17 September 2020
EMA/526836/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Deltyba

International non-proprietary name: delamanid

Procedure No. EMEA/H/C/002552/II/0040

Note

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

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List of abbreviations

AUC	Area under the concentration-time curve
$AUC_{0\text{-}24h}$	Area under the mean concentration-time curve from time 0 to 24 hours
BID	twice daily (bis in die)
CHMP	Committee for Medicinal Products for Human use
C_{max}	Maximum (peak) plasma drug concentration
C_{min}	Minimum (trough) plasma drug concentration
DLM	Delamanid
DOT	Directly observed therapy
DPF	Delamanid paediatric formulation
ECG	Electrocardiogram
EMA	European Medicines Agency
ERA	Environmental risk assessment
GCP	Good Clinical Practice
IMP	Investigational medicinal product
INN	International non-proprietary name
MAH	Marketing authorisation holder
MDR-TB	Multidrug-resistant tuberculosis
NOAEL	No observed adverse effect level
OBR	Optimised background regimen
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PEC	Predicted environmental concentration
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PL	Package Leaflet
QTc	Corrected QT interval
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's fornula
SD	Standard deviation
SmPC	Summary of Product Characteristics
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TK	Toxicokinetic(s)
ULN	Upper limit of normal
WHO	World Health Organisation
XDR-TB	Extensively-drug resistant tuberculosis

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Otsuka Novel Products GmbH submitted to the European Medicines Agency on 26 August 2019 an application for a variation.

The following variation was requested:

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

Extension of indication to include adolescents and children above 6 years with a body weight of at least 30 kg. As a consequence, sections {4.1, 4.2, 5.1 and 5.2} of the SmPC and corresponding, relevant sections of the PL are updated accordingly. The updated RMP version 3.2 has also been submitted. Furthermore, the PI is being brought in line with the latest QRD template.

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

Information relating to orphan designation

Deltyba was designated as an orphan medicinal product EU/3/07/524 on 01/02/2008. Deltyba was designated as an orphan medicinal product in the following indication: Treatment of multi drug resistant tuberculosis.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0271/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0271/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

2. Scientific discussion

2.1. Introduction

Deltyba has a conditional marketing authorisation, obtained on 28 April 2014, for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. The recommended dose in adults is 100 mg twice daily (BID) for 24 weeks. Delamanid is a film-coated tablet for oral use. Deltyba has mycobacteria-specific antibacterial activity.

The PIP for delamanid in paediatric MDR-TB patients aims to determine whether delamanid plasma exposure in children of all ages with MDR-TB is similar to the efficacious plasma exposure in adults; thereby determining the appropriate paediatric dose (using both the adult and paediatric formulations) and documenting safety and tolerability. The PIP for Deltyba (PIP P/0271/2019, EMEA-001113-PIP01-10-M02) essentially consists of 3 clinical trials in addition to the paediatric formulation development and juvenile toxicity assessment: a pharmacokinetic (PK) trial (Trial 242-12-232) in children of all ages with MDR-TB on therapy with optimised background regimen (OBR), followed by a 24-month safety and tolerability extension trial (Trial 242-12-233) in the same patient population, and a bioavailability/bioequivalence trial (Trial 242-12-245) in adults to investigate the comparative bioavailability of the paediatric formulation (5- and 25-mg immediate-dissolving tablets) with the delamanid 50-mg tablet adult formulation. At the cut-off date of 13 Dec 2016, all children from the first two age groups (ages 6 - 17 years) have completed the 24-month safety and tolerability long-term Trial 242-12-233 including the 6-month delamanid treatment in conjunction with an OBR, the overall 6 month post-treatment and follow-up periods, and the additional 12-month treatment outcome follow-up period. The trial is still ongoing in younger children (age groups 0 - 2 and 3 - 5 years) and trial finalisation will be in March 2020 in agreement with the PIP. The aim of this Type II variation is to already extend the delamanid MDR-TB indication to children 6 to 17 years of age.

Childhood TB disease is different from adult TB disease. These differences include time from exposure to disease onset, epidemiologic differences in contagiousness, pathophysiology, bacillary load, and clinical and radiographic manifestations. Most cases of childhood TB have a short period between exposure to a contagious individual and manifestation of symptoms. Differences in the pathophysiology and clinical presentation of TB in children make diagnosis more challenging in children than in adults and definitions of latent infection and active disease are not as clear. Children are also at a much higher risk of progression to active disease than adults. This risk is greatest for infants and children under 2 years of age.

Infants have a particularly high rate of morbidity and mortality from TB. Children under the age of 5 years are frequently affected by peripheral lymphadenopathy and 65% to 75% of these children have a thoracic and mediastinal location. In a setting with a high incidence of TB and ongoing transmission, the most common clinical presentation of TB in young children, i.e., age ≤ 5 years, is likely to be pulmonary TB.

Older children and adolescents (> 10 years) often present with adult-type cavitary disease with a high bacillary load. Pleural TB typically has been considered a disease of adulthood and is estimated to comprise approximately 4% of disease cases. However, TB pleural effusions can complicate 12% to 38% of cases in children with untreated pulmonary TB. Pleural involvement is more common among adolescents, and the mean age at diagnosis is 13 years. Adult-type disease is a phenomenon that suddenly appears around puberty and is distinguished by cavitation that occurs predominantly in the lung apices.

Overall, the lifetime risk of progression from infection to active disease is 5% to 20% for immunocompetent older children and 40% to 50% for children in the first 2 years of life. Adolescents have a slightly higher risk of disease progression than adults.

The diagnosis of childhood TB is challenging. Microbiological confirmation is often not available due to the paucibacillary nature of disease and the difficulty of specimen collection (especially sputum) in younger children. The diagnosis usually relies on nonspecific clinical and radiologic signs, as well as a history of exposure (i.e., close contact with a TB case). Fever (possibly intermittent or low grade), weight loss or failure to thrive, and persistent cough for > 2 weeks are the most important clinical signs for pulmonary TB.

Children are diagnosed with either confirmed or presumed MDR-TB. Confirmed disease occurs when an organism is isolated from the child and is shown either genotypically or phenotypically to be resistant to isoniazid and rifampicin. Presumed disease occurs when TB is diagnosed in combination with either known contact with an MDR-TB case or after failure of appropriate first-line therapy when adherence has been verified. Incident cases of childhood TB reflect recent transmission, which implies that drug resistance patterns observed among paediatric TB cases reflect primary (transmitted) drug resistance within the community. If a child presenting with TB is a known contact of an adult with MDR pulmonary TB, the child is a probable MDR-TB case and should be managed accordingly.

Treatment of drug-resistant TB is long, expensive and associated with frequent adverse events. In children, treatment is further complicated by limited data on appropriate dosing and safety, and a lack of child-friendly formulations. New anti-TB drugs are urgently needed to improve treatment tolerability and outcome, particularly for MDR-TB cases with additional second-line drug resistance, for whom identifying at least four active drugs is difficult with the current armamentarium of drugs.

The principles for treating adults with MDR-TB have demonstrated over time that they generally apply to infants, children, and adolescents, and the regimens recommended by the WHO for childhood-type TB continue to be essentially the same as for adult-type TB.

Children with MDR-TB are managed in much the same way as adults, although there are some differences. Confirmation of MDR-TB may not be possible in children and child TB cases in recent close contact with an adult MDR-TB case or failing to respond to adherent first-line treatment should be empirically treated as MDR-TB cases. Because of the paucibacillary nature of early primary disease (contained primary lung lesion or uncomplicated hilar/mediastinal lymph node enlargement), these children may need fewer drugs and shorter durations of treatment, although there are no randomised studies to confirm this.

The EMA Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to *Mycobacterium tuberculosis* (EMA/CHMP/EWP/14377/2008 Rev. 1, 20 July 2017) gives the following recommendations on the paediatric population:

- The presentation and treatment of pulmonary tuberculosis is similar in adults and paediatric patients aged from approximately 10 years so that an extrapolation of safety and efficacy data obtained from adults is acceptable. Sponsors may also consider including adolescent patients with tuberculosis in trials conducted in adults.

- The presentation of clinical disease may be different in children aged less than approximately 10 years compared to adults but the response to treatment may be comparable at least from the age of five years upwards, supporting the possibility of extrapolating efficacy documented in adults (and possibly also adolescents if they are enrolled into the same trials as adults) to this age group.

- There are recognised difficulties in diagnosing pulmonary tuberculosis in children aged less than 5 years in whom extrapulmonary disease occurs more often and the clinical presentation and radiological findings may differ from those in older children and adults. Nevertheless, an extrapolation of efficacy data in adults to paediatric age groups is considered to be possible provided that appropriate age-specific dose regimens can be established using pharmacokinetic data obtained in children with tuberculosis and the safety profile is shown to be acceptable. The diagnosis of tuberculosis in these children should be based on age-specific criteria recommended by internationally-recognised expert bodies.

- Sponsors may also consider establishing post-authorisation registries for collecting data on treatment outcomes from paediatric patients.

2.2. Quality aspects

2.2.1. Suitability of the existing dosage form for the proposed age group

The MAH provided data to justify the acceptability of the existing dosage form for the proposed age group. In trial 242-12-233, the dose which applied to children 12 to 17 years of age was the adult dose of 100 mg delamanid BID and the dose which applied to children 11 to 6 years of age was 50 mg delamanid BID. Both age groups received the already approved tablet formulation (50 mg film-coated tablet) in the paediatric trials while younger children received delamanid dispersible tablets (in the paediatric investigation plan [PIP] named "delamanid paediatric formulation" [DPF]). In agreement with the PIP, assessment of the acceptability/palatability has been performed only for the DPF and not for the approved tablet formulation and therefore such information for the approved tablet formulation could not be presented in the dossier. As the trial was still ongoing in younger age groups receiving DPF, final assessment of acceptability/palatability of DPF has not been available or applicable for this indication extension.

Regarding the suitability of Deltyba 50 mg film-coated tablets for children aged 6 to 17 years, the MAH stated that according to the "Guideline on Pharmaceutical Development of medicines for paediatric use" (hereafter named "Guideline") and the Reflection Paper "Formulations of Choice for the Paediatric Population" (hereafter named "Reflection Paper"), tablets can be considered appropriate pharmaceutical forms for children aged 6 years and older. In particular, Table 3.1 of the "Reflection Paper" shows that tablets are coded as "preferred acceptability" (age 6 to 11 years) and "dosage form of choice" (age 12 to below 18 years). Furthermore, the EU guidance documents state that training can improve the acceptability of tablets and that with appropriate training, even children younger than 6 years may be able to swallow tablets (see "Guideline" Section 6.2.1 and "Reflection Paper" Section 2.1.7). This should apply particularly to indications requiring long term treatment, such as MDR-TB. Although the tablets are relatively large (11.7 mm in diameter), they were tolerated in the clinical trials. The excipients of the delamanid 50 mg film-coated tablets should also not raise concerns regarding the use in paediatric patients aged 6 years and older. The only excipient with a known effect requiring specific information in the SmPC and package leaflet is lactose, see "Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'". Lactose is a well-established excipient, and according to the Annex to the Excipients Guideline referenced above, this information is already included in the approved Deltyba SmPC and package leaflet and the information provided is also considered acceptable for children aged 6 years and older. Finally, it has to be taken into consideration that the therapeutic indication limits the use of the approved film-coated tablets to paediatric patients with a body weight of at least 30 kg who are expected to be significantly older than 6 years.

The CHMP noted that the included patients were 7 to 17 years of age. No difficulties were reported regarding tablet acceptability. Tablet acceptability issues were never reported as a reason for study

discontinuation. Monitoring the acceptability of the 50 mg film-coated tablets was not an endpoint of this study and is likely an underestimation of potential problems. No further data can be obtained from trial 242-12-233 in the patients aged 6 to 17 years of age as this study part has been completed.

The CHMP noted that according to the EMA reflection paper on the formulations of choice for the paediatric population, tablets are an acceptable formulation for children (6-11 y) and adolescents (12-18 years of age). No unacceptability of the tablets, e.g. due to the size, has been reported in the clinical study, though this was not a predefined study outcome.

Although not explicitly assessed, no negative reports from study sites, children or parents, respectively, on the excipients, tablet size, swallowability, acceptability, palatability or administration instructions became available nor was there a drop-out case reported because of unacceptability. All patients 6 to 17 years of age who received the delamanid 50 mg adult tablet tolerated the tablet without reported difficulties.

The MAH stated that the diameter of the film-coated tablet is 11.7 mm and that crushing of the film-coated tablets is difficult because the tablets are very hard due to the film-coating and would require use of appropriate equipment. Splitting should not raise specific safety concerns because the pharmaceutical form is for immediate release but another important disadvantage of splitting the tablets is the expected sensation of unpleasant taste. The 50 mg film-coated tablets are not scored and very hard, therefore they are not considered suitable for splitting. Although there are no specific safety concerns regarding crushing or splitting of the film-coated tablets, the MAH does not propose addition of such proposals to SmPC or package leaflet.

The CHMP considered that the tablet size is acceptable and agreed that the 50 mg film-coated tablets are not scored and very hard. An unpleasant taste is expected when the tablets will be crushed. Therefore, the tablets are not considered suitable for splitting and it is considered appropriate that no information on splitting or crushing the tablets is added to the SmPC or PL.

With regard to the potential administration of delamanid through feeding tubes, the MAH referred to the "Guideline", Section 6.2.3 which states that administration through feeding tubes needs to be addressed if this either a main route or a very likely option. MDR-TB as such is not a disease which requires administration of food or medicinal products through feeding tubes. Use of feeding tubes in MDR-TB would be more the result of concomitant diseases (e.g., acute diseases requiring intensive care) or very poor general health conditions (e.g., elderly patients, preterm neonates). For patients with such poor general health conditions or concomitant acute diseases, it is more likely that treatment of MDR-TB will be discontinued until the general health conditions of the patients have been improved.
The MAH therefore concluded that MDR-TB is a disease where potential administration of delamanid through feeding tubes is very unlikely.

The CHMP was of the view that administration of MDR-TB treatment through feeding tubes is not very likely. Possibly, the delamanid paediatric formulation, a dispersible tablet, might be a better solution for administration via feeding tubes.

2.2.2. Conclusion on the quality aspects

The acceptability of the existing dosage form for the proposed age group has not been investigated in the paediatric clinical studies for children of 6 to 17 years of age. It was noted that no difficulties were reported regarding tablet acceptability and tablet acceptability issues were never reported as a reason for study discontinuation.

2.3. Non-clinical aspects

2.3.1. Introduction

The MAH submitted an ERA addendum. No other new non-clinical PK/PD or toxicology data have been submitted in this application. However, in the Deltyba Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006 (EMEA/H/C/002552/P46/007, 20/09/2018), the following table is included:

Table 1 Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non-clinical study

Product Name: Deltyba Active substance: Delamanid

Study title	Study number	Date of completion	Date of submission of final study report
Ten-week Repeated Oral-Dose Toxicity Study of OPC-242 (SD powder) in Juvenile Rats with 4-week Recovery Test	report No. 028620 (PIP: Study 2 OTS-PAED:RAT	05/12/2012	26 Mar 2015

The 10w juvenile rat study report has been submitted to the PDCO for PIP compliance check, but was not formally submitted for CHMP assessment.

From the PDCO report, it seems that the NOAEL in males is the lowest dose tested:

Study design

OPC-242 (SD powder) was administered orally by gavage to juvenile Sprague-Dawley rats [Crl:CD(SD), 4 days of age at the start of administration, 43 or 67 animals of each sex] once daily for 10 weeks at dose levels of 0 (5 w/v% gum arabic solution), 0 (control article: 0% OPC-242 (SD powder)), 3, 30 and 300 mg/kg/day as OPC-242.

Study results

Males and females showed prolongation of activated partial thromboplastine time, males showed prolongation and females showed a tendency toward prolongation of prothrombine time, and females showed a high value in motor activity and a low value in the number of corpora lutea in the 300 mg/kg group, and males in the 30 and 300 mg/kg groups showed suppressed body weight gain in association with low food consumption from Week 3 of administration, it was judged that the nontoxic dose level was 3 mg/kg in males and 30 mg/kg in females.

The MAH provided an addendum to the non-clinical overview and the study report with the results of the 10-week juvenile rat study. The addendum non-clinical overview concludes that "the toxicity observed in juvenile animals was similar to those seen in the adult animal, i.e., the juvenile animal does not appear to be uniquely sensitive to the toxicity of delamanid" Based on this conclusion, the MAH proposed to add the following statement to the SmPC Section 5.3: "In juvenile toxicity studies in rats, all delamanid treatment-related findings were consistent with those noted in adult animals". This is agreed by the CHMP

<u>Dose-range finding (DRF) study:</u>

Design: SD rats PND 4, 4 weeks dosing, oral, once daily, 0, 10, 30, 100, 300 mg/kg

Plasma concentrations were determined in a subset of animals at Day 35 of administration. There were no treatment-related deaths during the conduct of the study. There were also no treatment-related effects on body weight, food consumption, haematology, or gross necropsy.

Results: 1 animal died in the HD group, cause of death unknown. Otherwise, there were no test article-related changes in any examination in either sex.

Definitive JAS study:

Design: SD Rats PND 4 oral 10 week + 4 week recovery, dose levels were 0, 3, 30, 300 mg/kg/day

Main cohort (evaluated for behaviour, and pathology; necropsy at Weeks 2, 5, or 10), Recovery cohort (sensory and motor function, motor activity, learning performance, ophthalmology, urinalysis, and pathology), Mating cohort (evaluated for behaviour, learning performance, sexual maturation, fertility and reproductive function) and Toxicokinetic (TK) cohort (blood collection at Weeks 2, 5 or 10). In the Mating cohort, male and female animals were cohabitated for a maximum of 2 weeks starting in Week 6 of the recovery period.

Both the DRF and definitive JAS studies were conducted in compliance with GLP.

Results: One male in the placebo control group and 1 male and 2 females in the 300 mg/kg group died during the lactation period between Day 5 and Day 17 of administration (1 female due to worsened general condition, 2 others cause of death unknown). No effects on general condition, detailed clinical observation, manipulative test, grip strength, learning performance (Water-filled Multiple T-maze Test), observation of external differentiation, ophthalmological examination, urinalysis, blood chemistry examination, organ weight, necropsy or histopathological examination.

Summary of main findings in the high dose group of 300 mg/kg:
- body weights of male animals were lower than those of the vehicle control group at various periods during the dosing phase and remained lower throughout the recovery period. Males in the 30 and 300 mg/kg groups in the mating cohorts also showed suppressed body weight gain.
- Motor activity was increased in females at week 10 of dosing and week 4 of recovery.
- prolonged PT and aPTT in males and females at Week 2 and/or Week 10, which resolved by Week 4 of recovery.
- low values in urine volume, sodium, potassium, chloride and creatinine in males.
- lower number of corpora lutea, implantations, and live embryos.

The NOAELs were considered to be 3 mg/kg/day in juvenile male rats ($AUC_{0\text{-}24h}$: 18760 ng.h/mL) and 30 mg/kg/day in juvenile female rats ($AUC_{0\text{-}24h}$: 49060 ng.h/mL).

The CHMP considered that regarding the toxicokinetics, it appears from the data obtained in the DRF study that in the 100 and 300 mg/kg groups, C_{max} and AUC values were similar to or lower than 30 mg/kg. From the table below, and the TK data from the definitive JAS study, it seems that especially in the low dose groups, the exposure was abnormally high. This has not been explained but is not considered as a concern given that the exposures in the definitive study generally increased in a dose-related manner.

Table 2 Toxicokinetic parameters of OPC-242 in week 5 of administration in juvenile rats

Sex	Analyte	Week 5							
		C_{max} (ng/mL)				AUC_{24h} (ng·h/mL)			
		Dose (mg/kg/day)				Dose (mg/kg/day)			
		10	30	100	300	10	30	100	300
Male	OPC-242	2988	4106	4737	4260	45090	61950	68860	66580
Female	OPC-242	3171	4289	3260	4267	48990	64170	39960	70610

C_{max}: maximum plasma concentration after administration
AUC_{24h}: area under the concentration-time curve from time zero to 24 hours after administration
Each value represents the mean of three animals.

- In the definitive JAS study, there was **unexpected contamination** in the vehicle and placebo control group at week 2 (plasma concentrations from 294.7 ng/mL to 707.4 ng/mL in the vehicle control group, and from 127.6 ng/mL to 1380 ng/mL in the placebo control). In weeks 5 and 10, all values were below the LLOQ.
- In Week 2, the C_{max} and AUC_{24h} of OPC-242 were increased in a dose-related manner for both sexes. In Weeks 5 and 10, the AUC_{24h} of OPC-242 was increased in a dose-related manner for both sexes; however, the C_{max} of OPC-242 in the 300 mg/kg group was similar to that of the 30 mg/kg group for both sexes.
- There were no sex differences in TK.

Sex	Dose (mg/kg/day)	C_{max} (ng/mL)			AUC_{24h} (ng·h/mL)		
		Week 2	Week 5	Week 10	Week 2	Week 5	Week 10
Male	3	1473	1264	1472	25750	14400	18760
	30	4030	3551	3110	66430	40250	37730
	300	10380	3452	3049	180900	53370	58620
Female	3	1651	890.2	1107	29090	11400	13420
	30	5050	4013	3456	84010	50060	49060
	300	8392	3912	4056	157100	61590	71100

- Age-related differences in TK have not been discussed. From the table above, it is noted that there were no significant TK differences between week 5 and 10, which is not unexpected in view of the age of animals, i.e. between PND 32/39 and PND 67/74, respectively. There were some age-related increases in exposure in week 2 (animals PND 11-18) when comparing to week 10 (adult age), which may have been linked to immature metabolism in the youngest group, however, the differences were limited to a ~2-fold increase in AUC.

