 (50.0)
Excluding subjects with congenital systemic-to-pulmonary shunt					
a. Overall b. < 7 year c. ≥ 7 year NDA d. ≥ 7 year DA	26 (61.9) 2 (4.8) 7 (16.7) 17 (40.5)	35 (63.6) 12 (21.8) 5 (9.1) 18 (32.7)	51 (66.2) 21 (27.3) 10 (13.0) 20 (26.0)	112 (64.4) 35 (20.1) 22 (12.6) 55 (31.6)	37 (61.7) 12 (20.0) 7 (11.7) 18 (30.0)

[1] Subjects who were randomised to study treatment and received ≥1 dose of study treatment. Denominators for the subgroup percentages are based on the ITT population.

Surgical repairs include e.g atrial, ventricular septal defects; patent ductus arteriousis.

DA: developmentally able. NDA: none developmentally able.

The baseline efficacy characteristics are presented in the following table (Table 10).

Table 10: A1481131 Baseline Efficacy Endpoint Characteristics

	Sildenafil Group				
	Low	Medium	High	Combined	Placebo
Number of subjects (developmentally able only)	24	26	27	77	29
Mean (SD) peak VO_2, mL/kg/minute	17.37 (4.36)	18.03 (4.70)	17.43 (3.70)	17.61 (4.22)	20.02 (3.80)
Mean (SD) time to peak VO_2, seconds	414.54 (123.13)	452.27 (141.88)	433.81 (108.69)	434.04 (124.44)	466.43 (139.14)
Mean (SD) predicted peak VO_2, %	43.15 (10.46)	45.32 (12.25)	46.07 (10.84)	44.91 (11.15)	51.16 (12.18)
Number of subjects					
Mean (SD) RER	1.10 (0.07)	1.10 (0.12)	1.09 (0.09)	1.10 (0.09)	1.11 (0.13)
Mean (SD) mPAP, mmHg	66.3 (22.2)	61.9 (18.1)	61.6 (23.9)	62.8 (21.7)	59.4 (21.6)
Mean (SD) PVRI, Wood units*m^2	23.5 (15.2)	19.0 (13.8)	20.9 (19.0)	20.9 (16.6)	16.1 (12.0)
Mean (SD) Cardiac Index, L/minute/m^2	2.95 (1.16)	3.40 (1.85)	3.73 (2.09)	3.44 (1.84)	4.08 (2.31)
WHO Class, n (%)					
I	9 (22.5)	20[b] (37.0)	21 (27.6)	50 (29.4)	25 (41.7)
II	22[b] (55.0)	25 (46.3)	43 (56.6)	90 (52.9)	29 (48.3)
III	9 (22.5)	8 (14.8)	12 (15.8)	29 (17.1)	6 (10.0)
IV	0	1 (1.9)	0	1 (0.6)	0
Missing	2	1	1	4	0

Source: A1481131 CSR Tables 5.2.1.1, 5.5.1.1, 5.6.1.1a, 5.15.6.1, 5.3.1, 5.4.1, 5.8.1, and 5.11.1
SD = standard deviation, RER = respiratory exchange ratio, PVRI = pulmonary vascular resistence index, mPAP = Mean Pulmonary Arterial Pressure, WHO = World Health Organisation

- ***Main efficacy results***

a) Peak V02

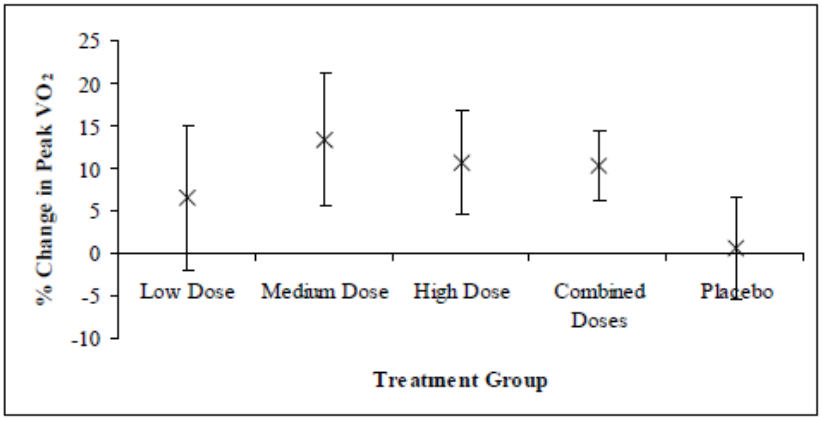
There were mean increases in peak VO2 percentage change from baseline with all 3 sildenafil dose groups (table 11; fig 5) with little change with placebo (0.53%). In the primary analysis, which adjusted for baseline peak VO_2, aetiology and weight group, the increase in percentage change in peak VO_2 on sildenafil (combined sildenafil groups) compared to placebo was 7.71% (95% CI: -0.19% to 15.60%; p-value =0.056).
While the reduced effect with the low dose sildenafil group was useful with respect to making dose recommendations, the lack of treatment effect in this group diminished the effect of the sildenafil combined group versus placebo leading to the overall borderline non-significance.

Table 11: Percentage Change from Baseline[a] in Peak VO_2 at Week 16 – ITT[b]

	Sildenafil				
Treatment Group	**Low**	**Medium**	**High**	**Combined**	**Placebo**
Number of subjects	24	26	27	77	29
Mean (SD) VO_2, mL/kg/minute					
Baseline	17.37 (4.36)	18.03 (4.70)	17.43 (3.70)	17.61 (4.22)	20.02 (3.80)
Week 16	18.40 (5.61)	20.39 (6.16)	19.00 (3.59)	19.28 (5.21)	20.01 (4.44)
Change from baseline	1.03 (3.41)	2.36 (3.36)	1.57 (2.56)	1.67 (3.13)	-0.01 (3.34)
Percentage change from baseline	6.44 (20.16)	13.40 (19.50)	10.58 (15.51)	10.24 (18.39)	0.53 (15.91)
Mean difference versus placebo (SE)	3.81 (5.00)	11.33 (4.84)	7.98 (4.85)	7.71 (3.98)	NA
95% Confidence interval[c]	-6.11, 13.73	1.72, 20.94	-1.64, 17.60	-0.19, 15.60	NA
P-value[c]	NA	NA	NA	0.056	NA

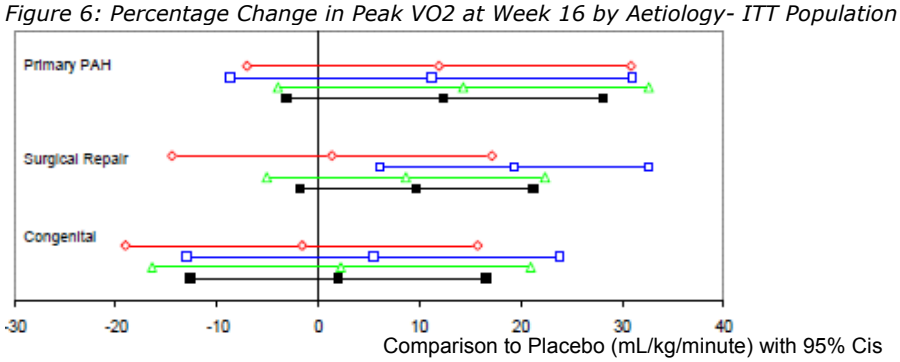
ITT=intention-to-treat population; SE=standard error; SD=standard deviation; NA=not applicable
[a] Baseline was the average of all assessments on or before the first day of study treatment
[b] ITT subset of developmentally able subjects
[c] Analyses were performed using analysis of covariance with aetiology, weight and baseline peak VO_2 as the covariates

Figure 5: Treatment Difference in Percentage Change from Baseline in Peak VO2 at Week 16: Mean and 95% CI ITT



Based on etiology, a better response was observed in the subgroup of primary PAH and surgical repairs in the mean percent change from baseline compared to placebo [12.5% (95% CI: -3.1%, 28.2% and 9.8% (95% CI: -1.7%, 21.3%)] respectively, unlike the congenital systemic-to-pulmonary shunt subgroup of a 2.0% (95% CI: -12.6%, 16.6%) (fig 6).

Figure 6: Percentage Change in Peak VO2 at Week 16 by Aetiology- ITT Population



Low dose; ☐ Medium Dose; ☐ High Dose; ■ Combined sildenafil; Congenital = Congenital systemic-to pulmonary shunt; CIs = Confidence intervals

b) Time to Peak VO_2

The sildenafil combined group showed a 9.24% mean increase compared to placebo in percentage change in time to peak VO2 (95% CI: -3.05%, 21.54%; p= 0.139).
Mean RER (ratio of carbon dioxide produced to oxygen consumed [VCO2/VO2]), values are consistent with achievement of maximal exercise (RER >1) in all treatment groups, although the range across individuals was 0.7 to 1.6, suggesting that some subjects did not reach maximum exercise.

c) Haemodynamic Endpoints: mPAP, PVRI and Cardiac Index

mPAP and PVRI demonstrated a dose response over the dose range. Increases from baseline in mean cardiac index were observed for all sildenafil groups, though a dose response was not as clear. The combined sildenafil showed significant changes in PVRI and CI compared to placebo (tables 12, 13 and 14).

Table 12: Change from Baseline in mPAP at Week 16 – ITT

	Sildenafil				
Treatment Group	**Low**	**Medium**	**High**	**Combined**	**Placebo**
Number of subjects	39	55	71	165	56
Mean (SD) mPAP, mmHg					
Baseline	66.3 (22.2)	61.9 (18.1)	61.6 (23.9)	62.8 (21.7)	59.4 (21.6)
Week 16	67.1 (24.4)	57.9 (19.4)	54.2 (20.6)	58.5 (21.6)	59.0 (20.3)
Change from baseline	0.9 (12.3)	-3.9 (12.0)	-7.4 (15.4)	-4.3 (13.9)	-0.4 (15.9)
Mean difference versus placebo[b] (SE)	1.6 (3.1)	-3.5 (2.7)	-7.3 (2.6)	-3.1 (2.2)	NA
95% Confidence interval[b]	-4.5, 7.6	-8.9, 1.9	-12.4, -2.1	-7.5, 1.3	NA
P-value[b]	NA	NA	NA	0.172	NA

Table 13: Change from Baseline in PVRI at Week 16 – ITT

	Sildenafil				
Treatment Group	**Low**	**Medium**	**High**	**Combined**	**Placebo**
Number of subjects	36	49	67	152	50
Mean (SD) PVRI, Wood units*m^2					
Baseline	23.5 (15.2)	19.0 (13.8)	20.9 (19.0)	20.9 (16.6)	16.1 (12.0
Week 16	23.6 (16.0)	16.0 (11.0)	15.8 (13.5)	17.7 (13.7)	17.7 (13.8
Change from baseline	0.1 (10.9)	-2.9 (11.5)	-5.1 (14.7)	-3.2 (13.0)	1.6 (9.2)
Mean difference versus placebo (SE)	-0.6 (2.7)	-4.5 (2.4)	-7.2 (2.3)	-4.1 (2.0)	NA
95% Confidence interval[b]	-5.9, 4.7	-9.3, 0.3	-11.7, -2.7	-8.0, -0.2	NA
P-value[b]	NA	NA	NA	0.041	NA

