22 July 2021
EMA/543612/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

**Deltyba**

International non-proprietary name: delamanid

Procedure No. EMEA/H/C/002552/X/0046/G

**Note**

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BID</td>
<td>twice daily</td>
</tr>
<tr>
<td>DDI</td>
<td>Drug-drug interaction</td>
</tr>
<tr>
<td>DPF</td>
<td>Delamanid paediatric formulation</td>
</tr>
<tr>
<td>DS-TB</td>
<td>drug-susceptible tuberculosis</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>HFM</td>
<td>High-Fat Meal</td>
</tr>
<tr>
<td>LC-MS/MS</td>
<td>high-performance liquid chromatography-tandem mass spectrometry</td>
</tr>
<tr>
<td>PZA</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>SM</td>
<td>Standard Meal</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TEAE</td>
<td>Treatment-emergent adverse event</td>
</tr>
<tr>
<td>UPLC-MS/MS</td>
<td>ultra-performance liquid chromatography-tandem mass spectrometry</td>
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</table>
1. Background information on the procedure

1.1. Submission of the dossier

Otsuka Novel Products GmbH submitted on 24 July 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

<table>
<thead>
<tr>
<th>Variation(s) requested</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.I.6.a</td>
<td>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</td>
</tr>
<tr>
<td></td>
<td>II</td>
</tr>
</tbody>
</table>

Extension application to introduce a new pharmaceutical form (dispersible tablets) associated with a new strength (25 mg), grouped with a type II extension of indication variation (C.I.6.a) to include the treatment of multidrug-resistant tuberculosis (MDR-TB) of children of at least 10 kg of body weight for the approved Deltyba 50 mg film-coated tablets; as a consequence, sections 3, 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly. Version 3.3 of the RMP has been submitted and Annex II is updated to remove the specific obligation related to an in vitro study using the HFS-TB model.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Deltyba was designated as an orphan medicinal product EU/3/07/524 on 30/04/2014 in the following condition: treatment of multidrug-resistant tuberculosis (MDR-TB).

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

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 completed.

The PDCO issued an opinion on compliance for the PIP P/0271/2019 eligible for the reward.

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 MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is authorised orphan medicinal product for a condition related to the proposed indication.

It is considered that Deltyba 25mg is not similar to Sirturo, Granupas and Dovprela (Previously Pretomanid FGK) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.
**Protocol assistance**

The MAH did not seek Protocol assistance at the CHMP.

**1.2. Steps taken for the assessment of the product**

The Rapporteur appointed by the CHMP was:

Rapporteur: Christophe Focke

<table>
<thead>
<tr>
<th>Step</th>
<th>Date</th>
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<tbody>
<tr>
<td>The application was received by the EMA on</td>
<td>24 July 2020</td>
</tr>
<tr>
<td>The procedure started on</td>
<td>13 August 2020</td>
</tr>
<tr>
<td>The Rapporteur's first Assessment Report was circulated to all CHMP members on</td>
<td>13 November 2020</td>
</tr>
<tr>
<td>The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on</td>
<td>11 November 2020</td>
</tr>
<tr>
<td>The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on</td>
<td>26 November 2020</td>
</tr>
<tr>
<td>The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on</td>
<td>10 December 2020</td>
</tr>
<tr>
<td>The MAH submitted the responses to the CHMP consolidated List of Questions on</td>
<td>19 March 2021</td>
</tr>
<tr>
<td>The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on</td>
<td>23 April 2021</td>
</tr>
<tr>
<td>The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on</td>
<td>06 May 2021</td>
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<tr>
<td>The CHMP agreed on the consolidate List of Outstanding Issues to be sent to the MAH on</td>
<td>20 May 2021</td>
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<tr>
<td>The MAH submitted the responses to the CHMP List of Outstanding Issues on</td>
<td>22 June 2021</td>
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<tr>
<td>The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on</td>
<td>07 July 2021</td>
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<tr>
<td>The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension to the marketing authorisation and extension of indication to Deltyba on</td>
<td>22 July 2021</td>
</tr>
<tr>
<td>The CHMP adopted a report on similarity of Deltyba with Sirturo, Granupas and Dovprela on (Appendix 1)</td>
<td>22 July 2021</td>
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2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The therapeutic indication for Deltyba is its use, as part of an appropriate combination regimen, for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children and infants with a body weight of at least 30 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

The Company is applying for an extension of the indication in infants and children with a body weight of at least 10 kg. In a previous variation procedure (EMEA/H/C/002552/II/0040) extension of the indication from adults to adolescents and children with a body weight of at least 30 kg was granted.

2.1.2. Epidemiology

It is estimated that 3.6% of the tuberculosis (TB) cases worldwide are multidrug-resistant (MDR); i.e.: 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.

2.1.3. Biologic features Aetiology and pathogenesis

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.

2.1.4. Clinical presentation, diagnosis

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 (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. 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.

2.1.5. Management

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.

**About the product**

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis, ATC code: J04AK06.

**Mechanism of action**

The pharmacological mode of action of delamanid involves inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid.

The mechanism of action has not been fully elucidated for delamanid. Delamanid requires intracellular activation for their biological function. Under aerobic conditions, delamanid disrupts the formation of mycolic acids, major constituents of the cell envelope of Mycobacterium tuberculosis. Under anaerobic conditions, delamanid acts by respiratory poisoning through generation of reactive nitrogen species, including nitric oxide.

These activities require nitro-reduction of the active substance within the mycobacterial cell by a deazaflavin-dependent nitroreductase (Ddn), which is dependent on the reduced form of the cofactor F420. Reduction of F420 is accomplished by the F420-dependent glucose-6-phosphate dehydrogenase, Fgd1.

**Paediatric formulation**

The 50 mg tablet formulation used in the paediatric population weighing more than 30 kg is the same formulation and strength as used in adults. This adult formulation has been approved. A paediatric formulation of delamanid (DPF) was developed as immediate-release dispersible tablets containing 25-mg of delamanid, intended to be reconstituted in water as an extemporaneous suspension for oral ingestion. This new DPF is subject of the current line extension procedure.

**Posology**

For the currently approved 50 mg tablet formulation:

The recommended dose for adults is 100 mg twice daily for 24 weeks.

**Paediatric population**

Paediatric patients with a body weight of

- $\geq 30$ to $< 50$ kg: the recommended dose is 50 mg twice daily for 24 weeks
- $\geq 50$ kg: the recommended dose is 100 mg twice daily for 24 weeks
For patients with a body weight below 30 kg Deltyba 25 mg dispersible tablets should be used.

The proposed posology for the 25 mg dispersible tablets is:

Paediatric patients with a body weight of
- \(\geq 10 \text{ to } < 20 \text{ kg}\): the recommended dose is 25 mg twice daily for 24 weeks
- \(\geq 20 \text{ to } < 30 \text{ kg}\): the recommended dose is 50 mg every morning and 25 mg every evening for 24 weeks

2.2. Quality aspects

2.2.1. Introduction

This application is a line extension to the already approved Deltyba 50 mg film-coated tablets. The scope is to add 25 mg dispersible tablets and extend the indication to infants and children with a body weight of at least 10 kg.

The finished product is presented as dispersible tablets containing 25 mg of delamanid.

Other ingredients are: hypromellose phthalate, povidone (K-25), all-rac-\(\alpha\)-tocopherol, mannitol, crospovidone, sucralose, silica colloidal hydrated, cherry micron OT-22685 and calcium stearate.

The product is available in aluminium/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

Deltyba 25 mg dispersible tablets introduced with this line extension application contain the same active substance, delamanid, used to manufacture the already approved Deltyba 50 mg film-coated tablets. No new information on the active substance has been provided within this application.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Deltyba 25 dispersible tablets are white to off white, round, debossed with “DLM” and “25” on one side.

The aim of the development was to obtain a formulation for paediatric use.

Delamanid is a white to pale yellow crystalline powder. The active substance is practically insoluble in water and its solubility increases only slightly under a lower pH (under 4).

The excipients used in the formulation are hypromellose phthalate, povidone (K-25), all-rac-\(\alpha\)-tocopherol, mannitol, crospovidone, sucralose, silica colloidal hydrated, cherry micron OT-22685 and calcium stearate. These are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. and USP/NF standards, except for the flavouring agent cherry micron OT-22685 that is controlled by an in-house specification. The flavouring agent is composed of the following ingredients: flavourings, starch sodium octenyl succinate and reduced palatinose. A statement was given declaring its compliance with the EU Flavouring Regulation 1334/2008. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of the excipients with the active substance was confirmed during preliminary stability studies. Delamanid showed no compatibility issues with all the excipients used in the formulation.
The manufacturing process for delamanid 25 mg dispersible tablets consists of the following processes: dispersion of the active substance in a polymer matrix, powder blending and the tableting process.

A risk evaluation was performed to identify the factors potentially affecting the proposed critical quality attributes (CQA) throughout the manufacturing process of the dispersible tablets. Each of these factors was reviewed to identify critical unit operations which needed further investigation. The critical steps were identified. Based on the CQAs, process parameters for the critical steps were evaluated and the proven acceptable ranges (PARs) were identified.

The dissolution method for delamanid dispersible tablets is the same as for the approved delamanid 50 mg film-coated tablets.

The data demonstrates that the developed 25 mg dispersible tablets and manufacturing process deliver a product compliant with the defined QTTP and CQAs.

The clinical and intended commercial dispersible tablets are exactly the same formula except that the clinical dispersible tablets have no debossing letters.

The primary packaging is an aluminum/aluminum foil blister. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Two manufacturers are involved in the manufacturing process. Both manufacturers are the same as the ones used for the already authorised Deltyba 50 mg film-coated tablets. As indicated above, the manufacturing process consists of: dispersion of the active substance in a polymer matrix, powder blending and tableting.

The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. A concurrent validation approach is proposed for the validation of the dispersible tablets at the commercial manufacturing site. The results from formal stability batches, trial batches and site transfer justification batches show a robust process that is also supported by prior knowledge and appropriate quality risk management and risk mitigation. The concurrent process validation scheme provided is acceptable.

To justify the manufacturing process for the proposed commercial 25 mg dispersible tablets, the process validation at the proposed commercial production scale will be performed prior to marketing of the dispersible tablets. The applicant should commit to immediately notify the CHMP of any non-compliance.

Product specification

The finished product release and shelf-life specification includes appropriate tests for this kind of dosage form: identification (visual), identification of tocopherol (HPLC with PDA), degradation products (HPLC), fineness of dispersion (HPLC), content uniformity (HPLC), disintegration (Ph. Eur.), dissolution (Ph. Eur.), assay of delamanid (HPLC), assay of tocopherol (HPLC) and microbial limit test (Ph. Eur.).

The specification for the 25 mg dispersible tablets is based on the one established for Deltyba 50 mg film-coated tablet. The proposed specification is considered acceptable.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk...
assessment and the presented batch analysis data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identification and assay testing has been presented.

The finished product is released onto the market based on the above mentioned release specifications, through traditional final product release testing.

A risk assessment concerning the presence of nitrosamine impurities in the finished product was based on the combined recommendations from health authorities, Questions and answers for Marketing Authorisation Holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products (EMA/409815/2020), and the assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products (EMA/369136/2020). It was concluded that there is no risk of N-nitrosamine contamination and there is no risk related to the presence of nitrosamine impurities in the product. Therefore, no changes to the control strategy for Deltyba are necessary to mitigate potential contamination by nitrosamines.

Batch analysis results are provided for four clinical and production scale batches that have been placed on formal stability studies confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

**Stability of the product**

Stability data from three representative production batches stored for up to 18 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Additionally, stability studies have also been performed on bulk tablets stored for up to 18 months at 30 °C / 75% RH. Samples were tested for description, assay (delamanid and tocopherol), impurities/degradation products, dissolution, microbial limit test, water content, disintegration (37°C), hardness, and friability. No significant changes were observed on any of the measured parameters under any condition.

In addition, an open dish stress study, a photostability study and a cycling stress study have been completed on one representative scale batch of Deltyba 25 mg dispersible tablets. The photostability study, performed in accordance with ICHQ1B, indicates that the unpackaged delamanid dispersible tablets are sensitive to light whereas the open dish stress study indicates that unpackaged dispersible tablets tend to be sensitive to moisture. Therefore, a specific caution for to protect the tablets from light and moisture is required.

Based on available stability data, the proposed shelf-life of 30 months and a storage restriction "Store in the original package in order to protect from light and moisture " as stated in the SmPC (section 6.3) is acceptable.

**Adventitious agents**

No excipients derived from animal or human origin have been used.
2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the 25 dispersible tablets to enable administration of delamanid to infants and children with a body weight of at least 10 kg has been presented in a satisfactory manner. The development of the formulation was based on the existing 50 mg film-coated tablets. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

A recommendation with regards to the concurrent validation approach asking the applicant to present batch analysis data on dispersible tablets manufactured at the proposed commercial site has been raised (see section 2.2.6).

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

The following post-authorisation measure (recommendation) is included:

- Development batches were already manufactured at the proposed commercial scale (e.g. stability batches) or larger scale (trial batch) but not at the proposed commercial manufacturing site. A preliminary site transfer ‘justification’ study is successfully done with one batch of each strength. However, batch analysis data on dispersible tablets manufactured at the proposed commercial site are not available yet. It is assumed that such data will only be available once site transfer and validation activities are initiated as part of the concurrent validation approach. The commercial tableting process will be validated with concurrent validation approach for the first three commercial batches and full validation report as well as batch analysis results will be provided. Submission of these batch data should be addressed as a post-authorisation measure (recommendation).

2.3. Non-clinical aspects

2.3.1. Pharmacology

No additional data.

2.3.2. Pharmacokinetics

No additional data.

2.3.3. Toxicology

In support of paediatric development, 2 GLP-compliant juvenile toxicity studies (027779 and 028620) were completed in line with delamanid’s paediatric investigation plan EMEA-001113-PIP01-10. These results were already submitted on occasion of type II variation EMEA/H/C/002552/II/0040.
Daily dosing with delamanid up to 300 mg/kg for 10 weeks, and starting in juvenile rats from PND 4, resulted in treatment-related findings consistent with those noted in adult animals. Based on the young starting age of the animals, the study is considered to support paediatric development from birth. There were no notable sex differences in TK parameters for delamanid in neonatal rats. Age-related differences in TK were limited to a ~2-fold increase in AUC (animals PND 11-18) when comparing to week 10 (adult age).

The NOAELs were considered to be 3 mg/kg/day in juvenile male rats (AUC0-24h: 18760 ng.h/mL) and 30 mg/kg/day in juvenile female rats (AUC0-24h: 49060 ng.h/mL), significantly exceeding the intended systemic clinical exposure.

2.3.4. Ecotoxicity/environmental risk assessment

Although the approval of the paediatric indication for Deltyba may increase the environmental exposure, delamanid is not expected to pose a risk to the environment.

2.3.5. Discussion on non-clinical aspects

No non-clinical issues have been identified.

The proposed wording for section 5.3 is agreed.