The CHMP considered that regarding the main findings in the high dose group of 300 mg/kg:
- Motor activity was increased in females at week 10 of dosing and week 4 of recovery. Since the motor activity was slightly higher than the historical background data, the relation to administration of the test article could not be ruled out. However, this change is estimated to be of little toxicological significance since there were no changes suggestive of increased motility/reactivity relating to the high value in motor activity in clinical observation and detailed clinical observation, although the mechanism for the occurrence of this change remains unclear.
- prolonged PT and aPTT in males and females at Week 2 and/or Week 10, which resolved by Week 4 of recovery. Similar findings have been reported in previous repeated dose toxicity studies with delamanid.
- low values in urine volume, sodium, potassium, chloride and creatinine in males. According to the study report, these changes were reversible and judged to be within the range of physiological variations.
- lower number of corpora lutea, implantations, and live embryos. No effects on any of these parameters were observed in previous rat studies including FEED study in rats and rat EFD study. In rabbit EFD, an

increase in pre-implantation loss and early resorptions as observed but was considered secondary to maternal toxicity.

Figure 1 Ten-week Repeated Oral Dose Toxicity Study of OPC-242 (SD powder) in Juvenile Rates with 4-week Recovery Test

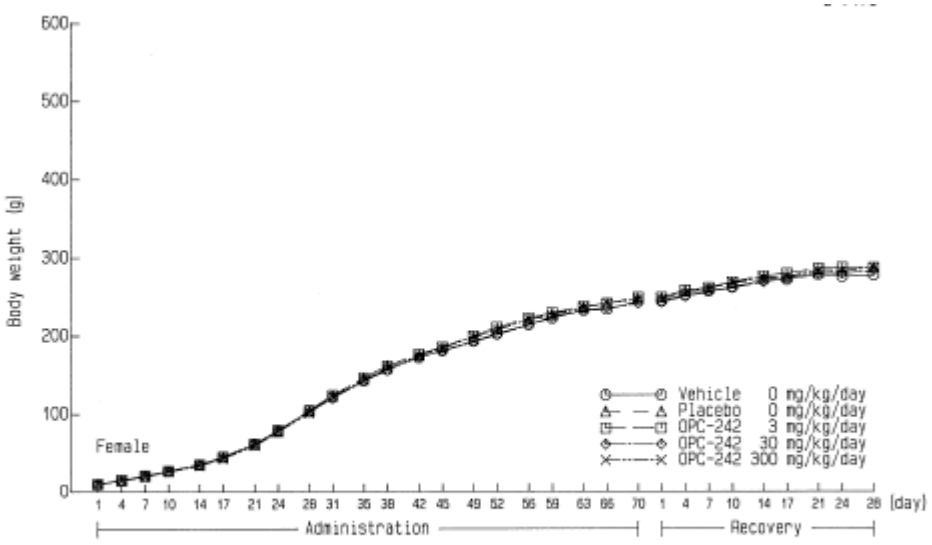


Fig.8 Ten-week Repeated Oral Dose Toxicity Study of OPC-242 (SD powder) in Juvenile Rats with 4-week Recovery Test

——— Body weight (Mating group) ———

The MAH was requested to discuss the clinical relevance (incl. safety margins) of the observed effects on corpora lutea, implantation and live embryos in the high dose females especially as such effects have not been reported in any of the previous adult rats studies including the FEED and EFD studies in rats administered the same dose. Similar effects were observed in the rabbit EFD study, albeit in the presence of maternal toxicity. However, the effects observed in the juvenile rat study are reported in the absence of any effects on body weight in the female animals.

The MAH provided data showing that although the mean number of corpora lutea was significantly reduced at 300 mg/kg/day, the mean number corpora lutea at the 300 mg/kg/day dose group (mean = 10.7) falls within the historical control range for this species of rats (mean of 9 to 18.3). In addition, delamanid had no effect on number of estruses, mean oestrous cycle, number of days until copulation, or fertility index. Furthermore, histopathological examination of the main cohort animals showed no abnormal findings in the ovary. Based on the totality of data, the CHMP agreed that the reduced number of corpora lutea in the 300 mg/kg/day is likely an incidental finding and does not reflect a toxic effect of delamanid. The CHMP was therefore of the view that the effects on corpora lutea are not considered to be related to delamanid.

As the product is to be approved for a paediatric population, the CHMP considered it appropriate to include the following paragraph in section 4.8 of the SmPC, following the tabulated list of adverse drug reactions, to describe the safety profile seen in this population:

"Paediatric population

Based on a study (see section 5.1) in 13 children and adolescents aged 6 – 17 years, the frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Clinical study safety data are not available for children under 6 years."

2.3.2. Pharmacology

No new data.

2.3.3. Pharmacokinetics

No new data.

2.3.4. Toxicology

No new data.

See discussion above on the juvenile animal data.

2.3.5. Ecotoxicity/environmental risk assessment

The MAH submitted an ERA addendum stating that since the initial PEC calculations were not limited to adult patients, a new ERA is not needed for an extension to paediatric patients.

2.3.6. Discussion on non-clinical aspects

The approval of the paediatric indication for Deltyba may increase the environmental exposure to delamanid. However, in the initial ERA, the PEC calculations were not limited to adult patients. The calculation of a refined PEC was based on published epidemiological data (WHO report from 2009) for all tuberculosis patients in the EU (data from 2007). Although the epidemiological data seem outdated, the provided justification for not providing a new ERA is considered acceptable. It can be concluded that no new environmental risk assessment is required.

2.3.7. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication may lead to an increase in environmental exposure further to the use of delamanid. Nevertheless, considering the above data, delamanid is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

Trial 242-12-233 has been conducted in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable local laws and regulatory requirements.

- Tabular overview of clinical studies

Type of Study (Study Phase)	Protocol Number Location of Study	Study Report Location	Study Objective(s)	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled/ Treated/ Completed	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of Report
PK	242-12-232 Multi-national	Section 5.3.3.2	To determine PK, safety and tolerability of delamanid in combination with OBR in paediatric MDR-TB subjects. To determine the palatability of the delamanid paediatric formulation.	Multicenter, open-label, multiple-dose, age de-escalation trial	Group 1: Delamanid 100 mg BID (administered as 2 × 50-mg film-coated tablet) + OBR Group 2: Delamanid 50 mg BID (administered as 1 × 50-mg film-coated tablet) + OBR Group3: Delamanid 25 mg BID (administered as 1 × 25-mg dispersible tablet) + OBR Group 4: • Subjects with weight > 10 kg received delamanid 10 mg BID (administered as 2 × 5-mg dispersible tablets) + OBR • Subjects with weight > 8 and ≤ 10 kg received delamanid 5 mg BID (administered as 1 × 5-mg dispersible tablet) + OBR • Subjects with weight ≥ 5.5 kg and ≤ 8 kg received delamanid 5 mg QD (administered as 1 × 5-mg dispersible tablet) + OBR	7/7/7 6/6/6 12/12/12 12/12/12	paediatric MDR-TB	10 days	Complete; Full CSR

Type of Trial (Trial Phase)	Protocol Number Location of Trial	Trial Report Location	Trial Objective(s)	Trial Design and Type of Control	Investigational Medicinal Product; Dosage Regimen; Route of Administration[b]	Number of Subjects Enrolled[a]	Healthy Subjects or Diagnosis of Subjects	Treatment Duration	Trial Status; Type of Report
Patient PK and Initial Tolerability Study Reports									
PK, safety, and efficacy; (Phase 2)	242-12-233 Philippines, South Africa	Section 5.3.3.2 [Synopsis]	To evaluate the long-term safety and tolerability of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in paediatric MDR-TB subjects; to report delamanid and metabolite plasma con-centrations at each visit day by age groups and to conduct a population PK analysis	Open-label, multi-dose, age de-escalation, long-term extension trial	Delamanid 50 mg or 25 mg oral tablet, with meals for 180 days Group 1 (ages 12 - 17 years): 100 mg BID + OBR Group 2 (ages 6 - 11 years): 50 mg BID + OBR Group 3 (ages 3 - 5 years): 25 mg BID + OBR Group 4 (ages birth - 2 years): > 10 kg: 10 mg BID + OBR > 8 kg and ≤ 10 kg: 5 mg BID + OBR ≥ 5.5 kg and ≤ 8 kg: 5 mg QD + OBR	Group 1: 7 Group 2: 6 (As of the data cutoff 13 Dec 2016)	Paediatric MDR-TB subjects on therapy with an OBR who had completed Trial 242-12-232	6 months	Ongoing; Synoptic report
Population PK Study Reports[c]									

BID = twice daily; DLM = delamanid; MDR-TB = multidrug-resistant tuberculosis; OBR = optimized background regimen; PK = pharmacokinetics; QD = once daily.

[a]Data is not included for Groups 3 and 4.

[b]Children in Groups 3 and 4 were given delamanid as an extemporaneous suspension using the delamanid pediatric dispersible tablet formulation.
[c]Report of population PK study in Section 5.3.3.5 includes the following:
242-19-259: Population pharmacokinetic/pharmacodynamic analysis of delamanid in paediatric patients from Trials 242-12-232 and 242-12-233.

2.4.2. Pharmacokinetics

Three clinical trials were performed in accordance with the PIP for Deltyba:

- Trial 242-12-232: a pharmacokinetic (PK) trial in children of all ages with MDR-TB on therapy with optimised background regimen (OBR)
- Trial 242-12-233: a 24-month safety and tolerability extension trial of trial 242-12-232 in the same patient population
- Trial 242-12-245: a bioavailability/bioequivalence trial in adults to investigate the comparative bioavailability of the paediatric formulation (5- and 25-mg immediate-dissolving tablets) with the delamanid 50-mg tablet adult formulation

In view of the scope of this Type II variation, which concerns the extension of the MDR-TB indication to children 6-17 years of age, the first two trials are of interest as the third trial concerns the bioequivalence between the actual delamanid tablets formulation and the paediatric formulation, which has only been used in children 0-5 years of age. It is important to note that the 50 mg tablet formulation used in the paediatric population is the same formulation and strength as used in adults. Only children from the first two age groups (ages 6 - 17 years) have completed the 24-month safety and tolerability trial long-term Trial 242-12-233 including the 6-month delamanid treatment in conjunction with an OBR, the overall 6 month post-treatment and follow-up periods, and the additional 12-month treatment outcome follow-up period. The trial is still ongoing in younger children (age groups 0 - 2 and 3 - 5 years) and trial finalisation will be in March 2020.

Trial 242-12-232 (Trial 232) was designed to define the paediatric dose in subjects between 0 to 17 years of age that will result in a delamanid systemic exposure equivalent to that observed in the pivotal adult trials. Further objectives of that trial were the safety and tolerability of delamanid in combination with OBR treatment and the palatability of delamanid paediatric formulation (DPF). Results of this trial were already introduced and assessed as part of the Article 46 of Regulation (EC) No1901/2006 in July 2018 (EMA/H/C/002552/P46/007). Below a summary of the PK results and the conclusions of this trial can be found. Trial 242-12-233 (Trial 233) is a 6-month treatment extension trial evaluating the long-term safety and tolerability of the age-specific delamanid doses used in Trial 232 and to characterise the pharmacokinetics (PK) of delamanid in this population. Delamanid PK data from this trial were combined with PK data from the Trial 232 and analysed using population PK methods.

Trial 242-12-232: Phase 1, Open-label, Multiple-dose, Age De-escalation Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Delamanid (OPC-67683) in Paediatric Multidrug-resistant Tuberculosis Patients on Therapy with an Optimised Background regimen.

Trial 242-12-232 was a phase 1, multicentre, open-label, uncontrolled, multiple-dose, age de-escalation trial to assess the safety and tolerability of delamanid in paediatric subjects with MDR-TB who were also receiving OBR. The goal of this trial was to define the paediatric dose for delamanid in children from birth (0) to 17 years of age that results in delamanid plasma exposure similar to the plasma exposure in adult patients that has been demonstrated to be safe and effective for the treatment of Multidrug-resistant Tuberculosis (MDR-TB).

Objectives

- To determine the PK of delamanid and its metabolites in combination with OBR in paediatric MDR-TB subjects.
- To determine the safety and tolerability of delamanid in combination with OBR in paediatric MDR-TB subjects.
- To determine the palatability of the delamanid paediatric formulation.

Study design

The trial was conducted sequentially in 4 groups of paediatric subjects: Group 1 (ages 12 – 17 years, inclusive, n = 6), Group 2 (ages 6 - 11 years, inclusive, n = 6), Group 3 (ages 3 – 5 years, inclusive, n = 12), Group 4 (ages birth - 2 years, inclusive, n = 12).

Subjects who dropped out or who completed this trial (Trial 242-12-232) and decided not to participate in the 6-month extension trial (Trial 242-12-233) were replaced.

Delamanid was administered to study subjects for 10 days with 8 days of safety follow-up and PK sampling was performed on Days 1, 2, 10, 11, 13 (Groups 1 and 2 only), 15, and 18.

Study population /Sample size

A total of 44 subjects were screened for this trial. The trial enrolled 37 males and females ages birth to 17 years, inclusive, who were receiving OBR for confirmed or presumptive MDR-TB.

All enrolled subjects who completed Trial 242-12-232 were rolled over to Trial 242-12-233, an open-label, uncontrolled, 6-month extension trial to evaluate the long-term safety, tolerability, and PK of delamanid administered BID for Groups 1, 2, and 3; and once or twice daily, depending upon body weight for Group 4, for 6 months in paediatric subjects with MDR-TB. Trial 242-12-233 was initiated as required under the approved Paediatric Investigation Plan.

Treatments

Group 1 (ages 12 - 17 years, inclusive) received adult formulation delamanid 100 mg dosing twice per day (BID) + OBR (n = 7)

Group 2 (ages 6 - 11 years, inclusive) received adult formulation delamanid 50 mg BID + OBR (n = 6)

Group 3 (ages 3 - 5 years, inclusive) received delamanid paediatric formulation (DPF) 25 mg BID + OBR (n = 12)

Group 4 (ages birth - 2 years, inclusive) received the following DPF dose based on body weight during baseline visit (n = 12):

- Subjects > 10 kg received DPF 10 mg BID + OBR
- Subjects > 8 and ≤ 10 kg received DPF 5 mg BID + OBR
- Subjects ≥ 5.5 kg and ≤ 8 kg received DPF 5 mg QD + OBR

The morning dose of the delamanid BID regimen was given within 30 minutes after the start of a standard breakfast meal. The evening dose of the BID dose regimen was given 10 hours post morning dose and within 30 minutes after the start of a standard dinner meal. For the QD regimen, delamanid was

administered within 30 minutes after the start of a standard breakfast meal. Food composition was typical for the children's age and needs.

The second-line medications were those generally used in developing OBR for MDR-TB subject treatment.

PK Outcomes/endpoints

For each subject, the following PK parameters were determined for delamanid and delamanid metabolite (DM-6705):

- C_{max}, t_{max}, AUC_{0-24h} on Day 1 and Day 10
- $t_{½}$ z on Day 10
- Rac Day 10/Day 1 for AUC_{0-24h}, and apparent total clearance (CLss/F) for delamanid only

Statistical Methods

Determination of Sample Size:

This was a phase 1, open-label trial to assess the PK parameters, safety and tolerability of delamanid. No formal statistical hypothesis testing was planned. Thus, no formal sample size calculation based on statistical power was required. All statistical presentations are descriptive.

The following delamanid PK parameters were determined using noncompartmental analysis:

- Peak (maximal) concentration of drug in plasma (C_{max}), time of peak concentration of drug (t_{max}), area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24h}) on Day 1 and Day 10
- Accumulation ratio Day 10/Day 1 for AUC_{0-24h}
- Apparent terminal phase elimination half-life ($t_{1/2z}$) and apparent total clearance

PK analysis of delamanid metabolite (DM-6705) plasma concentrations was performed where feasible.

- The following PK parameters were determined for DM-6705 using noncompartmental analysis: C_{max}, t_{max}, AUC_{0-24h} on Day 1 and Day 10 and $t_{1/2z}$.

Plasma concentrations and PK parameters when determined, were reported with descriptive statistics in the PK report. No prior inferential statistical comparisons were performed.

Bioanalytical Results

A total of 582 plasma samples were received by the bioanalytical laboratory. Concentration results for delamanid and DM-6705 were generated for 556 samples; the remaining 26 samples were backups and were not analysed.

PK Results

Median plasma delamanid concentration versus time profiles following oral doses of delamanid on Day 1 and Day 10 to paediatric subjects with MDR-TB (Group 1 - 100 mg BID, Group 2 - 50 mg BID, Group 3 - 25 mg BID, Group 4 - 5 to 20 mg) are presented in **Figure 2** and **Figure 3**. Pharmacokinetic assessment of CSF was not conducted

Figure 2 Median Delamanid Plasma Concentrations Following Delamanid Administration on Day 1 of Pediatric Subjects with MDR-TB Ages 17 years and Younger.

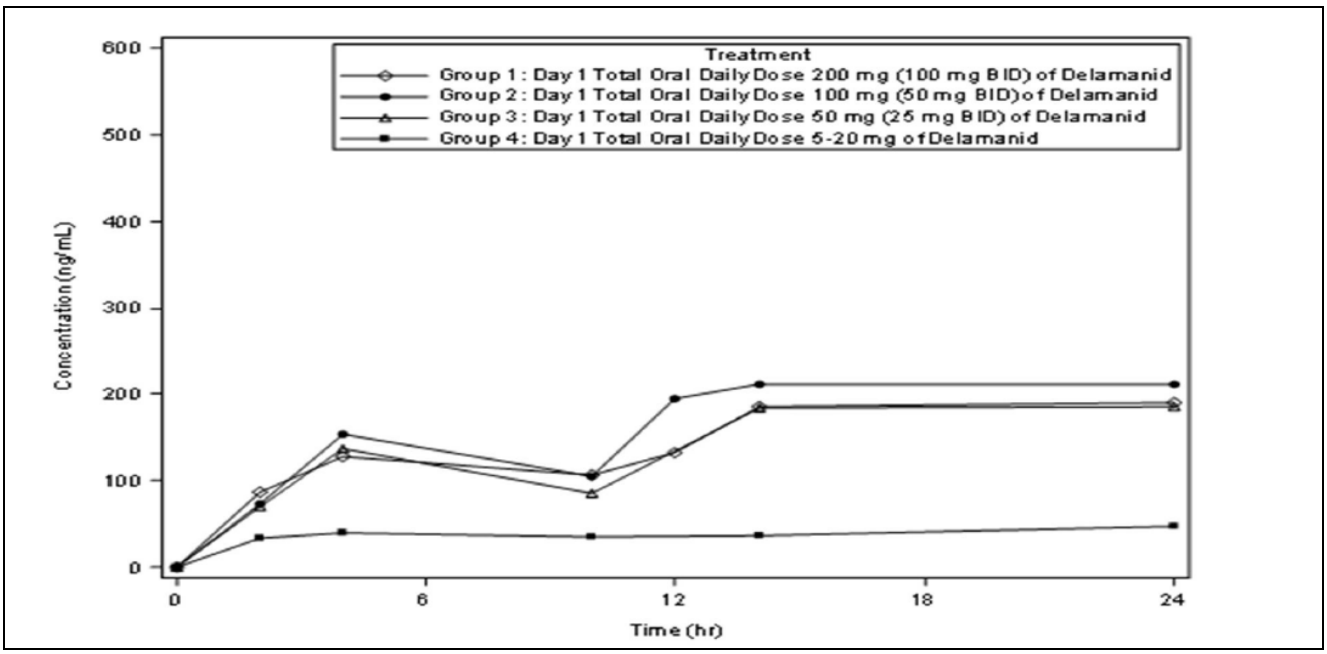
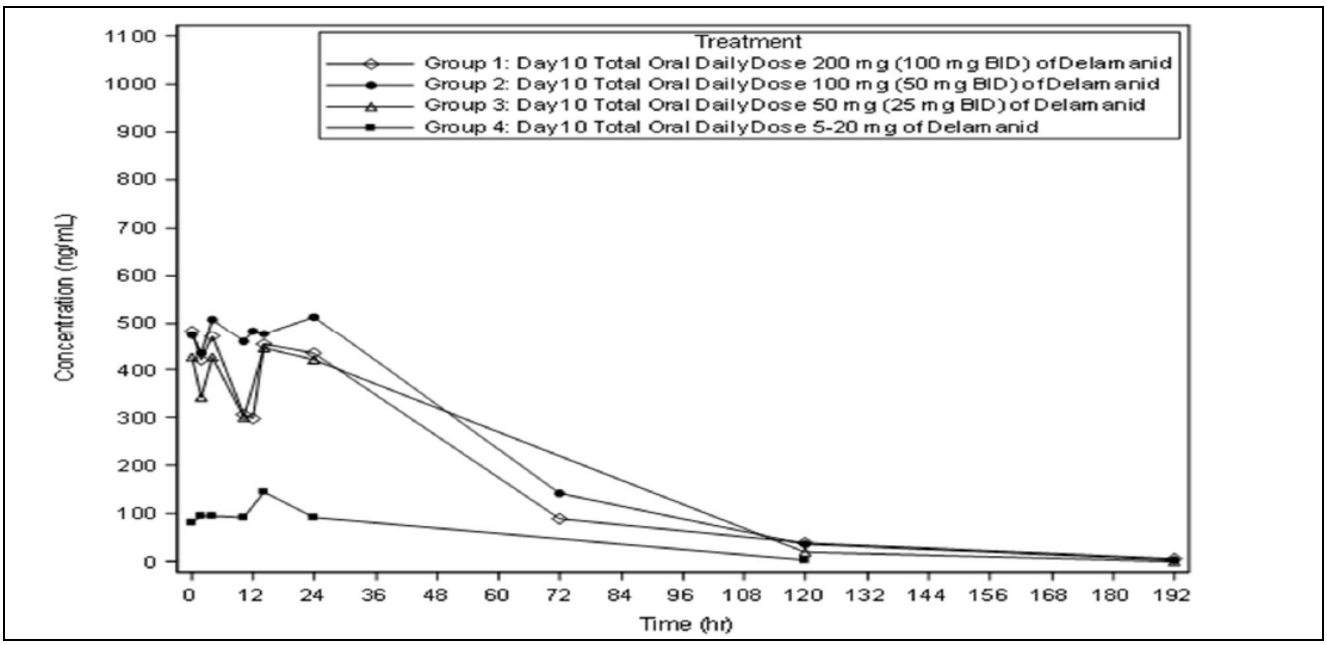


Figure 3 Median Delamanid Plasma concentrations Following Delamanid Administration on Day 10 to Pediatric Subjects with MDR-TB Ages 17 years and Younger



DM-6705 PK Profiles:

Median plasma DM-6705 concentration versus time profiles following oral doses of delamanid on Day 1 and Day 10 to paediatric subjects with MDR-TB (Group 1 - 100 mg BID, Group 2 - 50 mg BID, Group 3 - 25 mg BID, Group 4 - 5 to 20 mg) are presented in **Figure 4** and **Figure 5**.