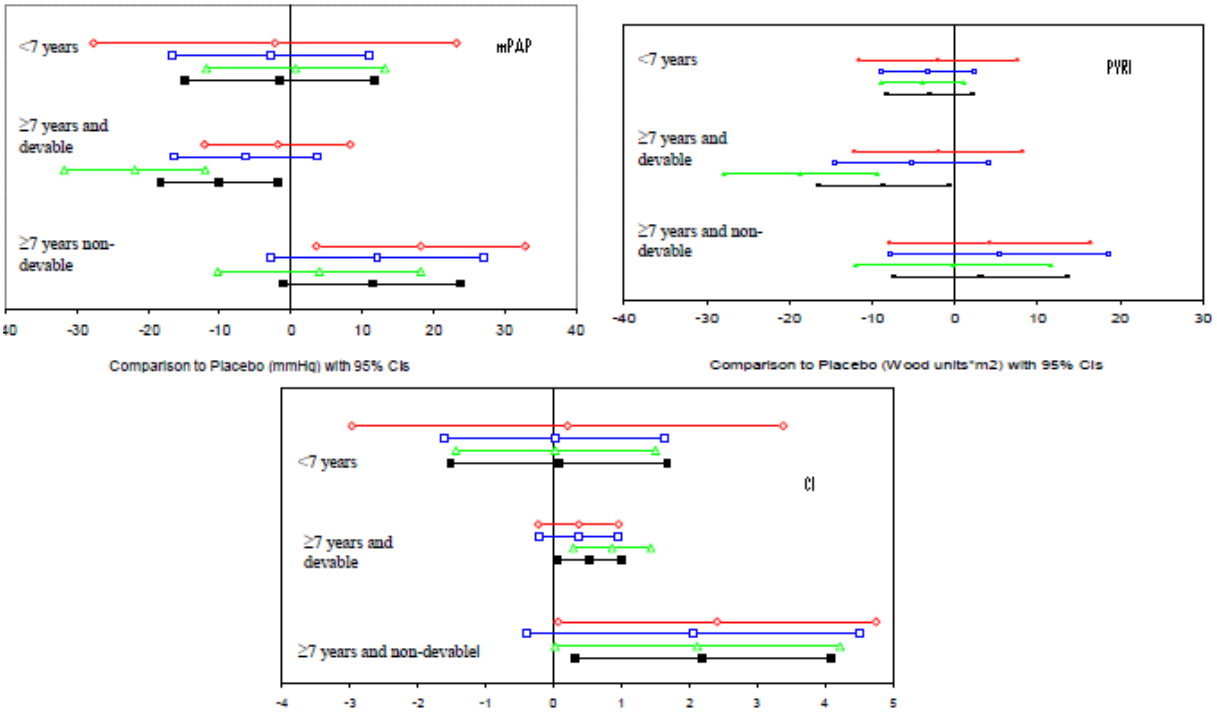
Table 14: Change from Baseline in Cardiac Index at Week 16 – ITT

	Sildenafil				
Dose	**Low**	**Medium**	**High**	**Combined**	**Placebo**
Number of subjects	37	49	68	154	52
Mean (SD) Cardiac Index, L/minute/m^2					
Baseline[a]	2.95 (1.16)	3.40 (1.85)	3.73 (2.09)	3.44 (1.84)	4.08 (2.31)
Week 16	3.15 (1.37)	3.42 (1.94)	3.97 (2.23)	3.60 (1.98)	3.48 (1.41)
Change from baseline	0.20 (1.17)	0.02 (1.44)	0.24 (2.19)	0.16 (1.76)	-0.60 (2.12)
Mean difference versus placebo (SE)[b]	0.71 (0.41)	0.61 (0.37)	0.89 (0.35)	0.74 (0.30)	NA
95% Confidence interval[b]	-0.10, 1.52	-0.12, 1.35	0.21, 1.58	0.14, 1.34	NA
P-value[b]	NA	NA	NA	0.015	NA

d) Aetiology subgroups

Results presented by age and developmental ability are presented in the following figure (7).

Figure 7: Change in mPAP, PVRI and CI from baseline distributed by age and developmental ability (excluding subjects with congenital systemic to pulmonary shunts)



Low dose; ☐ Medium Dose; High Dose; ■ Combined sildenafil; Devable= Developmental ability; CIs = Confidence incidences

Subjects in the ≥7 year developmentally able subgroup (n=115) demonstrated dose related improvements in mPAP and PVRI which were associated with increases in Cardiac Index. The combined sildenafil group, in comparison to placebo, was statistically significant for all endpoints. Mean changes from baseline in the <7 years of age subgroup (n=63), in comparison to placebo, were small in mPAP, PVRI and Cardiac Index. This may be due in part to the fact that subjects in the <7 years of age subgroup had lower mean mPAP and PVRI values at baseline than the other subgroups and for Cardiac Index, mean baseline values were generally higher. As there were only 2 evaluable subjects in the low dose group with this subgroup only the medium and high dose groups are potentially interpretable.
These improvements in haemodynamic parameters (Table 15) are consistent with those seen in the adult PAH sildenafil pivotal study (study A1481140).

Table 15: Mean Changes from Baseline in Haemodynamics

Study	Dose Group	mPAP (mmHg)	PVRI (Wood units*m^2)	Cardiac Output (L/min)
A1481131	Placebo	-0.4	1.6	-0.45
	Low	0.9	0.1	0.29
	Medium	-3.9	-2.9	0.10
	High	-7.4	-5.1	0.44
A1481140	Placebo	0.6	1.4	-0.08
	20mg	-2.1	-2.8	0.39
	40mg	-2.6	-3.0	0.41
	80mg	-4.7	-5.7	0.68

No clear relationship to the sub-etiology was observed in the haemodynamic parameters i.e patients with congenital heart disease showed comparable improvements.
The applicant submitted several analyses that could explain the better results of Revatio in primary PAH compared to the secondary forms. The sub-analysis involved very few patients, which complicate their interpretation. In general, it can be observed that recruited patients with primary PAH might have

suffered from more severe disease, indicated by worse haemodynamic data and FC; such patients usually show better response. Another possible reason could be the inclusion of a higher proportion of patients with Down syndrome in the secondary forms. These patients may be less responsive to vasodilator therapy. In an analysis excluding patients with Down's syndrome from the secondary forms, results of PVRI and CI appear comparable for both primary and secondary aetiologies. Regarding the worse haemodynamic response in general, this could be attributed to inclusion of patients with Down syndrome who may be less responsive to vasodilator therapy. Haemodynamic effect in non-developmentally able subjects who did not have Down syndrome was comparable to the effect shown in developmentally subjects irrespective of age.

In conclusion, the explanations are plausible. However no robust conclusions can be made regarding possible different efficacy based on aetiology due to the limited number of patients.

e) Changes from baseline in WHO Class

Overall 32.6%, 51.7%, 15.2% and 0.4% of subjects had WHO Class I, II, III and IV respectively at baseline. The weighting towards Class I was highest in the placebo group. The data suggest a dose response with changes in functional class, with odds ratios for the sildenafil low, medium and high dose groups compared to placebo of 0.6 (95% CI: 0.18, 2.01), 2.25 (95% CI: 0.75, 6.69) and 4.52 (95% CI: 1.56, 13.10), respectively (table 16).

Table 16: Changes from Baseline in World Health Organisation (WHO) Functional Class for Subjects with PAH Class I to IV at Baseline

		Sildenafil				
Treatment Group		**Low**	**Medium**	**High**	**Combined**	**Placebo**
Baseline WHO Class						
WHO Class I	Number of subjects	9	20	21	50	25
No change		6	18	20	44 (88%)	21 (84%)
Worsened by 1 class		3	2	1	6 (12%)	4 (16%)
Worsened by 2 classes		0	0	0	0	0
WHO Class II	Number of subjects	22	25	43	90	29
No change		20	23	35	78 (86.7%)	27 (93.1%)
Improved by 1 class		2	2	8	12 (15.3%)	2 (6.9%)
Worsened by 1 class		0	0	0	0	0
Worsened by 2 classes		0	0	0	0	0
WHO Class III/IV	Number of subjects	9	9	12	30	6
No change		5	1	3	9 (30%)	4 (66.6%)
Improved by 1 class		4	8	8	20 (66.7%)	2 (33.3%)
Improved by 2 classes		0	0	1	1 (3.3%)	0
Worsened by 1 class		0	0	0	0	0

1.5.1.3. Discussion on efficacy results

Choice of primary end points
In the developmentally able children (mostly above 7 years), the primary efficacy results showed a borderline non-significant increase in ***peak VO_2*** of the combined sildenafil group compared to placebo (7.7% CI: -0.19- 15.6; p=0.056). Several issues could have influenced the results. CPX may not have been a good choice as a primary endpoint. Differences in center training are important factors that could impact the results. Considering that 32 centers contributed to the current paediatric trial, it is not feasible to request analysis by center. Recruiting patients in less severe forms i.e WHO I could have also influenced the results as these patients are already known to exhibit lesser improvements in exercise capacity compared to the more severe forms.

However, the improvement seen in VO_2 can be considered numerically in line with another study performed in children, but in a different indication (Moalla at al., 2005). Focusing on the medium dose which is the currently advocated dose by the MAH, it is agreed that the results of this group are the best ones.

Haemodynamic parameters are considered by some experts to be the appropriate primary endpoints for paediatric studies, considering the difficulty in performing exercise tests.

Upon CHMP request, additional data provided in the group of children who could exercise showed modest correlations between PVRI/CI/FC/physician global assessment and VO2. However the results are in line with the adult pivotal study which is reassuring regarding clinical relevance of the results.

The applicant pointed out several points which may theoretically favor the use of CPET over 6MWT in children. Results of CPET are expected to give a broader assessment of the patient than those of 6-MWT. However the 6-MWT is more widely used in PAH probably because of its convenience and consequently no PAH drug has been approved based on CPET results. In one of the pivotal studies of the sitaxentan initial application both tests were performed. Sitaxentan showed significant improvement using the 6MWT while results of CPET were equivocal. The question remains about this disparity of the results for which the most relevant explanation given at that time was the improper training in the performance of CPET of some centers. This issue can not be excluded either in this application.

Study results
Children above 7 years
The results in the paediatric study show a positive trend for improvement in exercise capacity, generally accompanied with improvements in other endpoints, mainly the haemodynamic parameters. Results are comparable to those observed in the adult studies, indicating a significant clinical improvement (analysis shows equivalent exercise response in adults (6MWT) and paediatrics (CPET) compared to placebo).

Children below 7 years
It is recognized that exercise testing in children below 7 years is problematic and there is some understanding that in this age category, haemodynamic data may be the only available proof of efficacy. In the present study, no significant haemodynamic improvements was shown in terms of absolute differences in children below 7 years, but the data were found to be skewed and baseline differences should be taken into account. A difference in the efficacy of sildenafil is not foreseen between patients above and below 7 years, except when this is confounded by difference in disease stage. Younger patients may present less advanced disease as manifested by better preserved haemodynamics compared to the older group. The number of patients below 7 years administered sildenafil is limited (n=35) in the present application.
At recruitment, haemodynamic parameters were better in patients <7 years, PVRI: 12.3 compared to 20.7 wood units.m^2 in patients ≥ 7 years; CI: 4.2 L▪m^2/min versus 3.2 L▪m^2/min; mPAP 54.2 mmHg versus 64.7 mmHg. This may partly explain the lack of significant effect in the lower age group. To assess the differences in treatment effect sizes across populations, baseline was used as a covariate and the resulting performed analysis (including baseline as a covariate) showed that effects on PVRI and CI were consistent in the 2 populations (<7 and ≥7 years). With the medium dose, PVRI (ratio to placebo) was 0.77 compared to 0.83 respectively and CI (ratio to placebo) was 1.06 compared to 1.04 for 7 and ≥7 years respectively.
The changes in mPAP are not comparable between the groups, and no dose response is shown in patients younger than 7 years. It is recognized that both PVR and CI constitute more sensitive indices for response of treatment.
Based on the above, it can be accepted that the efficacy of Revatio was also shown in patients <7 years. This is reflected in section 5.1 of the SmPC.

WHO functional class
Regarding WHO functional class, a dose response in improvement in WHO Functional class (FC) could be observed. The results are supportive to the general efficacy data.
It can be agreed with the applicant that the evidence based recommendations of the ESC guideline are limited by the availability of data from randomised clinical trials. There are many similarities between the adult and paediatric forms of PAH, but patient presentation may be different. Exercise intolerance and fatigue frequent symptoms in adults may be less manifest in children, who present with more severe symptoms like syncope or pre syncope. This is however, accompanied with preserved right ventricular function and better haemodynamics.
The rate of deterioration in children is also faster than in adults. Without treatment, estimated median survival after diagnosis of patients with iPAH is reported to be 0.8 years in children compared to 2.8 years in adult. These issues probably prompt earlier intervention with specific PAH therapies, although this is not specifically mentioned in PAH treatment guidelines. Also, this may hinder recruitment of paediatrics in clinical trials even in the earlier stages of disease.
The recruited paediatric patients reflect the recruitment criteria in clinical practice according to one database (Barst et al., 2009). However, according to a Dutch registry (van Loon et al., 2010) and a Swiss registry (Fasnacht et al 2007) for paediatric PAH patients, the diagnosis of paediatric patients in Functional Class I is rare (2% and zero respectively). Data stratified by FC show inconsistent VO2 peak

values and the results should be interpreted with caution considering the small number of patients. Generally, the result show that patients with severe FC groups have the most benefit, as could be expected. Haemodynamic data show that improvements in both PVRI and CI in patients with FC I are comparable in magnitude to those seen in FC II-IV when medium or high doses of sildenafil are administered. It was not considered feasible to include FC in the paediatric indication, considering that there are no clear treatment recommendations for patients in FC I. This choice was also taken to avoid a complicated wording of the indication considering that different endpoints were investigated in different age groups, and that FC is essentially applicable in the developmentally able patients. Still, a description of the number and percent of children included in study A1481131 by functional class at baseline is included in section 5.1 of the SmPC.