2.3.6. Conclusion on the non-clinical aspects

Based on the review of the non-clinical data, the application for a line-extension and an extension of indication for Deltyba, is considered approvable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies
The PIP 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.
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 relative bioavailability trial (Trial 242-12-245) in adults to investigate the comparative bioavailability of the paediatric formulation (5- and 25-mg dispersible tablets) with the delamanid 50-mg tablet adult formulation.

Trials 242-12-232 and 242-12-233 are age de-escalation trials that were performed sequentially in four groups: Group 1 (ages 12 - 17 years, inclusive), Group 2 (ages 6 - 11 years, inclusive), Group 3 (3 - 5 years, inclusive), and Group 4 (ages birth - 2 years, inclusive).

The paediatric formulation of delamanid was developed as immediate-release dispersible tablets containing either 5- or 25-mg of delamanid, intended to be reconstituted in water as an extemporaneous suspension for oral ingestion. The dispersible tablet formulation of delamanid was used for the younger age groups in Trial 242-12-232 and 242-12-233, and relative bioavailability was conducted to compare the dispersible tablet formulation for paediatric subjects with the marketed tablet formulation. Further objectives regarding the formulation were the palatability of the dispersible tablets.

Trials 242-12-232 and 242-12-233 were conducted in paediatric subjects ages 0.7 to 17 years with MDR-TB who received either the delamanid tablet formulation (6-17 years) or the delamanid paediatric formulation (DPF) (< 6 years) in dosing regimens ranging from 100 mg BID to 5 mg QD in an age de-escalating design. A population PK analysis was performed on data from the 2 trials (Trial 242-12-232 and Trial 242-12-233) to determine the doses in paediatric subjects which would provide delamanid exposures similar to those observed in adult subjects with MDR-TB. In addition, an exposure-response analysis of delamanid plasma concentrations versus QTc was also conducted on data from the 2 trials.

Trial 242-12-245 was a randomized, 2 sequence, open-label, single-dose, 2-way crossover trial to compare the dispersible tablet formulation for paediatric subjects with the marketed tablet formulation and to determine the effect of a high-fat meal on delamanid PK. Further objectives regarding the formulation were the palatability of the dispersible tablets.

A population PK analysis has been conducted by using data from Trials 242-12-232 and 242-12-233 in order to describe the PK of delamanid, evaluate the effect of covariates on the variability of PK of delamanid in the paediatric population, and define the paediatric doses for patients with 0 to 17 years of age that would result in a delamanid systemic exposure comparable to that in adults following the approved dose. Dosing paradigms to provide exposure comparable to adult dosing were determined based on simulations.

**2.4.2. Pharmacokinetics**

**Analytical Methods**

Methods of Analysis of Delamanid and DM-6705 in Plasma for Protocol 242-12-245

- A method utilizing ultra-performance liquid chromatography and tandem mass spectrometry (UPLCMS/MS) was developed and validated for the analysis of delamanid (OPC-67683) and 8 metabolites in human plasma.

Analysis of plasma samples for OPC-67683 and DM-6705 with the LC/MS/MS method are presented in the bioanalytical report (TSLR14–253) and the results are correctly described. The different deviations, rejections of analytical runs and reanalysis of study samples have been discussed in an appropriate way. It can be concluded that there is no impact on the quality of the data or the integrity of the study.
- A method utilizing liquid chromatography and tandem mass spectrometry (LC-MS/MS) was developed and validated for the analysis of delamanid (OPC-67683) and DM-6705 in human plasma samples.

**Method of Analysis of Delamanid and DM-6705 in Plasma for Protocol 242-12-233**

A method utilizing liquid chromatography and tandem mass spectrometry (LC-MS/MS) was developed and validated for the analysis of delamanid (OPC-67683) and DM-6705 in human plasma.

The quantifications of OPC-67683 and DM-6705 in plasma by LC/MS/MS are presented in the final bioanalytical report and the results are correctly described. The different deviations, contaminations, failed analytical runs, reinjected runs and repeat analysis have been discussed in an appropriate way. It can be concluded that there is no impact on the quality of the data or the integrity of the study.

**Absorption**

**Bioavailability**

Peak plasma concentrations are reached in approximately 4 hours post-dose, regardless of food intake.

There is no data on the absolute bioavailability. In light of the very long plasma half-life and slow accumulation of metabolites observed in clinical studies a single dose absolute bioavailability study is unlikely to contribute to the better understanding of delamanid absorption and metabolism.

**Bioequivalence**

**Study n° 242-12-245**

Study 242-12-245 was a randomized, open-label, single-dose, two-way crossover, relative bioavailability study comparing a 100-mg Oral Dose of Delamanid Tablets and a 100 mg Oral Dose of the Delamanid Paediatric Formulation in Healthy Adult Subjects.

Each subject received a single 100-mg dose of DLM as the reference formulation and a 100-mg dose of DPF as the test formulation. Subjects were randomly allocated to one of 2 cohorts in which each cohort received the same 3 treatments (A, B, and C) given consecutively but a different sequence (ie, ABC, BAC).

The treatments A, B, and C were as follows:

- Treatment A: 100 mg DLM (2 x 50-mg tablets) with a standard meal (DLM + SM)
- Treatment B: 100 mg DPF (4 x 25-mg tablets) with a standard meal (DLM + SM)
- Treatment C: 100 mg DPF (4 x 25-mg tablets) with a high-fat meal (DPF + HFM)

The palatability of the DPF was assessed at 30 minutes following each dose of IMP using a standard 9-point hedonic scale (1 = worst; 9 = best).

The proposed study design is appropriate for an immediate release formulation. Blood sampling occurred during most of the trials at 1, 2, 3, 4, 5, 6, 8, ... hours post-dosing. The median time of peak concentration (tmax) of the delamanid film-coated tablet was 4 hours with a range of 2 to 6 hours; the tmax of the paediatric dispersible tablet was 5 hours with a range of 3 to 8 hours. Therefore, the sampling was adequate to identify C_max.

The certificate of analysis has been submitted for both the test and reference product. The batch sizes of the test products used in the relative bioavailability study were full production scale batch sizes.
Geometric mean ratios (test [DPF]/reference[DLM]) and 90% CIs for delamanid $C_{\text{max}}$ and $\text{AUC}_{\infty}$ are presented in the table below.

### Table 1: Geometric Mean Ratios and 90% Confidence Intervals for Delamanid Pharmacokinetic Parameters Following Administration of 100 mg Delamanid Tablets (2 x 50-mg Tablets) and 100 mg Delamanid Paediatric Formulation (4 x 25-mg Tablets) to Healthy Subjects

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PK Parameter</th>
<th>GMR$^a$</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg of DPF</td>
<td>$C_{\text{max}}$</td>
<td>0.753</td>
<td>(0.701, 0.809)</td>
</tr>
<tr>
<td>Versus</td>
<td>$\text{AUC}_{\infty}$</td>
<td>0.840</td>
<td>(0.775, 0.909)</td>
</tr>
<tr>
<td>100 mg of DLM</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Geometric mean ratio between 100 mg of DPF with a standard meal versus 100 mg of DLM with at standard meal (T/R), estimated from a mixed effect linear model with cohort, period, and treatment as fixed effects and subject as random effect nested within cohort.

Based on the statistical results, 100 mg of DPF was not bioequivalent to 100 mg of DLM as the 90% CIs for the delamanid PK parameters ($C_{\text{max}}$ and $\text{AUC}_{\infty}$) were outside the 0.80 - 1.25 bioequivalence limits. The GMR for both the PK parameters following DPF administration was lower than that from DLM.

Results of the palatability assessment using a 9-point hedonic scale (1 = worst; 9 = best) are summarized in the table below.

### Table 2: Summary of Palatability Hedonic Scale: Safety Sample

<table>
<thead>
<tr>
<th>Hedonic Scale</th>
<th>DLM</th>
<th>DPF + SM</th>
<th>DPF + HFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>53</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.1 (1.8)</td>
<td>7.1 (1.9)</td>
<td>7.0 (1.9)</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Range</td>
<td>1.0 - 9.0</td>
<td>2.0 - 9.0</td>
<td>1.0 - 9.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Differences (T$^a - R$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1.0</td>
</tr>
</tbody>
</table>

$^a$The test treatment is DLM. The reference treatment is DPF + SM.

$^b$The estimate is the Hodges-Lehman estimator for the median paired difference associated with Wilcoxon’s signed-rank test.

$^c$The CI is from Moses’ procedure for determining a distribution-free CI for paired difference based on Wilcoxon’s signed-rank test.

$^d$The p-value is based on the Wilcoxon’s signed-rank test of whether the median paired difference equals zero.

A statistically significant difference in the mean score was observed for DLM (6.1) versus DPF + SM (7.1), $p = 0.0013$.

A palatability assessment (visual hedonic scale) was performed longitudinally for subjects in Groups 3 and 4. The vast majority of subjects in both Group 3 (3 to 5 years group) and Group 4 (0 to 2 years group) selected “like very much” at all timepoints. No subjects selected “dislike very much” at any of the timepoints, and only a few subjects selected “dislike a little.” A summary of the palatability of delamanid dispersible tablets is presented in Table 11.4.1.2.4-1 of the 242-12-233 CSR. Importantly, no subjects in the study exhibited adherence problems, discontinued study medication, or discontinued participation in the trial due to issues related to drug palatability.
A hedonic scale and investigational medicinal product (IMP) acceptability assessment worksheet was used in the study. The results of the palatability assessment conducted confirm that the dispersible formulation is palatable to paediatric patients and would result in enhanced ease of administration, adherence to the medication as well as preserve bioavailability.

**Influence of food**

Pharmacokinetics have been previously studied and systemic exposure was greater when delamanid was taken with food: about 2-fold greater with a standard meal and 4-fold greater with a high-fat meal, and hence the effect of high-fat meal on the DPF was studied.

Delamanid $C_{\text{max}}$ and $AUC_{\infty}$ values were 1.4- to 2.1-fold higher following DPF administration with a high-fat meal compared to that with a standard meal.

In the paediatric clinical trials conducted, delamanid was administered with food that was typical for the children’s ages and nutritional requirements. The delamanid dose estimation modelling (for either the film-coated or the dispersible formulation) is therefore based on PK data that was measured under 'real-world’ conditions and therefore the corresponding delamanid exposure should reflect exposure following regular food consumption by paediatric patients in the real-world. In particular, in younger children, the actual typical age specific 'standard’ meals might not vary much with respect to fat content reflecting the reliance on breast milk/formula feed as the main energy source with limited consumption of complementary food in this age group.

Therefore, the SmPC recommends intake of delamanid with food.

**Distribution**

Delamanid and primary metabolites DM-6704, DM-6705, and DM-6706 extensively binds to all plasma proteins (> 99.5%) and most extensively (> 97%) to albumin and lipoproteins. Delamanid has a large apparent volume of distribution ($V_{\text{z/F}}$ of 2,100 L).

**Elimination**

**Excretion**

The elimination half-life ($t_{1/2}$) of delamanid is about 30 to 38 hours, allowing steady state to be reached after 10 to 14 days of dosing. The elimination half-life of its major metabolite (DM-6705) is approximately 230 hours, and steady state is reached by 8 weeks. The single-dose $^{14}$C-delamanid trial indicated that delamanid and its metabolites were predominantly excreted in the faeces while renal excretion is a negligible pathway for elimination.

**Metabolism**

In vitro data suggest that delamanid is essentially metabolized by albumin, resulting in the formation of the primary metabolites DM-6705, which in turn is metabolized to DM-6704 and DM-6706. Eight metabolites have been identified in human plasma following multiple oral doses, though present at low concentrations after 10 to 14 days of dosing, representing all together about 1% to 10% of parent delamanid.

**Inter-conversion**

Delamanid is the R enantiomer of a chiral compound. Delamanid does not undergo chiral inter-conversion *in vivo.*
Pharmacokinetics of metabolites

Delamanid and primary metabolites DM-6704, DM-6705, and DM-6706 extensively binds to all plasma proteins (> 99.5%) and most extensively (> 97%) to albumin and lipoproteins.

Consequences of possible genetic polymorphism

Delamanid does not show clinically meaningful induction and/or inhibitory effects on cytochrome P450 (CYP) isoenzyme activity.

Dose proportionality

After single or multiple oral doses in healthy subjects, as well as drug-susceptible tuberculosis (DS-TB) and multidrug-resistant tuberculosis (MDR-TB) patients, delamanid plasma concentrations increase less than dose proportionally.

Time dependency

The twice daily (BID) dosing regimen for phase 2 was selected based on the fact that for a total daily dose of 300 mg, the 150 mg BID and the 100 mg three times daily (TID) dosing regimens showed higher exposure (1.93-fold to 2.23-fold higher) compared with the 300 mg once daily (QD) dosing regimen (Trial 242-08-211).

Intra- and inter-individual variability

A moderate intra- and inter-individual variability has been reported for the PK parameters of delamanid.

The inter-individual variability (CV%) for C_{max} and AUC_{∞} of DPF dispersible tablet under standard meal was 27.1% and 34.6%, respectively (CSR 245-12-245, PKT-9). The CV% for C_{max} and AUC_{∞} of delamanid film-coated tablet under standard meal was 21.6% and 21.9%, respectively (CSR 245-12-245, PKT-8). The intra-individual variability for C_{max} and AUC_{∞} is 22.1% and 24.6%, respectively (CSR 245-12-245, derived from Tables STAT-1.1 and STAT-1.2, using CV% = 100 * sqrt (exp (S2 within) −1), whereas S2 within is the residual error).

Special populations

Impaired renal function

Less than 5% of an oral dose of delamanid is recovered from urine. Mild renal impairment (50 mL/min < CrCLN < 80 mL/min) does not appear to affect delamanid exposure. Therefore, no dose adjustment is needed for patients with mild or moderate renal impairment. It is not known whether delamanid and metabolites will be significantly removed by haemodialysis or peritoneal dialysis.

Impaired hepatic function

No dose adjustment is considered necessary for patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment.

Gender

The POPPK models submitted in the original submission investigated the following covariate parameters:
Intrinsic factors (body size [BW, LBW, BSA], age, gender, race, geographic region, disease status [MDR-TB vs. XDR-TB], and laboratory values [CRCL, CRCLN, MDRD]). Exposure-related PK parameters were independent of gender.

**Race**

An approximately 50% higher exposure to delamanid was observed in Asian compared to non-Asian populations.

**Weight**

The POPPK models submitted in the original submission investigated the covariate the body size [BW, LBW, BSA]. Delamanid clearance was independent of weight.

**Elderly**

No patients of ≥ 65 years of age were included in clinical trials.

**Children**

In trial 242-12-232, in Groups 1 to 4, the median delamanid C<sub>max</sub> on Day 10 was 557, 573, 500, and 179 ng/mL, respectively; the median AUC0-24h on Day 10 was 9790, 12000, 9290, and 2740 ng*h/mL, respectively. The C<sub>max</sub> and the AUC0-24h ranges were reasonably similar for Groups 1 to 3 but were much lower for Group 4. A summary of delamanid pharmacokinetic parameters following delamanid administration on Day 10 is presented in Table 3.