Figure 4 : Median DM-6705 Plasma Concentrations Following Delamanid administration on Day 1 to Paediatric Subjects with MDR-TB Ages 17 Years and younger

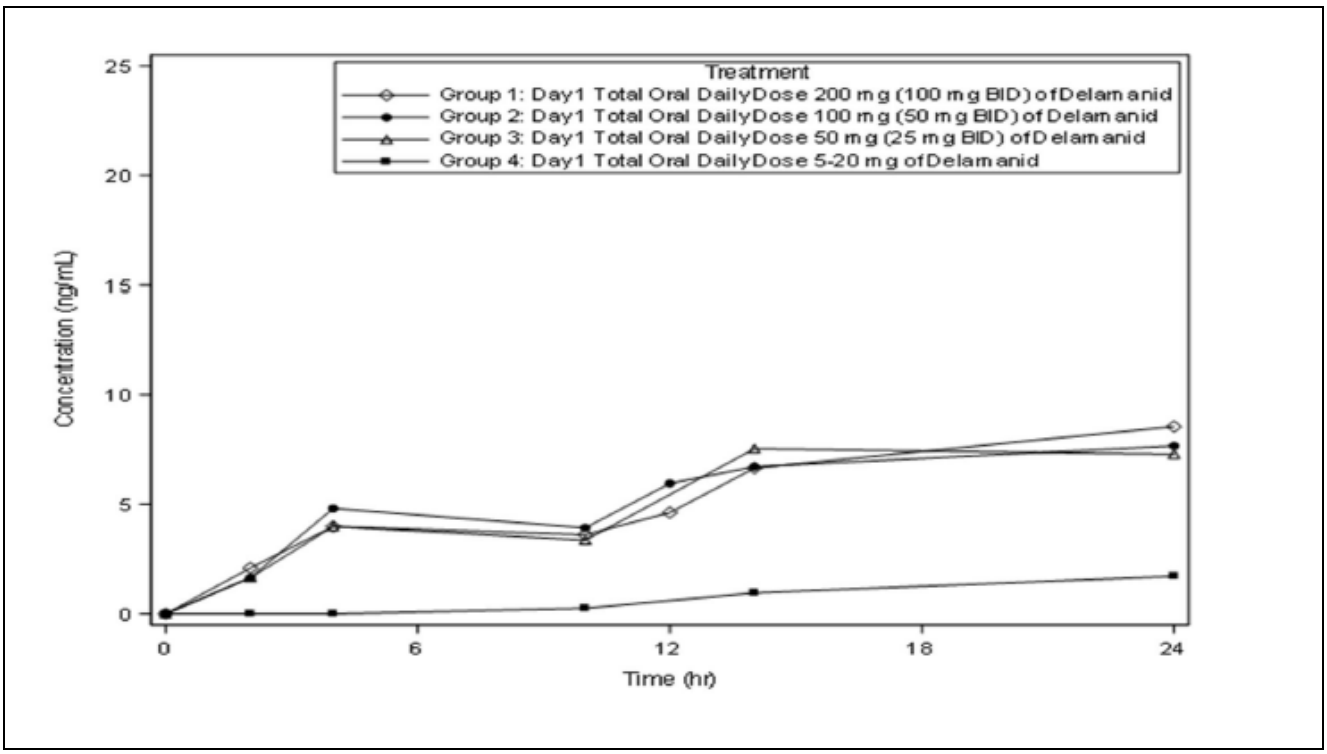
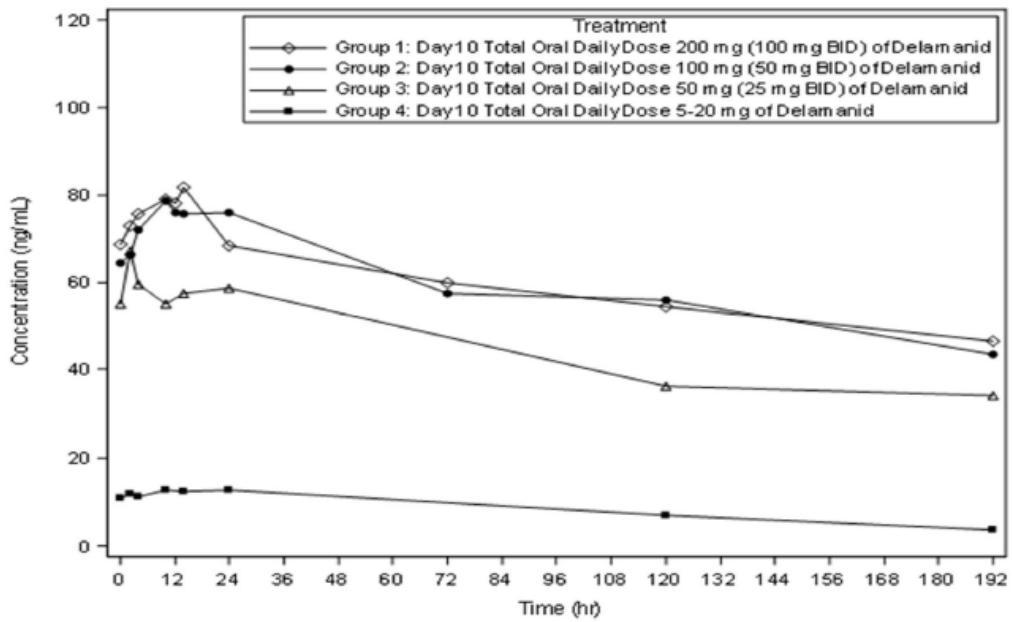


Figure 5 Median DM-6705 Plasma Concentrations Following Delamanid Administration on Day 10 to Pediatric Subjects with MDR-TB Ages 17 years and younger



Delamanid PK Parameters:

A summary of delamanid pharmacokinetic parameters following delamanid administration on Day 1 and Day 10 are presented in **Table 3** and **Table 4**, respectively.

Table 3 Delamanid Median (Range) PK Parameters on Day 1 Following 100 mg BID (Group 1), 50 mg BID (Group 2), 25 mg BID (Group 3) or 5-20 mg (Group 4) of Delamanid to Pediatric MDR-Subjects

Parameter	Group 1	Group 2	Group 3	Group 4
N	7	6	12	12
C_{max} (ng/mL)	268 (164-420)	315 (205-454)	207 (150-364)	80.3 (26.2-121)
t_{max} (h)	14·0 (2·05-24·0)	11.98 (2·0-24·0)	23·96 (14·0-24·03)	7.03 (2·0-24·0)
AUC_{0-24h} (ng.hr/mL)	3910 (1910-5270)	4080 (3240-7090)	3580 (1940-4920)	949 (262-1930)

Table 4 Delamanid Median (Range) PK Parameters on Day 10 Following 100 mg BID (Group 1), 50 mg BID (Group 2), 25 mg BID (Group 3) or 5-20 mg (Group 4) of Delamanid to Pediatric MDR-Subjects

Parameter	Group 1	Group 2	Group 3	Group 4
N	7	6	12	12
C_{max} (ng/mL)	557 (304-803)	573 (485-682)	500 (287-919)	179 (45.2-298)
t_{max} (h)	3·98 (0·0 - 24·0)	11.98 (2·0 - 24·0)	4·00 (0·0 - 24·0)	13·75 (2·0 - 23·97)
AUC_{0-24h} (ng.hr/mL)	9790 (6170-13000)	12000 (9810-13300)	9290 (5180-12900)	2740 (701-4910)
CL/F (mL/min)	341 (257–541)	139 (125-170)	89.8 (64.5-161)	87.4 (67.9-123)
$t_{1/2,z}$(h)	30.4 (19.7 – 54.7)	23.7 (19.1-82.1)	20.5 (16.8-31.3)	ND
$R_{ac}AUC_{0-24h}$	2.68 (1.86 – 4.71)	2.55 (1.72-4.11)	2.70 (1.85-4.00)	2.69 (1.24-4.20)

ND = No data.

Pharmacokinetic parameters:

A summary of DM-6705 pharmacokinetic parameters following delamanid administration on Day 1 and Day 10 are presented in **Table 5** and **Table 6**, respectively.

Table 5 DM-6705 Median (Range) Pharmacokinetic Parameters on Day 1 Following 100 mg BID (Group 1), 50 mg BID (Group 2), 25 mg BID (Group 3) or 5-20 mg (Group 4) of Delamanid to Pediatric MDR-Subjects

Parameter	Group 1	Group 2	Group 3	Group 4
N	7	6	12	12
C_{max} (ng/mL)	8.60 (6.86-15.5)	7.68 (6.07-23.1)	8.35 (5.03-15.1)	2.01 (0.5-4.17)
t_{max} (h)	24·0 (14.0-24·03)	18.98 (11·95-24·0)	23·98 (14·0-24·03)	24·0 (4·0-24·02)
AUC_{0-24h} (ng.hr/mL)	114 (89.4-224)	122 (81.1-351)	120 (77.9-223)	25.2 (2.49-61.8)

Table 6 DM-6705 Median (Range) Pharmacokinetic Parameters on Day 10 Following 100 mg BID (Group 1), 50 mg BID (Group 2), 25 mg BID (Group 3) or 5-20 mg (Group 4) of Delamanid to Pediatric MDR-Subjects

Parameter	Group 1	Group 2	Group 3	Group 4
N	7	6	12	12
C_{max} (ng/mL)	81.7 (52.9-93.2)	90.0 (62.4-112)	68.7 (33.7-95.0)	14.2 (2.38-35.9)
t_{max} (h)	12.0 (10·0 - 14·0)	12.0 (2·0 - 24·0)	3·00 (0·0 - 24·0)	10.49 (1.97 – 24.0)
AUC_{0-24h} (ng.hr/mL)	1780 (1210-2010)	1880 (1210-2210)	1370 (671-2160)	291 (49.6-774)
$t_{1/2,z}$(h)	237.3 (217.0 – 350.5)	ND	155.4 (88.8-341.8)	128.2 (70.0-201.4)
$R_{ac}AUC_{0-24h}$	12.90 (7.87 - 19.95)	11.0 (6.3 - 23.44)	11.15 (6.15 - 19.83)	15.19 (5.23 - 65.26)
Ratio of Delamanid/ DM-6705 AUC_{0-24h}	0.18 (0.155 – 0.198	0.148 (0.123 – 0.181)	0.164 (0.119 – 0.190)	0.12 (0.071 – 0.161)

In Groups 1 to 4, the median delamanid C_{max} on Day 10 was 557, 573, 500, and 179 ng/mL, respectively; the median AUC_{0-24h} on Day 10 was 9790, 12000, 9290, and 2740 ng*h/mL, respectively. The C_{max} and the AUC_{0-24h} ranges were reasonably similar for Groups 1 to 3 but were much lower for Group 4.

The MAH notes that the ratio of AUC_{0-24h} on Day 10 of DM-6705 to delamanid appears to decrease with decreasing age, indicating that either the formation of DM-6705 is decreasing or its elimination is increasing or a combination of the two scenarios. The median terminal elimination half-life of DM-6705 was 237.3 hours in Group 1 and 128.2 hours for Group 4, indicating a more rapid elimination with decreasing age.

In order to compare the exposures across the groups, the weight normalised oral clearance, was calculated for each regimen. The median weight-normalised oral clearance on Day 10 for delamanid was 8.92, 6.11, 6.68, and 8.34 for Groups 1 to 4, respectively.

The results indicated that the clearances for all groups, including most subjects in Group 4, were within a narrow range and the lower exposures observed in Group 4 were due to this group receiving lower doses of delamanid.

The CHMP noted that no subjects had missing PK data. Delamanid exposures in children aged 2 years to <18 years in Groups 1 to 3, were comparable to each other but higher than in adults. When considering all age groups, delamanid exposures were the lowest for the youngest children aged from birth to less than 2 years (Group 4).

The dosing regimen for Group 4 was determined by modelling PK data from the previous three groups and it was thus expected that the delamanid doses used would have a higher predicted bioavailability for children in this age cohort. However, the current data suggest that a higher delamanid dose is needed in the youngest children. As this Type II variation applies to extend the indication to children 6-17, this will not be further discussed in this AR, but the MAH is reminded of the conclusions of the outcome of their Article 46 application, that further paediatric development is needed for these young children as, at this stage, the available data do not fully determine the benefit-risk of delamanid in this youngest population.

Trial 242-12-233: Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC-67683) in Pediatric Multidrugresistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs over a 6-Month Treatment Period

Trial 242-12-233 (Trial 233) is a 6-month treatment extension trial evaluating the long-term safety and tolerability of the age-specific delamanid doses used in Trial 232 and to characterise the pharmacokinetics

(PK) of delamanid in this population. The trial will also assess the palatability (Groups 3 and 4 only) of the paediatric formulation using an age-appropriate visual hedonic scale and clinical assessment.

Objectives

The primary objectives of this trial are:

- To evaluate the long-term safety and tolerability of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in paediatric subjects with MDR-TB for the age-specific delamanid doses determined in Trial 232
- To report delamanid and metabolite plasma concentrations at each visit day by age groups and to conduct a population PK analysis of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in paediatric subjects with MDR-TB

The secondary objectives are:

- To evaluate the PK/PD relationship of delamanid and its metabolite plasma concentrations and change in QTc when delamanid is administered in combination with OBR during a 6-month treatment period in paediatric subjects with MDR-TB
- To evaluate the efficacy of delamanid when administered in combination with an OBR during a 6-month treatment period in paediatric subjects with MDR-TB
- To determine the palatability of the DPF (applicable for Groups 3 and 4 only)

Study design

Both Trial 232 and Trial 233 are age de-escalation trials in which paediatric subjects are enrolled in 4 age groups: adolescents ages 12 to 17 years, inclusive (Group 1); children ages 6 to 11 years, inclusive (Group 2); children ages 3 to 5 years, inclusive (Group 3); and newborns and infants ages birth to 2 years, inclusive (Group 4).

All subjects must have completed the paediatric PK Trial 232 prior to enrolment into Trial 233. Those subjects who have completed Trial 232 and choose to enter Trial 233 must rollover from Trial 232 within 30 days of completing that trial. Subjects who terminate Trial 233 early are not replaced.

Blood samples were taken for determination of delamanid and metabolite (DM-6705) plasma concentrations.

An interim analysis was conducted focusing on groups (Groups 1 and 2) treated with the adult formulation. As of the cutoff date of 13 Dec 2016, all subjects enrolled into Groups 1 and 2 have completed the 24-month MDR-TB therapy including the 6-month delamanid treatment, the overall 6-month posttreatment and follow-up periods, and the 12-month treatment outcome follow-up.

Study population /Sample size

At least 36 males and females ages birth to 17 years, inclusive, who have successfully completed Trial 232, and meet all of the inclusion criteria and none of the exclusion criteria, and are receiving OBR for confirmed or presumptive MDR-TB were planned to be enrolled in 4 treatment groups based on age. As of the cutoff date, 13 subjects have been enrolled in the trial. Seven subjects were enrolled into Group 1 (12 to 17 years) and 6 subjects into Group 2 (6 to 11 years). All subjects were treated with the IMP and no subject discontinued. Overall, 6 male and 7 female subjects with a mean (standard deviation [SD]) age of 12.7 (3.4) years and a mean (SD) weight of 32.4 (9.3) kg were enrolled at 3 sites in the Philippines (2 sites) and South Africa (1 site).

Treatments

Eligible subjects are assigned to 1 of 4 treatment groups based on age and receive delamanid for 182 days:

- Group 1 (ages 12 to 17 years, inclusive): Adult formulation delamanid 100 mg twice daily (BID) + OBR (n = 6 [target enrolment number])
- Group 2 (ages 6 to 11 years, inclusive): Adult formulation delamanid 50 mg BID + OBR (n = 6)
- Group 3 (ages 3 to 5 years, inclusive): DPF 25 mg BID + OBR (n = 12)
- Group 4 (ages birth to 2 years, inclusive): DPF dose based on body weight during baseline visit (n = 12):
    - Subject > 10 kg will receive DPF 10 mg BID + OBR
    - Subject > 8 and ≤ 10 kg will receive DPF 5 mg BID + OBR
    - Subject ≤ 8 kg will receive DPF 5 mg once daily (QD) + OBR
    - Delamanid dose will be adjusted as needed for Group 4 subjects based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).

PK Outcomes/endpoints

For each subject, the following PK parameters were determined for delamanid and delamanid metabolite (DM-6705):

- C_{max}, t_{max}, $AUC_{0\text{-}24h}$ on Day 1 and Day 10
- $t_{½\ z}$ on Day 10
- Rac Day 10/Day 1 for $AUC_{0\text{-}24h}$, and apparent total clearance (CLss/F) for delamanid only

Statistical Methods

Determination of Sample Size:

This was a phase 1, open-label trial to assess the PK parameters, safety and tolerability of delamanid. No formal statistical hypothesis testing was planned. Thus, no formal sample size calculation based on statistical power was required. All statistical presentations are descriptive.

The following delamanid PK parameters were determined using noncompartmental analysis:

- Peak (maximal) concentration of drug in plasma (C_{max}), time of peak concentration of drug (t_{max}), area under the plasma concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24h}$) on Day 1 and Day 10
- Accumulation ratio Day 10/Day 1 for $AUC_{0\text{-}24h}$
- Apparent terminal phase elimination half-life ($t_{1/2z}$) and apparent total clearance

PK analysis of delamanid metabolite (DM-6705) plasma concentrations was performed where feasible.

- The following PK parameters were determined for DM-6705 using noncompartmental analysis: C_{max}, t_{max}, $AUC_{0\text{-}24h}$ on Day 1 and Day 10 and $t_{1/2z}$.

Plasma concentrations and PK parameters when determined, were reported with descriptive statistics in the PK report. No prior inferential statistical comparisons were performed.

PK Results

No PK/pharmacodynamic (PD) data are summarised or listed in the synoptic clinical study report (CSR) as the analysis is ongoing. Those results will be included either in the final CSR or reported separately.

Population PK analysis

A population PK model was developed for delamanid in the paediatric population with the data collected in Trials 232 and 233 in order to define the dose in the paediatric patients.

The objectives of the analyses described herein were to:

- Develop the population PK model and evaluate the effect of the covariates on the variability of PK of delamanid in the paediatric population.
- Define the paediatric doses for patients between 0-17 years of age that will result in a delamanid systemic exposure comparable to that in adults following the approved

An internal interim population PK model of delamanid was used as the starting point for the base model building. A 2-compartment model with transit compartment modelled absorption (number of transit compartments = 1) and linear elimination (with interindividual variability on clearance [CL] and central volume of distribution [Vc]; inter-occasional variability on bioavailability [F1] and mean absorption time [MAT]) was determined to adequately fit the data. Weight was determined to be significant covariate on CL, Vc, inter-compartmental clearance (Q) and peripheral volume of distribution (Vp) in the model. Age was a significant covariate on F1 only for age < 2 y. A summary of the covariates that may be evaluated and the PK parameters on which each were to be tested was provided. Covariates were selected based on known or hypothetical factors that could affect the PK. The relationships between covariates and model parameters were explored graphically using the empirical Bayesian estimates (EBEs) from the final base model. Also, to screen for other covariate relationships unanticipated.

Potential covariates were tested in a stepwise process on key PK parameters. The covariate selection was performed using forward addition process followed by a backward deletion approach. In order to be retained in the final model, a potential covariate will be required to offer statistically significant improvement in the model fit as estimated by the Likelihood Ratio Test (LRT).

A number of standard diagnostic plots was used throughout model development to assess the ability of each model to describe the observed data. These diagnostic plots include observed vs. individual and population predicted concentrations (PRED), weighted residuals/CWRES/ normalised prediction distribution errors vs. PRED or time.

Bootstrap re-sampling techniques was used to evaluate the stability of the final model and to estimate confidence intervals for the model parameters. Visual Predictive Checks (VPCs) were used to evaluate the predictive ability of the final model.

Stochastic simulation scenarios potentially examined a range of doses and regimens to support dose selection. The final population PK model was used as a basis for these simulations. Demographic information (i.e. age, body weight) was extracted from two studies in paediatric TB patients. Study 1 is observational study in MDR-TB paediatric patients, while Study 2 is hospital-based study for paediatric patients who started TB treatment (not MDR). Both studies were conducted in South Africa. For the source of adult exposure, data from adult subjects with MDR-TB who received 100 mg BID treatment regimen of delamanid (Study 242-07-204) was used.

The CHMP was of the view that the population PK modelling approach used to inform doses to be used in children of 6 to 17 years of age, assuming that similar PK exposure as in adults should lead to similar response to delamanid, is acceptable in principle provided that other factors that also impact overall response to treatment are also comparable in adult and paediatric populations: these include disease stage and concomitant medications.

Childhood tuberculosis (TB) is heterogeneous manifesting as pleural effusions, disseminated (miliary) disease, lymph node disease, central nervous system disease, congenital TB, skeletal disease, and (later in childhood) adult-type disease.

Clinical information on efficacy of delamanid in adults is not available other than for pulmonary MDR-TB; however, there is little evidence in general on treatment of MDR-TB in children at this time and therefore the treatment of MDR-TB and extensively-drug resistant tuberculosis (XDR-TB) in paediatric patients is guided by the same principles and uses the same second-line drugs as the treatment in adult patients. Accordingly, programmes for treating children with MDR-TB use the World Health Organisation (WHO) guidelines applied for treatment of adult patients. With respect to concomitant medication administered specifically to children, the principles for concomitant drug administration specified in the Deltyba SmPC are applicable.

As regards the Pop PK model development and evaluation, the CHMP considered overall that the methods used are state of the art, and noted that the MAH provided a discussion on the scientific plausibility of the covariates tested on the different model parameters and presented the collinearity/correlation between categorical vs continuous covariates. Results show overall good estimation of parameters. Only the intercompartmental clearance was estimated with a RSE of>50%. Results of graphical evaluation are also overall acceptable.