Regional differences
The study was conducted in 32 centres from 16 different countries. Given that management of PAH in children may differ depending on the geographic region, the applicant provided additional information by country and geographic region (US, European Union and rest of the world) for the main efficacy and safety results. Differences in medical practice between the 16 participating centers throughout the 5 years can not be excluded. However importantly, no PAH specific therapy was allowed.
For VO2 peak, it is difficult to comment on the results considering the very low numbers. For the presented haemodynamic data, some dose response relation can be observed, however again the numbers are too low to draw definite conclusions.

The applicant submitted the number and nature of the patient's subgroup: secondary PAH with congenital systemic to pulmonary shunt. In many cases the shunt was categorized "other" or "shunt not specified or not recorded" as according to the applicant this information was not required to be collected.

Concomitant medications:
TTSpecific therapy for PAH (eg, bosentan, NO donors or prostacyclins) was prohibited during the study. The use of non-specific background therapy to treat hypertension (including calcium channel blockers), diuretics, ACEi, digoxin, beta-blockers or warfarin were permitted but not very frequently used, according to the data provided. Most children were not in an advanced stage of the PAH disease in the study and the use of concomitant therapies was balanced between groups. Therefore, an effect of concomitant medications of study results can be reasonably excluded.
A paragraph is included in the description of the study in section 5.1 of the SPC regarding the "naive" nature of children recruited into the study with respect to specific PAH therapies (i.e. endothelin-A receptor antagonists, NO donors or prostacyclins).

1.5.2. Study A1481156- Extension to A1481131

1.5.2.1. Methodology

This was a multi-center, long-term extension study including subjects who completed study A1481131. To prevent un-blinding in study A1481131, subjects received the different doses of sildenafil in a blinded phase until study A1481131 was un-blinded (02 August 2008), after which subjects were also un-blinded to treatment in study A1481156. Subjects randomised to receive sildenafil in study A1481131, who consented to participate in this extension study, were maintained on their A1481131 sildenafil dose. Subjects in the A1481131 placebo group were stratified by their weight prior to entry into Study A1481156 (≥8-20 kg, >20-45 kg, >45 kg), to ensure a balance across treatment groups with respect to this factor and randomised to receive 1 of the 3 doses of sildenafil. Subjects were randomly assigned to treatment groups according to the following schedule:
- Subjects in the low weight stratum (≥8-20 kg) were assigned to sildenafil medium dose, or sildenafil high dose in a 1:2 ratio (sildenafil medium dose:sildenafil high dose), according to the schedule in Table 2.
- Subjects in the medium (>20-45 kg) and high (>45 kg) weight strata were assigned to sildenafil low dose, sildenafil medium dose, or sildenafil high dose in a 1:1:1 ratio.

The placebo patients were randomised to blinded doses of sildenafil following completion of the 16 week treatment period in Study A1481131 and therefore at 1 year had received 36 weeks of active treatment. This study is currently ongoing.

The ***primary objective*** of Study A1481156 was to assess the safety and tolerability of oral sildenafil in the chronic treatment of paediatric subjects with PAH. The ***secondary objective*** was to describe long-term (≥1 year) efficacy of oral sildenafil in these subjects.

In addition to the Week 8 and Week 16 CPX tests in Study A1481131 a further CPX test was performed for developmentally able subjects at Week 36 (Week 52 following randomisation in study A1481131). Other endpoints included WHO functional class, patients assessments and change in background therapy. All randomised and treated subjects in Study A1481131 (placebo or sildenafil) were also included, where appropriate, in survival analyses, including data of post-discontinuation survival status where available. The statistical methods for the analysis of efficacy data mainly comprised of simple descriptive summaries and estimated treatment group differences (with 95% CIs) for each parameter.

1.5.2.2. Results

Of the 228 subjects who completed Study A1481131, 220 entered the extension Study A1481156 and 55 placebo subjects from Study A1481131 were allocated to low (13 subjects), medium (19 subjects) and high (23 subjects) dose sildenafil. As of this data-cut (15 May 2009) 206 patients (94%) have received ≥1 year of therapy (from the start of Study A1481131), 129 (59%) have received ≥2 years of therapy and 88 (20%) have received ≥3 years of therapy within Study A1481131/A1481156. Across Studies A1481131 and A1481156, duration of treatment for individual subjects currently ranges from 3-1815 days. The baseline demographic characteristics are presented in table 17.

Table 17: Patient Demography by A1481156 Treatment Group

Treatment Group	Low	Medium	High
Number of subjects	55	74	100
Male, n (%)	21 (38.2)	32 (43.2)	34 (34.0)
Female, n (%)	34 (61.8)	42 (56.8)	66 (66.0)
Age (years), n (%):			
1-4	1 (1.8)	12 (16.2)	21.0 (21.0)
5-12	36 (65.5)	38 (51.4)	50.0 (50.0)
13-17	18 (32.7)	24 (32.4)	29.0 (29.0)
Mean (SD)	11.2 (3.2)	9.7 (4.5)	8.7 (4.5)
Range	4-17	2-17	1-17
Weight, kg			
Mean (SD)	36.9 (16.7)	31.5 (16.4)	26.3 (14.2)
Range	19.5-105.0	8.6-106.0	8.2-61.0

By this data cut-off, just over two-thirds of subjects were still ongoing (159/234 subjects, 67.9%) and just under one-third of subjects had discontinued (75/234 subjects, 32.1%). The percentage of discontinuations was similar for all weight subgroups (around 30%) (table 16, in safety). A greater proportion of primary PAH subjects withdrew (30/77 subjects, 39.0%) compared to subjects with secondary PAH (21/68 subjects [30.9%] for surgical repair, 19/84 subjects [22.6%] for congenital systemic-to-pulmonary shunt). Of the 15 withdrawals due to death, 10 subjects had primary PAH (13.0% of the primary PAH subjects).

Main efficacy results

a) PeakV02

Increases in mean percentage change from baseline in peak VO2 at Year 1 were observed for all sildenafil treatment groups (maximum percentage change of 11.2% in the sildenafil low dose group (Table 18). For the sildenafil low, medium, and high dose groups, improvements >10% at Year 1 were similar across treatment groups: 15/38 subjects (39.5%), 12/36 subjects (33.3%), and 13/40 subjects (32.5%). The low dose group showed a greater proportion of subjects improving between 0%-10% at 1 year (28.9%) compared to the medium (11.1%) and high (17.5%) dose groups. Hence no deterioration (ie, no change or some improvement) was observed for 26/38 subjects (68.4%), 16/36 subjects (44.4%), and 20/40 subjects (50.0%), in the low, medium, and high dose groups, respectively. A similar proportion of subjects had discontinued, died or had missing values at Year 1 across the three groups (approximately 11%-13%). It is important to highlight that these data should be interpreted with caution as all discontinuations and missing values were taken as deteriorations and hence values are possibly biased.

Table 18: Summary of Peak VO_2 (mL/kg/min) at Year 1 by A1481156 Treatment Group - ITT Population

	Sildenafil Low Dose (N=33)	**Sildenafil Medium Dose (N=32)**	**enafil High Dose (N=35)**
Baseline			
Mean (SD)	18.30 (4.54)	18.11 (4.44)	17.78 (3.65)
Year 1			
Mean (SD)	19.97 (5.17)	18.69 (5.92)	17.93 (4.02)
Mean (SD) Change from Baseline	1.67 (3.64)	0.58 (5.22)	0.15 (3.44)
Mean (SD) % Change from Baseline	11.19 (22.98)	5.37 (31.62)	2.56 (21.46)
Comparison with Low Dose:			
Mean Difference (SE)		-7.02 (6.10)	-9.84 (5.92)
95% Confidence Interval		-19.13, 5.09	-21.60, 1.93
Comparison with Medium Dose:			
Mean Difference (SE)			-2.82 (6.01)
95% Confidence Interval			-14.75, 9.11

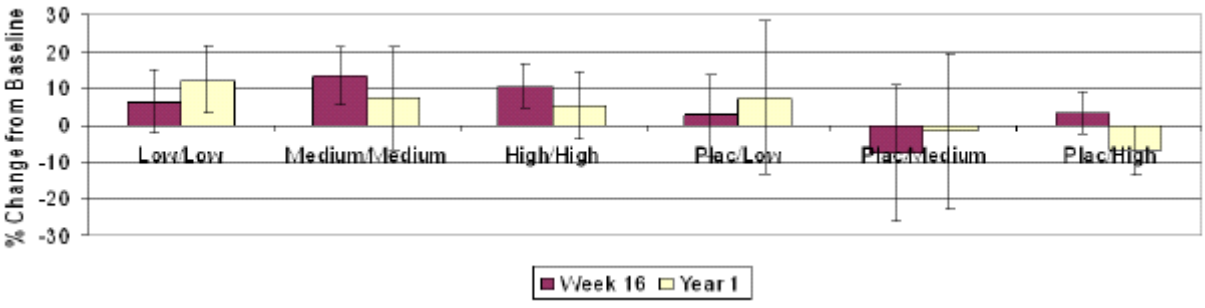
VO_2 = volume of oxygen consumed; ITT = intent-to-treat; N = number of subjects in analysis; SD = standard deviation; SE = standard error
ITT population for this table refers only to the subset of the ITT population who were developmentally able.
Baseline was the average of all assessments on or before the first day of study treatment.
Analyses were performed using analysis of covariance with aetiology, weight, day of assessment and baseline peak VO_2 as the covariates

Improvements at Year 1 from baseline, with the low dose group were observed with both those subjects who were randomised to the low dose in Study A1481131 and those who received placebo in Study A1481131 and then received low dose in Study A1481156. Improvements at Year 1 from baseline were also seen for the medium and high dose groups. Subjects who received placebo in Study A1481131, and then went on to receive medium or high dose in Study A1481156 showed mean deteriorations from baseline at Year 1 (table 19 and fig 8).

Table 19: Percentage Change from Baseline in Peak VO2 at Year 1 by A1481131/A1481156 Treatment Sequence

Number (%) of Subjects	Sildenafil Low/ Low Dose (N=25)	Sildenafil Medium/ Medium Dose (N=25)	Sildenafil High/ High Dose (N=27)	Placebo/ Low Dose (N=8)	Placebo/ Medium Dose (N=7)	Placebo/ High Dose (N=8)
Baseline						
Mean (SD)	17.32 (4.27)	17.45 (4.61)	17.39 (3.69)	21.36 (5.14)	20.45 (2.97)	19.08 (3.40)
Year 1						
Mean (SD)	19.05 (4.45)	18.36 (6.36)	18.02 (4.44)	22.83 (6.48)	19.86 (4.17)	17.63 (2.29)
Mean (SD) Change from Baseline	1.73 (3.01)	0.91 (5.41)	0.62 (3.70)	1.46 (5.41)	-0.59 (4.66)	-1.45 (1.70)
Mean (SD) % Change from Baseline	12.37 (22.78)	7.33 (33.84)	5.32 (23.45)	7.49 (24.81)	-1.62 (22.64)	-6.76 (8.12)

Figure 8: Percentage Change from Baseline in Peak VO2 at Year 1 by A1481131/A1481156 Treatment Sequence



b) Changes from baseline in WHO class

The percentage of subjects showing maintenance (no change or improvement) was generally similar for all sildenafil dose groups, being 67.3%, 75.7%, and 71.0% in Year 1, and 48.4%, 46.3%, and 50.0% in Year 3, for the low, medium, and high dose groups, respectively.

c) Survival Status

The investigation of time to death included the 234 subjects who received at least 1 dose of study medication in Study A1481131. The analysis included post-treatment survival follow-up data from subjects who discontinued study treatment. Time to death was taken relative to either the start of sildenafil treatment or from the start of Study A1481131, and was censored on the last day on which the subject was known to be alive. Across all dose groups, the probability of survival at Year 1, Year 2 and Year 3, relative to Day 1 of active therapy (derived from the life table estimates of deaths), was 99.6%, 94.8%, and 90.2%, respectively. However, these data should be interpreted with caution as subjects who were lost to follow-up were censored at the last date they were known to be alive. If their survival was worse than those for whom survival is still being assessed then the survival estimates above will be upwardly biased.