**Table 3: Delamanid Median (Range) PK Parameters on Day 10 Following 100 mg BID (Group1), 50 mg BID (Group 2), 25 mg BID (Group 3) or 5-20 mg (Group 4) of Delamanid to Paediatric MDR-TB subjects**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>6</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>557 (304-803)</td>
<td>573 (485-682)</td>
<td>500 (287-919)</td>
<td>179 (45.2-298)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>3.98 (0.0 - 24.0)</td>
<td>11.98 (2.0 - 24.0)</td>
<td>4.00 (0.0 - 24.0)</td>
<td>13.75 (2.0 - 23.97)</td>
</tr>
<tr>
<td>AUC0-24h (ng.hr/mL)</td>
<td>9790 (6170-13000)</td>
<td>12000 (9810-13300)</td>
<td>9290 (5180-12900)</td>
<td>2740 (701-4910)</td>
</tr>
<tr>
<td>CL/F (mL/min)</td>
<td>341 (257-541)</td>
<td>139 (125-170)</td>
<td>89.8 (64.5-161)</td>
<td>87.4 (67.9-123)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>30.4 (19.7 - 54.7)</td>
<td>23.7 (19.1-82.1)</td>
<td>20.5 (16.8-31.3)</td>
<td>ND</td>
</tr>
<tr>
<td>R&lt;sub&gt;ae&lt;/sub&gt;AUC0-24h</td>
<td>2.68 (1.86 - 4.71)</td>
<td>2.55 (1.72-4.11)</td>
<td>2.70 (1.85-4.00)</td>
<td>2.69 (1.24-4.20)</td>
</tr>
</tbody>
</table>

The paediatric investigation plan (PIP) for delamanid in paediatric multidrug-resistant tuberculosis (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.
A population PK analysis was conducted for this purpose. All nonlinear mixed effects modelling analyses was performed using NONMEM software (Version 7.4.3).

The final population PK model was used to simulate steady-state exposure in paediatric patients in different age/body weight groups, which were then compared with exposure in adults. Based on these results, estimated paediatric doses were determined, which will result in an exposure comparable to that in adults following the approved adult dose.

Several issues were identified with the approach taken by the Applicant for population PK model building during the first round of evaluation. Based on the comment made, the Applicant has updated the POPPK model. The updated version of the POPPK model is judged suitable to serve as a basis to compare PK exposure in adults and children.

- The structural model selection as described by the applicant was judged very confusing. It was stated that the starting point was a 2 compartment model with a transit absorption, and still simpler models (one compartment, lag time, etc.) seemed to have been tested and criteria for model selection were vague and variable: some models were discarded for longer run times and other for lack of fitting improvement. This approach was not endorsed during the first round. Longer run time is not considered a valid argument to discard a model with better fitting performances (e.g. based on results of loglikelihood ratio tests). The Applicant was requested to restart the model building with structural model selection starting from the simpler and progressing in complexity and base the structural model selection on fitting performance (Log likelihood ratio tests) and on parsimony.

The Applicant has rerun the model: the newly retained structural model was a 2 compartments model with transit absorption (N=4).

- Regarding covariate model building, it was noted/anticipated that some of the covariate tested were highly correlated: these include formulation vs bodyweight vs age. This was judged very concerning given that the covariate model building was performed using a pure data driven approach. The Applicant was requested during the first assessment round to provide the results of correlation analyses for all the combinations of potential covariates and to also provide a mechanistic discussion of the reason why each covariate was tested on the chosen PK parameter.

The updated information provided by the applicant adequately addresses the issues raised from the initial submission.

- It was particularly noted that, given that adult formulation was administered to older children (groups 1 & 2) while dispersible tablets were administered to younger children (groups 3&4), it would very probably not be possible, only using paediatric data from study 232 to disentangle the formulation and the age/body side effects on F and CL. Of note the formulation effect was not detected in the popPK analysis while the bioequivalence results showed that the two formulations are not bioequivalent: this is an additional evidence that the POPPK analysis as performed by the applicant was not sensitive enough to detect the actual effects of formulation, age and body size on PK. This was considered an important issue for the reliability of the dosing recommendation based on POPPK results. The Applicant was requested during the 1st assessment to redo the POPPK analysis including the adult bioequivalence PK data in the analysis dataset. This would allow adequate description of the absorption phase (which was hampered by the data sparsity) and better characterization of the covariate effects (formulation vs body size vs maturation vs dose) on the absorption (rate and extent) parameters.

The Applicant has made some efforts to better understand the impact of age and formulation on the absorption of the drug. The data available did not allow estimation of the related parameters. Formulation effects was modelled as a fixed parameter and age effect estimated. The overall fitting performances on the paediatric data are now acceptable.
- It was noted that, without any explanation, a fixed value of 0.58 was used for the effects of Fractional Change by Dose < 100 mg on F1. The Applicant was requested during the 1st assessment round to justify and provide the source for any fixed value used during the updated model building to be fitted to the extended dataset.

The data source and explanation were provided for the fixed value used for the dose effect on F1.

- The Applicant was requested to provide pcVPC splitted by age groups for the updated model to ensure that model fitting performances are acceptable for each age group. In addition, the applicant was asked to provide pcVPC stratified on body weight during the 1st evaluation round.

The Applicant provided pcVPC splitted by age and bodyweight groups for the updated model. Overall, the model fitting performances are now acceptable.

- The applicant was asked during the 1st assessment round to present simulations from the updated popPK model, comparing adult exposure to paediatric exposure, and discussing the adequacy of the proposed paediatric dosing. Please refer to MSWP Q&A (https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answer) for details on the better manner to present these results.

Comparable AUCs and $C_{\text{max}}$ values are now displayed for the recommended paediatric and the adult doses. The methodology used to implement the simulations and to generate the related plots/results were well-described and the codes were provided.

Based on these simulations, Table 4 summarizes the simulated doses for patients with different age/weight groups that will result in an exposure comparable to that in adults following the approved adult dose.

**Table 4. Summary of Simulated Doses to Provide Equivalent AUC**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Weight Group</th>
<th>Formulation</th>
<th>Dose</th>
<th>AUC Ratio vs Adult</th>
<th>$C_{\text{max}}$ Ratio vs Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD dosing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGE&gt;2</td>
<td>&lt;10kg</td>
<td>Film-Coated</td>
<td>25mg-30mg</td>
<td>0.901-1.08</td>
<td>1.14-1.36</td>
</tr>
<tr>
<td></td>
<td>10-20kg</td>
<td></td>
<td>35mg-50mg</td>
<td>0.855-1.22</td>
<td>1.12-1.60</td>
</tr>
<tr>
<td></td>
<td>20-30kg</td>
<td></td>
<td>50mg-100mg</td>
<td>0.825-1.05</td>
<td>1.03-1.30</td>
</tr>
<tr>
<td></td>
<td>30-40kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40-50kg</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>&gt;=50kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGE&lt;=2</td>
<td>&lt;10kg</td>
<td></td>
<td>40mg-50mg</td>
<td>0.885-1.11</td>
<td>1.04-1.30</td>
</tr>
<tr>
<td></td>
<td>10-20kg</td>
<td></td>
<td>40mg-50mg</td>
<td>0.855-1.07</td>
<td>0.982-1.23</td>
</tr>
<tr>
<td>AGE&gt;2</td>
<td>&lt;10kg</td>
<td>Dispersible</td>
<td>30mg-40mg</td>
<td>0.895-1.19</td>
<td>1.07-1.43</td>
</tr>
<tr>
<td></td>
<td>10-20kg</td>
<td></td>
<td>50mg-100mg</td>
<td>0.968-1.23</td>
<td>1.17-1.48</td>
</tr>
<tr>
<td></td>
<td>20-30kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30-40kg</td>
<td></td>
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<tr>
<td></td>
<td>40-50kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;=50kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not Achievable up to 100 mg
As a result of the analysis, the following posology is being proposed for subjects weighing ≥ 10 kg. A BID regimen was selected for the posology as QD regimens at body weight > 30 kg would not achieve the adult AUC target of 7500 ng*h/mL at doses up to 100 mg, as compared to a BID regimen.

Table 5. Proposed Delamanid Dosing Regimen for Paediatric Subjects

<table>
<thead>
<tr>
<th>Weight Group</th>
<th>Dosing Regimen</th>
<th>Formulation</th>
<th>AUC Ratio versus Adult</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; Ratio versus Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - 20 kg</td>
<td>25 mg BID</td>
<td>Dispersible</td>
<td>0.968 (Age&gt;2)/1.07 (Age≤2)</td>
<td>0.988 (Age&gt;2)/1.06 (Age≤2)</td>
</tr>
<tr>
<td>20 - 30 kg</td>
<td>50 mg (am) + 25 mg (pm)</td>
<td>Dispersible</td>
<td>1.02</td>
<td>1.04</td>
</tr>
<tr>
<td>30 - 40 kg</td>
<td>50 mg BID</td>
<td>Film-Coated</td>
<td>1.18</td>
<td>1.25</td>
</tr>
<tr>
<td>40 - 50 kg</td>
<td>50 mg BID</td>
<td>Film-Coated</td>
<td>0.987</td>
<td>1.03</td>
</tr>
<tr>
<td>&gt; 50 kg</td>
<td>100 mg BID</td>
<td>None</td>
<td>1.09</td>
<td>1.13</td>
</tr>
</tbody>
</table>

AUC/C<sub>max</sub> ratio was calculated as a ratio of simulated median AUC/C<sub>max</sub> with recommended dose. (N = 200 for each) to that in adults following the approved adult dose (100 mg BID in Trial 242-07-204).

For children with a body weight < 10 kg, administration of delamanid is currently not recommended by the MAH. In Trials 242-12-232 and 242-12-233 only 5 children with a body weight below 10 kg were included, whereby their weights were distributed around the upper limit (10 kg), with a lowest weight of 8 kg. It is therefore uncertain whether the simulation is strong for body weights below 10 kg. In addition, all 5 children were assigned to Group 4, and delamanid doses (5 mg BID >8kg and ≤10 kg or 5 mg QD ≥ 5.5 kg and ≤8 kg) administered in the trials resulted in plasma exposure essentially lower than the targeted effective adult exposure. Delamanid’s safety profile has therefore not been investigated for the model informed therapeutic dose (20-25 mg BID) as currently proposed by the MAH for this weight group.
**Interactions**

Some drug-drug interactions have been determined during previous clinical drug-drug interaction (DDI) studies. However, the complete metabolic profile of delamanid and mode of elimination of delamanid have not yet been elucidated, and there is a potential for drug-drug interactions with other co-administered medicinal products, if significant unknown metabolites are discovered.

This is adequately reported in the SmPC.

There is continued concern that there is a large portion of drug-related material circulating in plasma that is unidentified (96%) and unexplained by the very limited metabolite profiling that was performed during the mass balance study. Without identification of what is circulating in plasma, it cannot be concluded that the major circulating metabolites of delamanid are known. Therefore, it cannot be concluded that the potential for delamanid to have an effect on co-administered drugs has been adequately characterised.

**Exposure relevant for safety evaluation**

In the two paediatric studies, the administered doses in patients 0-2 years were considerably lower than the revised doses proposed by the Applicant to achieve adult exposure levels (See Section “Children” above). Consequently, plasma exposures achieved in all study patients <10 kg were considerably lower than the target exposure (median AUC 2740 ng*hr/mL in children 0-2 years vs 7500 ng*hr/mL in adults). The available data in patients <10kg are therefore not sufficiently informative to support an extension of the lower weight limit.

**2.4.3. Pharmacodynamics**

The pharmacological mode of action of delamanid involves inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid.

For the paediatric population, an exposure-response analysis of delamanid and its metabolite, DM-6705, plasma concentrations versus QT interval corrected for heart rate (QTc) was conducted on data from the 2 trials conducted in paediatric subjects ages 0.7 to 17 years with multidrug-resistant tuberculosis (Trial 242-12-232 and Trial 242-12-233).

**PK/QTc analysis**

The final PK/QT dataset contained 354 valid QT measurements with time-matched delamanid/DM-6705 plasma concentrations from 37 subjects. Also, corresponding time-matched baseline QT measurements were obtained on Day -1.

The relationships between QTc and plasma concentrations of both delamanid and one of the primary metabolites of delamanid, DM-6705 were examined.

First, an exploratory analysis was implemented. The Graphical evaluation of the relationship between heart rate and QT/QTc intervals (QT, QTcB and QTcF) was evaluated via scatterplots using data at baseline to assess the need and the most appropriate method for heart rate correction. Before fitting the model, the following assumptions were evaluated: i) QTcB or QTcF as the sufficient HR correction method, ii) lack of drug effect on HR, iii) lack of time delay between drug concentration and ΔQTc, and iv) the presence of a linear concentration-QTc relationship.

Subsequently, a linear mixed effects model was used to examine the relationship between the time-matched change from baseline in QTc and plasma concentration of delamanid or DM-6705.
The relationship between RR and QT/QTC intervals were evaluated via scatterplots using data at drug-free state on Day -1. The slope and correlation coefficient (Rsq) was smaller in QTcB (slope 0.03, Rsq = 0.044) than that in QTcF (slope 0.128, Rsq = 0.484). Thus, QTcB was determined to be a sufficient and more adequate correction method for heart rate than QTcF, even though QTcF was the primary QT variable specified in the protocol.

Based on the linear mixed effects modelling, the concentration of delamanid does not have a significant impact on ΔQTcB (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) as seen in the figure below. Slight over-prediction was observed especially at higher exposure range.

![Graph](image.png)

Grey closed circles represent observed values. Blue closed circles and vertical bars represent binned observed data. Solid black line and grey shaded area represent model fit and 90% CI.

**Figure 1. Goodness-of-fit Plot: Observed and Model-Predicted ΔQTcB versus Observed DM-6705 Concentration**

The fixed effect parameter estimates for the delamanid/QTcF model are listed in Table 6. The typical population slope estimate was 0.0154 ms/[ng/mL] (90% CI: 0.00703, 0.0237), which suggests delamanid concentration is a significant predictor of ΔQTcF.

Using the developed linear mixed effects model, ΔQTcF values were predicted at delamanid concentrations of interest and the results are provided in Figure 2.

**Table 6. Parameter Estimates for the Linear Mixed Effects Model for Delamanid/ΔQTcF**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept (ms)</td>
<td>0.466</td>
<td>1.58</td>
<td>-2.63, 3.57</td>
</tr>
<tr>
<td>Slope (ms/[ng/mL])</td>
<td>0.0154</td>
<td>0.00426</td>
<td>0.00703, 0.0237</td>
</tr>
<tr>
<td>Baseline QTcF effect (ms)</td>
<td>-0.0365</td>
<td>0.0549</td>
<td>-0.144, 0.0711</td>
</tr>
</tbody>
</table>

Source: pkqt 232 233.csv, Appendix 10.6.7, File Path: 01 Data
Figure 2. Goodness-of-fit Plot: Observed and Model-Predicted ΔQTcF versus Observed Delamanid Concentration

The fixed effect parameter estimates for the DM-6705/QTcF model are listed in Table 7. The typical population slope estimate was 0.117 ms/[ng/mL] (90%CI: 0.0797, 0.155), which suggests delamanid concentration is a significant predictor of ΔQTcF.