Results of simulation results were shown for C_{max} and AUCs. However, the only comparison with adult results was the AUC ratios for AUCs (presumably) medians and the MAH was therefore requested to provide box plots displaying comparisons of distributions of AUC, C_{max} and C_{min} between adults and different range of bodyweight in children should be provided. The MAH was also requested to present, compare and discuss the relevance of C_{min} and provide distributions of C_{min} for comparison between adults and paediatric subjects.

The MAH provided data summarising the median steady state area under the concentration-time curve (AUC) and C_{max} ratios of paediatric patients vs adults at the recommended dosage for paediatric patients in **Table 7**. Box plots displaying comparisons of distributions of AUC and maximum (peak) plasma concentration of the drug (C_{max}) between adults and children in different ranges of body weight are shown in **Figure 6** and **Figure 7** respectively. The source of AUC values for adults used in the calculations was the observed data from adult subjects with multidrug resistant-tuberculosis (MDR-TB) who received a 100 mg twice daily (BID) treatment regimen of delamanid in Trial 242-07-204. The data for the adult C_{max} values were derived from the adult patients with post-hoc parameter estimates in the Population Pharmacokinetic (Pop PK) model. Since non-clinical and clinical pharmacokinetic/pharmacodynamic (PK/PD) analysis suggested AUC/minimum inhibitory concentration is considered an efficacy driver of delamanid (Otsuka Report No. 025547), the minimum (trough) plasma concentration of the drug (C_{min}) may not be relevant justification of the paediatric dosage. The box plots and median ratio for C_{min} are also presented in **Figure 8** and **Table 7**, respectively, as requested.

Table 7 Summary of Recommended Dose in Paediatric Patients

Age Group	Weight Group	Dose	AUC Median Ratio vs Adult	$C_{max,ss}$ Median Ratio vs Adult	$C_{min,ss}$ Median Ratio vs Adult
QD dosing					
Age ≤ 2 years	< 10 kg	40-50 mg	0.871-1.17	359-447	1.03-1.29
	10 to 20 kg	40-50 mg	0.891-1.09	334-430	0.962-1.24
Age ≥ 2 years	< 10 kg	25-35 mg	0.81-1.13	318-449	0.916-1.29
	10 to 20 kg	40-50 mg	0.867-1.13	358-437	1.03-1.26
	20-30 kg	100 mg	0.952	344	0.991
	30-40 kg	Not achievable up to 100 mg			
	40-50 kg				
	≥ 50 kg				
BID dosing					
Age ≤ 2 years	< 10 kg	20 to 25 mg	0.87-1.16	312-388	0.899-1.12
	10 to 20 kg	20 to 25 mg	0.886-1.1	294-381	0.847-1.1
Age ≥ 2 years	< 10 kg	15-20 mg	0.955-1.22	336-430	0.968-1.24
	10 to 20 kg	20 to 25 mg	0.883-1.18	307-380	0.885-1.09
	20-30 kg	30-40 mg	0.862-1.16	297-411	0.856-1.18
	30-40 kg	35-**50 mg**	0.81-1.14	269-387	0.775-**1.12**
	40-50 kg	**50**-100 mg	0.931-1.2	319-418	**0.919**-1.2
	≥ 50 kg	50-**100 mg**	0.834-1.02	278-346	0.801-**0.997**

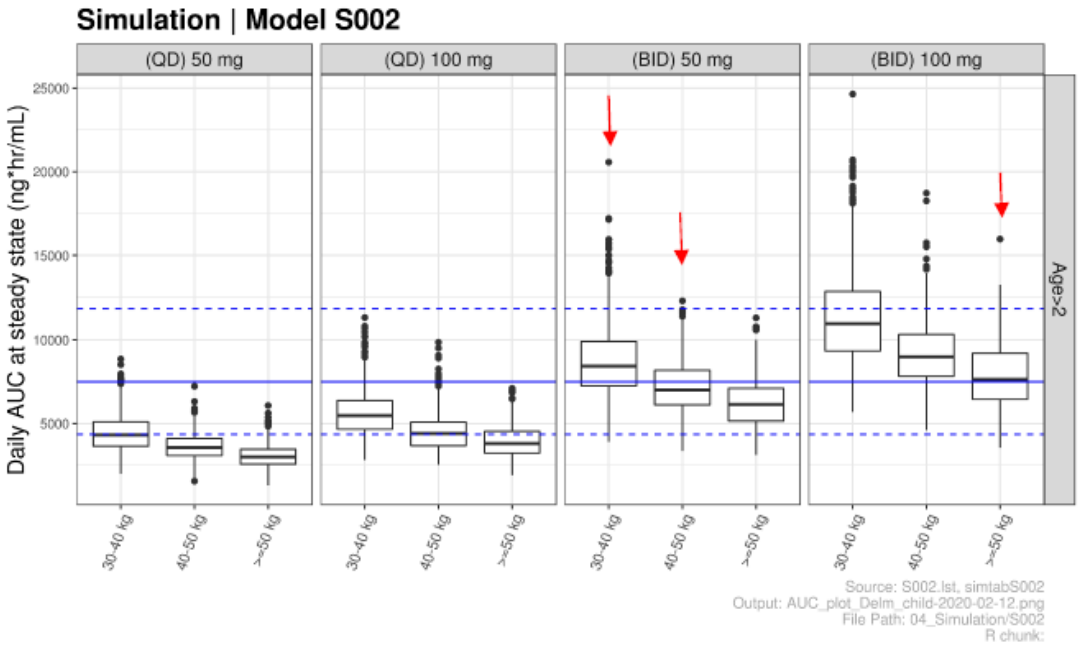
$C_{max,ss}$ = maximum (peak) steady-state drug concentration in the plasma during a dosing interval;

$C_{min,ss}$ = minimum (trough) steady-state drug concentration in the plasma during a dosing interval;

QD = once daily.

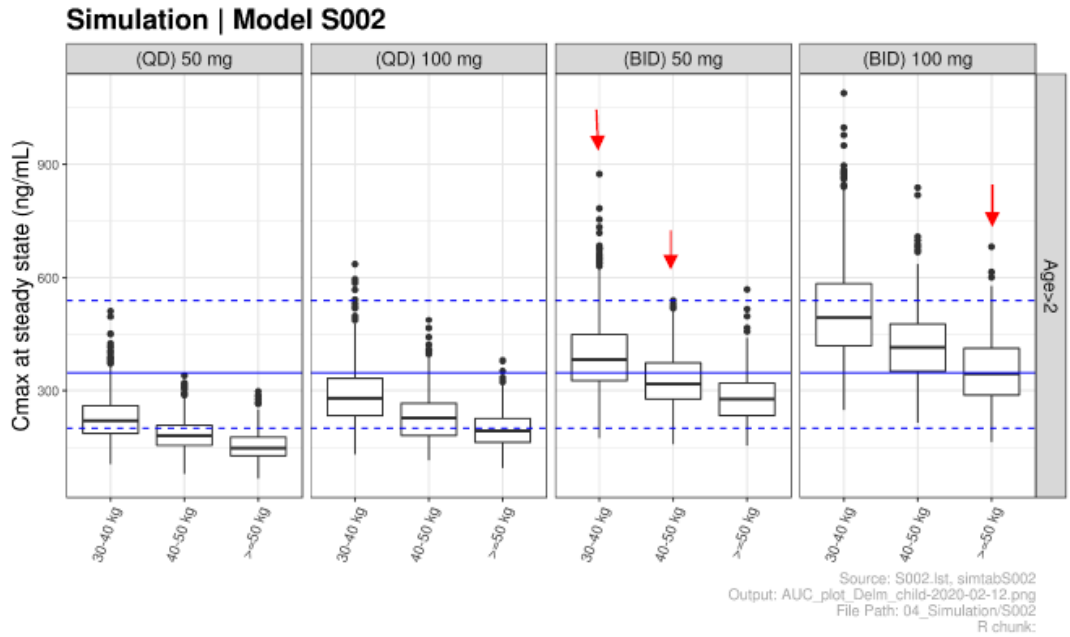
Note: Underlines represent current proposed dosage regimens.

Figure 6 Simulated Daily AUC at Steady State in Each Age, Weight Group at different dosages



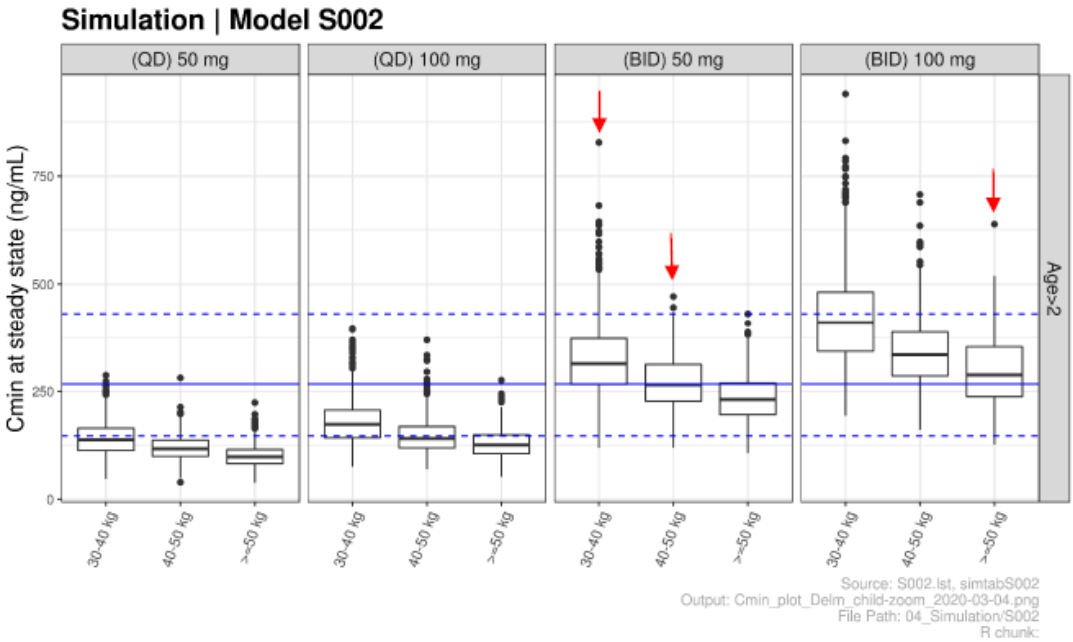
Note: Upper plots include all weight categories; lower plots include only 30-50 weight categories.
Note: Blue solid and dashed line represent median and 5-95th percentiles of adult exposure with 100 mg BID in clinical study report (CSR) 242-07-204. Red arrows represent current proposed dosage regimens.

Figure 7 Simulated C_{max} at Steady State in Each Age, weight Group at different dosages



Note: Upper plots include all weight categories; lower plots include only 30-50 weight categories.
Note: Blue solid and dashed line represent median and 5-95th percentiles of adult exposure with 100 mg BID in Trial 242-07-204. Red arrows represent current proposed dosage regimens.

Figure 8 Simulated C_{min} at Steady State in Each Age, weight Group at different dosages



Note: Upper plots include all weight categories; lower plots include only 30-50 weight categories.

Note: Blue solid and dashed line represent median and 5-95th percentiles of adult exposure with 100 mg BID in Trial 242-07-204. Red arrows represent current proposed dosage regimens

The CHMP assessed the boxplots of distributions of AUC_{ss}, C_{maxss} and C_{minss} in the paediatric weight groups as requested, compared to the corresponding PK metrics in adults receiving 100 mg BID. The CHMP was of the view that the results are consistent with the proposed dose of 50 mg BID in 30-50 kg. For the >50 kg group, the adult dose is proposed consistently with the fact the median weight in the adult study was 55 kg. This is endorsed.

The CHMP assessed the choice of weight bands proposed by the MAH and the selected threshold of 30 kg selected for children with an age limit of 6 years and older. For the 40 kg to 50 kg weight band, it is predicted that both 50 mg and 100 mg BID provide similar AUC (i.e., the AUC ratio of paediatric patients to adults is 0.931 and 1.21, respectively, in the Pop PK report (Otsuka Report No. 242-19-259, Table 8-5). Since DOSE = 100 mg is treated as categorical covariate of relative bioavailability, it is difficult to simulate the exposure between 50 mg and 100 mg. By comparing the point estimates and distribution, 50 mg BID is considered to be closer to the exposure in adults, thus 50 mg BID is selected as the optimal dose.

In agreement with the PIP children recruited for the paediatric Trial 242-11-232 and Trial 242-11-233 have been subdivided into 4 age groups (0 to 2, 3 to 5, 6 to 12, and 13 to 17 years of age) and dosed according to age groups. Doses applied to children 12 to 17 years of age were the adult dose of 100 mg delamanid BID and to children 11 to 6 years of age 50 mg delamanid BID when both age groups received the adult tablet formulation (50-mg film-coated tablet) in paediatric trials while younger children received delamanid DPF. However, PK/PD analysis in paediatric patients assessing the paediatric dose for children that will result in delamanid systemic exposure comparable to that in adults following the approved dose suggests weight-based dosing in children. The current line extension for the use of delamanid in children 6 to 17 years of age is based on an interim analysis of Trial 242-12-233 for these paediatric age groups, which had completed the trial whereas the trial was still ongoing in younger children.

When delamanid dosing is suggested based on the simulation results, children with a weight of < 30 kg should receive the DPF, which is available in 5 mg and 25 mg dispersible tablet strength. As the clinical Trial 242-12-233 using the DPF was still ongoing and final results on safety and efficacy for the use of the DPF were not available at the time of the interim analysis (data cut-off 13 Dec 2016), the current indication extension proposes that the 30 kg threshold be used. Additionally, the interim analysis included only children older than 6 years of age and therefore using a conservative approach, the MAH suggested the age (> 6 years) as well as the weight band (> 30 kg). For children with a body weight < 30 kg the existing 50 mg film-coated tablets would not be considered the optimal strength. Therefore, dosing proposals for these children will be included in the upcoming 2nd type II variation addressing the younger age groups. With this variation the MAH will also submit an extension application to establish the delamanid dispersible tablets which are more appropriate for administration in children with younger age and lower body weight.

Of note, the > 50 kg subgroup was underrepresented in the model building dataset (only 3 children included), and the model-based simulations are therefore not reliable for this subgroup. The dose proposed is the adult dose, which is agreed since the median weight in the adult Pop PK data (Trial 242-17-256) population is 55 kg.

2.4.3. Pharmacodynamics

No specific studies have been conducted in the paediatric population. The presentation and treatment of pulmonary tuberculosis is similar in adults and paediatric patients aged from approximately 10 years so that an extrapolation of safety and efficacy data obtained from adults is acceptable.

The presentation of clinical disease may be different in children aged less than approximately 10 years compared to adults but the response to treatment may be comparable at least from the age of five years upwards, supporting the possibility of extrapolating efficacy documented in adults to this age group.

2.4.4. PK/PD modelling

A PK/PD modelling analysis including trial 233 data to determine the relationship between delamanid and DM-6705 plasma concentrations and changes in QTc interval will be performed.

2.4.5. Discussion on clinical pharmacology

A population PK modelling approach was used to inform doses to be used in children of 6 to 17 y, assuming that similar PK exposure as in adults should lead to similar response to delamanid. This is acceptable as other factors that also impact overall response to treatment are also comparable in adult and paediatric populations: these include disease stage and concomitant medications. Additionally, it should be kept in mind that Deltyba obtained a conditional approval and that there is still uncertainty on the optimal dose in the adult population.

As regards the Pop PK model development and evaluation, the methods used are overall considered state of the art. The MAH provided a discussion on the scientific plausibility of the covariates tested on the different model parameters. Collinearity/correlation were tested between continuous covariates and between categorical vs continuous.

The boxplots of distributions of AUC_{ss}, C_{maxss} and C_{minss} in the paediatric weight groups, compared to the corresponding PK metrics in adults receiving 100 mg BID, are consistent with the proposed dose of 50 mg BID in 30-50 kg. For the >50 kg group, the adult dose is proposed consistently with the fact the median

weight in the adult study was 55 kg. This is endorsed.

In the absence of a concentration-corrected-QT interval modelling analysis (PK/PD) with completed Trial 242-12-233, it is hard to assess the available laboratory data on the prolongation of the QTc interval. Linear QTc/RR regression is a well-known and easy to apply technique providing an accurate estimate of the remaining influence of the RR-interval on the corrected QT-intervals. Optimal QTc correction should be independent of the RR-interval, the linear regression slope and R^2 should be 0. The CHMP noted the MAH commitment to submit the detailed report on the concentration-corrected-QT interval modelling analysis in the upcoming 2nd Type II variation addressing the younger age groups.

While awaiting this analysis to support the safety assessment of the proposed paediatric dose regimen, the MAH was requested to provide a thorough discussion of the risk of QT-interval in more detail, in particular the relationship between QT-prolongation, dosages given/weight, time to onset, and data on serum concentration of DM-6705 at time of event, if possible. The MAH was also asked to discuss the clinical consequences of the increase of this surrogate marker in the paediatric population.

The MAH stated that *in vitro* studies have shown that delamanid inhibits hERG channel (cardiac potassium channel); however, in pre-clinical studies, prolongation of the QT interval corrected for heart rate (QTc) was observed only with repeated delamanid dosing, while single doses of delamanid showed no effect on electrocardiograph (ECG) QTc interval. It has been postulated that metabolites of delamanid, and in particular DM-6705 (which results from metabolism of delamanid in plasma by albumin), may be primarily responsible for prolongation of QTc. This hypothesis is supported by the *in vitro* effect of DM-6705 and other delamanid metabolites on HEK-293 and CHO-K1 cells that express hERG channels.

In the delamanid Phase 2 clinical Trial 242-07-204, Day 56 C_{max} values were used to compute predictions for QTc change from baseline, and the highest DM-6705 concentrations were observed on Day 56, and the QTc prolongation reversed after drug was discontinued on the same day. Therefore, DM-6705 concentrations were identified as a surrogate marker for QTc prolongation. Around 3% of patients experienced an increase of 60 ms in QTc interval corrected for heart rate by Fredericia's formula (QTcF) or greater at some point during the trial, and QTcF greater than 500 ms was observed in 10% and 13% of patients receiving delamanid 100 mg BID and 200 mg BID, respectively. However, no clinical cardiac manifestations, Torsades de Pointes (TdP) arrhythmias, or temporary related arrhythmias were reported among those patients. The QTc interval prolongation developed slowly over time in the first 6 to 10 weeks of treatment and remained stable thereafter, corresponding to the time to steady state of DM-6705.

A concentration-corrected-QT interval modelling analysis (PK/PD) is completed and results are integrated in the updated PopPK/PD report (Otsuka Report No. 242-19-259).

Based on the linear mixed effects modelling, the concentration of delamanid does not have a significant impact on ΔQTc interval corrected for heart rate by Bazett's formula (QTcB) (slope for delamanid: 0.00792 ms/[ng/mL], 90% confidence interval [CI]: −0.00132, 0.0172), whereas a significant positive correlation was detected for the concentration of DM-6705 (slope for DM-6705: 0.0613 ms/[ng/mL], 90% CI: 0.016, 0.107). Based on this regression model between QTcB and DM-6705 and the observed metabolic ratio to DM-6705 in Trial 242-12-232, ΔQTcB are simulated with the recommended regimen and the results are found in **Table 8**

Due to lack of placebo data, ΔΔQTcB cannot be derived in this analysis. However, the model-predicted that the upper bounds of the 90% CIs of ΔQTcB values were all less than 1 ms at the simulated C_{max} of DM-6705 following the recommended regimen, suggesting that there is unlikely to be a clinically meaningful effect on the QT interval.

Table 8 Model Predicted ΔQTcB with Recommended Dose

Age Group	Weight Group	Maximum Recommended Dose	Simulated[a] Median C_{max} of DM-6705 (ng/mL)	Model-Predicted ΔQTcB Point Estimate (ms, 90% CI)
QD Dosing				
Age ≤ 2	< 10 kg	50 mg	82.6	5.07 (1.80, 8.33)
	10-20 kg	50 mg	80.5	4.93 (1.76, 8.11)
Age > 2	< 10 kg	35 mg	81.9	5.02 (1.79, 8.26)
	10-20 kg	50 mg	78.8	4.83 (1.72, 7.95)
	20-30 kg	100 mg	65.9	4.04 (1.44, 6.64)
	30-40 kg	Achievable up to 100 mg	–	–
	40-50 kg		–	–
	≥ 50 kg		–	–
BID Dosing				
Age ≤ 2	< 10 kg	25 mg	71.3	4.37 (1.55, 7.19)
	10-20 kg	25 mg	68.4	4.19 (1.49, 6.90)
Age > 2	< 10 kg	20 mg	75.6	4.64 (1.65, 7.62)
	10-20 kg	25 mg	73.3	4.49 (1.60, 7.39)
	20-30 kg	40 mg	70.6	4.33 (1.54, 7.11)
	30-40 kg	50 mg	67.9	4.16 (1.48, 6.84)
	40-50 kg	100 mg	75.2	4.61 (1.64, 7.59)
	≥ 50 kg	100 mg	59.6	3.65 (1.30, 6.01)

[a]Calculated as median C_{max} of Delamanid × 0.180 (Median Ratio of Delamanid/DM-6705 $AUC_{0 \text{ to } 24h}$ in Age Group 1 in Trial 242-12-232)
Source: PDATA-9 (19Feb2020).

The overall incidence of drug-induced TdP is generally unknown for paediatric populations, but paediatric cases of QTc interval prolongation and TdP have been associated with various drugs, including dopamine antagonists (domperidone, risperidone), antiarrhythmic agents (amiodarone, procainamide, and sotalol), and antifungals (fluconazole and voriconazole).

A literature review involving multiple prospective cohorts in various age groups among children receiving domperidone, none of the patients had a QTc interval above 500 ms or experienced an increase in QTc interval of more than 60 ms relative to the pre-treatment value; however, drug-induced QTc interval prolongation to greater than 450 ms has been noted as a reason for concern. Fortunately, none of the patients in this analysis experienced TdP or sudden cardiac death.