1.5.2.3. Discussion

Most of the patients who finished A1481131 (n=228) were recruited in its long term extension study A1481156 (n=220), which is still ongoing. The cut-off date of the presented data is 15 May 2009. The study is open label and not controlled limiting its value for interpretation of efficacy, but can still be helpful in providing data on maintenance of efficacy.

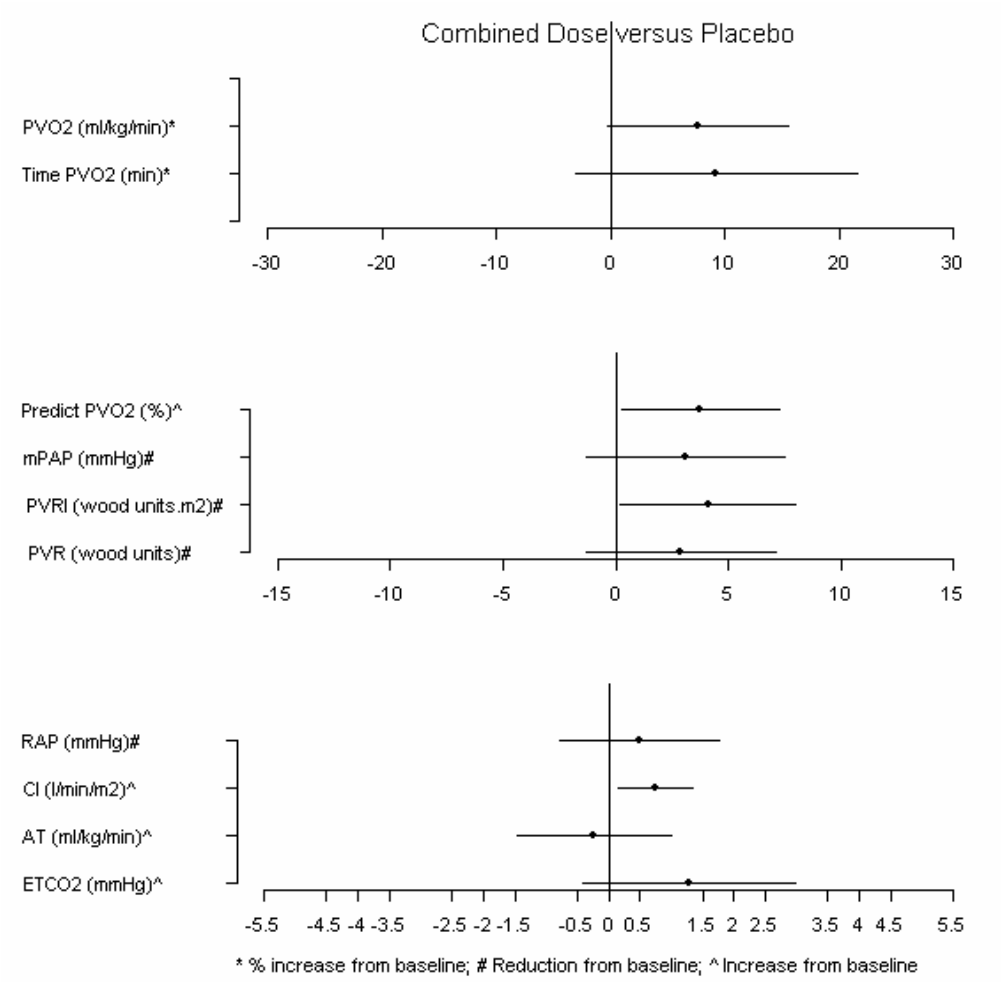
Increases in peak VO2 are observed at one year ranging from 2.56% to 11.19%. Time to maximum peak VO2 was also increased ranging from 3.74% to 24.43, however with an inverse dose response in both cases.

It is acknowledged that the inverse dose response for peak VO2 and time to peak VO2 was not significantly different. The applicant explored several factors that could explain such an observation e.g evaluable population, baseline demographics and baseline severity. A possible influence of either the evaluable population or their baseline severity could be excluded. Younger patients were administered the lower dose however, using the age as covariate, there was still a difference between doses. Using other parameters of efficacy (WHO, FC and physician global assessment questionnaire) did not indicate the same direction of results. In summary, in the long term study, there was an unexplained trend for better VO2 results with lower doses however this did not correlate with other efficacy assessments.

Patients originally randomised to placebo in the short term placebo-controlled study A1481131 kept exhibiting lower VO_2 than those originally randomised to active treatment during the follow up in the long term extension study. This is in line with the observations of the adult studies.

According to the MAH, the overall efficacy data generated from studies A1481131 and A1481156 show that administration of Revatio is associated with improvements in clinical endpoints that are relevant to the treatment of PAH, including exercise capacity, pulmonary haemodynamics and WHO functional class. The consistency of these effects with specific reference to exercise capacity and haemodynamics is illustrated in figure 9.

Figure 9: Summary of efficacy results.



Predicted peak VO2, Time to peak VO2, PVR= Pulmonary Vascular Resistance, RAP= Right Atrial Pressure, AT= Anaerobic threshold and ETCO2= End Tidal Carbon Dioxide)

The applicant was also requested to present an analysis of time to clinical worsening (TTCW). Four different definitions of time to clinical worsening (TTCW) (frequency of patients experiencing first event) were investigated post-hoc, of which definition 2 (Death and/or heart/lung transplant and/or SAE associated with disease progression and/or addition of PAH specific therapy and/or discontinuations due to an adverse event associated with disease progression/death; data censored at time of discontinuation; 'ordinary' discontinuations not counted as events; sildenafil up-titrations excluded as events) was most similar to that used in study A1481131.
With this definition, the highest hazard ratio comparing the high and low dose groups was 1.59 (95%CI: 0.70 to 3.63), compared to 1.28 (95%CI: 0.64 to 2.58) in the high- and medium-dose groups. Based on this post-hoc analysis of TTCW events, there is no compelling evidence that the higher doses of sildenafil, relative to lower doses, are related to a beneficial effect in the TTCW.

1.6. Discussion on clinical efficacy

The main study in the current application study A1481131 is the largest placebo-controlled paediatric study conducted so far, recruiting around 230 drug-naive patients and lasting 5 years. The efforts of the company are acknowledged.
Several critical issues have been raised during the initial assessment of this application. The choice of CPET as a measure of exercise capacity in PAH clinical studies has always been problematic. Theoretically, CPET can give more broad information about the patients exercise capacity than the 6MWT, however the 6MWT is easier to use and is accordingly more popular in clinical trials. The clinical significance of the results of the CPET is also difficult to interpret due to the limited experience. The results of CPET in this paediatric study do show a positive trend for improvement in exercise capacity, of unclear significance. They were generally accompanied with improvements in other endpoints as

well, mainly the haemodynamic parameters which are comparable to those observed in the adult studies. For the group of children who could exercise, modest but significant correlations were shown between PVRI/CI/Functional class/Physician global assessment and VO2. The same modest correlations were also shown in the pivotal adult study, which is reassuring.
Another issue is the recruitment of patients in functional class WHO I (32.6%). Paediatric treatment guidelines usually follow those of the adult guidelines, due to the similarities in the disease, though patient presentation may be different. The rate of deterioration in children is also faster. This may justify earlier intervention, though this is not explicitly mentioned in the guidelines. Data stratified by FC show inconsistent VO2 peak values, but it can be generally seen that patients with severe FC groups have the most benefit, as could be expected. Haemodynamic data show that there are improvements in both PVRI and CI in patients with FC I comparable in magnitude to that seen in FCII-IV when medium or high doses of sildenafil are administered. These results could justify their inclusion. Importantly, analysis of patients in WHO II/III, who are the target group show appropriate haemodynamic responses.
Another major issue was the efficacy in children below 7 years. In this patient group, haemodynamic results appeared equivocal. A difference in the efficacy of sildenafil is not foreseen between patients above and below 7 years, however further analysis was requested. The responses of the applicant show that at recruitment, haemodynamic parameters were better in patients <7 years. This may partly explain the lack of significant effect in the lower age group. Further analysis (including baseline as a co-variety) shows that effects on PVRI and CI were consistent in the 2 populations (<7 and ≥7 years). Based on analysis of the haemodynamic data, it can be accepted that efficacy in patients less than 7 years was demonstrated. The limited experience in this patient group should be mentioned in the SPC.
In the long term study, there was an unexplained trend for better VO2 results with lower doses, but this was not seen with other efficacy assessments (WHO FC and physician global assessment questionnaire).
There was a trend for higher mortality, higher rate of SAEs and higher rate of patients with first events of clinical worsening with the higher sildenafil dose as compared with the lower doses in the initial and long-term extension treatment sequence (A1481131/A1481156), but a direct causal relation is not made in any of the cases. The data should be interpreted cautiously, considering the uncontrolled nature of the long-term extension study, and the possible confounding by disease severity. However, the overall long-term data do no support that the higher sildenafil doses provide a significant benefit over lower doses. Appropriate information has been included in sections 4.2 and 5.1 of the SmPC.

The proposed dose based on the PK/PD simulations is accepted. The medium dose shows the best results in exercise testing, supported by appropriate haemodynamic data against an acceptable safety profile.

1.6.1. Conclusion on clinical efficacy

In the developmentally able children (mostly above 7 years), the primary efficacy results showed a borderline non-significant increase in peak VO2 of the combined sildenafil group compared to placebo. Several issues could have influenced the results and were further investigated and discussed. Additional post hoc analyses on haemodynamic end points by age groups provided further confirmation of clinical relevance of the efficacy data in developmentally able children (mostly above 7 years), and not developmentally able children (mostly below 7 years). Exploratory analyses in different subpopulations data suggest that some beneficial effects on peak VO2 and on some haemodynamic parameters may exist in some subgroups.

In conclusion, the overall efficacy data generated from studies A1481131 and A1481156 show that administration of Revatio is associated with improvements in clinical endpoints that are relevant to the treatment of PAH, including exercise capacity, pulmonary haemodynamics and WHO functional class. The consistency of these effects with specific reference to exercise capacity and haemodynamics was further discussed and finally agreed.
It is agreed that the data support an indication in children aged 1 to 17 years old with pulmonary arterial hypertension.

1.7. Clinical safety

1.7.1. Patient exposure

The safety database comprises six completed studies, of which four were conducted in the paediatric population. Two studies (a controlled study A1481131 and its long-term extension A1481156, ongoing

and presented with a cut-off date of 15 May 2009) were for oral sildenafil for the treatment of paediatric PAH. The MAH refers to IV administration in paediatrics, but the focus will be on the two oral studies. In addition, the MAH makes reference to post marketing data, as well as to available literature.

Study A1481131 and A1481156 combined

The paediatric clinical development program included 234 treated subjects in the placebo-controlled Study A1481131. The majority (228; 97.4%) completed 16 weeks of per protocol treatment in study A1481131, and 220 of these subjects continued into the extension Study A1481156.
Sixty of the 234 treated subjects in Study A1481131 received placebo. Subjects who received placebo in Study A1481131 were randomly assigned to a sildenafil dose level for the long-term extension study A1481156.
As of 15 May 2009 interim data-cut, 206 of these 234 patients (88%) have received ≥1 year of therapy (from the start of A1481131), 129 (59%) have received ≥2 years of therapy and 88 (20%) have received ≥3 years of therapy (for the 60 placebo-treated subjects in A1481131, this includes 12 weeks of placebo treatment). This corresponds to 206/234 (88.0%), 129/173 (74.6%) and 88/133 (66.2%) of those subjects who had the potential to reach 1, 2 and 3 years duration, respectively.

The most common reasons for discontinuation were death (15 subjects) and subjects not willing to continue participation in the study (14 subjects). Seven subjects withdrew due to 'lack of efficacy' (3 and 4 subjects receiving low and high dose sildenafil, respectively) and 4 subjects withdrew due to AEs considered to be treatment related (2 subjects in each of the low and high dose groups).
Two subjects were reported as protocol violators due to treatment non-compliance, which was not due to tolerability issues: all other subjects received 80%-120% of their prescribed dose. A total of 28 subjects temporarily discontinued dosage for >5 days (table 20).