Table 7. Parameter Estimates for the Linear Mixed Effects Model for DM-6705/ΔQTcF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept (ms)</td>
<td>-0.871</td>
<td>1.57</td>
<td>-3.94, 2.20</td>
</tr>
<tr>
<td>Slope (ms/[ng/mL])</td>
<td>0.117</td>
<td>0.0191</td>
<td>0.0797, 0.155</td>
</tr>
<tr>
<td>Baseline QTcF effect (ms)</td>
<td>-0.0445</td>
<td>0.0558</td>
<td>-0.154, 0.0649</td>
</tr>
</tbody>
</table>

Using the developed linear mixed effects model, ΔQTcF values were predicted at delamanid concentrations of interest and the results are provided in Figure 3.
2.4.4. Discussion on clinical pharmacology

Two trials (Trial 242-12-232 and Trial 242-12-233) were conducted in paediatric subjects ages 0.7 to 17 years with multidrug-resistant tuberculosis (MDR-TB) who received either the delamanid tablet formulation (6-17 years) or the delamanid paediatric formulation (DPF) (< 6 years) in dosing regimens ranging from 100 mg twice per day (BID) to 5 mg once per day (QD) in an age de-escalating design. The paediatric formulation of delamanid was developed as immediate-release dispersible tablets containing 5- and 25-mg of delamanid, intended to be reconstituted in water as an extemporaneous suspension for oral ingestion.

A bioequivalence study was conducted to compare the relative bioavailability of delamanid following a single 100-mg oral dose of DLM tablets compared with a single 100-mg oral dose of the DPF and to determine the effect of a high-fat meal on the DPF (Trial 242-12-245).

Based on the statistical results from bioequivalence study 242-12-245, 100 mg of Delamanid Paediatric Formulation is not bioequivalent to 100 mg of Delamanid Tablets with respect to rate and extent of absorption as the lower bound of the 90% confidence interval of the GMR for both $C_{\text{max}}$ and $AUC_{\infty}$ are lower than 0.8.

Based on an age appropriate visual hedonic scale and clinical assessment, there was a statistically significant difference in favour of DPF in the palatability when administered with a standard meal compared with DLM when administered with a standard meal. In the current relative bioavailability trial, the delamanid $C_{\text{max}}$ and $AUC_{\infty}$ values were 1.4- to 2.1-fold higher following DPF administration with a high-fat meal compared to that with a standard meal.

No new safety findings were reported in this trial.

A population pharmacokinetic (PK) analysis (clinical study report [CSR] 242-19-259) was performed on data from the 2 trials to determine the doses in paediatric subjects which would provide delamanid exposures similar to those observed in adult subjects with MDR-TB.

A nonlinear mixed effects modelling analysis was performed using NONMEM software (Version 7.4.3). First order conditional estimation with $\eta-\epsilon$ interaction was used for the modelling.
In answer to the previous round’s questions, the Applicant has provided an updated version of the modelling and simulation results that addressed most of the issues raised in a satisfactory manner. A new model was developed with an approach which is state of the art and the results of model evaluation and related dose selection where provided using appropriate tools.

The final population PK model was used to simulate steady-state exposure in paediatric patients in different age/body weight groups, which were then compared with exposure in adults. Based on these results, estimated paediatric doses were determined, which will result in an exposure comparable to that in adults following the approved adult dose. The methodology used to implement the simulations and to generate the related plots/results were well-described and the codes were provided.

The DPF doses used in group 3 (3-5 years) were 25 mg BID and in group 4 (0-2 years) 10 mg BID for patients > 10 kg, 5 mg BID for patients >8 and ≤ 10 kg. All patients in group 3 had a body weight between 10 and 20.5 kg at baseline. Therefore, the recommended doses identified by simulation, 25 mg BID for patients 10-20 kg corresponds with the one used in group 3 during trial 233. In group 4, the recommended dose identified by simulation would be 20-25 mg BID. In this group a lower dose (5 or 10 mg BID) has been used in the studies.

Consequently, plasma exposures achieved in all study patients <10 kg were considerably lower than the target exposure (median AUC 2740 ng*hr/mL in children 0-2 years vs 7500 ng*hr/mL in adults). The available data in patients <10kg are therefore not sufficiently informative to support an extension of the lower weight limit.

For children with a body weight < 10 kg, administration of delamanid is currently not recommended by the Applicant. In group 4 in trial 232, 5 patients with a body weight below 10 kg at baseline have been included. In group 4 of trial 233, 4 patients still had a body weight below 10 kg at baseline. A patient under 2 years old with a BW under 10 kg died shortly after starting delamanid treatment in trial 233; the patient had developmental parameters below the 3rd percentile at baseline and it was determined that the death was not related to delamanid treatment. Exposure in these patients was indeed below the targeted effective adult exposure and the model estimates that a 4-5 times higher dose would be needed in this population.

In addition, an exposure-response analysis of delamanid plasma concentrations versus QT interval corrected for heart rate (QTc) was also conducted on data from trial 232 and 233. This type of model is normally used to rule out a QT prolonging effect.

In a previous QTc vs concentration analysis in adults, there was a significant correlation between delamanid concentration and ΔQTcB/ΔQTcF.

By linear mixed effects modelling of delamanid/ΔQTcB, no significant impact of delamanid was detected on ΔQTcB. For DM-6705, significant positive correlation was detected in a concentration-corrected-QT interval ΔQTcB modelling analysis, using the linear mixed effect model. The point estimate of slope for DM-6705 (0.0613 ms/[ng/mL]) is consistent with the value in adults (0.0795 ms/[ng/mL]). The typical population slope estimate for the delamanid/QTcF model was 0.0154 ms/[ng/mL] (90%CI: 0.00703, 0.0237), which suggests delamanid concentration is a significant predictor of ΔQTcF. The typical population slope estimated for the DM-6705/QTcF model was 0.117 ms/[ng/mL] (90%CI: 0.0797, 0.155), which suggests DM-6705 concentration is a significant predictor of ΔQTcF.

Administration of delamanid has been shown to result in QT interval prolongation in the adult population and based on the exposure response simulation, this is also the case in adolescents, children and infants. Appropriate warning on QT interval prolongation is included in the SmPC.
2.4.5. Conclusions on clinical pharmacology

The use of model informed approach for paediatric dose selection is supported.

As for the adult population, an effect of delamanid administration (mainly via its DM-6705 metabolite) is noticed on the QTc interval in the paediatric population in the exposure response simulation.

2.5. Clinical efficacy

A tabular overview trial 233 is given below:

<table>
<thead>
<tr>
<th>Type of Trial (Trial Phase)</th>
<th>Protocol Number Location of Trial</th>
<th>Trial Report Location</th>
<th>Trial Objective(s)</th>
<th>Investigational Medicinal Product; Dosage Regimen; Route of Administrationa</th>
<th>Number of Subjects Enrolled</th>
<th>Healthy Subjects or Diagnosis of Subjects</th>
<th>Treatment Duration</th>
<th>Trial Status; Type of Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient PK and Initial Tolerability Study Reports</td>
<td>PK, safety, and efficacy; (Phase 2)</td>
<td>242-12-233 Philippines, South Africa</td>
<td>Section 5.3.3.2 [Appendix; Synopsis]</td>
<td>Open-label, multi-dose, age-deciles, long-term, extension trial</td>
<td>Delamanid 50 mg oral tablet or 5 mg or 25 mg oral dispersible tablet, with meals for 180 days</td>
<td>Group 1: 7</td>
<td>Paediatric MDR-TB subjects on therapy with an OBR who had completed Trial 242-12-232</td>
<td>6 months</td>
</tr>
</tbody>
</table>

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

aChildren in Groups 3 and 4 were given delamanid as an extemporaneous suspension using the delamanid paediatric dispersible tablet formulation.

bThe population PK analysis will be reported separately.

Part of the results of trial 233, namely the subgroup of children aged 6 to 17 years who had completed the trial and follow-up period, have been submitted in a previous variation EMEA/H/C/002552/II/0040 and lead to an extension of the indications from adults to adults, adolescents and children with a body weight of at least 30 kg.

The results of trial 233 for the two youngest age groups (0-5 years of age) are submitted in this line extension procedure. The aim of this variation is to provide a justification for extension of the delamanid MDR-TB indication to ‘Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children and infants with a body weight of at least 10 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)’. 

2.5.1. Main 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 Paediatric Multidrug-resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs over a 6 Month Treatment
Trial 242-12-233 is an age de-escalation trial to assess the long-term safety, tolerability, PK, and efficacy of delamanid plus OBR over a 6-month period in pediatric subjects with MDR-TB who had successfully completed Trial 242-12-232.

**Methods**

**Study Participants**

Subjects met the following inclusion criteria prior to enrolment:

- Successfully completed Trial 242-12-232
- Male or female
- Age birth to 17 years, inclusive
- Confirmed diagnosis of MDR-TB, ie, 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 (eg, cerebrospinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of TB disease
  - Persistent cough lasting > 2 weeks
  - Fever, weight loss, and failure to thrive
  - Findings on recent chest radiograph (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
  - Trial-specific written informed consent/assent obtained

**Treatments**

Trial duration was up to 760 days including the following periods:

- 30-day screening,
- 182-day treatment,
- 56-day post-treatment,
- additional follow-up through Day 365 (ie, 6 months after the last delamanid dose), and treatment outcome follow-up at Day 730 (Month 24) + 2 months (ie, 1 year after the Day-365 follow-up visit).
Figure 4. Schematic trial design for Trial 242-12-233

According to the country-specific DOT plan for Trial 242-12-233, 1 dose per day for a minimum of 5 days per week is to be given under direct observation. All delamanid dispersible tablet doses are recommended to be administered with water and under fed conditions in the morning and evening within 30 minutes of the start of a meal. Optimally, OBR medications should be given at least 1 hour prior to or 1 hour after dosing of delamanid dispersible tablets.

The delamanid treatment administered did depend on the age group:

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

Objectives

The primary objectives of this trial were:

1. 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 242-12-232.
2. 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 were:

3. To evaluate the PK/pharmacodynamic relationship of delamanid and its metabolite DM-6705 plasma concentrations and change in corrected QT interval (QTc) when delamanid is administered in combination with OBR during a 6-month treatment period in paediatric subjects with MDR-TB.

4. 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.

5. To determine the palatability of the delamanid paediatric formulation (DPF) (applicable for Groups 3 and 4 only).

**Outcomes/endpoints**

The efficacy of delamanid in treating paediatric MDR-TB subjects was based on World Health Organization (WHO)-recommended treatment outcomes. Efficacy endpoints included chest radiography (subjects with pulmonary disease), body weight/height, and resolution of TB symptoms (based on investigator evaluation). There were no summary tables produced for sputum culture conversion or drug susceptibility due to the limited availability of data.

Blood samples were taken for determination of delamanid and metabolite plasma concentrations. Electrocardiograms and PK measurements for determination of the relationship between delamanid and DM-6705 plasma concentrations and changes in QTc interval were collected. Delamanid PK data from this trial were combined with PK data from the Trial 242-12-232 and analysed using population PK methods.

The palatability of the paediatric formulation (ie, dispersible tablets) was assessed using an age-appropriate visual hedonic scale and clinical assessment (Groups 3 and 4 only), within 25-30 minutes after the morning dose.

**Statistical methods**

All statistical presentations are descriptive due to the small sample sizes.

**Results**

**Participant flow**

Thirty-seven subjects ages birth to 17 years were enrolled into Trial 242-12-233. Of the 37 subjects that were enrolled in the trial, 35 (94.6%) were administered IMP for ≥ 6 months. Thirty-five (94.6%) subjects completed the trial, ie, were evaluated at the last scheduled visit of the trial (the Day 365 follow-up visit).
Table 8. Subject Disposition trial 233

<table>
<thead>
<tr>
<th></th>
<th>12-17 YEARS (N=7)</th>
<th>6-11 YEARS (N=6)</th>
<th>3-5 YEARS (N=12)</th>
<th>0-2 YEARS (N=12)</th>
<th>TOTAL (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NUMBER OF:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCREENED</td>
<td>7 (100.0)</td>
<td>6 (100.0)</td>
<td>12 (100.0)</td>
<td>12 (100.0)</td>
<td>37 (100.0)</td>
</tr>
<tr>
<td>ENROLLED</td>
<td>7 (100.0)</td>
<td>6 (100.0)</td>
<td>12 (100.0)</td>
<td>12 (100.0)</td>
<td>37 (100.0)</td>
</tr>
<tr>
<td>TREATED</td>
<td>7 (100.0)</td>
<td>6 (100.0)</td>
<td>12 (100.0)</td>
<td>12 (100.0)</td>
<td>37 (100.0)</td>
</tr>
<tr>
<td>COMPLETED TRIAL&lt;sup&gt;d&lt;/sup&gt;</td>
<td>7 (100.0)</td>
<td>6 (100.0)</td>
<td>11 (91.7)</td>
<td>11 (91.7)</td>
<td>35 (94.6)</td>
</tr>
<tr>
<td>DISCONTINUED TRIAL</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>LOST TO FOLLOW-UP</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>ADVERSE EVENT</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>DEATH</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>2 (5.4)</td>
</tr>
</tbody>
</table>

<sup>1</sup>Percentages were based on subjects who took at least 1 dose of trial medication.
<sup>2</sup>Subjects who signed informed consent and enrolled in the trial.
<sup>3</sup>Subjects who took at least 1 dose of trial medication.
<sup>4</sup>Subjects who were evaluated at the last scheduled visit of the trial, the day 365 follow-up visit.

Source: CT-2.

At the Day 365 follow-up visit, two subjects discontinued due to adverse events (AEs), one patient in group 3 and one in group 4. Both patients died due to pneumonia.

At 24 months, 2/37 (5.4%) subjects were considered lost to follow-up, 1 patient in group 1 and 1 patient in group 3, and 2/37 (5.4%) subjects died from pneumonia.

Baseline data

Overall, 18 male and 19 female subjects with a median age of 4.55 years, age range 0.78 – 17.60 years, and a median weight of 15.0 kg were enrolled at 3 sites in the Philippines (2 sites) and South Africa (1 site). The race was Asian for 25 subjects (67.6%), “Other” for 10 subjects (27.0%), and black or African American for 2 subjects (5.4%).

In group 4 in trial 232, 5 patients with a body weight below 10 kg at baseline have been included kg.

In group 4 of trial 233, 4 patients still had a body weight below 10 kg at baseline). A patient under 2 years old with a BW under 10 kg died shortly after starting delamanid treatment in trial 233; this patient had developmental parameters below the 3<sup>rd</sup> percentile at baseline and it was determined that the death was not related to delamanid treatment.