Drug-induced QTc interval prolongation and TdP are usually attributed to predisposing risk factors including female sex; advanced age (> 65 years); hypokalaemia, hypomagnesemia, or hypocalcaemia; heart failure with reduced ejection fraction; bradycardia; treatment with more than 1 QTc interval-prolonging drug; and conditions leading to elevated plasma concentrations of such drugs, such as kidney or liver disease, drug interactions, and rapid IV administration. It is generally unknown which of these risk factors would apply to paediatric populations; however, hypokalaemia, hypomagnesemia, bradycardia, and elevated plasma concentrations of QTc interval-prolonging drugs have been postulated as potential risk factors for paediatric patients similar to adults. Additionally, female sex at or following puberty has been identified as a risk factor for QTc interval prolongation and TdP.

In the delamanid Phase 2 clinical Trial 242-07-204 in adult patients, the QTc interval prolongation developed slowly over time in the first 6 to 10 weeks of treatment and remained stable thereafter, corresponding to the time to steady state of DM-6705.

Regarding the modelling-based proposed dose regimen in the paediatric population with a body weight above 30 kg, the MAH completed the concentration-corrected-QT interval modelling analysis (PK/PD). The results are integrated in the updated PopPK/PD report (Otsuka Report No. 242-19-259). This updated study report has not been provided by the MAH, but the results of the model predicted ΔQTcB interval are provided and discussed. Based on the linear mixed effects modelling, there was a significant positive correlation between the concentration of DM-6705 and ΔQTcB. The upper bounds of the 90% CIs of ΔQTcB values were all less than 10 ms at the simulated C_{max} of DM-6705 following the recommended regimen.

The C-QT modelling using linear mixed effects approach is in principle only valuable to model observed concentrations when large enough concentration ranges are covered (including at least 2x therapeutic), in order to be able to exclude or not a clinically relevant effect (10ms) on the average. A 6-7ms prolongation at therapeutic dose can definitely lead to >10ms at supratherapeutic concentrations, and therefore a QT effect cannot be ruled out. Nothing precise can be concluded on the actual effect size when only therapeutic doses are used.

The CHMP noted that the MAH only reported ΔQTcB. As stated in the EMA guideline on the through QT analysis, Bazett's correction is frequently used in clinical practice and in the medical literature. In general, however, Bazett's correction overcorrects at elevated heart rates and under corrects at heart rates below 60 bpm and hence is not an ideal correction. Fridericia's correction is more accurate than Bazett's correction in subjects with such altered heart rates and the MAH was therefore asked to also report model predicted ΔQTcF.

In the QTC concentration-response analysis in trial 242-09-213 for the adult population, predicted mean placebo-adjusted ΔQTcF values were slightly higher than the corresponding predicted mean placebo-adjusted ΔQTcB values. The highest placebo-adjusted ΔQTcF was predicted for DM-6705 at Week 8, with the value of 7.10 ms and upper bound of one-sided 95% CI of 8.14 ms predicted by the nonlinear model. The corresponding values from the linear model were 6.93 ms and 7.75 ms.

The currently provided data suggest that if 50 mg BID is used for paediatric patients weighing 30-50 kg and 100 mg BID for those above 50 kg, the model-predicted ΔQTc values will be in the same range as those observed in the adult population.

The MAH stated that from a scientific perspective the QT correction method used should show no relationship between QT interval and RR[1]. The MAH therefore evaluated the relationship between RR and QT/QTc intervals via scatterplots using data at drug-free state on Day −1. As shown in **Figure 9**, QTc by Fridericia's correction showed significant correlation with heart rate ($P < 0.01$, $R2 = 0.484$), while this correlation was greatly reduced after the Bazett's correction ($P = 0.026$, $R2 = 0.044$).
Thus, QTcB was determined to be a more adequate correction method for heart rate than QTcF for the current population. This observation is consistent with a previous article that evaluated various heart rate correction formulas in children[2]. This article concluded that "The Fridericia's correction may work well for adults, in whom average heart rates tend to be 60 - 90 bpm. However, children, especially infants, tend to have average heart rates well above 100 bpm. Therefore, the Bazett correction may be more appropriate for drug safety trials and clinical studies involving infants and young children."

[1] Garnett C, Bonate PL, Ferber G, Huang D, Liu J, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodynam 2018;45:383–397.
[2] Phan DQ, Silka MJ, Lan YT, Chang RK. Comparison of formulas for calculation of the corrected QT interval in infants and young children. J Pediatr. 2015;166(4):960- 964.

Figure 9 Linear regression of QT, QTcB and QTcF versus RR Plots

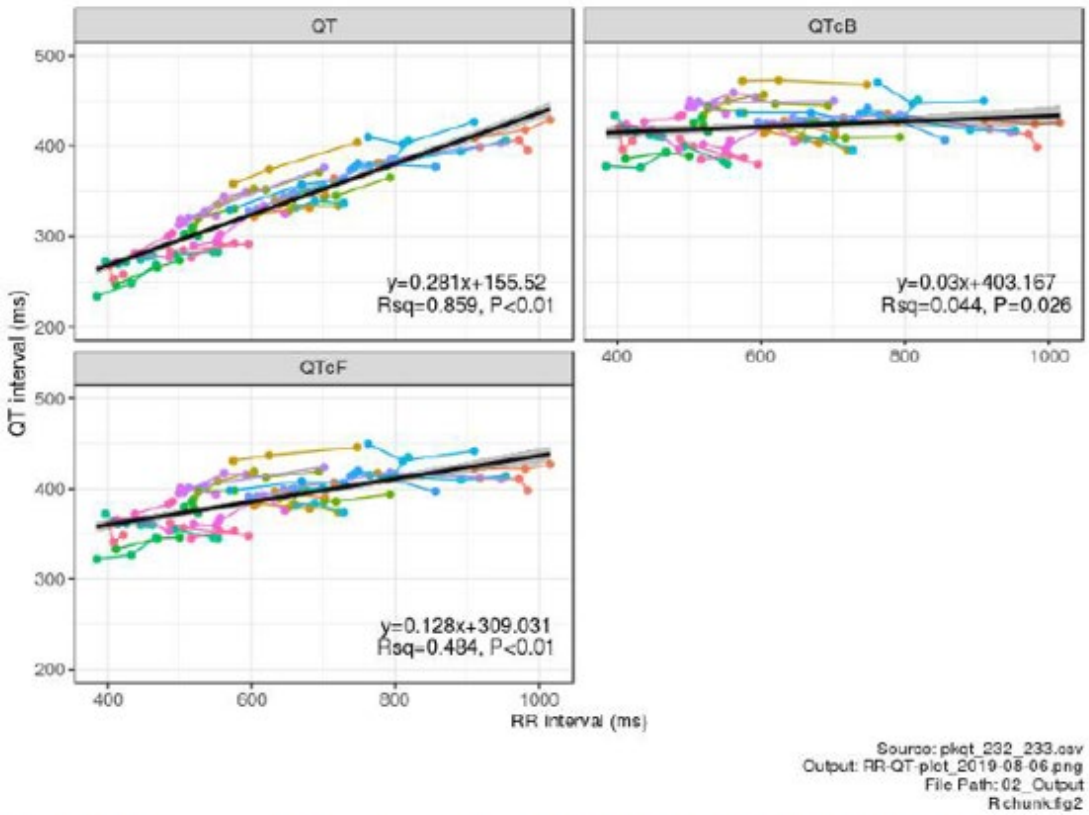


Figure 1.2.1-4 Linear regression of QT, QTcB and QTcF versus RR Plots

Rsq: R squared
Closed circles represent observed data.
Each line represents data from one subject.
Black solid line with grey shaded area represent linear regression line with 90% CI.

Although QTcF was concluded as not appropriate for the current population, as per the CHMP request, a linear regression analysis was conducted between ΔQTcF and the concentration of delamanid and DM-6705, separately. Based on the linear mixed effects modelling, a significant positive correlation was detected for the concentration of delamanid and DM-6705 (slope for delamanid: 0.0154 ms/[ng/mL], 90% CI: 0.00703 to 0.0237; slope for DM-6705: 0.117 ms/[ng/mL], 90% CI: 0.0797 to 0.155). By using these regression models between ΔQTcF and delamanid/DM-6705, ΔQTcFs are simulated with recommended regimen in Table 9. The model-predicted upper bounds of the 90% CIs of ΔQTcF value were greater than 10 ms at the simulated Cmax of DM-6705 following all dosing regimens of interest. Although this evaluation might not be appropriate, since the effect of heart rate on QT is not sufficiently corrected by QTcF, the model predicted ΔQTcF and ΔQTcB point estimates show no clinical meaningful differences. Therefore, it can be concluded that the results from the model estimating ΔQTcF re-confirm the initially reported results.

Table 9 Model Predicted ΔQTcF with Recommended Dose

Age Group	Weight Group	Maximum Recommended Dose	Model-Predicted ΔQTcB Point Estimate by C_{max} of DM-6705[a] (ms, 90% CI)	Model-Predicted ΔQTcF Point Estimate by C_{max} of Delamanid (ms, 90% CI)	Model-Predicted ΔQTcF Point Estimate by C_{max} of DM-6705[a] (ms, 90% CI)
BID dosing					
Age ≤ 2 years	< 10 mg	25 mg	4.37 (1.55, 7.19)	6.09 (3.02, 9.15)	7.72 (5.32, 10.1)
	10 - 20 mg	25 mg	4.19 (1.49, 6.90)	5.84 (2.90, 8.78)	8.35 (5.75, 10.9)
Age > 2 years	< 10 mg	20 mg	4.64 (1.65, 7.62)	6.46 (3.21, 9.70)	8.01 (5.52, 10.5)
	10 - 20 mg	25 mg	4.49 (1.60, 7.39)	6.26 (3.11, 9.40)	8.86 (6.10, 11.6)
	20 - 30 mg	40 mg	4.33 (1.54, 7.11)	6.03 (2.99, 9.06)	8.58 (5.91, 11.2)
	30 - 40 mg	50 mg	4.16 (1.48, 6.84)	5.79 (2.88, 8.71)	8.27 (5.70, 10.8)
	40 - 50 mg	100 mg	4.61 (1.64, 7.59)	6.42 (3.19, 9.66)	7.95 (5.48, 10.4)
	≥ 50 mg	100 mg	3.65 (1.30, 6.01)	5.09 (2.53, 7.65)	8.81 (6.07, 11.6)

R chunk: sim-QTc-recom

[a]Calculated as median Cmax of delamanid × 0.180 (median ratio of delamanid/DM-6705 AUC0-24h in age group 1 in Trial 242-12-232)

Note: Model-predicted ΔQTcB point estimate by C_{max} of delamanid was not shown, since the slope for delamanid was not statistically significant on ΔQTcB.

The CHMP was of the view that QT correction methods developed for adults do not automatically apply to children. Linear QTc/RR regression is a well-known and easy to apply technique providing an accurate estimate of the remaining influence of the RR-interval on the corrected QT-intervals. Optimal QTc correction should indeed be independent of the RR-interval, the linear regression slope and R^2 should be 0[3]. Wernicke et al[4] proposed, for clinical trials, to derive a population-specific correction factor 'e' in the formula $QTc = QT/RR^e$, based on pre-treatment ECG data from the population being studied.
In their study, ECG data were obtained from a meta-analysis of seven clinical trials for attention deficit/hyperactivity disorder (ADHD) involving 2,288 children and adolescents 6 to 17 years of age. The most appropriate formula for children and adolescents included in this database was found to be $QTc = QT/RR^{0.38}$. This is closer to Fridericia's correction $QTc = QT/RR^{0.33}$ than to Bazett's correction $QTc = QT/RR^{0.5}$.

In this case, the MAH followed a similar methodology evaluating the relationship between RR and QT/QTc intervals via scatterplots using data at drug-free state on Day −1. The optimal correction factor exponent 'e' was not determined, but the analysis showed that Bazett's correction was closer to the optimal correction (slope = 0.03, R^2 = 0.044) than Fridericia's correction (slope = 0.128, R^2 = 0.484). It is, therefore, considered appropriate to use Bazett's correction for the current paediatric population from 6 to 17 years of age in the paediatric study.

Regarding the modelling-based proposed dose regimen in the paediatric population with a body weight above 30 kg, the MAH previously completed the concentration-corrected-QT interval modelling analysis (PK/PD). Based on the linear mixed effects modelling, there was a significant positive correlation between the concentration of DM-6705 and ΔQTcB. The upper bounds of the 90% CIs of ΔQTcB values were all

[3] Vandenberk B, Vandael E, Robyns T, Vandenberghe J et al. QT correction across the heart rate spectrum, in atrial fibrillation and ventricular conduction defects. Pacing Clin Electrophysiol. 2018;41(9):1101-1108.
[4] Wernicke JF, Faries D, Breitung R, Girod D. QT correction methods in children and adolescents. J Cardiovasc Electrophysiol. 2005;16(1):76-81.

less than 10 ms at the simulated C_{max} of DM-6705 following the recommended regimen. The upper bounds of the 90% CIs of ΔQTcF values were above 10 ms at the simulated C_{max} of DM-6705 following the recommended regimen. However, in this population from 6 to 17 years of age, Bazett's correction is to be preferred.

Administration of delamanid has been shown to result in QT interval prolongation in the adult population and based on this simulation, this is also the case in children and adolescents aged 6 to 17 years. Appropriate warning on QT interval prolongation is included in the SmPC.

2.4.6. Conclusions on clinical pharmacology

The proposed dosing regimen for children is supported.

2.5. Clinical efficacy

2.5.1. Main study

Title of Study

Trial 242-12-233: Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC-67683) in Pediatric Multidrugresistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs over a 6-Month Treatment Period

Methods

This is a phase 2, open-label, multi-dose, multi-centre trial to assess the safety, tolerability, PK, and efficacy of delamanid tablets plus OBR in paediatric subjects with MDR-TB over a 6-month period. This long-term trial is an extension of Trial 232, and only subjects who have completed Trial 232 are eligible to participate in this trial (Trial 233).
Trial 233 is conducted sequentially in 4 groups of paediatric subjects.

As Trial 242-12-233 is still ongoing, all results presented in this efficacy update are based on an interim analysis of children 6 to 17 years of age, all of whom have completed the study.

This trial is being conducted at 3 sites qualified to treat paediatric subjects with MDR-TB.

Study participants

At least 36 male and female paediatric MDR-TB patients ages birth to 17 years of age, inclusive, who successfully completed paediatric PK trial 232 and must rollover from trial 232 within 30 days of completing that trial.

Subjects were assigned to 1 of 4 treatment groups based on age:

- Group 1: ages 12 to 17 years (minimum of 6 subjects, at least 2, but no more than 5 females)
- Group 2: ages 6 to 11 years (minimum of 6 subjects)
- Group 3: ages 3 to 5 years (minimum of 12 subjects)
- Group 4: ages birth to 2 years (minimum of 12 subjects)

Additional inclusion criteria:

- Confirmed diagnosis of MDR-TB, i.e., culture positive for Mycobacterium tuberculosis with isoniazid and rifampicin resistance on drug-susceptibility testing, or a positive rapid test demonstrating resistance to rifampicin alone or to rifampicin and isoniazid

  OR

- Presumptive diagnosis of pulmonary or extrapulmonary MDR-TB such that the treating physician has decided to treat for MDR-TB the subject who has one of the following:
    - Clinical specimen (e.g., cerebral spinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue specimen) suggestive of TB disease
    - Persistent cough lasting > 2 weeks
    - Fever, weight loss, and failure to thrive
    - Findings on recent chest radiograph or other imaging studies (prior to Visit 1) consistent with TB
    - And Household contact of a person with known MDR-TB or a person who died while appropriately taking drugs for drug-sensitive TB
    - Or on first-line TB treatment but with no clinical improvement
- Negative urine pregnancy test for female subjects who have reached menarche
- Written informed consent/assent

Key Exclusion Criteria:

- Patients who have not completed Trial 232
- Children with laboratory evidence of active hepatitis B or C
- Children with body weight < 5.5 kg
- For patients with HIV co-infection, CD4 cell count ≤ 1000/mm3 for children 1-5 years old, and ≤ 1500/mm3 for children less than 1 year old
- History of allergy to metronidazole and any disease or condition in which metronidazole is required
- Use of amiodarone within 12 months prior to the first dose of investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within 30 days prior to the first dose of IMP
- Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment)
- Pre-existing cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds
- Abnormalities in screening electrocardiogram (ECG) (including atrioventricular block, bundle branch block or hemi-block, QRS prolongation > 120 msec, or QT interval corrected using Fridericia's method (QTcF) > 450 msec in both males and females)

- A concomitant condition such as renal impairment characterised by serum creatinine levels > 1.5 mg/dL, hepatic impairment (alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of normal [ULN]), or hyperbilirubinemia characterised by total bilirubin > 2x ULN
- Concurrent diagnosis of severe malnutrition or kwashiorkor
- Positive urine drug screen (Groups 1 and 2 only)
- Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP and/or any prior or concurrent use of bedaquiline
- Lansky Play Performance Score < 50 (not applicable for children < 1 year old) or Karnofsky Score < 50
- Administered an IMP within 1 month prior to Visit 1 other than delamanid given as IMP in Trial 232
- Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form (Groups 1 and 2 only)

Treatments

Delamanid was administered for 6 months (182 days)

- Group 1: Adult formulation delamanid 100 mg twice daily (BID) + OBR
- Group 2: Adult formulation delamanid 50 mg BID + OBR
- Group 3: DPF 25 mg BID + OBR
- Group 4: DPF dose based on body weight during baseline visit:
    - Subject > 10 kg will receive DPF 10 mg BID + OBR
    - Subject > 8 and ≤ 10 kg will receive DPF 5 mg BID + OBR
    - Subject ≤ 8 kg will receive DPF 5 mg once daily (QD) + OBR
    - Delamanid dose will be adjusted as needed for Group 4 subjects based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).

One dose per day for a minimum of 5 days per week will be given under direct observation. It is recommended that all delamanid doses be administered under fed conditions in the morning and evening. It is also recommended that delamanid be dosed within 30 minutes of the start of a meal, if possible. Optimally, OBR medications should be given at least 1 hour prior to or 1 hour after dosing of delamanid.

Delamanid is added to an optimised background regimen (OBR) for the treatment of MDR-TB as per the World Health Organization Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis, relevant national guidelines for treating MDR-TB, and the investigator's best clinical judgment. OBR generally comprises 4 or more classes of first-line (other than isoniazid and rifampicin) and second-line anti-TB medications to which the patient's strain of MTB has suspected or documented susceptibility based on previous treatment history and epidemiologic and clinical factors.
Whenever possible, 5 or more classes of drugs are preferred for use in treatment, particularly in the initial stage of treatment. The components of OBR include:

1) Any remaining first-line anti-TB medications to which the patient's isolates are likely susceptible such as pyrazinamide

2) An anti-TB medication given by injection; preferred order of selection: amikacin > kanamycin >Capreomycin

3) Fluoroquinolone class; preferred order of selection: moxifloxacin, levofloxacin, gatifloxacin > ofloxacin (gatifloxacin to be used with caution secondary to rare but severe side effect of dysglycaemia; ciprofloxacin not recommended for use). Moxifloxacin causes QT interval prolongation and should not be used in this trial

Other medications include (but are not limited to):

4) Ethionamide or prothionamide

5) Cycloserine

6) Para-aminosalicyclic acid

Objectives

The primary objectives of this trial are:

- To evaluate the **long-term safety and tolerability** of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in paediatric subjects with MDR-TB for the age-specific delamanid doses determined in Trial 232
- To report delamanid and metabolite plasma concentrations at each visit day by age groups and to conduct a **population PK analysis** of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in paediatric subjects with MDR-TB

The secondary objectives are:

- To evaluate the **PK/PD** relationship of **delamanid and its metabolite** plasma concentrations and **change in QTc** when delamanid is administered in combination with OBR during a 6-month treatment period in paediatric subjects with MDR-TB
- To evaluate the **efficacy** of delamanid when administered in combination with an OBR during a 6-month treatment period in paediatric subjects with MDR-TB
- To determine the **palatability** of the DPF (applicable for Groups 3 and 4 only)

Outcomes/endpoints

The primary endpoints in this trial are:

- Safety and tolerability: Changes in physical examination including visual testing and audiometry during screening, TEAEs, vital signs, ECGs, Holter monitoring (if applicable), and clinical laboratory tests.
- Pharmacokinetics: Descriptive statistics of delamanid and metabolite plasma concentrations. Delamanid PK data from this trial will be combined with PK data from the Trial 232 and analysed using population PK methods.

The secondary endpoints in this trial are:

- Pharmacokinetics/Pharmacodynamics: PK/PD analysis for changes in QTc as a function of delamanid and metabolite (DM-6705) plasma concentrations.
- Efficacy: Culture conversion, normal chest radiography results, resolution of TB symptoms.

The efficacy of delamanid tablets in treating paediatric MDR-TB subjects is assessed by chest radiography (subjects with pulmonary disease), body weight/height, and resolution of TB symptoms (based on investigator evaluation). In addition, when available, sputum culture conversion (for culture-positive subjects) will be assessed in subjects who are able to produce sputum (or provide other biological specimens) for microbiological evaluation. Although microbiological assessment of sputum or other biological specimens is not required as part of this protocol, if collected by the investigator as part of routine subject management, all available results for smear microscopy, culture, identification, and drug susceptibility will be captured as an unscheduled visit. The final treatment outcome is a World Health Organisation (WHO) defined outcome and will be assessed by the investigator at 24 months of initial investigational medicinal product (IMP) dose. For the assessment of treatment outcome, culture and/or other clinical results could be taken into account.

- Palatability: The palatability of the DPF (Groups 3 and 4 only) is assessed using an age-appropriate visual hedonic scale and clinical assessment.

Sample size

No formal sample size calculations were performed.

Randomisation

Randomisation of patients was not planned.

Blinding (masking)

This is an open-label, non-controlled trial.

Statistical methods

No formal statistical analysis is planned due to the small sample sizes; all statistical presentations are descriptive.