Table 20: Studies A1481131 and A1481156 Combined: Subject Disposition by A1481131/A1481156 Treatment Sequence

Number (%) of Subjects	All	Sildenafil Low/ Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-Randomised
Screened	324							
Assigned to Study Treatment	235	42	56	77	13	19	23	5
Treated	234[a]	42	55[a]	77	13	19	23	5
Discontinued	75 (31.9)	13 (31.0)	17 (30.4)	26 (33.8)	4 (30.8)	4 (21.2)	6 (26.1)	5 (100)
Subject died	15 (6.4)	2 (4.8)	4 (7.3)	9 (11.7)	0	0	0	0
Related to study drug	11 (4.7)	3 (7.1)	0	3 (3.9)	2 (15.4)	0	3 (13.0)	0
Adverse event	4 (1.7)	1 (2.4)	0	2 (2.6)	1 (7.7)	0	0	0
Lack of efficacy	7 (3.0)	2 (4.8)	0	1 (1.3)	1 (7.7)	0	3 (13.0)	0
Not related to study drug	49 (20.9)	8 (19.0)	13 (23.6)	14 (18.2)	2 (15.4)	4 (21.1)	3 (13.0)	5 (100)
Adverse event	6 (2.6)	0	2 (3.6)	2 (2.6)	0	1 (5.3)	1 (4.3)	0
Did not enter A1481156	8 (3.4)	2 (4.8)	2 (3.6)	1 (1.3)	0	0	0	3 (60.0)
Lost to follow-up	6 (2.6)	1 (2.4)	0	1 (1.3)	0	1 (5.3)	2 (8.7)	1 (20.0)
Other	15 (6.4)	3 (7.1)	6 (10.9)	5 (6.5)	0	1 (5.3)	0	0
No longer willing to participate	14 (6.0)	2 (4.8)	3 (5.5)	5 (6.5)	2 (15.4)	1 (5.3)	0	1 (20.0)
Ongoing at Cut-Off 15 May 09	159 (67.7)	29 (69.0)	38 (67.9)	51 (66.2)	9 (69.2)	15 (78.9)	17 (73.9)	0
Analysed for Safety								
Safety	234 (99.6)	42 (100)	55 (98.2)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Adverse Events	234 (99.6)	42 (100)	55 (98.2)	77 (100)	13 (100)	19 (100)	23 (100)	5 (100)
Laboratory Data	233 (99.1)	42 (100)	55 (98.2)	76 (98.7)	13 (100)	19 (100)	23 (100)	5 (100)

1.7.2. Adverse Events

The most common AEs were upper respiratory tract infection URTI (58/229 subjects, 25.3%), headache (53/229 subjects, 23.1%), and vomiting (52/229 subjects, 22.7%).
For the all causality AEs, an apparent dose response was observed for some AEs (eg, URTI, nausea, pneumonia). None of the episodes of URTI or pneumonia were considered to be treatment-related, and there was no evidence of a relationship between dose and treatment-related episodes of nausea.
The most common treatment-related AEs TRAEs were headache (30/229 subjects, 13.1%) and vomiting (15/229 subjects, 6.6%). No dose response was observed. Most of these TRAEs were mild or moderate in severity (table 21).

Table 21: Summary of Most Frequent Treatment-Related Adverse Events by Preferred Term by A1481131/A1481156 Treatment Sequence

Number (%) of Subjects	All (N=234)	Sildenafil Low/ Low Dose (N=42)	Sildenafil Medium/ Medium Dose (N=55)	Sildenafil High/ High Dose (N=77)	Placebo/ Low Dose (N=13)	Placebo/ Medium Dose (N=19)	Placebo/ High Dose (N=23)	Placebo Non-Randomised (N=5)
Headache	31 (13.2)	6 (14.3)	7 (12.7)	9 (11.7)	4 (30.8)	2 (10.5)	2 (8.7)	1 (20.0)
Vomiting	16 (6.8)	4 (9.5)	3 (5.5)	8 (10.4)	0	0	0	1 (20.0)
Abdominal pain	8 (3.4)	0	1 (1.8)	4 (5.2)	2 (15.4)	0	1 (4.3)	0
Cough	6 (2.6)	1 (2.4)	1 (1.8)	4 (5.2)	0	0	0	0
Dyspepsia	6 (2.6)	1 (2.4)	3 (5.5)	1 (1.3)	0	1 (5.3)	0	0
Epistaxis	5 (2.1)	1 (2.4)	0	3 (3.9)	0	1 (5.3)	0	0
Flushing	5 (2.1)	1 (2.4)	1 (1.8)	0	0	2 (10.5)	1 (4.3)	0
Spontaneous penile erection	5 (2.1)	0	3 (5.5)	1 (1.3)	0	0	1 (4.3)	0

Table 22 (below) gives an overview of the incidence of Treatment Emergent AEs reported in >3% of subjects in Study A1481131 compared with treated adult subjects from Study A1481140.

Table 22: Incidence of Treatment-Emergent Adverse Events Reported in ≥3% of Subjects in Study A1481131 Combined Sildenafil Treatment Groups compared to Adult Subjects Treated for PAH (Study A1481140)

	Study A1481131	**Study A1481140**
Subjects evaluable for AEs	174	207
Number of AEs	348	1061
Number (%) of subjects with AEs	126 (72.4)	186 (89.9)
Number (%) of subjects with Adverse Event[a]		
Headache	23 (13.2)	95 (45.9)
Upper respiratory tract infection	20 (11.5)	13 (6.3)
Pyrexia	20 (11.5)	13 (6.3)
Vomiting	19 (10.9)	15 (7.2)
Diarrhea	12 (6.9)	22 (10.6)
Cough	8 (4.6)	14 (6.8)
Nausea	8 (4.6)	22 (10.6)
Bronchitis	8 (4.6)	5 (2.4)
Nasopharyngitis	8 (4.6)	16 (7.8)
Pharyngitis	7 (4.0)	3 (1.4)
Dizziness	6 (3.4)	26 (12.6)
Epistaxis	6 (3.4)	15 (7.2)
Abdominal pain upper	6 (3.4)	17 (8.2)

AE=Adverse event a AEs that occurred in ≥3% of subjects in any treatment group

Events that depend on self-reporting (for example, headache, upper abdominal pain, and dizziness) are more frequent in the adult population, while more objective events such as URTI, pyrexia and vomiting are more frequent in the paediatric population. There were no treatment-emergent deaths during Study A1481131.

When comparing the incidence of AEs in paediatric and adult clinical trials it is worth noting that the incidence of URTI (with or without pharyngitis and nasopharyngitis), bronchitis, pyrexia and vomiting are apparently more frequent among paediatric patients than in the adult population. The MAH attributes this misbalance to the fact that more objective events (such as those showing a higher incidence among paediatric patients) are more frequent in the paediatric population.

As requested, the MAH has included other URTI terms such as nasopharyngitis, pharyngitis, rhinitis, laryngitis, sinusitis, tonsillitis, viral sinusitis, and viral URTI, leading to a higher number of patients in each treatment arm. When all these terms were included the incidence of URTI is still slightly higher

among sildenafil treated patients compared to placebo (table 23) and it seems that this difference is mainly due to a high incidence of URTI in low weight patients (table 24).

Table 23: URTI Adverse Events in Study A1481131

	Treatment Group				
	Low N = 42	Medium N = 55	High N = 77	Combined N = 174	Placebo N = 60
Subjects, n (%)	11 (26.2)	16 (29.1)	16 (20.8)	43 (24.7)	14 (23.3)
N Adverse Events*	14	20	18	52	15

*: If a subject had more than one same preferred term AEs reported, these AEs are counted as one event.

Table 24: Subjects with URTI Adverse Events in Study A1481131 by Weight Group

	Treatment Group				
Weight	Low N = 42	Medium N = 55	High N = 77	Combined N = 174	Placebo N = 60
≤ 20 kg, Subjects (%)	N/A	8/ 15 (53.3)	9/35 (25.7)	17/50 (34.0)	4/18 (22.2)
>20 kg subjects (%)	11/42 (26.2)	8/40 (20.0)	7/42 (16.7)	26/124 (20.1)	10/42 (23.8)

A higher incidence of all causality bronchitis and pneumonia was also reported (4.6% and 2.9% in the combined sildenafil group vs 1.7% and 0 in the placebo group, respectively). None of these cases were considered treatment related by the investigator, and also a causal relationship is not foreseen. However, considering that at least bronchitis is included as a common AE in the adult data, the MAH is requested to submit further analysis (see further discussion under RMP section)

1.7.3. Severe adverse events and deaths.

Treatment related SAEs (convulsion, hypersensitivity, stridor, hypoxia, ventricular arrhythmia, respiratory tract infection, and unspecified death (included in the total of 23 deaths)) were reported by 6 subjects.

In total 23 deaths have been reported, of which 17 deaths have been reported in the safety database (not including the 2 subjects who died before they were randomised into study A1481131). None of the deaths were considered to be treatment related by the investigator. An additional 6 deaths, none of which were on study treatment, were reported when subjects who discontinued were followed up for survival status. The number of deaths in each of the treatment groups at the cut-off for this submission is 13/100 (13%) in the high dose treatment group, 7/74 (9%) in the medium dose treatment group and 3/55 (5%) in the low dose treatment group (table 25).

Table 25: Studies A1481131 and A1481156 Combined: Deaths Resulting from an On-Treatment Serious Adverse Events

Sex/ Age (years)	Weight (kg)	Total Daily Dose (mg)	Cause of Death Preferred Term	Study Day of Death Relative to A1481131 Baseline	Causality
Sildenafil Low/Low Dose					
M/11	23	120	Cardiac failure	535	Disease under study
F/17	52.6	120	Pulmonary haemorrhage	NR[a]	Not reported
M/18	52	80[b]	Cardiac failure	861	Disease under study
			Respiratory failure	861	Disease under study
Sildenafil Med/Med Dose					
M/13	50	120[b]	Pulmonary haemorrhage	430	Disease under study
M/18	38	20[b]	Death[c]	861	Other – unknown
M/14	42	60	Right ventricular failure	471	Disease under study
F/19	47	120	Pulmonary hypertension	1407	Disease under study
Sildenafil High/High Dose					
F/7	16.6	20[b]	Pulmonary hypertension	324	Disease under study
F/7	20	120[b]	Sudden cardiac death	1101	Disease under study
F9	15	60	Cardiac arrest	1112	Disease under study
F/3	10.5	60[b]	Pulmonary hypertension	370	Disease under study
F/12	31	120[b]	Cardiac failure	471	Disease under study
F/14	34	120[b]	Ventricular fibrillation	604	Other - vomiting during gastroenteritis stopped action of antiarrhythmic drug
M/16	55	240	Pulmonary hypertension	1191	Disease under study
M/14	35.8	40[b]	Cardiac failure	469	Other illness – bronchitis
F/19	48	80[b]	Cardiac failure	1093	Disease under study
Placebo/High Dose					
F/12	42	120	Death	815	Not reported
			Respiratory arrest	815	Not reported

The interim results of the study A1481156 raised concerns about a possible relationship between increased sildenafil doses and decreased survival and additional data were therefore provided during the procedure. As of 11 October 2010, 31 deaths were reported, whether on-treatment or reported as part of the survival follow-up. The incidence of deaths in the high, medium and low dose groups were 17% (17 of 100), 12% (9 of 74) and 9% (5 of 55) respectively. None of the deaths were considered to be treatment-related by the investigator. The majority of deaths were associated with functional class III or IV at baseline and primary pulmonary hypertension aetiology. After careful clinical review of the disease courses and causes for death, no biologically plausible explanation for the observed imbalance of deaths related to sildenafil dose has been found. As a precautionary measure, the higher sildenafil doses are not recommended in paediatrics with PAH. This information is included in section 5.1, in the subsection related to long-term extension data with a cross reference to section 4.2 of the SmPC.

The incidence of subjects with at least one SAE and the estimated number of subjects experiencing an SAE per 100 years is given below for each treatment sequence in Table 26.

Table 26: Estimated Number of Subjects Experiencing SAEs per 100 Years Exposure by A1481131/A1481156 Treatment Sequence – Studies A1481131 and A1481156

Treatment Sequence	Total Study Drug Exposure (Years)	Total Number of Subjects Reporting SAEs n/N (%)	Estimated Number of Subjects adjusted for exposure (n/ 100 years)
Sildenafil low/low dose	140.0	12/42 (28.6)	8.57
Sildenafil medium/medium dose	195.4	28/55 (50.9)	14.33
Sildenafil high/high dose	257.4	33/77 (42.9)	12.82
Placebo/low dose	45.9	1/13 (7.7)	2.18
Placebo/medium dose	66.7	4/19 (21.1)	6.00
Placebo/high dose	79.9	9/23 (39.1)	11.26
Placebo/non-randomised	1.2	0/5	0

Source: Table 9.3.618N and A1481156 November 2010 DMC Table 6.1.1.1

The estimated number of subjects/100 years exposure experiencing an SAE in the low/low treatment sequence (8.57) is fewer than the approximately equivalent medium/medium (14.33) and high/high (12.82) treatment sequences. The stratified hazard ratios (CI) by Cox regression stratified by weight group comparing high with low and medium with low are 1.71 (0.88, 3.36) and 1.69 (0.87, 3.27) respectively. As the confidence intervals both include 1 then one can't preclude this being a chance finding. The HR for SAEs between the high and low-dose of sildenafil (1.71) is consistent with the HR for the frequency of patients experiencing clinical worsening events (1.59) and death (1.9; 17% vs. 9%).