Table 9. Subject Demographics trial 233 (Safety sample)

<table>
<thead>
<tr>
<th>DEMOGRAPHIC CHARACTERISTICS</th>
<th>12-17 YEARS (N=7)</th>
<th>6-11 YEARS (N=6)</th>
<th>3-5 YEARS (N=12)</th>
<th>0-2 YEARS (N=12)</th>
<th>TOTAL (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (YEARS)</td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>7</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td>37</td>
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<td>MEAN</td>
<td></td>
<td></td>
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<tr>
<td>SD</td>
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<td>0.98</td>
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<td>MEDIAN</td>
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<td>9.65</td>
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<td>1.82</td>
<td>4.55</td>
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<td>SEX</td>
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<td></td>
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<tr>
<td>MALE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEMALE</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Assessment report
EMA/543612/2021
At baseline, most subjects had normal audiometry assessments (28 of 37 subjects [75.7%]) and visual assessments (34 of 37 subjects [91.9%]) and abnormal chest x-rays (35 of 37 subjects [94.6%], 1 subject [2.7%] not done) at baseline. The investigator-assessed sign and symptom with the highest incidence at baseline was findings on recent chest radiograph consistent with TB (32 of 37 subjects [86.5%]).

All subjects (37 [100.0%]) were treated with both a first-line and second-line regimen in their anti-TB treatment history.

Table 10. Anti-TB Treatment History (Trial 233)

<table>
<thead>
<tr>
<th></th>
<th>11-17 YEARS (n=7)</th>
<th>6-10 YEARS (n=6)</th>
<th>1-5 YEARS (n=11)</th>
<th>5-9 YEARS (n=11)</th>
<th>TOTAL (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTI-TB TREATMENT SETTLED WITH BOTH FIRST-LINE AND SECOND-LINE REGIMEN</td>
<td>7 (100.0)</td>
<td>6 (100.0)</td>
<td>12 (100.0)</td>
<td>12 (100.0)</td>
<td>37 (100.0)</td>
</tr>
<tr>
<td>INDICATION FOR DRUGS CONFIRMED (CULTURE POSITIVE, RESISTANCE TO ISONIAZID, AND RIFAMPICIN)</td>
<td>6 (85.7)</td>
<td>3 (50.0)</td>
<td>3 (27.3)</td>
<td>3 (27.3)</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td>DRUG RESISTANCE IN CHILD WITH NO CONTACT</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>SITE OF DISEASE PULMONARY</td>
<td>7 (100.0)</td>
<td>2 (33.3)</td>
<td>9 (81.8)</td>
<td>10 (90.9)</td>
<td>28 (75.7)</td>
</tr>
<tr>
<td>EXTRAPULMONARY</td>
<td>0 (0.0)</td>
<td>1 (16.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>BOTH</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

1. SOURCE WAS BASED ON THE NUMBER OF SUBJECTS WITH THE REQUIRED ASSESSMENT AT THE VISIT.

2. FIRST-LINE REGIMEN: ISONIAZID, Rifampicin, Pyrazinamide, PEP/ETP, ETP/M/P, ETH, and ETP/CO.

Numbers analysed

Outcomes and estimation

Efficacy assessment was evaluated for paediatric subjects 0 to 17 years of age, based on investigator-assessed WHO-recommended treatment outcome definitions (ie cure, treatment complete, treatment
failure, death, and lost to follow-up) based on a combination of clinical signs and symptoms (eg. weight gain/failure to thrive) and microbiologic data. A favourable WHO-recommended treatment outcome (number of subjects cured + number of subjects with treatment completed) has been reported in 33 of the 37 subjects [89.2%] aged 0 to 17 years (15 of the 37 subjects [40.5%] were cured, 18 of the 37 subjects [48.6%] completed treatment; [note: these 18 subjects completed treatment but did not have enough data to be considered cured]) and overall 4/37 (10.8%) subjects had an unfavourable outcome, (2 subjects [5.4%] were lost to follow-up and 2 subjects [5.4%] died) at 24 months. The 2 subjects who discontinued due to death were from Groups 3 and 4. See Table 11.

Table 11. Summary of Final Outcome at the End of Treatment as Assessed by Principal Investigator at 24 Months

<table>
<thead>
<tr>
<th>TREATMENT OUTCOME</th>
<th>12-17 YEARS (N=7)</th>
<th>6-11 YEARS (N=6)</th>
<th>3-5 YEARS (N=12)</th>
<th>0-2 YEARS (N=12)</th>
<th>TOTAL (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>CURED</td>
<td>4 (57.1)</td>
<td>3 (50.0)</td>
<td>3 (25.0)</td>
<td>5 (41.7)</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td>TREATMENT COMPLETED</td>
<td>2 (28.6)</td>
<td>3 (50.0)</td>
<td>7 (58.3)</td>
<td>6 (50.0)</td>
<td>18 (48.6)</td>
</tr>
<tr>
<td>FAVOURABLE (CURED + TREATMENT COMPLETED)</td>
<td>6 (85.7)</td>
<td>6 (100.0)</td>
<td>10 (83.3)</td>
<td>11 (91.7)</td>
<td>33 (89.2)</td>
</tr>
<tr>
<td>LOST TO FOLLOW-UP</td>
<td>1 (14.3)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>0 (0.0)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>DIED</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>UNFAVOURABLE (LOST TO FOLLOW-UP + DIED)</td>
<td>1 (14.3)</td>
<td>0 (0.0)</td>
<td>2 (16.7)</td>
<td>1 (8.3)</td>
<td>4 (10.8)</td>
</tr>
</tbody>
</table>

Note: Favourable = number of subjects cured + number of subjects with treatment completed; unfavourable = number of subjects lost to follow-up + number of subjects who died

Source: Module 5.3.3.2, CSR 242-12-233, Table 11.4.1.2.1-1.

Ancillary analyses

The overall mean baseline body weight of subjects was 19.5 kg and in Groups 1, 2, 3, and 4 were 38.4, 25.1, 14.8, and 10.3 kg, respectively. The total mean change and range in body weight at baseline and at last visit for Groups 1, 2, 3, and 4 were as follows:

Table 12. Mean Change from Baseline in Weight (Trial 233)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Group 1 12-17 Years</th>
<th>Group 2 6-11 Years</th>
<th>Group 3 3-5 Years</th>
<th>Group 4 0-2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean</td>
<td>Min</td>
<td>Max</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38.4</td>
<td>25.1</td>
<td>14.8</td>
<td>10.3</td>
</tr>
<tr>
<td>Last Visit</td>
<td>Mean</td>
<td>Min</td>
<td>Max</td>
<td></td>
</tr>
<tr>
<td></td>
<td>49.0</td>
<td>25.0</td>
<td>16.9</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Palatability assessment was only assessed for subjects in Groups 3 and 4 using an age appropriate visual hedonic scale and clinical assessment. No subjects selected “dislike very much” at all time points, and few subjects selected “dislike a little,” per either the investigator/sub-investigator/nurse score or parent/patient score. The majority of subjects in both Group 3 (3 - 5 years group) and Group 4 (0 - 2 years group) selected “like very much” at all time points for the palatability evaluation.

Also in trial 232, the majority of the subjects in Groups 3 and 4 found the paediatric formulation to be highly palatable.

In subjects aged 3 to 5 years (Group 3), it was reported at both Visit 3 and Visit 12 that the majority of the subjects liked the taste of delamanid “very much” based on the investigator or designee score.
and the parent/patient score. In subjects aged 0 to 2 years (Group 4), it was reported at Visit 3 and Visit 12 that the majority of the subjects liked the taste of delamanid "very much" or "a little" based on the investigator or designee score and the parent/patient score. A palatability rating of "dislike very much" was only reported by 1 (8.3%) subject aged 0 to 2 years at Visit 3 based on the investigator or designee score.

Summary of main study

The following table summarises the efficacy results from the main study 242-12-233 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of efficacy for trial 242-12-233

<table>
<thead>
<tr>
<th>Study identifier</th>
<th>242-12-233</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Open-label, and multiple-dose, age de-escalation trial to assess the long term safety, tolerability, PK, and efficacy of delamanid plus OBR over a 6-month period in pediatric subjects with MDR-TB who had successfully completed Trial 232</td>
</tr>
<tr>
<td>Duration of main phase:</td>
<td>Date of first signed informed consent: 20 Jul 2013</td>
</tr>
<tr>
<td>Duration of Run-in phase:</td>
<td>Date of last trial observation: 13 Jan 2020</td>
</tr>
<tr>
<td>Duration of Extension phase:</td>
<td>not applicable</td>
</tr>
<tr>
<td>Hypothesis</td>
<td>No hypothesis tested</td>
</tr>
<tr>
<td>Treatments groups</td>
<td>adult formulation delamanid 100 mg BID (administered as 2 × 50-mg tablets BID) + OBR for 6 months</td>
</tr>
<tr>
<td>Group 1 (12 - 17 years, incl.) n= 6 planned; n = 7 enrolled</td>
<td>adult formulation delamanid 50 mg BID (administered as 1 × 50-mg tablet BID) + OBR for 6 months</td>
</tr>
<tr>
<td>Group 2 (6 - 11 years, incl.) n=6</td>
<td>delamanid pediatric formulation 25 mg BID (administered as 1 × 25-mg dispersible tablet BID) + OBR for 6 months</td>
</tr>
<tr>
<td>Group 3 (3-5 years, incl.) n = 12</td>
<td></td>
</tr>
</tbody>
</table>
Group 4 (birth - 2 years, incl.)

n = 12

delamanid pediatric formulation dose based on body weight during baseline visit for 6 months:

1. Subjects > 10 kg received delamanid dispersible tablets 10 mg BID (administered as 2 × 5-mg dispersible tablet) + OBR

2. Subjects > 8 and ≤ 10 kg received delamanid dispersible tablets 5 mg BID (administered as 1 × 5-mg dispersible tablet) + OBR

3. Subjects ≤ 8 kg received delamanid dispersible tablets 5 mg QD (administered as 1 × 5-mg dispersible tablet) + OBR

4. Delamanid dose was adjusted as needed for Group 4 subjects based on the weight measurement at specified trial visits (Visits 5, 7, 9, 11 and 12).

Primary Endpoint

Long-term safety

Long-term safety and tolerability of delamanid and its metabolites when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric subjects with MDR-TB

popPK analysis

Report delamanid and metabolite plasma concentration and conduct a population PK analysis when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric subjects with MDR-TB

Secondary Endpoint

Efficacy of delamanid

Evaluate the efficacy of delamanid when administered in combination with an OBR during a 6-month treatment period in pediatric subjects with MDR-TB

PK/pharmacodynamic

Evaluate the PK/pharmacodynamic relationship of delamanid and its metabolite plasma concentrations and change in corrected QT interval (QTc)

Palatability of delamanid dispersible tablets

Determine the palatability of delamanid dispersible tablets

Results and Analysis

Analysis description

Efficacy Analysis

Analysis population and time point description

A total of 37 subjects were screened, enrolled in the trial, and received delamanid. Thirty-five (94.6%) subjects completed the trial, ie, were evaluated at the last scheduled visit of the trial (the Day 365 follow-up visit).

<table>
<thead>
<tr>
<th>Efficacy Endpoint</th>
<th>Final Outcome at the End of Treatment as Assessed by Principle Investigator at Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-17 years (N=7)</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>Cured</td>
<td>4 (57.1)</td>
</tr>
</tbody>
</table>

Assessment report
EMA/543612/2021
### Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

### Clinical studies in special populations

Not applicable.

### Supportive studies

Not applicable.

#### 2.5.2. Discussion on clinical efficacy

Part of the results of trial 233, namely the subgroup of children aged 6 to 17 years who had completed the trial and follow-up period, have been submitted in a previous variation EMEA/H/C/002552/II/0040 and lead to an extension of the indications from adults to adults, adolescents and children with a body weight of at least 30 kg.

The results of trial 233 for the two youngest age groups (0-5 years of age) are submitted in this line extension procedure.

The aim of this variation is to provide a justification for extension of the delamanid MDR-TB indication to 'Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children and infants with a body weight of at least 10 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)'.

### Design and conduct of clinical studies

The PIP for Deltyba (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.

Trials 242-12-232 and 242-12-233 are age de-escalation trials that were performed sequentially in four groups: Group 1 (7 patients, ages 12 - 17 years, inclusive), Group 2 (6 patients, ages 6 - 11

<table>
<thead>
<tr>
<th>Treatment completed</th>
<th>2 (28.6)</th>
<th>3 (50.0)</th>
<th>7 (58.3)</th>
<th>6 (50.0)</th>
<th>18 (48.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable Cured+Treat.com</td>
<td>6 (85.7)</td>
<td>6 (100.0)</td>
<td>10 (83.3)</td>
<td>11 (91.7)</td>
<td>33 (89.2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (4.3)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Died</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Unfavorable Lost to f.u.+died</td>
<td>1 (4.3)</td>
<td>0 (0.0)</td>
<td>2 (16.7)</td>
<td>1 (8.3)</td>
<td>4 (10.8)</td>
</tr>
</tbody>
</table>

**Analysis description**

No formal statistical analysis done due to the small sample sizes; all statistical presentations are descriptive.
years, inclusive), Group 3 (12 patients, 3 - 5 years, inclusive), and Group 4 (12 patients, ages birth - 2 years, inclusive). These trials have been completed. Based on the data in group 1 and 2, 6 to 17 years of age, an extension of the indication to adolescents and children with a body weight of at least 30 kg has been approved in a prior variation procedure. Trial 233 has now been completed and data from paediatric patients in group 3 and 4 are submitted to obtain a further extension of the indication to children and infants with a body weight of at least 10 kg. Patients in group 3 and 4 were administered the delamanid paediatric formulation.

The efficacy of delamanid in treating paediatric MDR-TB subjects was based on World Health Organization (WHO)-recommended treatment outcomes. Efficacy endpoints included chest radiography (subjects with pulmonary disease), body weight/height, and resolution of TB symptoms (based on investigator evaluation). There were no summary tables produced for sputum culture conversion or drug susceptibility due to the limited availability of data. It is agreed that the assessment of the microbiological response is often not possible in children due to the paucibacillary nature of paediatric TB and the fact that children do not readily produce sputum.

The dispersible tablet formulation of delamanid was used for the younger age groups in Trial 242-12-232 and 242-12-233, and relative bioavailability was conducted to compare the dispersible tablet formulation for paediatric subjects with the marketed tablet formulation. Further objectives regarding the formulation were the palatability of the dispersible tablets. This was assessed using an age-appropriate visual hedonic scale and clinical assessment (Groups 3 and 4 only), within 25-30 minutes after the morning dose. A hedonic scale and IMP acceptability assessment worksheets were used in the study. In the Operations Manual v4 dated 01 May 2017, the Palatability Assessment is described in Section 12.6, page 40. The results of this assessment have also been discussed in Section 3.3.7. Pharmacokinetics.