Subject Samples:

- Safety Sample: Comprises the subjects who have received any amount of study medication in Trial 233, regardless of any protocol deviation or violation.
- Efficacy Sample: Comprises all subjects with at least one efficacy endpoint available, the efficacy end points include: 1) chest radiograph result; 2) investigator assessed clinical signs and symptoms of tuberculosis; 3) microbiologic assessment of sputum; 4) evaluable change from baseline in body weight or height at treatment.

Safety parameters are summarised by incidence rates and their change from baseline if applicable. Change from baseline is summarised for observed cases at each scheduled post-baseline visit and for the last visit.

Results

Participant flow

Table 10 Subject Disposition

Number of	Group 1 (ages 12-17) n (%)	Group 2 (ages 6-11) n (%)	Total (ages 6-17) n (%)
Screened	7	6	13
Enrolled[a]	7 (100.0)	6 (100.0)	13 (100.0)
Treated[b]	7 (100.0)	6 (100.0)	13 (100.0)
Completed study[c]	7 (100.0)	6 (100.0)	13 (100.0)
Discontinued study	0 (0.0)	0 (0.0)	0 (0.0)

Note: Data cutoff was 13 Dec 2016.

[a]Subjects who signed informed consent and enrolled in the trial.

[b]Subjects who took at least one dose of IMP.

[c]Subjects who are evaluated at the last scheduled visit of the trial, the Day 365 Follow-up Visit.

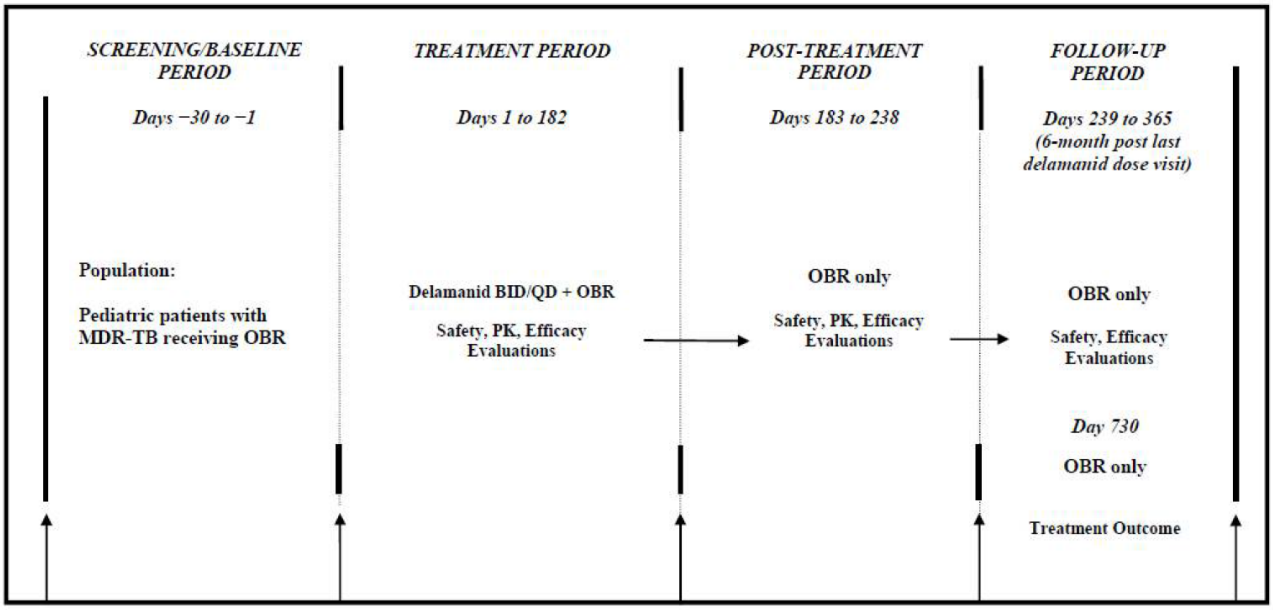
Patients who cannot be contacted on or before the scheduled M24 follow-up visit and who do not have a known reason for discontinuation (e.g., withdrew consent or AE) will be classified as "lost to follow-up" as the reason for discontinuation.

Recruitment

As of the cut-off date of 13 December 2016, 7 subjects have been enrolled into Group 1 (12 to 17 years) and 6 subjects into Group 2 (6 to 11 years).

Conduct of the study

Figure 10 Schematic trial design



Note: For the screening period, trial data will either be taken from screening or Day 10 of Trial 232 or will be performed during the post-Trial 232 thirty (30)-day screening period for Trial 233.

Trial 233 consists of: The screening period, baseline, treatment period (6 months DLM+OBR), post-treatment period (8 weeks OBR) and follow-up period with a visit at 6 months after the last delamanid dose and an additional treatment outcome follow-up one year after this last follow-up visit.
For the treatment outcome follow-up, all patients will either visit the clinic or be contacted by telephone for clinical assessment. Collection of treatment outcome information as routinely documented in the patient medical records or in national TB program.

Baseline data

Subjects were enrolled at 3 sites, 2 sites in the Philippines and 1 site in South-Africa. The race was Asian for 11 subjects (84.6 %).

Table 11 Subject Demographics (Safety Sample)

Characteristics	Group 1 (ages 12-17) (N^a = 7)	Group 2 (ages 6-11) (N^a = 6)	Total (ages 6-17) (N^a = 13)
Age (years)			
Mean (SD)	15.4 (1.6)	9.5 (1.5)	12.7 (3.4)
Median (Min, Max)	15.6 (13.4, 17.60)	9.6 (7.4, 11.46)	13.4 (7.4, 17.60)
Weight (kg)			
Mean (SD)	38.4 (6.1)	25.3 (7.1)	32.4 (9.3)
Median (Min, Max)	38.9 (26.9, 45.4)	25.0 (15.9, 34.5)	34.5 (15.9, 45.4)
Height (cm)			
Mean (SD)	151.9 (10.2)	123.3 (10.9)	138.7 (17.9)
Median (Min, Max)	154.0 (133.0, 163.0)	125.5 (105.0, 137.0)	137.0 (105.0, 163.0)
BMI (kg/m^2)			
Mean (SD)	16.6 (2.0)	16.3 (2.7)	16.5 (2.2)
Median (Min, Max)	16.2 (14.9, 19.6)	15.6 (14.4, 21.4)	16.2 (14.4, 21.4)
Sex (n [%][b])			
Male	4 (57.1)	2 (33.3)	6 (46.2)
Female	3 (42.9)	4 (66.7)	7 (53.8)
Ethnicity (n [%][b])			
Not Hispanic or Latino	7 (100.0)	6 (100.0)	13 (100.0)
Race (n [%][b])			
Asian	7 (100.0)	4 (66.7)	11 (84.6)
Other	0 (0.0)	2 (33.3)	2 (15.4)
Country (n [%][b])			
Philippines	7 (100.0)	4 (66.7)	11 (84.6)
South Africa	0 (0.0)	2 (33.3)	2 (15.4)

Abbreviation: BMI = body mass index
Note: Data cutoff was 13 Dec 2016.
[a]Subjects who took at least one dose of IMP.
[b]Percentage is based on number of total subjects in the age group.

The majority of the subjects had normal audiometry assessments (8 of 13 subjects [61.5%]) and visual assessments (11 of 13 subjects [84.6%]) at baseline and abnormal chest x-rays (12 of 13 subjects [92.3%]). Baseline was defined as the last pre-dose measurement prior to IMP administration.

Table 12 Audiometry, Chest X-ray and Visual Assessment

		12-17 YEARS (N=7)		6-11 YEARS (N=6)		TOTAL (N=13)	
CATEGORY	RESULT	n	(%)[1]	n	(%)[1]	n	(%)[1]
AUDIOMETRY ASSESSMENT	NORMAL	3	(42.8)	5	(83.3)	8	(61.5)
	ABNORMAL	4	(57.1)	1	(16.6)	5	(38.4)
CHEST X-RAY	NORMAL	0	(0.0)	1	(16.6)	1	(7.6)
	ABNORMAL	7	(100.0)	5	(83.3)	12	(92.3)
VISUAL ASSESSMENT	NORMAL	7	(100.0)	4	(66.6)	11	(84.6)
	ABNORMAL	0	(0.0)	1	(16.6)	1	(7.6)
	NOT DONE	0	(0.0)	1	(16.6)	1	(7.6)

The investigator-assessed sign and symptom with the highest incidence at baseline was findings on recent chest radiograph consistent with TB (11 of 13 subjects [84.6%]).

Table 13 Investigator-assessed sign and symptoms

		12-17 YEARS (N=7)		6-11 YEARS (N=6)		TOTAL (N=13)	
SIGNS AND SYMPTOMS	RESULT	n	(%)[1]	n	(%)[1]	n	(%)[1]
COUGH	YES	4	(57.1)	1	(16.6)	5	(38.4)
	NO	3	(42.8)	5	(83.3)	8	(61.5)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
FEVER	YES	0	(0.0)	0	(0.0)	0	(0.0)
	NO	7	(100.0)	6	(100.0)	13	(100.0)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
WEIGHT LOSS	YES	1	(14.2)	1	(16.6)	2	(15.3)
	NO	6	(85.7)	5	(83.3)	11	(84.6)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
FAILURE TO THRIVE	YES	0	(0.0)	0	(0.0)	0	(0.0)
	NO	7	(100.0)	6	(100.0)	13	(100.0)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
HEMOPTYSIS	YES	0	(0.0)	0	(0.0)	0	(0.0)
	NO	6	(85.7)	4	(66.6)	10	(76.9)
	NOT DONE	1	(14.2)	2	(33.3)	3	(23.0)
DYSPNEA	YES	1	(14.2)	0	(0.0)	1	(7.6)
	NO	6	(85.7)	6	(100.0)	12	(92.3)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
CHEST PAIN	YES	0	(0.0)	0	(0.0)	0	(0.0)
CHEST PAIN	NO	7	(100.0)	6	(100.0)	13	(100.0)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
NIGHT SWEATS	YES	1	(14.2)	0	(0.0)	1	(7.6)
	NO	3	(42.8)	5	(83.3)	8	(61.5)
	NOT DONE	3	(42.8)	1	(16.6)	4	(30.7)
LOSS OF APPETITE	YES	0	(0.0)	0	(0.0)	0	(0.0)
	NO	4	(57.1)	5	(83.3)	9	(69.2)
	NOT DONE	3	(42.8)	1	(16.6)	4	(30.7)
FINDINGS ON RECENT CHEST RADIOGRAPH CONSISTENT WITH TB	YES	7	(100.0)	4	(66.6)	11	(84.6)
	NO	0	(0.0)	2	(33.3)	2	(15.3)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
SPUTUM SMEAR POSITIVE FOR ACID-FAST BACILLI (AFB)	YES	2	(28.5)	0	(0.0)	2	(15.3)
	NO	5	(71.4)	6	(100.0)	11	(84.6)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
HOUSEHOLD CONTACT OF A PERSON WITH KNOWN MDR-TB	YES	1	(14.2)	1	(16.6)	2	(15.3)
	NO	6	(85.7)	5	(83.3)	11	(84.6)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
HOUSEHOLD CONTACT OF A PERSON WHO DIED WHILE APPROPRIATELY TAKING DRUGS FOR SENSITIVE TB	YES	0	(0.0)	1	(16.6)	1	(7.6)
HOUSEHOLD CONTACT OF A PERSON WHO DIED WHILE APPROPRIATELY TAKING DRUGS FOR SENSITIVE TB	NO	7	(100.0)	5	(83.3)	12	(92.3)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)
OTHER	YES	0	(0.0)	1	(16.6)	1	(7.6)
	NO	7	(100.0)	5	(83.3)	12	(92.3)
	NOT DONE	0	(0.0)	0	(0.0)	0	(0.0)

Anti-TB treatment history is summarised in the table below. All subjects (13 subjects [100.0%]) had been treated with both a first-line and second-line regimen.

Table 14 Anti-TB treatment history

		12-17 YEARS (N=7)		6-11 YEARS (N=6)		TOTAL (N=13)	
		n	(%)[1]	n	(%)[1]	n	(%)[1]
ANTI-TB TREATMENT	TREATED WITH BOTH FIRST-LINE AND SECOND-LINE REGIMEN[2]	7	(100.0)	6	(100.0)	13	(100.0)
INDICATION FOR MDR TREATMENT	CONFIRMED (CULTURE POSITIVE, RESISTANT TO ISONIAZID, AND RIFAMPICIN)	6	(85.7)	3	(50.0)	9	(69.2)
	PROBABLE (TB IN CHILD WITH MDR+CONTACT)	1	(14.2)	0	(0.0)	1	(7.6)
	SUSPECTED	0	(0.0)	3	(50.0)	3	(23.0)
SITE OF DISEASE	PULMONARY	7	(100.0)	2	(33.3)	9	(69.2)
	EXTRA PULMONARY	0	(0.0)	1	(16.6)	1	(7.6)
	BOTH	0	(0.0)	3	(50.0)	3	(23.0)

[2] First line regimen: isoniazid, rifampicin, rifampin, rifabutine, rifapentine, pyrazinamide, ethambutol and streptomycin. Second line regimen: amikacin, kanamycin and capreomycin.

The CHMP noted that the microbiological confirmation of the current treatment episode of MDR-TB is based on the patient's history and could have been several months before screening for trial 232 (and 233) – up to 5 months for group I and up to almost 1 year for group II. The CHMP therefore requested the MAH to discuss the patients' clinical, radiographic and culture response to the past tuberculosis treatment at baseline of trial 233 as the patients have already been treated for several months (before and during trial 232) for their current MDR-TB episode.

The MAH confirmed that all patients enrolled in Trial 242-12-232 and Trial 242-12-233 were required to have a recent diagnosis of confirmed or probable MDR-TB and to be on at least 2 weeks of an optimised background treatment regimen (OBR). At baseline, historical data including past TB treatment (that would include recent OBR), date of diagnosis, and site of disease were collected. In addition, signs and symptoms of active TB, along with smear microscopy data, were collected immediately prior to delamanid administration in order to establish a baseline status prior to the start of dosing. These data are summarised by age group in synoptic CSR 242-12-233, CT-3.2.2. As additional clinical data were not collected prior to the start of the initial background regimen, an assessment of the response of a patient to background treatment is not currently possible.

The CHMP was of the view that regarding the design of the trials, assessment of efficacy is not needed, rather it is presumed that these can be bridged from the adult population given similar PK, which is acceptable.

Concomitant anti-TB medications taken prior to the start of trial therapy were (Note that if a patient took more than one medication within a drug class, the patient was counted once for the drug class.):

Table 15 Concomitant anti-TB medications

DRUG CLASS MEDICATION PREFERRED NAME	12-17 YEARS (N=7) n	(%)	6-11 YEARS (N=6) n	(%)	TOTAL (N=13) n	(%)
TOTAL USING ONE OR MORE MEDICATIONS	6	(85.7)	6	(100.0)	12	(92.3)
AMINOSALICYLIC ACID AND DERIVATIVES	5	(71.4)	1	(16.7)	6	(46.2)
PARA-AMINOSALICYLIC ACID	4	(57.1)	0	(0.0)	4	(30.8)
PASER	1	(14.3)	1	(16.7)	2	(15.4)
ANTIBIOTICS	6	(85.7)	4	(66.7)	10	(76.9)
CYCLOSERINE	6	(85.7)	4	(66.7)	10	(76.9)
FLUOROQUINOLONES	6	(85.7)	6	(100.0)	12	(92.3)
LEVOFLOXACIN	6	(85.7)	6	(100.0)	12	(92.3)
HYDRAZIDES	0	(0.0)	2	(33.3)	2	(15.4)
ISONIAZID	0	(0.0)	2	(33.3)	2	(15.4)
OTHER AMINOGLYCOSIDES	6	(85.7)	3	(50.0)	9	(69.2)
AMIKACIN	0	(0.0)	1	(16.7)	1	(7.7)
KANAMYCIN	6	(85.7)	2	(33.3)	8	(61.5)
OTHER DRUGS FOR TREATMENT OF TUBERCULOSIS	2	(28.6)	4	(66.7)	6	(46.2)
ETHAMBUTOL	0	(0.0)	2	(33.3)	2	(15.4)
PYRAZINAMIDE	2	(28.6)	3	(50.0)	5	(38.5)
TERIZIDONE	0	(0.0)	2	(33.3)	2	(15.4)
THIOCARBAMIDE DERIVATIVES	1	(14.3)	5	(83.3)	6	(46.2)
ETHIONAMIDE	0	(0.0)	2	(33.3)	2	(15.4)
PROTHIONAMIDE	1	(14.3)	3	(50.0)	4	(30.8)

Numbers analysed

Outcomes and estimation

Results of chest x-ray and symptoms of TB assessments did not show consistent changes during treatment for both age groups.

Table 16 Chest x-ray results

CATEGORY	VISIT	RESULT	12-17 YEARS (N=7) n	(%)[1]	6-11 YEARS (N=6) n	(%)[1]	TOTAL (N=13) n	(%)[1]
CHEST X-RAY	BASELINE[4]	NORMAL	0	(0.0)	1	(16.6)	1	(7.6)
		ABNORMAL	7	(100.0)	5	(83.3)	12	(92.3)
	DAY 182	ABNORMAL	4	(100.0)	6	(100.0)	10	(100.0)
	DAY 365	NORMAL	0	(0.0)	1	(16.6)	1	(8.3)
		ABNORMAL	6	(100.0)	5	(83.3)	11	(91.6)
	ANY POST-BASELINE VISIT	ABNORMAL	7	(100.0)	6	(100.0)	13	(100.0)

Body weight

Results of changes in body weight show that subjects in Group 1 gained weight over the 12 months with a mean (SD) change of 4.6 (3.8) kg, and in Group 2, subjects lost a modest amount with a mean (SD) change of -0.4 (3.8) kg. Potentially clinically significant abnormalities in vital signs included changes ≥

5% in body weight. A decrease of ≥ 5% in body weight was only reported for 2 of the 6 subjects (33.3%) in Group 2; the percent change from baseline reported after 12 months (at Day 365) was -24.4% for one subject and −12.2% for the other subject. An increase of ≥ 5% in body weight was reported for 4 of the 7 subjects (57.1%) in Group 1 and for 2 of the 6 subjects (33.3%) in Group 2; the percent change from baseline reported for the subjects after 12 months (at Day 365) varies from 15.1% to 27.8% in Group 1 and was 23.3% and 10.2% in Group 2.

During trial 233, there was only one patient with a smear positive result for acid-fast bacilli. MGIT and solid cultures during trial 233 were either not performed or were culture negative. The MAH was therefore asked to discuss the patients' clinical, radiographic and culture response to the tuberculosis treatment at the patients' visits of trial 233 where these have been assessed. For the treatment outcome follow-up at 24 months, all patients will either visit the clinic or be contacted by telephone for clinical assessment. Therefore, a summary and discussion of the data from the last follow-up visit at 6 months after the last delamanid dose was also requested.

The MAH presented the numbers of subjects with specific signs and symptoms of TB assessed by the investigator at baseline, at 6 months, and at 6 months after the last dose of delamanid in Trial 242-12-233. Overall, there was a trend towards a reduction in cough over the course of the trial, notably in the oldest age group. There were no consistent changes in signs and symptoms exhibited by subjects overall or within age groups over the course of the first year. Cough and weight loss were observed more frequently than any of the other signs/symptoms assessed with 20 of 37 (55.5%) subjects exhibiting cough and 24 of 37 (66.6%) subjects showing weight loss during the study. However, an examination of changes in body weight from baseline to the end of the 6-month follow-up period showed that 29 of 36 (80.6%) subjects had clinically significant (⩾ 5%) increases in body weight. Increases in body weight in paediatric TB patients is suggestive of a positive clinical response. Body weights at baseline, at 6 months, and at 6 months follow up are presented for each subject by age group. All but 1 of 36 (97.2%) subjects had abnormal findings on chest x-rays at baseline. At 6 months, 4 of 33 (12.1%) subjects had normal chest x-rays and at 6 months follow up, 3 of 31 (8.8%) subjects had normal chest x-rays. A total of 4 of 37 (8.8%) subjects had a sputum smear test positive for AFB at baseline. No subjects tested positive on any postbaseline sputum test performed.

The CHMP assessed the data provided by the MAH and considered that no clear trends could be derived. As the line extension is based on the presumption that efficacy can be bridged from the adult population, given similar PK, this is accepted.

Summary of final outcome at the end of treatment as assessed by the principal investigator at 24 months based on the safety sample:

Table 17 Treatment outcome at 24 Months (Safety Sample)

Treatment outcome		Group 1 (ages 12-17) (N = 7) n (%)	Group 2 (ages 6-11) (N = 6) n (%)	Total (ages 6-17) (N = 13) n (%)
Favorable	Cured	4 (57.1)	3 (50.0)	7 (53.8)
	Treatment completed	2 (28.6)	3 (50.0)	5 (38.5)
Unfavorable	Lost to follow-up	1 (14.3)	0 (0.0)	1 (7.7)
	Treatment failed	0 (0.0)	0 (0.0)	0 (0.0)
	Died	0 (0.0)	0 (0.0)	0 (0.0)

In Groups 1 and 2, 57.1% and 50.0% of subjects, respectively were cured.

The MAH was requested to clarify on which data the conclusion of cure as treatment outcome is based (chest radiography results, resolution of TB signs and symptoms or culture conversion) and to provide the

data supporting the treatment outcomes as well as definitions of the categories 'Cure', 'Treatment completed', 'Treatment failed'.

The MAH stated that all patients who completed Trial 242-12-233 were assessed on Day 730 (Month 24) + 2 months for clinical assessment. Determination of final treatment outcomes was not prescribed by the protocol; nevertheless, final outcomes were assessed by the treating clinician as per local and/or WHO guidance, which in general were based on the standard definitions listed in **Table 18**. The MAH provided the results of these assessments for Trial 242-12-233 in PDATA-15 (19/02/2020).

Table 18 Treatment Outcomes for RR-TB/MDR-TB/XDR-TB Patients treated using Second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: - lack of conversion[b] by the end of the intensive phase[a], or - bacteriological reversion[b] in the continuation phase after conversion[b] to negative, or - evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or - adverse drug reactions
Died	A TB patient who dies for any reason during the course of treatment
Lost to follow up	A TB patient whose treatment was interrupted for 2 consecutive months or more

[a]For treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.

