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EMEA/H/C/002552/P46
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Deltyba

delamanid

Procedure no: EMEA/H/C/002552/P46/007

Note

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

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1. Introduction

On 20th June 2018, the MAH submitted a completed paediatric study for delamanid, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are generated as part of the Paediatric Investigation Plan (PIP) for delamanid (Deltyba) agreed upon by the European Medicines Agency's decision P/275/2011 on 11 November 2011.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study 242-12-232 (Phase 1, Open-label, Multiple-dose, and Age De-escalation Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Delamanid [OPC-67683] in Paediatric Multidrug-resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs) is part of a clinical development program. The extension application consisting of the full relevant data package (containing several studies) is expected to be submitted by 05/20. A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Delamanid was granted conditional marketing authorisation in the EU via a centralised procedure in 2014. This authorisation was renewed in February 2018. It is currently registered and approved in 39 countries but not currently licensed in the US. Delamanid is indicated for use as part of an appropriate combination regimen for the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults only, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. It is not currently licensed for use in children since the safety and efficacy of delamanid in children below 18 years of aged have not yet been established.

In Study 242-12-232, delamanid was administered to paediatric MDR-TB subjects on optimised background regimen (OBR) therapy and was supplied in labelled blister cards as 5 mg, 25 mg, and 50 mg tablets. Delamanid 50 mg film-coated tablets is the currently licensed adult formulation and was administered to children from the age of 6 years. For patients younger than 6 years, specific paediatric formulations, developed as part of an agreed PIP, were used. A dispersible 25mg tablet was administered to children aged 3 to 5 years and a 5 mg dispersible delamanid paediatric formulation (DPF) was given to children under the age of 3 years. The DPF was mixed with water and administered orally as an extemporaneous suspension.

Delamanid was administered with water and food in both a morning and an evening dose, approximately 10 hours apart. Food composition was typical for the children's age and needs.

Assessor's comments:

Study 242-12-232 is part of a Paediatric Investigation Plan (PIP), first agreed by the Paediatric Committee (PDCO) in November 2011. There were 5 subsequent modifications, the last modification, EMEA-001113-PIP01-10-M05, was agreed in the August 2016. The latest EMA decision for this modified PIP, P/0269/2016, was published on 7th October 2016. The indication targeted for paediatric development is the "*treatment of multi drug resistant tuberculosis*." There are no waivers agreed in the

PIP for the development for this product.

The PIP contains 5 studies: 1 paediatric formulation development study, a juvenile toxicity assessment and 3 clinical studies. Trial 242-12-232 is study 4 of the agreed PIP. All studies are completed with the exception of the 6-month open label extension trial which is currently ongoing and due to be completed by November 2019.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

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

2.3.2. Clinical study

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

Description

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

Methods

Objectives

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

Study design

This trial was conducted at two (2) Phase 1 sites qualified to treat paediatric subjects with MDR-TB. The protocol was approved by the appropriate national competent authorities (CAs) and the respective

IRBs/IECs. Compliance with any other regional or local notification or approval requirements was met and maintained.

The trial was conducted sequentially in 4 groups of paediatric subjects: Group 1 (ages 12 – 17 years, inclusive, n = 7), Group 2 (ages 6 - 11 years, inclusive, n = 6), Group 3 (ages 3 – 5 years, inclusive, n = 12), Group 4 (ages birth - 2 years, inclusive, n = 12).

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

The study population included male and female subjects between birth and 17 years of age, inclusive, with a confirmed diagnosis of MDR TB culture positive for *Mycobacterium tuberculosis* (MTB) with isoniazid and rifampicin resistance on drug sensitivity testing (DST), or a positive rapid test demonstrating resistance to rifampicin alone, or to rifampicin and isoniazid, OR a presumptive diagnosis of pulmonary or extrapulmonary MDR-TB, such that the treating physician had decided to treat the subject for MDR-TB. Subjects also had one of the following criteria:

1) Clinical specimen (e.g., cerebrospinal fluid [CSF], pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of tuberculosis disease;

2) Persistent cough lasting > 2 weeks;

3) Fever, weight loss, and failure to thrive;

4) Findings on recent chest radiograph (prior to Visit 1) consistent with TB;

5) AND household contact with a person with known MDR-TB or with a person who died while appropriately taking drugs for sensitive TB; OR on first-line TB treatment but with no clinical improvement.