**Efficacy data and additional analyses**

The use of delamanid in addition to OBR in paediatric trial 233 resulted in a favourable treatment outcome at 24 months in 10 of the 12 subjects (83.3%) aged 3 to 5 years at 24 months (3 of these 12 subjects (25.0%) were cured and 7 of the 12 subjects (58.3%) completed treatment) and in a favourable treatment outcome in 11 of the 12 subjects (91.7%) aged 0-2 years (5 of these (41.7%) were cured and 6 of the 12 subjects (50.0%) completed treatment), even though the dose administered in this population aged 0-2 years was too low based on the modelling of a dose equivalent to the adult posology. Two patients died due to pneumonia, one in group 3 and one in group 4.

Overall, 15/37 (40.5%) subjects were considered cured at the end of treatment and a total of 18/37 (48.6%) subjects achieved treatment completion, as assessed by the investigator at 24 months. Subjects were defined as treatment completed per WHO guidance as those subjects who completed treatment but did not have enough data to be considered cured. There were 2/37 (5.4%) subjects who were considered lost to follow up and 2/37 (5.4%) subjects died due to pneumonia.

This limited number of patients included in the trial is acceptable as it is considered that the efficacy in children can be extrapolated from achieving delamanid exposures comparable to effective exposure in adults.

The majority of the subjects in Groups 3 and 4 found the paediatric formulation to be highly palatable. In trial 233, no subjects selected “dislike very much” at all time points, and few subjects selected “dislike a little,” per either the investigator/sub-investigator/nurse score or parent/patient score. The majority of subjects in both Group 3 (3 - 5 years group) and Group 4 (0 - 2 years group) selected “like
very much” at all time points for the palatability evaluation. Also in trial 232, the majority of the subjects in Groups 3 and 4 found the paediatric formulation to be highly palatable.

2.5.3. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy in children can be extrapolated from achieving delamanid exposures comparable to effective exposure in adults.

2.6. Clinical safety

Patient exposure

All 37 subjects enrolled in Trial 242-12-232, received all doses of IMP for 10 days, completed the trial and were enrolled in Trial 242-12-233.

Of the 37 subjects enrolled in Trial 242-12-233, 35 (94.6%) were exposed to at least 6 months of the investigational medicinal product (IMP). One subject in Group 4 (ages 0 - 2) had exposure of less than 1 week and one subject in Group 1 (ages 12 - 17) missed all doses for the last 80 days of treatment. The total subject days of IMP exposure, defined as the total duration of IMP exposure for all subjects under the same age group, was assessed resulting in 6487 days in total. In Group 1 (ages 12 - 17), total subject days of IMP exposure was 1196 days for the 7 subjects, 1092 days for the 6 subjects in Group 2 (ages 6 - 11), 2190 days for the 12 subjects in Group 3 (ages 3 - 5), and 2009 days for the 12 subjects in Group 4 (ages 0 -2)).

Adverse events

In trial 233, a total of 246 treatment-emergent adverse events (TEAEs) were experienced in all age groups. Of these events, 185 occurred before end of IMP administration and were reported in 36 subjects (97.3%). The 4 most frequently reported AEs were upper respiratory tract infection (14/37 subjects [37.8%] – 12 mild, 2 moderate cases), hyperuricaemia (10/37 subjects [27.0%] – 9 mild, 1 moderate case), headache (10/37 subjects [27.0%] – 10 mild cases), and arthralgia (8/37 subjects [21.6%] – 6 mild, 2 moderate cases).

The incidence of on treatment TEAEs per 100 patient-days IMP exposure was 5.2 for group 1 (12-17 years of age), 2.4 for group 2 (6-11 years of age), 2.1 for group 3 (3-5 years of age) and 2.5 in the youngest patient group 4 (0-2 years of age).

In trial 233, potentially related TEAEs defined as those having a possible or definitive relationship to the IMP were reported for 9 subjects (24.3%). The most commonly reported potentially IMP-related TEAEs were prothrombin time prolonged (3/37 [8.1%] subjects), blood corticotrophin increased, liver function test increased, and butterfly rash (2/37 [5.4%] subjects for each).

The number of patients with potentially IMP-related TEAEs was higher in younger age groups: 1 patient in group 1 and 2 (12-17 and 6-11 years of age, 14.3% and 16.7%, respectively), 2 patients in group 3 (3-5 years of age, 25%) and 4 patients in group 4 (0-2 years of age, 33.3%). The 2 patients with severe IMP-related TEAEs were in group 4, one patient with immune thrombocytopenic purpura and one patient with bronchial hyperreactivity discussed in the next section on serious adverse events.

In trial 232, of 37, 9 subjects (24.3%) 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.
**Adverse events of special interest** – important potential and identified risks in the EU RMP

**QT interval prolongation** is discussed in section on laboratory findings.

**Paraesthesia, Hypoaesthesia, and Tremor:** There was a low occurrence of neurological symptoms in Trial 242-12-233. No SAEs were reported for paraesthesia, hypoaesthesia, or tremor. Paraesthesia of mild intensity and not related to IMP was present in 1 subject (7.7%) in Group 1 (ages 12 - 17 years) and resolved. No subjects reported hypoaesthesia or tremor.

**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 - 17 years) and resolved. Mild insomnia was also reported by 1 subject (7.7%) in Group 2 (ages 6 - 11 years) and resolved. Both events were not related to IMP. There were no reports of anxiety.

**Gastrointestinal Disorders (Nausea, Vomiting, and Gastritis):** There were no SAEs reported for nausea, vomiting, or gastritis. There were 7 events of vomiting experienced by 6 subjects (16.2%) total; 2 subjects each in Group 1 (ages 12 - 17 years) and Group 3 (ages 3 - 5 years), and 1 subject each in Group 2 (6 - 11 years) and Group 4 (0 - 2 years). All events were mild and all but one were unrelated, and all but one resolved. Per the AE listing, 1 subject (2.7%) in Group 2 (6 - 11 years) had 2 events of vomiting where 1 resolved and the event of **intermittent vomiting did not resolve**; and 1 subject (2.7%) in Group 3 had 1 event of vomiting possibly related to IMP. There were no reports of nausea or gastritis.

No incidence of **Tinnitus** or **Blurred vision** was reported in Trial 233.

**Hypokalaemia** occurred infrequently: 1 subject (2.7%) in Group 1 (ages 12 - 17 years) experienced 3 AEs of mild hypokalaemia which resolved and were unrelated to IMP. No SAEs were reported.

**Liver disorders:** There were no SAEs of liver disorders.

Reported potentially IMP-related TEAEs were **prothrombin time prolonged** (3/37 [8.1%] subjects, 1 subject in Group 3 [ages 3 - 5 years] and 2 subjects in Group 4 [ages 0 - 2 years]); **liver function test increased** (2/37 [5.4%] subjects, 1 subject each in Group 3 [ages 3 - 5 years] and Group 4 [ages 0 - 2 years]); **alanine aminotransferase increased**, **hepatic enzyme increased** (1/37 [2.7%] subject for each TEAE-in Group 3 [ages 3 - 5 years]); and **coagulation time prolonged** (1/37 [2.7%] subject Group 4 [ages 0 - 2 years]).

Reported TEAEs that were unrelated to IMP were prolonged activated partial thromboplastin (1/37 [2.7%] subject in Group 1 [ages 12 - 17 years]), and liver function test increased (1/37 [2.7%] subject, 1 subject in Group 3 [ages 3 - 5 years]).

All events were mild and resolved, and none resulted in discontinuation from the IMP or trial. In seven of eight children there was no action taken with delamanid, while in one case rechallenged with delamanid was negative.

See section on laboratory findings.

**Cortisol level increased:** There were no events of cortisol level increased in Trial 242-12-233. However, blood corticotrophin increased was reported overall in 3/37 (8.1%) subjects; assessed as potentially related to IMP (2/37 [5.4%] subjects, both in Group 3 [ages 3 - 5 years]) and assessed as not related to IMP (1/37 [2.7%] subject Group 4 [ages 0 - 2 years]).

All events were mild and resolved, and none resulted in discontinuation from the IMP or trial.

**Drug Use during Pregnancy and Breastfeeding:** See section Safety in special populations.
**Serious adverse event and deaths**

In trial 233, there were 8/37 (21.6%) subjects with serious TEAEs (5/12 [41.7%] subjects in Group 4 [0 - 2 years group], 2/12 [16.7%] subjects in Group 3 [3 - 5 years group], and 1/6 [16.7%] subject in Group 2 [6 - 11 years group]). Serious TEAEs deemed possibly related or related by the investigator were immune thrombocytopenic purpura and bronchial hyperreactivity, both in group 4 patients. The company assessed immune thrombocytopenic purpura as not related as onset was 214 days after the last dose of delamanid. The company assessed the bronchial hyperreactivity as not related to delamanid due to subject’s underlying MDR-TB and medical history of reactive airway disease.

All other serious TEAEs for these subjects, pneumonia, lethargy, lower respiratory tract infection, and non-Hodgkin’s lymphoma were judged as unlikely related or not related to IMP by the investigator.

There were 2 deaths during the trial, one in Group 3 [3 - 5 years group] and one in Group 4 [0 - 2 years group], neither fatal events were assessed as causally related to IMP by the investigator or the company, but related to the treated MDR-TB.

**Laboratory findings**

The assessment of clinical laboratory tests did not show any clinically relevant changes from baseline across all age groups or any significant effect of delamanid. Clinically significant laboratory test abnormalities for serum chemistry were reported for 3 subjects: 1 subject in Group 4 had an elevated potassium of 6.7 mEq/L at the Day 182 visit; 1 subject in Group 3 had an elevated uric acid of 12.5 mg/dL at the Day 56 visit; 1 subject in Group 1 had an elevated uric acid of 14.6 mg/dL at an unscheduled visit and a value of 12.9 mg/dL at the Day 56 visit. This subject also had a TEAE of mild, nonserious hyperuricemia.

No subjects met the criteria for elevated liver enzymes and potential drug-induced liver injury.

Clinically significant laboratory test abnormalities for haematology were reported for 4 subjects: 1 subject in Group 2 had an elevated partial thromboplastin time (PTT) value of 22.4 sec at the Day 365 visit; 2 subjects in Group 3 had an elevated PTT value of 29.1 sec at the Day 28 visit and a PTT value of 18.8 sec at the Day 182 visit, respectively. 1 subject in Group 4 had a low platelet count at the visit at day 365 and subsequent unscheduled visits. This subject had a serious TEAE of thrombocytopenia purpura at day 395 and day 520.

There were no newly acquired clinically significant laboratory test abnormalities from baseline for urinalysis.

**Electrocardiogram – QT-interval prolongation**

In trial 232, 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. In trial 233, there were no SAEs or any AEs of QT prolongation and no clinical signs were seen in conjunction with QTc abnormalities.

In trial 232 – 10 days delamanid treatment -, new onset changes > 480 msec in QTcB were experienced by 3 of 37 subjects (8.1%) (3 of 12 subjects [25.0%] in Group 3). New onset changes > 450 msec in QTcB were experienced by 15 of 37 subjects (40.5%) (2 of 7 subjects [28.5%] in Group 1, 2 of 6 subjects [33.3%] in Group 2, 8 of 12 subjects [66.6%] in Group 3, and 3 of 12 subjects [25.0%] in Group 4). Changes of QTcB ≥ 30 and ≤ 60 msec were experienced by 19 of 37 subjects (51.3%) (2 of 7 subjects [28.5%] in Group 1, 1 of 6 subjects [16.6%] in Group 2, 9 of 12 subjects...
Changes of QTcB > 60 msec were experienced by 1 of 37 subjects (2.7%) overall (1 of 12 subjects [8.3%] in Group 3).

There were no new onset changes > 480 msec in QTcF. New onset changes > 450 msec in QTcF were experienced by 3 of 37 subjects (8.1%) (1 of 7 subjects [14.2%] in Group 1 and 2 of 12 subjects [16.6%] in Group 3). Changes of QTcF ≥ 30 and ≤ 60 msec were experienced by 9 of 37 subjects (24.3%) (1 of 7 subjects [14.2%] in Group 1, 5 of 12 subjects [41.6%] in Group 3, and 3 of 12 subjects [25.0%] in Group 4). There were no changes > 60 msec in QTcF.

New abnormal rhythm in ECG results were experienced by 30 of 37 subjects (81.0%) (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). New conduction abnormalities in ECG results (23 of 37 subjects [62.1%]) were the most frequently reported changes in clinically significant abnormalities or ECG results. There were no new onset changes > 500 msec in QTcB or QTcF.

In trial 233 – 6 months delamanid treatment, the effects of delamanid on QT interval prolongation in paediatric subjects with MDR-TB have been examined in 37 subjects aged 0 to 17 years in Trial 242-12-233. In this trial, the QT effect is not beyond that seen in adult delamanid trials, and the changes in ECG findings were within acceptable limits and in line with ECG and QT changes known to be associated with adult delamanid use. No clinical signs were seen in conjunction with QTc abnormalities. There were no SAEs or any AEs of QT prolongation.

In trial 233, clinically significant changes in QTcF were as follows: No new onset changes > 500 msec or > 480 msec in QTcF were experienced by any subjects. New onset changes > 450 msec in QTcF were experienced by 5/36 (13.9%) subjects. Changes of QTcF ≥ 30 and ≤ 60 msec were experienced by 22/36 (61.1%) subjects. Changes of QTcF > 60 msec were experienced by 2/36 (5.5%) subjects. Clinically significant changes in QT interval corrected by Bazett’s formula (QTcB) were as follows: No new onset changes > 500 msec in QTcB were experienced by any subjects. New onset changes > 480 msec in QTcB were experienced by 3/36 (8.3%) subjects. New onset changes > 450 msec in QTcB were experienced by 22/36 (61.1%) subjects. Changes of QTcB ≥ 30 and ≤ 60 msec were experienced by 25/36 (69.4%) subjects. Changes of QTcB > 60 msec were experienced by 3/36 (8.3%) subjects.

Safety in special populations

One pregnancy was reported during the trial for a subject in Group 1 after the last dose of IMP 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. The subject was not taking delamanid after delivery; thus, no events of drug use while breastfeeding were recorded.

Discontinuation due to adverse events

No subjects were discontinued due to TEAEs.

Post marketing experience

The Otsuka delamanid Compassionate Use Programme has 36 paediatric patients 3 to 17 years of age. From the cumulative post marketing data, within the paediatric population (≤ 17 years of age) there were 492 cumulative reported AEs that pertained to the following SOCs: injury, poisoning and procedural complications (182 events); investigations (52 events); gastrointestinal disorders (34 events); psychiatric disorders (33 events); nervous system disorders (32 events); general disorders.
and administration site conditions (31 events); respiratory, thoracic and mediastinal disorders (25 events); infections and infestations (20 events); metabolism and nutrition disorders (17 events); blood and lymphatic system disorders (15 events); hepatobiliary disorders (12 events); skin and subcutaneous tissue disorders (11 events); cardiac disorders (9 events); musculoskeletal and connective tissue disorders (5 events); eye disorders (4 events); endocrine disorders (2 events); renal and urinary disorders (2 events); surgical and medical procedures (2 events); vascular disorders (2 events); reproductive system and breast disorders (1 event); immune system disorders (1 event).