[b]The terms "conversion" and "reversion" of culture as used here are defined as follows:

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failed, reversion is considered only when it occurs in the continuation phase.

Source: WHO.[6]

The CHMP noted that as determination of final treatment outcomes was not prescribed by the protocol and it is not clear whether the WHO guidance has been followed, efficacy outcome should not be reported in the SmPC for the paediatric population. It is presumed that efficacy can be bridged from the adult population given similar PK. The SmPC is revised accordingly.

Ancillary analyses

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19 Summary of Efficacy for trial 242-12-233

Title: Phase 2, Open-label, Multi-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC-67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs Over a 6-Month Treatment Period			
Study identifier	Eudra CT No. 2012-004620-38		
Design	Open-label, non-controlled, age de-escalation trial 6-month treatment extension trial of trial 232		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months all subjects must rollover within 30 days of completing Trial 232 1.5 year	
Hypothesis	Descriptive only		
Treatments groups	Group 1: 12 - 17 years	DLM+OBR, 6 months, 7 patients	
	Group 2: 6 - 11 years	DLM+OBR, 6 months, 7 patients	
	Group 3: 3 - 5 years	DLM+OBR, ongoing	
	Group 4: birth - 2 years	DLM+OBR, ongoing	
Endpoints and definitions	Primary endpoint / Safety and tolerability	Changes in physical examination including visual testing and audiometry, TEAEs, vital signs, ECGs, Holter monitoring (if applicable), and clinical laboratory tests	
	Primary endpoint / PK	Descriptive statistics of delamanid and metabolite plasma concentrations. Combined with Trial 232 data and analysed using Pop PK	
	Secondary endpoint / PK/PD	For changes in QTc as a function of delamanid and metabolite (DM-6705) plasma concentrations	
	Secondary endpoint / Efficacy	Normal chest radiography results, resolution of TB symptoms, culture conversion	
	Secondary endpoint / Palatability	Not tested for group 1 and 2	
Database lock	Ongoing; Data cutoff 13 Dec 2016, ie, date of the last trial observation of subjects from Groups 1 and 2		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat – safety population End of study			
Descriptive statistics and estimate variability	Treatment group	Group 1: 12 - 17 years	Group 2: 6 - 11 years	Adults 100 mg BID
	Number of subject	7	6	
	ΔQTcF [msec]	21.6 after 4 months DLM trial 233	12.6 after 4 months DLM trial 233	12.1 (2 months DLM 100 mg BID trial 204)
	SD	23.4	9.3	
	PK: AUC_{0-24}	No details provided		
	Efficacy (Cure)	57.1 %	50.0 %	

Effect estimate per comparison	Not applicable		
Notes	Safety: PK/PD for changes in QTc as a function of delamanid and metabolite (DM-6705) plasma concentrations has not yet been performed. Efficacy: There are uncertainties related to the diagnosis of tuberculosis in the paediatric population and the assessment of treatment outcome.		

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical studies 232 and 233 are PIP compliant. There is little bias control: trial 233 is an open-label, non-controlled and non-randomised study. A very limited number of paediatric patients are included: 7 patients aged 12–17 years and 6 patients aged 6-11 years. Children with confirmed or presumptive diagnosis of pulmonary or extrapulmonary MDR-TB received delamanid during 6 months (the adult dosage, i.e. 100 mg BID for patients aged 12-17 years and 50 mg BID for patients aged 6-11 years) in addition to an optimised background regimen. Patients will continue on OBR, as prescribed by the investigator, and have post-delamanid treatment visits on Days 189, 196, 203, 210, 238 (2-month post last dose), and 365 (6-month post last dose). There is a treatment outcome follow-up at 24 months from the start of delamanid therapy. So, patients are closely followed until 2 months after stopping delamanid treatment. Thereafter, follow-up is limited with one visit 6 months after the last delamanid dose and an additional treatment outcome follow-up one year after this last follow-up, which makes it difficult to assess sustained SCC. The main endpoints of the study were the evaluation of safety and tolerability and PK evaluation. Efficacy was a secondary objective. The efficacy was assessed by chest radiography (in patients with pulmonary disease), body weight/height, and resolution of TB symptoms. When available, sputum culture conversion was assessed, although microbiological assessment of sputum or other biological specimens was not required as part of the protocol.

Efficacy data and additional analyses

Evaluation of efficacy is complicated by the more difficult diagnosis in younger patients: Six out of 7 patients aged 12-17 years had confirmed pulmonary MDR-TB, one probable pulmonary MDR-TB. In patient group II aged 6 to 11 years, only 50% had confirmed MDR-TB and 50% had suspected MDR-TB; 2 patients had pulmonary TB, one extra-pulmonary TB and 3 both pulmonary and extra-pulmonary TB. Secondly, microbiological confirmation of the current episode of MDR-TB is based on the patient's history and for some patients this was several months before screening for trial 232 (and 233) – up to 5 months for group I and almost 1 year for group II.

2.5.3. Conclusions on the clinical efficacy

The number of patients is too small to draw clear conclusions from the efficacy evaluation.

Based on the assumption that the response to treatment may be comparable from the age of 5 years upwards, approval of the indication in children from 6 to 17 years of age is based on the appropriateness of the age-specific dose regimens based on PK data and on an acceptable paediatric safety profile.

2.6. Clinical safety

Introduction

The most frequently observed adverse drug reactions in patients treated with delamanid + Optimised Background Regimen (OBR) (i.e. incidence > 10%) are nausea (32,9%), vomiting (29,9%), headache (27.6%), insomnia (27.3%), dizziness (22.4%), tinnitus (16.5%), hypokalaemia (16.2%), gastritis (15.0%), decreased appetite (13.1%), and asthenia (11.3%).

Safety concerns associated with the use of delamanid in the EU Risk Management Plan version 3.2 include the important identified risks of QT interval prolongation, paraesthesia, hypoaethesia, tremor, depression, anxiety, insomnia, drug resistance, and gastrointestinal disorders (nausea, vomiting, and gastritis), and the important potential risks of tinnitus, blurred vision, hypokalaemia, liver disorders, cortisol level increase, drug use during pregnancy, and breastfeeding.

Patient exposure

Trial 233

All but 1 of the 13 subjects analysed for the interim analysis of trial 233 were exposed to at least 6 months of the investigational medicinal product (IMP). One subject in Group 1 (ages 12 - 17) missed all doses for the last 80 days of treatment.

In trial 233, in Group 1 (ages 12 - 17), total subject days of IMP exposure was 1196 days for the 7 subjects and 1092 days for the 6 subjects in Group 2 (ages 6 – 11).

Trial 232 and 233

Total clinical trial exposure by duration of exposure and by age group and gender is given in the tables below:

Table 20 SIII.1 Clinical Trial Exposure to Delamanid (Cumulative for all indications)

Duration of Exposure	Persons	Person Time
≥ 1m	745	119198
≥ 3m	561	108693
≥ 6m	484	96033
≥ 12m	0	0
Total	**1371**	**123654**

Table 21 SIII.2: Clinical Trial Exposure to Delamanid by Age Group and Gender

Age Group	Persons		Person Time (days)	
	M	F	M	F
Age 0-2	6	6	1117	949
Age 3-5	6	6	1155	1140
Age 6-11	2	4	383	769
Age 12-17	4	3	735	490
Age 18-65	921	412	81704	35211
Age 65-75	1	0	1	0
Total	**940**	**431**	**85095**	**38559**

Current exposure in the paediatric population is very low and prohibits drawing clear conclusions on the clinical safety of delamanid in this population.

Adverse events

Trial 232 age 0 to 17 years

- Overall a total of 126 TEAEs were reported by 31 of 37 subjects (83.8%).
- The most frequently reported TEAEs were vomiting (9 of 37 subjects [24.3%]) followed by hyperuricaemia (5 of 37 subjects [13.5%]), nausea (5 of 37 subjects [13.5%]), and toothache (5 of 37 subjects [13.5%]).
- All 12 subjects (100.0%) aged 0 to 2 years experienced ≥ 1 TEAE during the trial followed by 9 of 12 subjects (75.0%) aged 3 to 5 years, 5 of 6 subjects (83.3%) aged 6 to 11 years, and 5 of 7 subjects (71.4%) aged 12 to 17. There was no clinically meaningful difference of TEAE incidences across all age groups.
- Most TEAEs were mild or moderate in intensity except for the TEAE of lower respiratory tract infection, which was considered to be severe in intensity.
- Of 37, 9 subjects (24.3%) subjects experienced ≥ 1 TEAE that was related to the IMP; the most frequently reporting terms were diarrhoea (2 subjects [5.4%]) and ECG QT prolongation (2 subjects [5.4%]).
- All IMP-related TEAEs were mild or moderate in severity.
- There were no IMP-related TEAEs experienced by subjects aged 12 to 17 years and 3 subjects each from all other age groups reported IMP-related TEAEs. There were no clinically meaningful differences between the age groups.
- Overall, eosinophilia (2 of 37 subjects (5.4%]; 1 subject aged 3 - 5 and 1 subject aged 0 - 2) and neutropenia (1 of 37 subjects (2.7%]; 1 subject aged 3 - 5) were the TEAEs reported for blood and lymphatic system disorders. One incidence of eosinophilia and neutropenia were assessed as IMP-related TEAEs.
- No subject had an abnormal physical examination finding that was considered to be clinically significant.
- Potentially clinically significant abnormalities in vital signs only included changes ≥ 5% in body weight for 8 subjects across all age groups. A decrease ≥ 5% in body weight was only reported for 1 of 37 subjects (2.7%). An increase of ≥ 5% in body weight was reported for 7 of 37 subjects (18.9%) which can be considered as a benefit for the purpose of this trial.
- Overall, 2 of 12 subjects (16.7%) aged 3 to 5 years experienced TEAEs related to ECGs; 1 subject experienced PR prolongation, QT prolongation, and presence of U wave and the other subject experienced QT prolongation. These incidences were reported as IMP-related TEAEs.
- No clinically relevant differences were noted for clinical laboratory results, ECGs, vital signs, physical findings, or other observations relating to safety parameters.

Trial 233

- As of the data cut-off date of 13 Dec 2016, the 13 subjects analysed for this interim analysis experienced a total of 105 treatment-emergent adverse events (TEAEs). Out of these, 88 TEAEs were on treatment, defined as TEAE occurring before end of IMP administration and were reported in all 13 subjects (100.0%).

- The 3 most frequently reported adverse events (AEs) were headache (8 subjects [61.5%]), upper respiratory tract infection (7 subjects [53.8%]), and arthralgia (5 subjects [38.5%]).
- Causally related TEAEs defined as those having a possible or definitive relationship to the IMP were reported for 2 subjects (15.4%). One subject experienced nonserious events of arthralgia, headache, and butterfly rash and for another subject a nonserious event of dizziness; all were assessed as possibly related to IMP.
- No notable findings were observed with audiometry and visual assessments.

Serious adverse event/deaths/other significant events

Trial 232 age 0 to 17 years

- No subject had a fatal outcome during the trial
- Two subjects (5.4%) each had a SAE; for one subject the SAE was hepatitis A (aged 3 to 5 years) and for the other subject the SAE was lower respiratory tract infection (aged 0 - 2 years). Both SAEs were not related to IMP.

Trial 233

- As of the cut-off date of 13 Dec 2016, no deaths have been reported in Trial 242-12-233.
- As of the cut-off date of 13 Dec 2016, 1 of 13 subjects (7.7%) experienced a serious adverse event. The subject was 10 years old and experienced an event of non-Hodgkin's lymphoma that was of severe intensity and not related to the IMP.

Laboratory findings

Trial 232 age 0 to 17 years

- Concurrent elevation of transaminases (≥ 3 × ULN) and bilirubin levels (≥ 2 × ULN) was experienced by 1 subject (2.7%) with diagnosed hepatitis A.
- No clinically relevant differences were noted for clinical laboratory results, ECGs, vital signs, physical findings, or other observations relating to safety parameters.

The CHMP noted that changes to ECGs were recorded in the majority of study patients, with the oldest group of paediatric patients (group 1) having fewer ECG abnormalities compared to the younger age cohorts. (4 of 7 subjects [57.1%] in Group 1, 5 of 6 subjects [83.3%] in Group 2, 10 of 12 subjects in Group 3 [83.3%], and 11 of 12 subjects [91.6%] in Group 4). The most commonly reported ECG rhythm abnormalities were sinus tachycardia and sinus bradycardia. Of the new ECG conduction abnormalities reported in 23 of 37 subjects (62.1%) the most frequently observed were intraventricular conduction defects, prolonged QTc and 1st degree AV block. Regarding the investigational TEAEs of special interest, no new onset changes > 500 msec in QTcB or QTcF were reported. None of the reported ECG changes led to withdrawal of study treatment. Overall, the CHMP considered the changes in ECG findings to be within acceptable limits. The ECG and QT changes described are known to be associated with adult delamanid use and are documented in Sections 4.4 and 4.8 of the SmPC.

Trial 233

The assessment of clinical laboratory tests did not show any clinically relevant changes from baseline for both age groups or any significant effect of delamanid. Although sporadic and transient excursions

outside the normal range were observed for laboratory values, no clinically relevant trends in clinical laboratory parameters were readily apparent or resulted in discontinuation from the trial.

QT interval prolongation is discussed further below in the section 'Adverse events of special interest'.

Adverse events of special interest

Safety concerns associated with the use of delamanid in the paediatric population are aligned with the EU Risk Management Plan version 3.2. These include the important identified risks of QT interval prolongation, paraesthesia, hypoaethesia, tremor, depression, anxiety, insomnia, drug resistance, and gastrointestinal disorders (nausea, vomiting, and gastritis), and the important potential risks of tinnitus, blurred vision, hypokalaemia, liver disorders, cortisol level increase, drug use during pregnancy, and breastfeeding.

There were no SAEs, no drug-related TEAEs, and no discontinuations of IMP due to any of these safety concerns reported for subjects in Group 1 (ages 12 to 17 years) or Group 2 (ages 6 to 11 years) in Trial 242-12-233.

QT interval prolongation

Administration of delamanid has been shown to result in QT interval prolongation, an effect associated primarily with DM-6705 plasma concentrations and to a lesser extent with delamanid and other metabolite plasma concentrations. DM-6705 accumulates slowly over time to reach maximal concentrations after 2 months of treatment. A 6-month open-label trial of delamanid in adults with MDR-TB (Trial 242-07-208) showed that QTcF interval prolongation did not increase beyond 2 months of treatment. In the placebo-controlled Trial 242-07-204, in MDR-TB adult patients receiving 100 mg delamanid twice daily, the mean placebo corrected increases in QTcF from baseline were 7.6 msec at 1 month and 12.1 msec at 2 months. Three percent of patients experienced an increase of 60 msec or greater at some point during Trial 242-07-204, and 1 patient exhibited a QTcF interval > 500 msec.

In the double-blind placebo-controlled Trial 242-09-213, the maximum mean placebo corrected value for QTcF reached 5.9 msec.

In the paediatric Trial 242-12-232, a clinical study with a delamanid treatment of 10 days, there were no clinically meaningful differences in the mean changes from baseline for the various ECG parameters across the age groups (0 to 17 years). The mean change from baseline for QTcF reached 4.4 msec at Day 10.

The effects of delamanid on QT interval prolongation in paediatric subjects with MDR-TB have been examined in a small number of subjects (13) aged 6 to 17 years in Trial 242-12-233. There were no SAEs or any AEs of QT prolongation. These data showed a mean change from baseline for QTcF of 17.5 msec. Five subjects (38.4%) [3 of 7 subjects (42.8%) in Group 1 (ages 12 to 17 years), 2 of 7 subjects (33.3%) in Group 2 (ages 6 to 11 years)] had new onset changes > 450 msec in QTcF. No subject exhibited a QTcF interval > 480 msec. Seven of 13 subjects in trial 233 experienced an increase ≥ 30 and ≤ 60 msec (5, 71.4 % in Group 1 and 2, 33.3 % in Group 2). For one patient from group 1 and one patient from group 2, this was reported during delamanid treatment and after D182, i.e. after the delamanid treatment period. One subject (1 of 13 subjects, 7.6%) [1 of 7 subjects (14.2%) in Group 1 (12-17 years)] experienced an increase of > 60 msec between Days 84 and 126, i.e. when delamanid was stopped for this patient. No cases of Torsades de Pointes were reported. Eleven of 13 patients reported a new conduction abnormality.

Table 22 Incidence of Clinically Significant ECG Test Abnormalities

Classification	Group 1 (ages 12-17) (N = 7) n (%)	Group 2 (ages 6-11) (N = 6) n (%)	Total (ages 6-17) (N = 13) n (%)
Ventricular rate outliners			
Notable decrease[a]	0 (0.0)	0 (0.0)	0 (0.0)
Notable increase[b]	1 (14.2)	0 (0.0)	1 (7.6)
PR outliners			
Notable changes[c]	0 (0.0)	0 (0.0)	0 (0.0)
QRS outliners			
Notable changes[d]	1 (14.2)	0 (0.0)	1 (7.6)
QT			
New onset (> 500 msec)[e]	0 (0.0)	0 (0.0)	0 (0.0)
QTcB			
New onset (> 500 msec)[e]	0 (0.0)	0 (0.0)	0 (0.0)
New onset (> 480 msec)[e]	1 (14.2)	1 (16.6)	2 (15.3)
New onset (> 450 msec)[e]	7 (100.0)	2 (33.3)	9 (69.2)
Change ≥ 30 and ≤ 60 msec	5 (71.4)	3 (50.0)	8 (61.5)
Change > 60 msec	1 (14.2)	0 (0.0)	1 (7.6)
QTcF			
New onset (> 500 msec)[e]	0 (0.0)	0 (0.0)	0 (0.0)
New onset (> 480 msec)[e]	0 (0.0)	0 (0.0)	0 (0.0)
New onset (> 450 msec)[e]	3 (42.8)	2 (33.3)	5 (38.4)
Change ≥ 30 and ≤ 60 msec	5 (71.4)	2 (33.3)	7 (53.8)
Change > 60 msec	1 (14.2)	0 (0.0)	1 (7.6)
U waves			
New abnormal U waves	0 (0.0)	0 (0.0)	0 (0.0)
ST segment			
New ST segment changes	0 (0.0)	0 (0.0)	0 (0.0)
T waves			
New T wave changes	0 (0.0)	0 (0.0)	0 (0.0)
Rhythm			
New abnormal rhythm	5 (71.4)	4 (66.6)	9 (69.2)
Conduction			
New conduction abnormality	6 (85.7)	5 (83.3)	11 (84.6)

QTcB = QT interval corrected by Bazett's formula
Note: Data cutoff was 13 Dec 2016.
Note: Baseline was defined as the average of the ECGs taken at Day 1.

[a] ≥ 25% decrease from baseline and ventricular rate < 50 bpm.

[b] ≥ 25% increase from baseline and ventricular rate > 100 bpm.

[c] ≥ 25% change from baseline when PR > 200 msec.

[d] ≥ 25% change from baseline when QRS > 100 msec.

[e] New onset (> 450, 480, 500 msec) means a subject who attains a value > 450, 480, 500 msec during treatment period but not at each baseline visit.

Table 23 QTC Mean Change from Baseline in Electrocardiogram Parameters (Fridericia correction)

TEST	AGE GROUP	VISIT	ORIGINAL VALUE N	MEAN	MED	SD	MIN	MAX	CHANGE[4] FROM BASELINE N	MEAN	MED	SD	MIN	MAX
QTC INTERVAL, FRIDERICIA (MSEC)	12-17 YEARS	BASELINE[1]	7	407.0	408.0	19.2	378.0	434.0						
		DAY 28	7	423.4	424.7	11.9	405.7	441.3	7	16.4	12.3	17.5	-2.0	46.7
QTC INTERVAL, FRIDERICIA (MSEC)	12-17 YEARS	DAY 56	7	417.1	420.3	16.0	384.3	432.3	7	10.1	7.3	15.5	-10.7	37.7
		DAY 84	7	427.9	434.3	17.1	403.0	442.0	7	20.9	10.3	20.8	7.0	64.0
		DAY 126	7	428.6	432.3	13.7	406.7	442.0	7	21.6	24.3	23.4	-16.7	62.0
		DAY 154	7	423.6	421.3	15.2	404.7	443.3	7	16.6	20.7	19.9	-12.7	40.0
		DAY 182	7	420.8	433.3	16.8	401.0	435.3	7	13.8	18.3	32.0	-33.0	57.3
		DAY 210	6	414.2	416.0	8.0	403.7	425.0	6	8.5	8.5	25.2	-28.0	47.0
		LAST VISIT	7	416.9	416.3	10.3	403.7	433.3	7	9.9	8.7	23.3	-28.0	47.0
	6-11 YEARS	BASELINE[1]	6	411.8	413.0	25.5	377.0	440.0						
		DAY 28	6	421.1	425.0	20.3	389.3	441.3	6	9.2	13.7	15.0	-16.0	25.0
		DAY 56	6	420.0	419.7	22.0	398.0	458.7	6	8.2	11.3	14.5	-17.3	22.3
		DAY 84	6	416.7	413.3	20.5	391.0	451.0	6	4.9	8.8	13.2	-21.0	14.0
		DAY 126	6	424.4	428.7	22.1	386.7	451.7	6	12.6	12.2	9.3	-2.3	25.3
		DAY 154	6	421.0	421.8	24.7	380.7	456.7	6	9.2	11.5	12.5	-12.0	23.7
QTC INTERVAL, FRIDERICIA (MSEC)	6-11 YEARS	DAY 182	6	420.9	422.7	23.2	384.0	448.7	6	9.1	8.2	5.5	1.3	18.0
		DAY 210	6	407.8	411.2	19.4	381.3	429.0	6	-4.0	-6.7	10.0	-14.3	10.7
		LAST VISIT	6	407.8	411.2	19.4	381.3	429.0	6	-4.0	-6.7	10.0	-14.3	10.7
	TOTAL	BASELINE[1]	13	409.2	408.0	21.5	377.0	440.0						
		DAY 28	13	422.3	424.7	15.6	389.3	441.3	13	13.1	12.3	16.2	-16.0	46.7
		DAY 56	13	418.5	419.7	18.2	384.3	458.7	13	9.2	7.3	14.4	-17.3	37.7
		DAY 84	13	422.7	426.7	18.9	391.0	451.0	13	13.5	10.3	19.0	-21.0	64.0
		DAY 126	13	426.7	432.3	17.4	386.7	451.7	13	17.5	16.7	18.2	-16.7	62.0
		DAY 154	13	422.4	421.3	19.2	380.7	456.7	13	13.2	14.7	16.6	-12.7	40.0
		DAY 182	13	420.8	429.7	19.1	384.0	448.7	13	11.6	10.3	23.0	-33.0	57.3
		DAY 210	12	411.0	415.2	14.5	381.3	429.0	12	2.3	1.0	19.4	-28.0	47.0
		LAST VISIT	13	412.7	415.7	15.2	381.3	433.3	13	3.5	4.3	19.1	-28.0	47.0

Baseline was defined as the average of the ECGs taken at Day 1

A concentration-corrected-QT interval modelling analysis is planned to be submitted with completed Trial 242-12-233.