Discontinuation due to adverse events

Dose Reductions or Temporary Discontinuations Due to Adverse Events
Over both A1481131 and A1481156, 31/234 subjects (13.2%) had 1 or more dose reductions or temporary discontinuation due to an AE. The AE of stridor (sildenafil high/high dose) resulted in both a temporary discontinuation and a subsequent permanent discontinuation. For 9/234 subjects (3.8%), such reductions/discontinuations were due to treatment-related AE. Six of these subjects were on the sequence sildenafil high/high dose.

Permanent discontinuations. Overall, 12 subjects permanently discontinued from Studies A1481131 and A1481156 combined due to AEs. These discontinuations were mainly considered to be related to the disease under study. Adverse events that were considered related to study drug included episodes of weight decreased, stridor, dyspnoea, hypoxia, and rash macular.

Specific Adverse Events.
Bleeding Events.
In study A1481131 the overall risk of bleeding events was 11.5% in the combined sildenafil arm and 10% in the placebo arm. During Study A1481156, an additional 23 bleeding events were reported by 20 subjects: 3 events occurred with the low-dose [epistaxis (1); anemia (1) menorrhagia (1)]; 12 events occurred with the medium dose [epixtasis (6); haemoptysis (2), haematemesis (1), petechiae (1), severe pulmonary haemorhage (1), and subdural haematoma (1)] and 8 events occurred with the high dose [epistaxis (4); anaemia (2), severe haemoptysis (1), and INR increased (1).
In summary, twenty subjects (11.5%) in the sildenafil groups combined had a total of 23 events, compared with 6 subjects (10.0%) with 6 events in the placebo group. The incidence of bleeding events did not increase with sildenafil dose. There were no severe adverse events and four moderate adverse events (2 in the high-dose sildenafil group and 2 in the placebo group); all other events were mild. The overall risk of bleeding events and events associated with increased risk of bleeding was lower in the placebo-controlled paediatric PAH study A1481131 (11.5% sildenafil, 10.0% placebo) than that in adults.

Ocular Events
All-causality AEs related to the eye reported in the placebo-controlled study were reported for 20 subjects receiving sildenafil (11.5%) and 9 subjects (15.0%) receiving placebo.
In both studies A1481131 and A1481156 combined, colour vision monitoring for 5 subjects had a worsening from baseline. These findings were similar to those reported in the adult clinical trials.

Paediatric Development Assessments

Studies A1481131 and A1481156 included assessments of cognitive and motor development. Most subjects were not limited in either their cognitive or their motor development at baseline. Changes in cognitive or motor development from baseline to Week 16 (end of Study A1481131) or at Week 52 in Study A1481156 were infrequent. The number of reports of deterioration was similar to the number of reports of improvement, and there were no apparent differences between treatment groups.

Regarding the long term safety of these patients, the submitted data do not indicate any specific safety issue that could be related to this age group, concerning ocular, motor or cognitive development.

Table 27: Summary of Adverse Events (All Causality), by Age and Ability Subgroups

Subgroup		Sildenafil	Placebo
< 7 year	N	47	16
	Subjects with AEs	34 (72%)	12 (75%)
	Subjects with SAEs	6 (13%)	2 (13%)
≥7 year NDA	N	42	14
	Subjects with AEs	31 (74%)	8 (57%)
	Subjects with SAEs	1 (2%)	0
≥7 year DA	N	85	30
	Subjects with AEs	61 (72%)	20 (67%)
	Subjects with SAEs	2 (2%)	0

Post marketing experience

Post-marketing data from the MAH's safety database has been reviewed during 8 periods since the approval of Revatio. The first seven periods are covered by the PSURs in Europe and the eighth period relates to a post-marketing line listing for the period 01 June 2009 through 30 October 2009 generated from the MAH's safety database specifically for this submission. Regarding the last period, of the 79 cases in patients treated with sildenafil for PAH that included information about the age of the patient, 11 (21 events) were in patients 17 years of age or younger, including 5 infants (less than 24 months of age), 4 children (2 to 11 years of age) and 2 adolescents (11 to 17 years of age). Seven of the cases were serious, and one case had a fatal outcome. A 9-month-old male born with trisomy 21 was hospitalized for pulmonary haemorrhage considered related to sildenafil treatment. This event resolved, but he died 20 days later of pneumonia, which was not considered related to sildenafil treatment. The assessment of the PSURs did not warrant changes in the current reference safety documentation regarding use in children (table 28).

Table 28: Summary of Post-Marketing Adverse Events Reported to the MAH during the period of 01 June 2009 through 30 October 2009

	All Ages			Age 17 and under		
Reporting Period	**Number of Cases (Number of events)**	**Number (%) of serious cases**	**Deaths (%)**	**Number of Cases (Number of events)**	**Number (%) of serious cases**	**Deaths (%)**
01 June 2009 through 30 October 2009	134 (235)	117 (87%)	76 (57%)	11 (21)	7 (64%)	1 (9%)

Post-Marketing Safety

As in the adult PAH population, AEs that can be attributed to the underlying PAH condition (e.g., dyspnoea, hypoxia, signs and symptoms of right cardiac failure) were found to dominate the clinical picture. Similarly events associated to the vasodilatory effect of sildenafil (e.g., headache, flushing) have been amongst the most frequently reported. In a number of cases, other PAH treatments such as bosentan, beraprost, and epoprostenol were associated with sildenafil in the therapeutic management of paediatric PAH (due to the severity of this condition). The role of these agents in the occurrence of some events cannot be ruled out (e.g. increased LFTs due to bosentan). The nature and the severity of the AEs remained similar over time.

A pharmacovigilance plan for assessing and monitoring safety in paediatric patients with PAH is described in the RMP.

It is accepted that post-marketing information for Sildenafil did not identify any additional risks for the paediatric population.

1.7.4. Discussion on clinical safety

The paediatric safety database for oral sildenafil is comprised by 234 treated subjects in the placebo controlled Study A1481131. The majority (228; 97.4%) completed 16 weeks of per protocol treatment in Study A1481131, and 220 of these subjects continued into the extension Study A1481156.

Study A1481131

In study A1481131, treatment-emergent AEs were experienced by similar proportions of subjects in each treatment group (66.7 to 80.0%) but the number of adverse events increased when sildenafil doses increased (All causality: low dose 77 vs medium dose 129 vs high dose 142; Treatment related: low 23 vs. medium 31 vs high 48). The most frequently reported AEs in the sildenafil combined group were headache (13.2% of subjects), upper respiratory tract infection (11.5% of subjects), pyrexia (11.5% of subjects) and vomiting (10.9%), which were generally higher than the corresponding rates for placebo. Thee were 19 SAEs in 11 subjects: sildenafil low-dose (4 SAEs in 1 subject); sildenafil medium-dose (3 SAEs in 1 subject), sildenafil high-dose (10 SAEs in 7 subjects) and placebo (2 SAEs in 2 subjects). Two of these SAEs (stridor and pyrexia with gastroenteritis), both in the sildenafil high-dose group, were considered as treatment-related. There were no deaths during study A1481131.

Although in study A1481131, the number of adverse events showed a trend to increase at increased sildenafil doses, no trend was observed when the number of AEs (all causality or treatment-related) was adjusted for exposure. Therefore, no significant exposure-safety relationship can be concluded from the safety data for the different dose groups.

Study A1481156

In study A1481156, the most common AEs were URTI (58/229 subjects, 25.3%), headache (53/229 subjects, 23.1%), and vomiting (52/229 subjects, 22.7%). An apparent dose response was observed for some AEs (eg, URTI, nausea, pneumonia), with a greater incidence of these AEs in the medium and high dose groups compared to the low dose groups. Many of these adverse effects occurred in the low weight subgroup (8-20 kg). The number of deaths in each of the treatment groups at the cut-off for this submission is 13/100 (13%) in the high dose treatment group, 7/74 (9%) in the medium dose treatment group and 3/55 (5%) in the low dose treatment group. In the interim A1481156 clinical study report a dose-related increase in the rate of children with SAEs is observed (all causality: low dose 7.7% vs. medium dose 15.8% vs. high dose 26.1%). Most of these SAEs correspond to cardiac and respiratory SAEs .A total of 7 SAEs occurring during study A1481156 have been considered as treatment-related (sildenafil low-dose: 0; sildenafil medium-dose: 1; sildenafil high-dose: 6). In study A1481131 the overall risk of bleeding events was 11.5% sildenafil and 10% placebo. During Study A1481156, an additional 23 bleeding events were reported by 20 subjects: 3 events occurred with the low-dose, 12 events occurred with the medium dose and 8 events occurred with the high dose. In studies A1481131 and A1481156 combined, colour vision monitoring for 5 subjects had a worsening from baseline. These findings were similar to those in the adult clinical trials.

1.7.5. Conclusion on clinical safety

The review of the paediatric clinical trial cases did not identify any new safety signal that would appear to be specific to the paediatric population, either considered as a whole or independently as its 3 components, i.e. neonates, infants, and children.

The adverse event profile for sildenafil in paediatric PAH trials was consistent with the adverse event profile of sildenafil in adult PAH clinical trials and for marketed Revatio in adults with PAH. Review of the published literature and of post-marketing information for Revatio did not identify any additional safety risks for the paediatric population.

Sildenafil was generally well tolerated at all doses studied in paediatric patients with PAH. In the placebo-controlled clinical trial, there were no treatment emergent deaths, and few discontinuations for adverse events.

In the combined sildenafil treatment groups, adverse drug reactions of vomiting, pyrexia, cough, and erection increased were experienced by more subjects than the placebo treatment group (5.2%, 1.7%, 1.7% and 9.0% compared to 1.7%, 0, 0 and 0, respectively).

Most of the serious adverse events reported were not considered treatment related. There was no evidence from the long-term safety study that frequently observed adverse events, or adverse events considered specific to sildenafil treatment, increased with time.

Ocular and developmental assessments during the studies of oral sildenafil in PAH did not reveal any significant findings.

In conclusion, the data presented support the use of Revatio in paediatric patients. Age appropriate formulations will also be made available specifically for the treatment of paediatric patients.

1.8. Risk Management Plan

An updated RMP was submitted in this type II variation.

Prior to this application, safety was limited in paediatric patients with PAH. The currently available paediatric safety data is discussed below.

- ***Non-clinical safety specifications***

With respect to the paediatric non-clinical safety specification, a full toxicology program was conducted for the sildenafil citrate registration package, with oral studies of duration up to 12, 18 and 24 months in dogs, mice and rats respectively. Embryofoetal, fertility and peri/ post- natal studies were also carried out. In addition, i.v. sildenafil base was administered to rats for 13 days at doses up to 10 mg/kg/day and to dogs for 14 days at doses up to 10 mg/kg/day. Intravenous sildenafil citrate was administered to rats and dogs for 1 month at doses up to 4 mg/kg/day. An intra-arterial irritation study has been conducted in rabbits. None of these studies produced findings that would preclude administration of intravenous sildenafil citrate to a paediatric population for the treatment of pulmonary hypertension and no additional toxicology studies in juvenile animals are proposed given the pharmacological profile of sildenafil.

- ***Clinical safety specifications***

Exposure data for the trials performed in paediatric patients (<17 years) has been added to the RMP. The post-marketing exposure in patients between 0 and 18 years old is 14429 patient-years.

A literature review for sildenafil citrate in PAH identified 23 paediatric controlled trials, case series and case reports dating from 1999 to 2009. Paediatric patients aged from 26 weeks old (gestational age) to 18 years are recorded as receiving sildenafil. The dose of sildenafil ranged from 0.25 mg/kg to 2 mg/kg and duration of therapy ranged from a single dose to over 15 months. In conclusion, review of the literature did not reveal specific additional safety issues for paediatric patients.

Two paediatric studies i.e. study A1481131 and its long-term extension study A1481156, constitute the clinical support to the submission for the use of Revatio in paediatric PAH.