As per request, the MAH performed an additional analysis of post-marketing data related to the important identified and potential risks reported in the EU Risk Management Plan (RMP) v.3.4, Part SVII.3.1, taking into consideration weight and delamanid dose in children with reported AEs. No AEs have been reported in children with weight ≤ 10 kg.

For the important potential risk of liver disorders, 23 AEs in 14 cases were reported post-marketing; 16 of these AEs were serious. In 11 of these cases, 2 co-suspect anti-TB drugs were administered. Given this high number and the imbalance seen in trial 233 for the reported potentially IMP-related TEAEs for liver disorders with a higher number of cases in the youngest age groups, the Applicant was asked to provide case reports and causality assessment of the three reported post marketing cases related to the important potential risk of liver disorders where nothing is mentioned about co-suspected drugs. All three cases were reported in 16 and 17 years old underweight adolescent patients and were very likely confounded by underlying drug-resistant TB and malnutrition. Although concomitant anti-TB drugs were not reported as co-suspected medications, their role in the development of the hepatic adverse events cannot be neglected.

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 optimized 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. Data for 13 patients aged 6-17 years has been analysed in a previous paediatric variation and data for paediatric population subset 0 to 5 years of age using a new dispersible tablet formulation is submitted with this variation. Both trials were in compliance with the PIP for delamanid.

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

All patients in trial 233 experienced TEAEs.

The incidence of “on treatment TEAEs” per 100 subject days exposure is highest in the oldest group (5.1 for Group 1), and the incidence for Group 2 (2.4) and Group 3 (2.1) is comparable with Group 4 (2.5) and the overall incidence (2.9) of “on treatment TEAEs” per 100 subject days exposure. The “on treatment TEAEs” per 100 subject days exposure were comparable for Weight Group ≤ 10 kg and > 10 kg with an incidence of 3.4 and 2.8 respectively. The number of subjects with serious TEAEs were higher in age Group 4 as well as in Weight Group ≤ 10 kg. However, in each weight group only one SAE was assessed as causally related to delamanid by the investigator and as causally not related by the company. All other SAE were assessed as causally not related to delamanid.

The number of patients with potentially IMP-related TEAEs was higher in younger age groups: 1 patient in group 1 and 2 (12-17 and 6-11 years of age, 14.3% and 16.7%, respectively), 2 patients in group 3
(3-5 years of age, 25%) and 4 patients in group 4 (0-2 years of age, 33.3%). Given the low number of patients included with a body weight ≤10 kg and the low delamanid exposure in group 4 patients, no conclusions can be drawn from the data in the weight group ≤10 kg. It is noted, however, that incidence of potentially drug-related TEAEs was slightly higher in group 3 patients than in group 1 and 2 patients as well. This difference was mainly seen in the SOC investigations, for increased blood corticotrophin, increased liver enzymes and prothrombin time prolongation. There was an imbalance in the reporting of adverse events related to the important potential risk of liver disorders with all except one case reported in the youngest age groups 3 and 4, though all events were mild and resolved, and none resulted in discontinuation from the IMP or trial. The effect of other concomitantly given medication, such as albendazole and PZA should be taken into consideration. Other risk factors are malnutrition, hypothyroidism and the age of children in Group 4. The potential risk of liver disorders will be followed-up further as liver disorders and blood cortisol level increase are included as important potential risks in the RMP.

The doses administered in group 4 (0-2 years of age) in the clinical trials (10 mg BID DPF > 10 kg and 5 mg BID DPF >8 and ≤10 kg) are below the ones that are currently predicted to be needed (20-25 mg BID) to obtain similar exposures as in the adult population. Consequently, plasma exposures achieved in all study patients <10 kg were considerably lower than the target exposure (median AUC 2740 ng*hr/mL in children 0-2 years vs 7500 ng*hr/mL in adults).

In trial 233, the 4 most frequently reported AEs were upper respiratory tract infection (14/37 subjects [37.8%] – 12 mild, 2 moderate cases), hyperuricaemia (10/37 subjects [27.0%] – 9 mild, 1 moderate case), headache (10/37 subjects [27.0%] – 10 mild cases), and arthralgia (8/37 subjects [21.6%] – 6 mild, 2 moderate cases).

In trial 232, 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%]).

In trial 233, potentially IMP-related TEAEs were reported for 9 subjects (24.3%). The most commonly reported potentially IMP-related TEAEs were prothrombin time prolonged (3/37 [8.1%] subjects), blood corticotrophin increased, liver function test increased, and butterfly rash (2/37 [5.4%] subjects for each). The number of patients with potentially IMP-related TEAEs was higher in younger age groups: 1 patient in group 1 and 2 (12-17 and 6-11 years of age, 14.3% and 16.7%, respectively), 2 patients in group 3 (3-5 years of age, 25%) and 4 patients in group 4 (0-2 years of age, 33.3%).

In trial 232, 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%]).

In trial 233, there were 7 events of vomiting experienced by 6 subjects (16.2%) total; 2 subjects each in Group 1 (ages 12 - 17 years) and Group 3 (ages 3 - 5 years), and 1 subject each in Group 2 (6 - 11 years) and Group 4 (0 - 2 years). All events were mild and all but one were unrelated, and all but one resolved.

There were no SAEs of liver disorders. Potentially IMP-related TEAEs were reported in group 3 and 4 only and involved prothrombin time prolonged, liver function test increased, alanine aminotransferase increased, hepatic enzyme increased and coagulation time prolonged. Significant laboratory test abnormalities for partial thromboplastin time were reported for 2 subjects in group 3 (one at Day 28 and one at Day 182) and 1 subject in group 2 at Day 365 visit (i.e. after delamanid treatment was stopped). One subject in group 4 had low platelet count at day 365 and subsequent unscheduled visits. This subject had a serious TEAE of thrombocytopenia purpura at day 395 and day 520, assessed as possibly related to delamanid by the investigators, although
confounding drugs have been administered and there was a prolonged latent period (first AE episode 214 days after the delamanid stop date).

There were no events of cortisol level increased in Trial 242-12-233. However, blood corticotrophin increased was reported overall in 2 patients in group 3 (assessed as potentially related to IMP) and 1 subject Group 4.

In trial 232, 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. In trial 233, there were no SAEs or any AEs of QT prolongation.

In trial 233, in age group 3 (3-5 years of age), half of the patients had a ΔQTcF increase between 30 and 60 msec. The mean and median increase was above 10 msec at the first month of delamanid treatment.

Also in the exposure response simulation for the QTc interval prolongation, an effect of delamanid administration on the QTc interval prolongation was shown.

Therefore, as observed in the adult population, an increase in QTc interval is noted in the paediatric population.

In trial 233, there were 8/37 (21.6%) subjects with serious TEAEs, 5 of these were subjects in Group 4. Serious TEAEs deemed possibly related or related by the investigator were immune thrombocytopenic purpura and bronchial hyperreactivity. Both patients with severe IMP-related TEAEs were in group 4. The company assessed immune thrombocytopenic purpura as not related as onset was 214 days after the last dose of delamanid. The company assessed the bronchial hyperreactivity as not related to delamanid due to subject’s underlying MDR-TB and medical history of reactive airway disease.

The observed laboratory test abnormalities of elevated levels of uric acid, elevated partial thromboplastin time and low platelet count are linked with adverse events reported in the adult population and included in the SmPC (thrombocytopenia, hyperuricaemia).

Opposite to the AE of hypokalaemia reported in the adult population a case of hyperkalaemia was reported in the youngest paediatric patient group. Based on the very low exposure of delamanid in this age group and a number of other anti-TB agents in the regimen, causality for delamanid is unlikely.

For the important potential risk of liver disorders, 23 AEs in 14 cases were reported post-marketing; 16 of these AEs were serious. For most of these patients administered doses were above the newly recommended ones achieving exposure similar to adults. In 11 of these cases, 2 co-suspect anti-TB drugs were administered. Given this high number and the imbalance seen in trial 233 for the reported potentially IMP-related TEAEs for liver disorders with a higher number of cases in the youngest age groups, the Applicant was asked to provide case reports and causality assessment of the three reported postmarketing cases related to the important potential risk of liver disorders where nothing was mentioned about co-suspected drugs. All three cases were reported in 16 and 17 years old underweight adolescent patients and were very likely confounded by underlying drug-resistant TB and malnutrition. Although concomitant anti-TB drugs were not reported as co-suspected medications, their role in the development of the hepatic adverse events cannot be neglected.

For children with a body weight < 10 kg, administration of delamanid is currently not recommended. In group 4 in trial 232, 5 patients with a body weight below 10 kg at baseline have been included. In group 4 of trial 233, 4 patients still had a body weight below 10 kg at baseline). A patient under 2 years old with a BW under 10 kg died shortly after starting delamanid treatment in trial 233; this patient had developmental parameters below the 3rd percentile at baseline and it was determined that
the death was not related to delamanid treatment. In addition, all 5 children were assigned to Group 4, and delamanid doses (5 mg BID >8kg and ≤10 kg or 5 mg QD ≥ 5.5 kg and ≤8 kg) administered in the trials resulted in plasma exposure essentially lower than the targeted effective adult exposure. Exposure in these patients was indeed below the targeted effective adult exposure (median AUC 2740 ng*hr/mL in children 0-2 years vs 7500 ng*hr/mL in adults) and the model estimates that a 4-5 times higher dose would be needed in this population. Delamanid’s safety profile has therefore not been investigated for the model estimated therapeutic dose (20-25 mg BID) for this weight group < 10 kg. Based on the above arguments (only 5 children with a body weight below 10 kg and a lower plasma exposure tested in the study in these children than the targeted effective adult exposure), administration of delamanid is currently not recommended in children with a body weight < 10 kg.

2.6.2. Conclusions on the clinical safety

The CHMP concluded that the observed safety data collected from trial 232 and 233 are consistent with the known safety profile of delamanid in adult subjects and no new safety signals have been identified.

2.7. Risk Management Plan

Safety concerns

The summary of safety concerns as per RMP version 3.5 is provided below:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT interval prolongation</td>
<td>Paraesthesia, hypoesthesia and tremor</td>
<td>Tinnitus</td>
<td>Drug use in paediatric patients (body weight &lt; 10 kg)</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders: Anxiety, Depression and Insomnia</td>
<td>Blurred vision</td>
<td>Drug use in elderly patients</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorders: Nausea, Vomiting and Gastritis</td>
<td>Hypokalaemia</td>
<td>Drug use in patients with HIV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood cortisol level increase</td>
<td>Drug use in patients with severe renal impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver disorders</td>
<td>Drug use in patients with severe hepatic impairment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug use during pregnancy</td>
<td>Drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug use during breastfeeding</td>
<td>Extended use (&gt; 24 weeks)</td>
</tr>
</tbody>
</table>

Pharmacovigilance plan

The following Table outlines the ongoing and planned additional pharmacovigilance activities in the RMP:
## Study Status

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Summary of objectives</th>
<th>Safety concerns addressed</th>
<th>Milestones</th>
<th>Due dates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>endTB NCT02754765</td>
<td>In order to further investigate the use of delamanid in different combination treatment regimens as well as safety, the MAH should submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomized, controlled Phase III trial in adults and adolescents with multi-drug-resistant tuberculosis conducted by Médecins Sans Frontières, including an additional analysis of the data with a focus on the evaluation of delamanid based on an agreed statistical analysis plan.</td>
<td>The following Safety objectives will be evaluated: 1) To compare, at 73 and 104 weeks, the proportion of patients who died of any cause in the experimental arms to that in the control arm 2) To compare, at 73 and 104 weeks, the proportion of patients who experience AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm 3) To compare, at 73 weeks, the proportion of patients who experience QTc prolongation in the experimental regimens to that in the control arm.</td>
<td>Final report</td>
<td>Q1 2023</td>
</tr>
<tr>
<td><strong>Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Category 3 - Required additional pharmacovigilance activities</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PASS 242-12-402 Ongoing</td>
<td>To monitor the usage of delamanid in a real-life setting when prescribed as part of an appropriate combination regimen designed by the treating physician.</td>
<td>All important identified and potential risks will be evaluated through the data analysis; Special interest: 1) Cardiac disorders (including QT prolongation) and 2) Suspected delamanid resistance (including</td>
<td>Annual reports Final report</td>
<td>Q2 2017 and yearly afterwards Q4 2022</td>
</tr>
</tbody>
</table>
**Study Status**

**Summary of objectives**

- guidelines for patients at the end of a full treatment period for MDR-TB up to 30 months
- To monitor the safety of delamanid in a real-life setting when prescribed as part of an appropriate combination regimen designed by the treating physician

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Summary of objectives</th>
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<th>Milestones</th>
<th>Due dates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>lack of delamanid effect</td>
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</tbody>
</table>

**Risk minimisation measures**

Routine and additional risk minimisation activities proposed to manage the safety concerns of the medicinal product are provided in the table below

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Risk Minimization Measures</th>
<th>Pharmacovigilance Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT Interval Prolongation</td>
<td>Routine risk minimization measures: SmPC Sections 4.3, 4.4, 4.5, 4.8 PIL Section 2</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td></td>
<td>Recommendation for ECG before initiation of treatment and monthly during the full course of treatment with delamanid is included in SmPC Section 4.4. It is further recommended that treatment not be initiated in patients with specific cardiac risk factors unless the possible benefit of delamanid is considered to outweigh the potential risks.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine.</td>
<td>In regard to the SOB002, the endTB study (NCT02754765) will provide additional information on delamanid’s safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients in the experimental arms with either QTc interval prolongation of ≥60 ms from baseline or QTc interval of &gt;500 ms at 73 weeks to that in the control arm as a secondary endpoint.</td>
</tr>
<tr>
<td></td>
<td>Additional risk minimization measures: Educational material for Healthcare Professionals and Patients</td>
<td></td>
</tr>
<tr>
<td>Paraesthesia, Hypoaesthesia and Tremor</td>
<td>Routine risk minimization measures: SmPC Sections 4.7, 4.8 PIL Section 4</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td>Safety Concern</td>
<td>Risk Minimization Measures</td>
<td>Pharmacovigilance Activities</td>
</tr>
<tr>
<td>--------------------------</td>
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<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Psychiatric Disorders:</td>
<td>Routine risk minimisation measures: SmPC Section 4.8 PIL Section 4</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td>Anxiety, Depression and</td>
<td>Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders: Nausea, Vomiting and Gastritis</td>
<td>Routine risk minimisation measures: SmPC Section 4.8 PIL Section 4</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>Routine risk minimisation measures: SmPC Section 4.8 PIL Section 4</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>Routine risk minimisation measures: None</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>Routine risk minimisation measures: SmPC Section 4.8</td>
<td>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None.</td>
</tr>
</tbody>
</table>