The CHMP noted that a significant prolongation of the QTc interval is observed in the paediatric population aged between 6 and 17 years in trial 233. The maximal mean change from baseline (patients on OBR) for QTcF was 17.5 msec after 4 months of delamanid addition to OBR. Given the relatively higher dose administered in these paediatric patients compared to adult patients, a larger prolongating effect on the QT interval could be expected. In that respect the QT effect seems to be consistent with the observations in adult patients. There were no SAEs or any AEs of QT prolongation observed. However, it should be kept in mind that in trial 233 patients with pre-existing cardiac conditions or abnormalities in screening ECG (including QTcF > 450 msec in both males and females) were excluded. Additionally the concomitant use of delamanid and moxifloxacin or bedaquiline was excluded.

Paraesthesia, Hypoaethesia, and Tremor

There was a low occurrence of neurological symptoms in Trial 233. No SAEs were reported for paraesthesia, hypoaethesia, or tremor. Paraesthesia of mild intensity was present in 1 subject (7.7%) in

Group 1 (ages 12 to 17 years) and resolved. No subjects reported hypoaesthesia or tremor.
No patients reported paraesthesia, hypoaesthesia or tremor in trial 232.

Anxiety, Depression, and Insomnia

No SAEs were reported for anxiety, depression, or insomnia. Depression of mild intensity was experienced by 1 subject (7.7%) in Group 1 (ages 12 to 17 years) and resolved. Mild insomnia was also reported by 1 subject (7.7%) in Group 2 (ages 6 to 11 years) and resolved. There were no reports of anxiety.
One patient reported insomnia in trial 232.

Gastrointestinal Disorders (Nausea, Vomiting, and Gastritis)

There were no SAEs reported for nausea, vomiting, or gastritis. Vomiting was experienced by 3 subjects (23.1%) total; 2 subjects in Group 1 (ages 12 to 17 years), and 1 subject in Group 2 (6 to 11 years). All events were mild and resolved. There were no reports of nausea or gastritis.
In study 232, 5/37 (13.5%) reported nausea, 9/37 (24.3%) vomiting and 1/37 (2.7%) gastritis.

Tinnitus

There was no incidence of tinnitus reported in Trial 242-12-233.

Blurred Vision

There was no incidence of blurred vision reported in Trial 242-12-233.

Hypokalaemia

Hypokalaemia occurred infrequently: 1 subject (7.7%) in Group 1 (ages 12 to 17 years) experienced an AE of mild hypokalaemia which resolved. No SAEs were reported.
One patient in trial 232 reported hypokalaemia. The AE was mild.

Liver Disorders

There were no SAEs of liver disorders. One subject (7.7%) in Group 1 (ages 12 to 17 years) experienced a mild event of prolonged activated partial thromboplastin time which resolved.

Cortisol Level Increase

There were no events of cortisol level increased in Trial 242-12-233.

Safety in special populations

Trial 233 – Pregnancy

One event of pregnancy was reported after the last dose of delamanid and before the last dose of OBR. The subject gave birth to a male newborn via vaginal delivery. No malformations were noted in the newborn.

Safety related to drug-drug interactions and other interactions

No new data in the paediatric population

Discontinuation due to adverse events

In trial 233 there were no discontinuations from the trial due to adverse events.

Post marketing experience

The safety profile of delamanid observed in the post-marketing use setting is in line with the overall safety profile of the product currently established and the safety profile of other OBR used concomitantly.

From the cumulative post-marketing data, within the paediatric population (≤ 17 years of age) the reported AEs pertained to the SOCs of injury, poisoning and procedural complications (126 events); investigations (35 events); gastrointestinal disorders (25 events); nervous system (23 events); general disorders and administration site conditions (20 events); infections and infestations (15 events); metabolism and nutrition disorders (13 events); psychiatric disorders (11 events); blood and lymphatic system disorders (10 events); respiratory, thoracic and mediastinal disorders (10 events); cardiac disorders (6 events); skin and subcutaneous tissue disorders (6 events); hepatobiliary disorders (5 events); eye disorders, (4 events); musculoskeletal and connective tissue disorders (2 events); endocrine disorders (2 events); and vascular disorder (1 event).

A review of cumulative paediatric data, including paediatric data analysed per important identified and potential risks, from all Otsuka safety data-base sources, does not support any increased risk in the paediatric population or varying safety profile from the safety profile of delamanid established in adults.

2.6.1. Discussion on clinical safety

Trial 242-12-232 was a phase 1, open-label, multiple-dose, and age de-escalation trial that investigated the pharmacokinetics and the safety and tolerability of delamanid in 37 paediatric MDR-TB patients administered with food for 10 days to subjects ages birth to 17 years, inclusive, who were also on therapy with an optimised background regimen.

Trial 242-12-233 (phase 2, open-label, multi-dose trial to assess the safety, tolerability, PK and efficacy of delamanid) is a 6-month extension to Trial 232. The trial has been completed and data analysed for 13 patients aged 6-17 years and is still ongoing for paediatric population subset 0 to 5 years of age.

Assessment of paediatric data on clinical safety

The safety data from these trials are consistent with the known safety profile of delamanid in adult subjects and no new safety signals have been identified.

Possibly IMP-related TEAEs occurring during trial 233 were reported for 2 subjects (15.4%) and comprised single events of arthralgia, headache, butterfly rash, and dizziness. All terms are listed in the published delamanid summary of product characteristics.

Safety concerns associated with the use of delamanid in the paediatric population are aligned with the EU Risk Management Plan.

In the adult population, QT prolongation is reported as a very common (≥ 1/10) adverse reaction potentially caused by delamanid. In adults QT prolongation seems to be related to increased concentrations of the metabolite DM-6705 that accumulates slowly over time to a maximum level after 2 months of treatment.

In Study 232 delamanid was used for 10 days and no meaningful clinical change from baseline was seen in ECG parameters.

Only 13 children were included in trial 233, but there were several cases with increase in QTcB and QTcF. In trial 233 (paediatric patients 6-17 years of age), the maximal mean change from baseline (patient on OBR) for QTcF was 17.5 msec, observed after 4 months of delamanid treatment. This is without placebo

correction. This is higher than the QTcF interval prolongation observed in adults: In trail 204 (adult population, 100 mg BID), the mean placebo corrected increase in QTcF was 12.1 msec at 2 months.

The above data suggest that the relatively higher exposure in the paediatric population aged 6-17 years relative to the adult population dosed 100 mg delamanid BID, would result in an increased risk for QTcF interval prolongation. In that respect, based on the current limited data, the QT effect seems to be consistent with the observations in adults, but no firm conclusions can be drawn at present.
There were no SAEs or any AEs of QT prolongation observed. However, it should be kept in mind that in trial 233 patients with pre-existing cardiac conditions or abnormalities in screening ECG (including QTcF > 450 msec in both males and females) were excluded. Additionally the concomitant use of delamanid and moxifloxacin or bedaquiline was excluded.

The currently proposed dose based on the Pop PK model is lower than the one used in study 233 for children aged 6-11 years and 12-17 years. The evaluation of the PK/PD relationship of delamanid and its metabolite DM-6705 plasma concentrations and change in QTc interval has not been conducted yet, as it is only planned after trial 233 has been completed. It is therefore hard to assess the potential for QTc interval prolongation (and its clinical consequences) without modelling.

2.6.2. Conclusions on clinical safety

The safety data from these trials are consistent with the known safety profile of delamanid in adult subjects and no new safety signals have been identified.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 3.2 is not acceptable. RMP version 3.1 remains as the latest approved.

The MAH chose to submit the updated RMP version 3.3 to address the outstanding RMP issues as part of ongoing EMEA/H/C/00255/X/0046G procedure; this procedure will also address the changes reviewed and agreed as part of the current variation. No revised RMP is therefore adopted as part of this procedure.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.1 and the Marketing Authorisation Holder (MAH) took the opportunity to make minor editorial changes.

The MAH initially proposed to extend the indication to adolescents and children aged 6 years and older with a body weight of at least 30 kg. As it is not likely that an average 6-year old child weighs 30 kg, there is a discrepancy between the age and weight limits selected (i.e. 6 years and 30 kg) and the CHMP

therefore agreed the following reworded indication:

"Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents and children with a BW of at least 30 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4.2, 4.4 and 5.1)."

2.8.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

It is estimated that 3.6% of the tuberculosis (TB) cases worldwide are multidrug-resistant (MDR); ie, resistant to isoniazid and rifampicin. Childhood TB comprises approximately 10% to 15% of the global TB disease burden, with higher rates in developing countries. Based on estimates of total MDR-TB cases this translates to a minimum global estimate of approximately 40 000 paediatric cases of MDR-TB per year.

Differences in the pathophysiology and clinical presentation of TB in children make diagnosis more challenging in children than in adults and definitions of latent infection and active disease are not as clear. Children are also at a much higher risk of progression to active disease than adults.

Microbiological confirmation is often not available due to the paucibacillary nature of disease and the difficulty of specimen collection (especially sputum) in younger children. The diagnosis usually relies on nonspecific clinical and radiologic signs, as well as a history of exposure (ie, close contact with a TB case). Fever (possibly intermittent or low grade), weight loss or failure to thrive, and persistent cough for > 2 weeks are the most important clinical signs for pulmonary TB.

Children are diagnosed with either confirmed or presumed MDR-TB. Confirmed disease occurs when an organism is isolated from the child and is shown either genotypically or phenotypically to be resistant to isoniazid and rifampicin. Presumed disease occurs when TB is diagnosed in combination with either known contact with an MDR-TB case or after failure of appropriate first-line therapy when adherence has been verified. Incident cases of childhood TB reflect recent transmission, which implies that drug resistance patterns observed among paediatric TB cases reflect primary (transmitted) drug resistance within the community.

If a child presenting with TB is a known contact of an adult with MDR pulmonary TB, the child is a probable MDR-TB case and should be managed accordingly.

The EMA Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to *Mycobacterium tuberculosis* (EMA/CHMP/EWP/14377/2008 Rev. 1, 20 July 2017) gives the following recommendations on the paediatric population:

- The presentation and treatment of pulmonary tuberculosis is similar in adults and paediatric patients aged from approximately 10 years so that an extrapolation of safety and efficacy data obtained from adults is acceptable.

- The presentation of clinical disease may be different in children aged less than approximately 10 years compared to adults but the response to treatment may be comparable at least from the age of five years upwards, supporting the possibility of extrapolating efficacy documented in adults (and possibly also adolescents if they are enrolled into the same trials as adults) to this age group.

3.1.2. Available therapies and unmet medical need

Treatment of drug-resistant TB is long, expensive and associated with frequent adverse events. In children, treatment is further complicated by limited data on appropriate dosing and safety, and a lack of child-friendly formulations. New anti-TB drugs are urgently needed to improve treatment tolerability and outcome, particularly for MDR-TB cases with additional second-line drug resistance, for whom identifying at least four active drugs is difficult with the current armamentarium of drugs.

3.1.3. Main clinical studies

Trial 242-12-232 was a phase I, open-label, multiple-dose, and age de-escalation trial that investigated the pharmacokinetics and the safety and tolerability of delamanid in 37 paediatric MDR-TB patients administered with food for 10 days to subjects ages birth to 17 years, inclusive, who were also on therapy with an optimised background regimen.

Trial 242-12-233 is a phase II, open-label, non-comparative, multi-dose trial to assess the safety, tolerability, PK and efficacy of delamanid and is a 6-month extension to Trial 232. Delamanid is added to OBR for 6 months. Patients safety, efficacy and PK are followed until 8 weeks after the last delamanid dose. There is a visit at 6 months after the last delamanid dose for safety and efficacy evaluation and an additional treatment outcome follow-up one year after this last follow-up visit. The trial has been completed and data analysed for age groups 6-17 years (13 patients) and is still ongoing for paediatric population subset 0 to 5 years of age.

Six children aged 6–11 years were administered a 50 mg BID dosing regimen, and seven adolescents aged 12–17 years were administered a 100 mg BID dosing regimen.

A population PK model was developed for delamanid in the paediatric population with the data collected in Trials 232 and 233 in order to define the dose in the paediatric patients.

3.2. Favourable effects

Deltyba has a conditional marketing authorisation, obtained on 28 April 2014, for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

A population PK modelling approach was used to inform doses to be used in children of 6 to 17 years of age, assuming that similar PK exposure as in adults should lead to similar response to delamanid. The use of delamanid in addition to OBR in paediatric trial 233 resulted in a favourable treatment outcome in 12 of the 13 subjects aged 6 to 17 years at 24 months; 7 of the 13 subjects (53.8%) were cured and 5 of the 13 subjects (38.5%) completed treatment.

Simulation results are showing the following optimal doses:

- 20-30 kg: 35 mg BID (AUC ratio: 1.05)
- 30-40 kg: 50 mg BID (AUC ratio: 1.1)
- 40-50 kg: 50 mg BID (AUC ratio: 0.9) AND 100 mg BID (AUC ratio: 1.2)
- >50 kg: 100 mg BID (AUC ratio: 1.2)

For the >50 kg group, the adult dose is proposed consistently with the fact the median weight in the adult study was 55 kg.

3.3. Uncertainties and limitations about favourable effects

Pop PK

A population PK modelling approach was used to inform doses to be used in children of 6 to 17 y, assuming that similar PK exposure as in adults should lead to similar response to delamanid. As stated above, this is presumed to be the case from the age of 5 years upwards.

Additionally, it should be kept in mind that Deltyba obtained a conditional approval and that there is still uncertainty on the optimal dose in the adult population.

As regards the Pop PK model development and evaluation, the methods used are overall considered state of the art.

Results show overall good estimation of parameters. Only the intercompartmental clearance was estimated with a RSE of>50%. Results of graphical evaluation are also overall acceptable. Results of simulation results were shown for C_{max}s, AUCs and C_{min}s. Boxplots of distributions have been provided.

PK data support dosing in children with a bodyweight < 30 kg, the existing film-coated tablets are not considered the optimal strength. Dosing proposals for these children will be included in the upcoming 2nd type II variation addressing the younger age groups. With this variation, the MAH will also submit an extension application to establish that delamanid dispersible tablets are more appropriate for administration in children with younger age and lower body weight.

Most patients included in trial 233, certainly in group I and II, were Asian. In Pop PK study 256 was stated that exposure was higher in Asian people. This could have an impact on the observed PK data. The race effect could be driven by the difference in body size between Asian and non-Asian population, but this is not definitely established. The lack of significance of the race effect in the paediatric Pop PK model can be driven by the high rate of patients with race 'unknown' (10/25): these results are considered inconclusive. This should be further explored in the planned modelling exercise in the younger children, data permitting.

Efficacy

Based on the current conclusions of the Pop PK simulation, the proposed doses are lower than the ones used in trial 232 and 233 in children 6 to 17 years of age.

Evaluation of efficacy is complicated by the more difficult diagnosis in younger patients. Especially for children below 10 years of age, the presentation of the clinical disease may be different in children than in adults and lesions are more likely to be of the extra-pulmonary TB type. Six out of 7 patients aged 12-17 years had confirmed pulmonary MDR-TB, one probable pulmonary MDR-TB. In patient group II aged 6 to 11 years, only 50% had confirmed MDR-TB and 50% had suspected MDR-TB; 2 patients had pulmonary TB, one extra-pulmonary TB and 3 both pulmonary and extra-pulmonary TB.

The microbiological confirmation of the current episode of MDR-TB is based on the patient's history and for some patients this was several months before screening for trial 232 (and 233) – up to 5 months for group I and almost 1 year for group II.

Determination of final treatment outcomes was not prescribed by the protocol; nevertheless, final outcomes were assessed by the treating clinician as per local and/or WHO guidance defining the categories 'Cure', 'Treatment completed' and 'Treatment failed'.

Efficacy of delamanid remains unclear in extra-pulmonary TB, especially in serious forms such as meningitis. Regarding TB meningitis, there are little data on the CNS penetration of delamanid. However, the MAH is only applying for an extension of the indication of pulmonary tuberculosis to paediatric patients from 6 to 17 years of age.

Several subgroups of the paediatric population have not been studied: There were no patients with HIV, hepatitis B or C included in the paediatric trials. In addition, patients with severe malnutrition were excluded.

3.4. Unfavourable effects

The safety data from these trials are consistent with the known safety profile of delamanid in adult subjects and no new safety signals have been identified. Possibly IMP-related TEAEs occurring during trial 233 were reported for 2 subjects (15.4%) and comprised single events of arthralgia, headache, butterfly rash, and dizziness. All terms are listed in the published delamanid summary of product characteristics.

In trial 233 (paediatric patients 6-17 years of age), there were several cases with increase in QTcB and QTcF, the maximal mean change from baseline for QTcF was 17.5 msec, observed after 4 months of delamanid treatment. This is higher than the QTcF interval prolongation observed in adults. There were no SAEs or any AEs of QT prolongation observed.

In a concentration-corrected-QT interval modelling analysis, using the linear mixed effect model, the concentration of DM-6705 does have a significant impact on ΔQTc interval corrected for heart rate by Bazett's formula (QTcB). The model-predicted that the upper bounds of the 90% CIs of ΔQTcB values were all less than 10 ms at the simulated C_{max} of DM-6705 following the new recommended regimen.

3.5. Uncertainties and limitations about unfavourable effects

Current exposure in the paediatric population is very low and prohibits drawing clear conclusions on the clinical safety of delamanid in this population.

Several subgroups with a higher risk profile were not studied. There were no patients with HIV, hepatitis B or C included in the paediatric trials. Also, patients with severe malnutrition and underlying hearth disease were excluded. Concomitant use of delamanid and moxifloxacin or bedaquiline was excluded.

The updated Pop PK/PD report (Otsuka Report No. 242-19-259) with the results from the concentration-corrected-QT interval modelling analysis (PK/PD) has not been provided and hence detailed evaluation was not possible. This is planned to be submitted with completed Trial 242-12-233. A 6-7ms prolongation at therapeutic dose can definitely lead to >10ms at supratherapeutic concentrations, and therefore a QT effect cannot be ruled out. The currently provided data suggest that if 50 mg BID is used for paediatric patients weighing 30-50 kg and 100 mg BID for those above 50 kg, the model-predicted ΔQTc values will be in the same range as those observed in the adult population.

3.6. Effects Table

Not applicable: A population PK modelling approach is used to inform doses to be used in children of 6 to 17 years of age, assuming that similar PK exposure as in adults should lead to similar response to delamanid. Approval of the indication in children from 6 to 17 years of age is mainly based on the

appropriateness of the age-specific dose regimens based on PK data and on an acceptable paediatric safety profile.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The number of patients is too small to draw clear conclusions from the efficacy evaluation.

Based on the assumption that the response to treatment may be comparable from the age of 5 years upwards, approval of the indication in children from 6 to 17 years of age is mainly based on the appropriateness of the age-specific dose regimens based on PK data and on an acceptable paediatric safety profile.

3.7.2. Balance of benefits and risks

A population PK modelling approach was used to inform doses to be used in children of 6 to 17 y, assuming that similar PK exposure as in adults should lead to similar response to delamanid. The proposed dosing regimen for children is based on body weight:

- 20-30 kg: 35 mg BID
- 30-50 kg: 50 mg BID
- >50 kg: 100 mg BID

For most patients this dosing regimen is lower than the dosing regimen used in the paediatric clinical trials 232 and 233.

The safety data suggest that the relatively higher exposure in the paediatric population aged 6-17 years in trial 233 relative to the adult population dosed 100 mg delamanid BID, would result in an increased risk for QTcF interval prolongation. Based on a concentration-corrected-QT interval modelling analysis, the predicted upper bounds of the 90% CIs of ΔQTcB values were all less than 10 ms at the simulated C_{max} of DM-6705 following the new recommended dose regimen. The currently provided data suggest that if 50 mg BID dose for paediatric patients weighing 30-50 kg and 100 mg BID for those above 50 kg are used, the model-predicted ΔQTc values will be in the same range as those observed in the adult population. A QT effect is not ruled out, but this risk would be acceptable, given the unmet need in the paediatric population, provided that appropriate precautions, specified in the SmPC, are followed.

The safety risk in children from 6 to 17 years of age enrolled in the trials seems to be consistent with what was observed in adults.

3.7.3. Additional considerations on the benefit-risk balance

Administration of 35 mg is not possible with the 50 mg film-coated tablets. The current extension of the indication is limited to adolescents and children with a body weight of at least 30 kg. The delamanid paediatric formulation, more appropriate for administration in children with younger age and lower body weight, will be introduced in a new extension application.

3.8. Conclusions

The overall benefit-risk of Deltyba for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adolescents and children with a body weight of at least 30

kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability is positive.

4. Recommendations

Outcome

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

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

Extension of indication to include adolescents and children with a body weight of at least 30 kg. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.2 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.1 and the Marketing Authorisation Holder (MAH) took the opportunity to make minor editorial changes.

The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB are recommended.

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

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0271/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Deltyba is not similar to Sirturo, Granupas and Pretomanid FGK within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.