The exclusion criteria are considered missing information. For most exclusion criteria statements are present in the SmPC of Revatio in the sections 4.3, 4.4, 4.5 and 4.6.

- ***Pharmacovigilance Plan***

The only action proposed by the MAH regarding safety in the paediatric population is data from ongoing clinical studies and enhanced pharmacovigilance using a data capture aid. Regarding clinical studies the only study ongoing is a long extension study (A1481156) that will continue until sildenafil is approved for marketing for treatment of PAH in children.

Risk Minimisation Plan

No population specific risk was identified in the clinical paediatric program that would justify pharmacovigilance/risk management activities beyond those currently in place for the adult population. However, the need for a clear and appropriate prescribing information to ensure safe use of the product has been addressed in the proposed product label, which focuses on: 1) the paediatric dosage recommendations, including the specifics of the extemporaneous preparation developed to ensure dosage flexibility in paediatric patients below the age of 6 years, and 2) the AEs reported in the paediatric trials that appear to be somewhat specific to that population.

For paediatric patients aged 1 to 17 years old, the recommended dose in patients ≤20 kg is 10 mg (1 ml of compounded suspension) 3 times a day and for patients >20 kg is 20 mg (2 ml of compounded suspension or 1 tablet) 3 times a day.

The extemporaneous preparation of a compounded suspension refers to a validated manipulation, by a trained pharmacist, of the authorized commercial sildenafil citrate tablet dosage form. The licensed pharmacist manipulation at the time of dispensing and the quality of the product prepared in this manner is validated, by the MAH during development, so that a robust product is delivered to the patient. Adopting this extemporaneous preparation approach enables the most rapid provision of a safe and effective preparation of assured quality for administration to the paediatric patient. To ensure final product quality and patient safety, appropriate quality data (e.g. stability, dose uniformity) and specific, detailed and standardized methods of preparation are provided in the proposed product SmPC to support the manipulation of the adult dosage form into the paediatric medicine. Compounding of an oral suspension, by a licensed pharmacist, following this procedure, will provide one patient with enough medication for a 30-day course of treatment (1 ml dosing volume, 10 mg dose) or a 15-day course of treatment (2 ml dosing volume, 20 mg dose).

Finally, based on the safety profile of the product established in the paediatric clinical development program several AEs associated with the use of Revatio appear to be somewhat more specific to the paediatric population, as compared to the safety profile derived from the adult clinical trials (i.e. Vomiting, Pyrexia, URTI). In the combined sildenafil treatment groups Vomiting, Pyrexia, URTI, and Erection increased were more frequent than in the placebo group.

The MAH was also asked to perform an analysis of the main characteristics of patients with URTI in the different arms of treatment but this analysis is not included. Additionally, the MAH does not provide a discussion of the possible reasons for the differences in the incidences of URTI. A higher incidence of all causality bronchitis and pneumonia was also reported. It is acknowledged that none of these cases were considered treatment related by the investigator, and also a causal relationship is not foreseen. However, considering that at least bronchitis is included as a common AE in the adult data, the MAH is requested to include other infections of the respiratory system in the requested analysis. In order to retrieve all cases related to respiratory infections, the MedDRA HLGT "Respiratory tract infections" should be used as search criteria and the analysis should be performed according to the PT. A statistic analysis of the differences in the incidence of different AEs should be applied:

1) To perform an analysis of the main characteristics of patients with URTI as well as patients with bronchitis and pneumonia and other possible AEs suggestive of a respiratory infection in the different arms of treatment of study A1481131. In order to retrieve all cases related to respiratory infections, the MedDRA HLGT "Respiratory tract infections" should be used as search criteria and the analysis should be performed according to the Preferred Term (PT). A statistical analysis of the differences in the incidence of different AEs should be applied

2) To discuss the possible reasons behind the differences in the incidences of URTI, bronchitis, pneumonia and other possible AEs suggestive of a respiratory infection.

The CHMP requested the MAH to commit to the submission an updated RMP, which should contain the requested analysis regarding upper and lower respiratory tract infections, and also include URTI, Bronchitis, and Pneumonia as potential risks in paediatric patients. (see letter of undertaking with commitment for submission as part of the next PSUR (July 2011).

In conclusion, this updated RMP version 5.3 discussed in this application is considered acceptable . However an updated RMP should further be submitted taking into account the above described comments.

1.9. Similarity with authorised orphan medicinal products

The CHMP is of the opinion the Revatio is not similar to iloprost (Ventavis), treprostinil (Remodulin), bosentan (Tracleer), ambrisentan (Volibris) within the meaning of Article 3 of Commission Regulation EC No. 847/2000 for the same therapeutic indication. (see annex)

1.10. Update of the Product information

As the result, the CHMP agreed with the changes in the SmPC as follows ;

1.10.1. Update of the Summary of Product Characteristics

The changes in the SmPC described below concern only the oral formulation unless otherwise mentioned.

- Update of section 4.1

The CHMP agreed to update the indication and add the following information.

Paediatric population

Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease (See section 5.1).

- Update of section 4.2

Posology
TTPaediatric Population
The safety and efficacy of Revatio in children below 1 year of age has not been established. No data are available.

For paediatric patients aged 1 year to 17 years old, the recommended dose in patients ≤ 20 kg is 10 mg (1 ml of compounded suspension) three times a day and for patients > 20 kg is 20 mg (2 ml of compounded suspension or 1 tablet) three times a day. Higher doses are not recommended in paediatric patients (see section 5.1).

For instructions on compounding of the medicinal product before administration, see section 6.6.

- Update of section 4.4

Two paragraphs are amended following the results of the paediatric studies. The final agreed text is detailed below :

The efficacy of Revatio has not been established in patients with severe pulmonary arterial hypertension (functional class IV). If the clinical situation deteriorates, therapies that are recommended at the severe stage of the disease (eg, epoprostenol) should be considered (see section 4.2). The benefit-risk balance of sildenafil has not been established in patients assessed to be at WHO functional class I pulmonary arterial hypertension.

Studies with sildenafil have been performed in forms of pulmonary arterial hypertension related to primary (idiopathic), connective tissue disease associated or congenital heart disease associated forms of PAH (see section 5.1). The use of sildenafil in other forms of PAH is not recommended.

This amendment is introduced also in the IV formulation.

- Update of section 4.5

The following information is added:

Paediatric Population
Interaction studies have only been performed in adults.

- Update of section 4.8

Paediatric Population

In the placebo-controlled study of Revatio in patients 1 to 17 years of age with pulmonary arterial hypertension, a total of 174 patients were treated three times a day with either low (10 mg in patients > 20 kg; no patients ≤ 20 kg received the low dose), medium (10 mg in patients ≥ 8-20 kg; 20 mg in patients ≥ 20-45 kg; 40 mg in patients > 45 kg) or high dose (20 mg in patients ≥ 8-20 kg; 40 mg in patients ≥ 20-45 kg; 80 mg in patients > 45 kg) regimens of Revatio and 60 were treated with placebo.

The adverse reactions profile seen in this paediatric study was generally consistent with that in adults (see table above). The most common treatment-related AEs (TRAEs) that occurred (with a frequency ≥ 1%) on Revatio (combined doses) with a frequency ≥ 1% over placebo, in the paediatric study were vomiting (5.2%), cough, pyrexia, (each 1.7%) and nausea, abdominal pain lower, abdominal pain upper, photophobia (each 1.1%). TRAEs erection increased and spontaneous penile erections occurred with a combined frequency of 9.0% in male subjects in the combined sildenafil group. Most of these TRAEs were mild or moderate in severity.

220 subjects who completed the 16 week placebo-controlled study entered a long-term extension study. Subjects who had been on active therapy continued in the same treatment regimen, whilst those who had been on placebo therapy for 16 weeks were randomised to low, medium or high dose groups of sildenafil.

At two years 184 subjects were still participating in the extension study. Over the first two years of sildenafil dosing a total of 4 of the 229 subjects who received sildenafil had a serious adverse reaction; 1 of 74 subjects in the medium dose group and 3 of 100 subjects in the high dose group. These 4 events were convulsion, hypersensitivity, hypoxia and ventricular arrhythmia.

From a data cut with a median subject duration of treatment of 2.2 years (range: 0 to 5.0 years) the most frequently reported treatment related AEs were: headache (13.2%), erection increased (9.0%), vomiting (6.8%), abdominal pain (3.4%) cough and dyspepsia (each 2.6%).

- Update of section 5.1

<u>Paediatric Population</u>
A total of 234 subjects aged 1 to 17 years were treated in a randomised, double-blind, multi-centre, placebo controlled parallel group, dose ranging study. Subjects (38% male and 62% female) had body weight ≥ 8 kg, and had primary pulmonary hypertension (PPH) [33%], or PAH secondary to congenital heart disease [systemic-to-pulmonary shunt 36%, surgical repair 30%]. 63 of 234 (27 %) patients were < 7 years old (sildenafil low dose = 2; medium dose = 17; high dose = 28; placebo = 16) and 171 of 234 (73%) patients were 7 years or older (sildenafil low dose = 40; medium dose = 38; and high dose = 49; placebo = 44). Most subjects were WHO Functional Class I (75/234, 32%) or II (120/234, 51%) at baseline; fewer patients were Class III (35/234, 15%) or IV (1/234, 0.4%); for a few patients (3/234, 1.3%), the WHO Functional Class was unknown.

Patients were naïve for specific PAH therapy and the use of prostacyclin, prostacyclin analogues and endothelin receptor antagonists was not permitted in the study, and neither was arginine supplementation, nitrates, alpha-blockers and potent CYP450 3A4 inhibitors.

The primary objective of the study was to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in paediatric subjects to improve exercise capacity as measured by the Cardiopulmonary Exercise (CPX) test in subjects who were developmentally able to perform the test, n = 115). Secondary endpoints included haemodynamic monitoring, symptom assessment, WHO functional class, change in background treatment, and quality of life measurements.

Subjects were allocated to one of three sildenafil treatment groups, low (10 mg), medium (10-40 mg) or high dose (20-80 mg) regimens of Revatio given three times a day, or placebo. Actual doses administered within a group were dependent on body weight (see Section 4.8). The proportion of subjects receiving supportive medications at baseline (anticoagulants, digoxin, calcium channel blockers, diuretics and/or oxygen) was similar in the combined sildenafil treatment group (47.7%) and the placebo treatment group (41.7%).

The primary endpoint was the placebo-corrected percentage change in peak VO_2 from baseline to week 16 assessed by CPX testing in the combined dose groups (Table 2). A total of 106 out of 234 (45%) subjects were evaluable for CPX test , which comprised those children ≥ 7 years old and developmentally able to perform the test. Children < 7 years (sildenafil combined dose = 47; placebo = 16) were evaluable only for the secondary endpoints. Mean baseline peak volume of oxygen consumed (VO2) values were comparable across the sildenafil treatment groups (17.37 to 18.03 mL/kg/min), and slightly higher for the placebo treatment group (20.02 mL/kg/min). The results of the main analysis (combined dose groups versus placebo) were not statistically significant (p = 0.056) (see Table 2). The estimated difference between the medium sildenafil dose and placebo was 11.33% (95%CI: 1.72 to 20.94) (see Table 2).

Table 2: Placebo Corrected % Change from Baseline in Peak VO2 by Active Treatment Group

Treatment Group	*Estimated Difference*	*95% Confidence Interval*
Low Dose (n=24)	*3.81*	*-6.11, 13.73*
Medium Dose (n=26)	*11.33*	*1.72, 20.94*
High Dose (n=27)	*7.98*	*-1.64, 17.60*
Combined Dose Groups (n=77)	*7.71 (p = 0.056)*	*-0.19, 15.60*

n=29 for placebo group
Estimates based on ANCOVA with adjustments for the covariates baseline peak VO2, etiology and weight group

Dose related improvements were observed with pulmonary vascular resistance index (PVRI) and mean pulmonary arterial pressure (mPAP). The sildenafil medium and high dose groups both showed PVRI reductions compared to placebo, of 18% (95%CI: 2% to 32%) and 27% (95%CI: 14% to 39%), respectively; whilst the low dose group showed no significant difference from placebo (difference of 2%). The sildenafil medium and high dose groups displayed mPAP changes from baseline compared to placebo, of -3.5 mmHg (95%CI: -8.9, 1.9) and -7.3 mmHg (95%CI: -12.4, -2.1), respectively; whilst the low dose group showed little difference from placebo (difference of 1.6 mmHg). Improvements were observed with cardiac index with all three sildenafil groups over placebo, 10%, 4% and 15% for the low, medium and high dose groups respectively.