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## Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommendation for very frequent monitoring of albumin levels, serum electrolytes, and ECG is included in SmPC Section 4.4, as hypokalaemia is a contributing factor to QTc interval prolongation. Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Blood Cortisol Level Increased</td>
<td>Routine risk minimisation measures: SmPC Section 4.8 PIL Section 4 Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Liver Disorders</td>
<td>Routine risk minimisation measures: SmPC Section 4.8 PIL Section 4 Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice The endTB study (NCT02754765) will provide additional information on delamanid’s safety profile when administered in different combination of treatment regimens. The study will assess the proportion of patients with AEs of Grade 3 or higher AEs or SAEs of any grade in the experimental arms to that in the control arm as a secondary endpoint.</td>
</tr>
<tr>
<td>Drug Use during Pregnancy</td>
<td>Routine risk minimisation measures: SmPC Sections 4.6, 5.3 PIL Section 2</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Use during Breastfeeding</strong></td>
<td>Routine risk minimisation measures: SmPC Sections 4.6, 5.3 PIL Section 2 Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Drug Use in Paediatric Patients (Body weight &lt; 10 kg)</td>
<td>Routine risk minimisation measures: SmPC Sections 4.2, 5.1, 5.2 PIL Section 2 Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Drug Use in Elderly Patients</td>
<td>Routine risk minimisation measures: SmPC Section 5.2 Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Drug Use in Patients with HIV</td>
<td>Routine risk minimisation measures: SmPC Sections 4.4, 4.5 PIL Section 2 Prescription only medicine. Additional risk minimisation measures: None.</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice</td>
</tr>
<tr>
<td>Drug Use in Patients with Severe Renal Impairment</td>
<td>Routine risk minimisation measures: SmPC Section 4.2, 5.2 PIL Section 2</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
</tbody>
</table>
Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Risk Minimization Measures</th>
<th>Pharmacovigilance Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescription only medicine.</td>
<td>Prescription only medicine.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice.</td>
</tr>
<tr>
<td>Additional risk minimisation measures: None.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Use in Patients with Severe Hepatic Impairment</td>
<td>Routine risk minimisation measures: SmPC Section 4.2, 4.4, 5.2 PIL Section 2</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice.</td>
</tr>
<tr>
<td></td>
<td>Additional risk minimisation measures: None.</td>
<td></td>
</tr>
<tr>
<td>Drug-drug Interactions</td>
<td>Routine risk minimisation measures: SmPC Sections 4.5, 5.2 PIL Section 2</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice.</td>
</tr>
<tr>
<td></td>
<td>Additional risk minimisation measures: None.</td>
<td></td>
</tr>
<tr>
<td>Extended Use (&gt; 24 weeks)</td>
<td>Routine risk minimisation measures: SmPC Section 4.2, 4.4</td>
<td>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.</td>
</tr>
<tr>
<td></td>
<td>Prescription only medicine.</td>
<td>Additional pharmacovigilance activities: PASS 242-12-402 - Study Assessing Medicinal Safety and Usage in Routine MDR-TB Medical Practice.</td>
</tr>
<tr>
<td></td>
<td>Additional risk minimisation measures: None.</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.
**Periodic Safety Update Reports submission requirements**

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.

**2.9. Significance of paediatric studies**

The CHMP is of the opinion that all studies, which are contained in the agreed Paediatric Investigation Plan, P/0271/2019 have been completed after 26 January 2007, are considered as significant.

**2.10. Product information**

**2.10.1. User consultation**

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Deltyba 50 mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

**2.10.2. Additional monitoring**

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Deltyba (delamanid) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU. In addition, Deltyba was granted a conditional marketing authorisation as per Article 14(7) of Regulation (EC) No 726/2004.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

**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.

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 optimized 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 had been completed and data analysed for age groups 6-17 years (13 patients) leading to an extension of the indication in adolescents and children with a body weight of 30 kg. This trial has now been completed for the subset 0 to 5 years of age.

The dispersible tablet formulation (DPF) of delamanid was used for the younger age groups in Trial 242-12-232 and 242-12-233. Twelve children aged 3-5 years (group 3) were administered DPF 25 mg BID + OBR and the twelve patients in aged 0 – 2 years (group 4) were administered a DPF dose based on body weight + OBR: Subjects > 10 kg received DPF 10 mg BID + OBR, Subjects > 8 and ≤ 10 kg received DPF 5 mg BID + OBR and Subjects ≤ 8 kg received DPF 5 mg once daily + OBR.

Relative bioavailability was conducted to compare the dispersible tablet formulation for paediatric subjects with the marketed tablet formulation and to determine the effect of a high-fat meal on delamanid PK (Trial 242-12-245).
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. (CSR 242-19-259)

The results of trial 232 have been submitted previously during procedure EMA/H/C/002552/P46/007. Part of the results of trial 233, namely the subgroup of children aged 6 to 17 years who had completed the trial and follow-up period, have been submitted in a previous variation EMEA/H/C/002552/II/0040 and lead to an extension of the indications from adults to adults, adolescents and children with a body weight of at least 30 kg.

The results of trial 233 for the two youngest age groups (0-5 years of age) are submitted in this line extension procedure. The aim of this variation is to provide a justification for extension of the delamanid MDR-TB indication to children and infants with a body weight of at least 10 kg.

3.2. Favourable effects

Deltiba 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 extension of this indication from adults to adolescents and children with a body weight of at least 30 kg was granted in October 2020.

A population PK modelling approach was used to inform doses to be used in children of 0 to 5 y, assuming that similar PK exposure as in adults should lead to similar response to delamanid.

The DPF doses used in group 3 (3-5 years) were 25 mg BID and in group 4 (0-2 years) 10 mg BID for patients > 10 kg, 5 mg BID for patients >8 and ≤ 10 kg. All patients in group 3 had a body weight between 10 and 20.5 kg at baseline. Therefore, the recommended doses identified by simulation, 25 mg BID for patients 10-20 kg corresponds with the one used in group 3 during trial 233. In group 4, the recommended dose identified by simulation would also be 20-25 mg BID.

The use of delamanid in addition to OBR in paediatric trial 233 resulted in a favourable treatment outcome in 10 of the 12 subjects (83.3%) aged 3 to 5 years at 24 months (3 of these 12 subjects (25.0%) were cured and 7 of the 12 subjects (58.3%) completed treatment) and in a favourable treatment outcome in 11 of the 12 subjects (91.7%) aged 0-2 years (5 of these (41.7%) were cured and 6 of the 12 subjects (50.0%) completed treatment).

The majority of the subjects in Groups 3 and 4 found the paediatric formulation to be highly palatable.

3.3. Uncertainties and limitations about favourable effects

PK
In children 0-2 years median AUC (2740 ng*hr/mL) was below the 7500 ng*hr/mL AUC in adults.

100 mg of Delamanid Paediatric Formulation (DPF) is not bioequivalent to 100 mg of Delamanid Tablets with respect to rate and extent of absorption.

In the bioavailability conducted in adults, systemic exposure was greater when delamanid was taken with a high-fat meal.

PopPK
Comparable AUCss and Cmax values are displayed for the recommended paediatric and the adult doses. The methodology used to generate these plots/results were well-described and the codes used were provided.
Efficacy

Based on the current conclusions of the popPK simulation, the proposed doses are different from the ones used in trial 232 and 233 for patients in group 4 aged 0-2 years. Plasma exposures achieved in all study patients <10 kg were considerably lower than the target exposure (median AUC 2740 ng*hr/mL in children 0-2 years vs 7500 ng*hr/mL in adults). Therefore, administration of delamanid has not been sufficiently investigated in children with a body weight < 10 kg.

Evaluation of efficacy is complicated by the more difficult diagnosis in younger patients. Both cured patients and patients with completed treatment were considered as having a favourable treatment outcome. Even though patients in group 4 were administered suboptimal doses in combination with an OBR, a favourable treatment outcome was noted in 11 of the 12 subjects (91.7%) aged 0-2 years (5 of these (41.7%) were cured and 6 of the 12 subjects (50.0%) completed treatment).

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.

In trial 233, the most commonly reported potentially IMP-related TEAEs were prothrombin time prolonged (3/37 [8.1%] subjects), blood corticotrophin increased, liver function test increased, and butterfly rash (2/37 [5.4%] subjects for each). In trial 232 this were diarrhoea (2 subjects [5.4%]) and ECG QT prolongation (2 subjects [5.4%]).

In trial 233, changes of QTcF ≥ 30 and ≤ 60 msec were experienced by 81.8% of patients in group 4 and by 50.0% of patients in group 3. Changes of QTcF > 60 msec were experienced by 1 subject in group 4. Though, no new onset changes > 450 msec in QTcF were experienced in group 3 and 4 patients. In trial 232, changes of QTcF ≥ 30 and ≤ 60 msec were experienced by 41.6% in Group 3 and 25.0% of patients in Group 4. New onset changes > 450 msec in QTcF were experienced 16.6% in Group 3.

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.

The number of patients with potentially IMP-related TEAEs was higher in younger age groups: 1 patient in group 1 and 2 (12-17 and 6-11 years of age, 14.3% and 16.7%, respectively), 2 patients in group 3 (3-5 years of age, 25%) and 4 patients in group 4 (0-2 years of age, 33.3%). Given the low number of patients included with a body weight ≤10 kg and the low delamanid exposure in group 4 patients, no conclusions can be drawn from the data in the weight group ≤10 kg. It is noted, however, that incidence of potentially drug-related TEAEs was slightly higher in group 3 patients than in group 1 and 2 patients as well. This difference was mainly seen in the SOC investigations, for increased blood corticotrophin, increased liver enzymes and prothrombin time prolongation. There is an imbalance in the reporting of adverse events related to the important potential risk of liver disorders with all except one case reported in the youngest age groups 3 and 4, though all events were mild and resolved, and none resulted in discontinuation from the IMP or trial. This will be followed-up further as liver disorders and blood cortisol level increase are included as important potential risks in the RMP.

The doses administered in group 4 (0-2 years of age) in the clinical trials (10 mg BID DPF > 10 kg and 5 mg BID DPF >8 and ≤10 kg) are below the ones that are currently predicted to be needed (20-25 mg BID) to obtain similar exposures as in the adult population.
Consequently, plasma exposures achieved in all study patients <10 kg were considerably lower than the target exposure (median AUC 2740 ng*hr/mL in children 0-2 years vs 7500 ng*hr/mL in adults). The available safety data in patients <10kg are therefore not sufficiently informative to support an extension of the lower weight limit.

As observed in the adult population, an increase in QTc interval is noted in the paediatric population. Also in the exposure response simulation for the QTc interval prolongation, an effect of delamanid administration on the QTc interval prolongation was shown, both in the adult and the paediatric population.

3.6. Benefit-risk assessment and discussion

3.6.1. 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 in the paediatric population is comparable to the adult population based on similar exposure, approval of the indication is dependent on the appropriateness of the age-specific dose regimens based on PK data and on an acceptable paediatric safety profile.

3.6.2. Balance of benefits and risks

A population PK modelling approach was used to inform doses to be used in children from birth to 5 years of age (included), assuming that similar PK exposure as in adults should lead to similar response to delamanid.

The safety risk in children from birth to 5 years of age (included) enrolled in the trials seems to be consistent with what was observed in adults and no new safety signals have been identified.

For children with a body weight < 10 kg, administration of delamanid is not recommended. In group 4 in trial 232, 5 patients with a body weight below 10 kg at baseline have been included). In group 4 of trial 233, 4 patients still had a body weight below 10 kg at baseline). A patient under 2 years old with a BW under 10 kg died shortly after starting delamanid treatment in trial 233; this patient had developmental parameters below the 3rd percentile at baseline and it was determined that the death was not related to delamanid treatment. Therefore, data for model validation in these patients is limited. In addition, all 5 children were assigned to Group 4, and delamanid doses (5 mg BID >8kg and ≤10 kg or 5 mg QD ≥ 5.5 kg and ≤8 kg) administered in the trials resulted in plasma exposure essentially lower than the targeted effective adult exposure. Exposure in these patients was indeed below the targeted effective adult exposure (median AUC 2740 ng*hr/mL in children 0-2 years vs 7500 ng*hr/mL in adults) and the model estimates that a 4-5 times higher dose would be needed in this population. Delamanid’s safety profile has therefore not been investigated for the model estimated therapeutic dose (20-25 mg BID) for this weight group.

Based on the above arguments (limited number of children with a body weight below 10 kg and a lower plasma exposure tested in the study in these children than the targeted effective adult exposure), administration of delamanid is currently not recommended in children with a body weight < 10 kg.
3.7. Conclusions

The overall B/R of Deltyba is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Deltyba 25 mg is not similar to Sirturo, Granupas and Dovprela (previously Pretomanid FGK) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Deltyba 25 mg dispersible tablets is favourable in the following indication:

- Use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children and infants with a body weight of at least 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

The CHMP therefore recommends the extension of the marketing authorisation for Deltyba subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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

Risk Management Plan (RMP)

The 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.

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.

Additional risk minimisation measures

Additional risk minimisation measures as per Annex II D of Deltyba Product Information: Conditions or Restrictions about the safe and effective use of the medicinal product include educational material for healthcare providers (HCPs) and for patients.

Objectives of:

Educational materials for HCPs:
• To inform the health care professionals about the appropriate usage and to minimize potentially associated risks from use of delamanid and
• To inform HCPs that delamanid should be used according to WHO/National guidelines for MDR TB management.

Educational materials for Patients:
• To reinforce and/or supplement the information provided in the patient information leaflet.

Rationale for the additional risk minimisation activity:

The educational materials for HCPs reinforce and supplement the EU SmPC information on the following safety/efficacy concerns in order to ensure the safe and effective use of delamanid: important identified risk of QT Interval Prolongation, important potential risks of Drug Use during Pregnancy and Drug Use during Breastfeeding, and the efficacy risk of Drug Resistance. Information for Patients addresses important potential risks of Drug Use during Pregnancy and Drug Use during Breastfeeding.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>In order to further investigate the use of delamanid in different combination treatment regimens as well as safety, the MAH should submit the results of the endTB (Evaluating Newly approved Drugs for multidrug-resistant TB) study, a randomized, controlled Phase III trial in adults and adolescents with multi-drug-resistant tuberculosis conducted by Médecins Sans Frontières, including an additional analysis of the data with a focus on the evaluation of delamanid based on an agreed statistical analysis plan.</td>
<td>Q1 2023</td>
</tr>
</tbody>
</table>

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.


**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.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change:

<table>
<thead>
<tr>
<th>Variation(s) requested</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.I.6.a</td>
<td>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</td>
</tr>
</tbody>
</table>

Extension application to introduce a new pharmaceutical form (dispersible tablets) associated with a new strength (25 mg), grouped with a type II extension of indication variation (C.I.6.a) to include the treatment of multidrug-resistant tuberculosis (MDR-TB) children of at least 10 kg of body weight for the approved Deltyba 50 mg film-coated tablets; as a consequence, sections 3, 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet and Labelling are updated accordingly. Version 3.3 of the RMP has also been submitted and Annex II is updated to remove the specific obligation related to an in vitro study using the HFS-TB model.