Significant improvements in functional class were demonstrated only in subjects on sildenafil high dose compared to placebo. Odds ratios for the sildenafil low, medium and high dose groups compared to placebo were 0.6 (95% CI: 0.18, 2.01), 2.25 (95% CI: 0.75, 6.69) and 4.52 (95% CI: 1.56, 13.10), respectively.

Long term extension data

Subjects enrolled into the placebo-controlled study were eligible to enter a long term randomised extension study with an initial blinded phase followed by open label administration of sildenafil using low, medium and high dose groups. Dose titrations were permitted.

From a data cut > 7 years after the study start 31 deaths were reported, whether on-treatment or reported as part of the survival follow-up. The incidence of deaths in the high, medium and low dose groups were 17% (17 of 100), 12% (9 of 74) and 9% (5 of 55) respectively. None of the deaths were considered to be treatment-related by the investigator. The majority of deaths were associated with functional class III or IV at baseline and primary pulmonary hypertension aetiology. The Kaplan-Meier estimate of survival at 2 years, in those subjects > 20kg in weight at baseline, was estimated as 95%, 95% and 92% for subjects in the low, medium and high dose groups respectively. The Kaplan-Meier estimate of survival at 2 years, in those subjects ☐ 20kg in weight at baseline, was estimated as 100% and 94% for subjects in the medium and high dose groups respectively.
These long-term data did not identify an additional survival benefit with higher doses of sildenafil compared to lower doses in paediatrics with PAH, therefore higher sildenafil doses are not recommended in paediatric patients with PAH (see also section 4.2).

Peak VO2 was assessed 1 year after the start of the placebo-controlled study. Of those Revatio treated subjects developmentally able to perform the CPX 50/85 subjects (59%) had not shown any deterioration in Peak VO2 from baseline. Similarly 123 of 174 subjects (71%) who had received sildenafil during the placebo-controlled study had either maintained or improved their WHO Functional Class at 1 year.

The European Medicines Agency has deferred the obligation to submit the results of studies with Revatio in newborns with Pulmonary Arterial Hypertension (see section 4.2 for information on paediatric use).

- Update of section 5.2

Based on the PK/PD data provided the following paragraph is added :

Paediatric Population
From the analysis of the pharmacokinetic profile of sildenafil in patients involved in the paediatric clinical trials, body weight was shown to be a good predictor of drug exposure in children. Sildenafil plasma concentration half-life values were estimated to range from 4.2 to 4.4 hours for a range of 10 to 70 kg of body weight and did not show any differences that would appear as clinically relevant. C_{max} after a single 20 mg sildenafil dose administered PO was estimated at 49, 104 and 165 ng/ml for 70, 20 and 10 kg patients, respectively. C_{max} after a single 10 mg sildenafil dose administered PO was estimated at 24, 53 and 85 ng/ml for 70, 20 and 10 kg patients, respectively. T_{max} was estimated at approximately 1 hour and was almost independent from body weight.

- Update of section 6.6

Compounding of an extemporaneously prepared oral suspension from Revatio 20 mg tablets (final concentration 10 mg/mL)

Compounding of an oral suspension, by a pharmacist, following this procedure, will provide one patient with enough medication for a 28-day course of treatment (1 mL dosing volume, 10 mg dose) or a 14-day course of treatment (2 mL dosing volume, 20 mg dose). The compounding of the Revatio suspension from Revatio 20 mg tablets uses Ora-Sweet and Ora-Plus diluents. Ora-Sweet and Ora-Plus® are registered trademarks of Paddock Laboratories.

Compounding Instructions for a Pharmacist

1. *Ensure Ora-Sweet and Ora-Plus have been equilibrated to room temperature.*
2. *Count 62 (sixty two) x 20 mg Revatio tablets.*
3. *Using a mortar and pestle, crush these 62 tablets, 2-10 tablets at a time, into a fine powder.*
4. *Measure out 30 mL Ora-Plus (cloudy white liquid), allowing time for any air bubbles to dissipate.*
5. *Add a portion (15-20 mL typical) of Ora-Plus from step 4 to the mortar and mix into a thick homogeneous paste. More Ora-Plus from step 4 may be added if necessary.*
6. *Transfer the paste to an amber glass or high density polyethylene (HDPE) bottle (≥ 150mL volume)*
7. *Rinse the mortar and pestle with the remaining Ora-Plus from step 4 and transfer rinses to the bottle to ensure complete transfer of the paste.*
8. *Measure 90 mL Ora-Sweet (clear pink liquid) allowing time for any air bubbles to dissipate.*
9. *Transfer approximately ½ the volume of the Ora-Sweet from step 8 to the bottle containing the formulation prepared above.*
10. *Cap bottle and shake vigorously for a minimum of 30 seconds.*
11. *Transfer the remaining Ora-Sweet from step 8 to the bottle and shake vigorously again for a minimum of 30seconds to achieve an homogenous suspension.*

    Put an ancillary label on the bottle warning "Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency, should not take this medicine". The ancillary label should also indicate "Shake well for a minimum of 10 seconds before each dosing".

12. *Include the patient's name, dosing instructions, expiry date , and drug name.*
13. *Instruct the person who is to administer the compounded product that any remaining material following completion of therapy must be discarded by either affixing an ancillary label to the bottle or adding a statement to the pharmacy label instructions.*
14. *Place an appropriate expiration date label according to storage condition (see Section 6.3).*

Note: The storage condition for the compounded oral suspension, using the Oraplus®/Orasweet® vehicle combination, in amber glass and HDPE bottles demonstrates stability for 28 days in a refrigerator at 2 to 8ºC. Stability studies have not been conducted or verified with other vehicles or bottle types.

Oraplus® (cloudy white liquid) contains: purified water, microcrystalline cellulose, sodium carboxymethylcellulose, xanthan gum, carrageenan, sodium phosphate, citric acid , antifoam emulsion and is preserved with methylparaben and potassium sorbate.

Orasweet® (clear pink liquid) contains: purified water, sucrose, glycerin, sorbitol, citric acid and sodium phosphate, flavouring and is preserved with methylparaben and potassium sorbate.

Consider dispensing the suspension with an appropriate graduated oral syringe for measuring the required volumes of suspension. If possible, mark or highlight the graduation corresponding to the appropriate dose (1 mL or 2 mL) on the oral syringe for each patient.

- Update of the Product information following QRD review

As agreed with the CHMP during the renewal application, the product information concerning both tablets and IV formulation is also updated taking into account QRD comments.

Furthermore, the MAH agreed to commit to update the paediatric statements of the product information according to the QRD review during the next variation.

Furthermore, the version number of the RMP (version 5.3) is updated taking into account the assessment performed in this application.

1.10.2. Update of the Package leaflet

Consequential changes related to the paediatric additions are introduced in the Package Leaflet.

2. Overall conclusion and benefit/risk assessment

The main study in the current application study A1481131 is the largest placebo-controlled paediatric study conducted so far, recruiting around 230 drug-naive patients and lasting 5 years.

The pivotal study A1481131 was a double-blind, multi-center, placebo-controlled parallel-group, dose-ranging paediatric study in PAH subjects, aged 1 to 17 years, body weight ≥8 kg, with different doses of sildenafil for 16 weeks. The primary objective was to assess peak VO2 in subjects who were able to perform the CPX test. However, all subjects who entered the study were assessed for haemodynamics, WHO functional class and the QoL measurements. A total of 234 subjects were treated with one of the 3 sildenafil doses (low, intermediate, high; according to body-weight ranges) or placebo and 115 children were able to perform CPX testing.

Interim efficacy and safety data from Study A1481156 the long-term extension study including subjects who completed Study A1481131 are also provided to support the above data.

The proposed dose based on the PK/PD simulations is accepted. The medium dose shows the best results in exercise testing accompanied with an acceptable safety profile.

The choice of endpoints in adult PAH is a recognized problem, and is even more complex in the paediatric population, due to the scarcity of patients and their inability to perform exercise testing.
Haemodynamic parameters are considered by some experts to be the appropriate primary endpoints for paediatric studies, considering the difficulty in performing exercise tests.
The main outcome Peak VO2 after cardiopulmonary exercise (CPX) testing has shown to be useful to assess patient prognosis and as a mean to quantify functional capacity, although experience is limited at present. Therefore, the peak VO2 should be interpreted in association with other harder endpoints (i.e., mortality, time to clinical worsening) and invasive haemodynamic measurements, leading to additional post hoc analysis requested to the applicant during the procedure.

It is concluded that efficacy data based on improvement of exercise capacity or pulmonary haemodynamics support an indication for the treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

The currently proposed indication reflects the results of the paediatric study and is generally formulated in line with the adult indication, except for omitting the WHO classification. The CHMP opted for this omission as the representation of the paediatric study (more WHO I and less WHO III) is different from that shown in adult studies. Furthermore, the ESC treatment guideline for PAH does not recommend specialized intervention in WHO I, however, this is mainly based on adult data. In the A1481131 study, improvement in haemodynamic parameters was shown in all three functional classes,

but results on VO2 max were inconsistent. There are experts who advocate early intervention in paediatrics (earlier than WHO II) considering that deterioration in paediatric patients is more rapid. However the number of patients with WHO 1 in the pivotal A1481131 study is too limited for any definite conclusions on the Benefit/Risk in this specific subgroup.

No new safety issues were identified with long term use of sildenafil in paediatric PAH patients.

It is important to highlight that the approval of this suspension for extemporaneous formulation is an interim measure temporally accepted. The MAH has committed to develop a suitable age appropriate formulation in a form of a powder for oral suspension (POS) which is currently under development.

In conclusion, based on the data provided in this application, the CHMP considers that the benefit/risk of Revatio is positive in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.

3. Conclusion

On 17 March 2011 the CHMP considered the following variation(s) for Revatio 20mg tablets to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, annex II, labelling and Package Leaflet

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

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

Follow-up measures undertaken by the marketing authorisation holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

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

Area[1]	Description	Due date[2]
Clinical	The MAH is requested to provide the final results of the ongoing study A1481156	Q1, 2012
Quality	The MAH is commits to develop and application for an age appropriate formulation (powder for oral suspension)	Q32011
Pharmacovigilance	The MAH commits to conduct and provide thefollowing: 1) To perform an analysis of the main characteristics of patients with URTI as well as patients with bronchitis and pneumonia and other possible AEs suggestive of a respiratory infection in the different arms of treatment of study A1481131. In order to retrieve all cases related to respiratory infections, the MedDRA HLGT "Respiratory tract infections" should be used as search criteria and the analysis should be performed according	To be submitted as part of an updated RMP accompanying the next expected PSUR # 9 (due July 2011).

	to the Preferred Term (PT). A statistical analysis of the differences in the incidence of different AEs should be applied 2) To discuss the possible reasons behind the differences in the incidences of URTI, bronchitis, pneumonia and other possible AEs suggestive of a respiratory infection.	
QRD	The MAH commits to incorporate the QRD changes identified by the EMA during application II/028 (paediatric application) into Annex I, II & III as appropriate.	Next variation after CHMP opinion for variation II/028 which involves Annex I, II & III updates

4. EPAR changes

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

EPAR scope:

Update of Summary of Product Characteristics, annex II, labelling and Package Leaflet to introduce a new indication in paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension.

The above extension of indication applies to the oral tablet formulation only.

Scientific discussion:

This application is based on quality and clinical data. The paediatric studies including clinical pharmacology data pertinent to this submission are Studies A1481134 and A1481157 with intravenous sildenafil in PAH (supportive for clinical pharmacology and safety data) and pivotal study A1481131 for PK/PD data with oral sildenafil, establishing population PK and PK-PD models, and driving the oral dose recommendation for the paediatric population. Interim data of study A1481156, the long term extension of study A1481131 are also supporting this application.

It is concluded that efficacy data based on improvement of exercise capacity or pulmonary haemodynamics support an indication for the treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.
The granted indication is as follows:

Paediatric population

Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

The granted indication concerns only the oral tablet pharmaceutical formation. The approval of this suspension for extemporaneous formulation is an interim measure temporally accepted. The MAH has committed to develop a suitable age appropriate formulation in a form of a powder for oral suspension (POS) which is currently under development.
In addition, minor amendments are introduced in the product information for both tablets and IV formulation based on QRD comments received from the renewal application.

[1] Areas: Quality, Non-clinical, Clinical, Pharmacovigilance.
[2] Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.