6) Negative urine pregnancy test for female subjects who had reached menarche.

Trial-specific written informed consent/assent obtained from a subject/guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol-required procedures. In addition, for Groups 1 and 2, the subjects were required provide informed nod at screening and be able to fully understand that he or she were able to withdraw from the trial at any time.

The trial comprised the following periods:

Pre-treatment Period

- Screening and eligibility assessment from Day −22 to Day −2 (Groups 1, 2, and 3); Day −31 to Day −2 (Group 4).
- Baseline safety assessment on Day −1.

Treatment Period: Day 1 to Day 18

- Delamanid administration from Day 1 to Day 10
- PK sampling on Days 1, 2, 10, 11, 13 (Groups 1 and 2 only), 15, and 18
- Safety assessments on Days 1, 10 (clinical laboratory tests and urinalysis were conducted only for Groups 1 and 2), and 18
- Discharge on Day 18 after completing all assessments

Follow-up Period: Day 19 to Day 40 (± 2 days)

All subjects who completed their last scheduled visit were contacted by telephone 28 to 30 days after the last dose of delamanid to assess any new or ongoing adverse events (AEs). This follow-up telephone contact occurred on Day 40 (± 2 days). Subjects who terminated from the trial prior to their last scheduled visit were contacted by telephone or home visit 14 days (± 2 days) after the last dose of delamanid to assess for any new or ongoing AEs.

Study population /Sample size

A total of 44 subjects were screened for this trial. The trial enrolled 37 males and females ages birth to 17 years, inclusive, who were receiving OBR for confirmed or presumptive MDR-TB. Subjects were to be enrolled in 4 sequential age groups.

- Group 1 (ages 12 - 17 years, inclusive) was expected to enrol a minimum of 6 subjects and must have enrolled at least 2, but not more than 5, females.
- Group 2 (ages 6 - 11 years, inclusive) was expected to enrol a minimum of 6 subjects.
- Group 3 (ages 3 - 5 years, inclusive) and Group 4 (ages birth - 2 years, inclusive) each were expected to enrol a minimum of 12 subjects.

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

Treatments

Delamanid was administered to study subjects for 10 days with 8 days of safety follow-up and PK sampling.

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

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

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

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

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

The morning dose of the delamanid BID regimen was given within 30 minutes after the start of a standard breakfast meal. The evening dose of the BID dose regimen was given 10 hours post morning dose and within 30 minutes after the start of a standard dinner meal. For the QD regimen, delamanid was administered within 30 minutes after the start of a standard breakfast meal. Food composition was typical for the children's age and needs.

The second-line medications generally used in developing OBR for MDR-TB subject treatment are as follows:

- Amikacin
- Capreomycin
- Cycloserine
- Ethambutol
- Ethionamide
- Prothionamide
- Gatifloxacin
- Levofloxacin
- Kanamycin
- Ofloxacin
- P-aminosalicylic acid
- Pyrazinamide
- Streptomycin

Medications with an unclear role in the treatment of MDR-TB and not recommended for routine use for MDR-TB treatment, though sometimes used for highly drug-resistant MDR-TB subjects, are described in the WHO Treatment Guidelines for MDR-TB. Moxifloxacin was excluded from the list of allowed medications.

Outcomes/endpoints

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

- Cmax, tmax, AUC0-24h on Day 1 and Day 10
- t ½ z on Day 10
- Rac Day 10/Day 1 for AUC0-24h, and apparent total clearance (CLss/F) for delamanid only

Safety of delamanid was assessed by the following variables:

- Reported treatment-emergent adverse events (TEAEs)
- Vital signs
- ECGs
- Holter monitoring (if applicable)
- Clinical laboratory assessments (haematology, serum chemistry, urinalysis, and other laboratory tests)

The palatability of the paediatric formulation was assessed using an age-appropriate visual hedonic scale and clinical assessment.

The palatability result was based on one of 5 responses: Dislike very much, Dislike a little, Neither liked nor disliked, Like a little, Like very much. The test was assessed only for Groups 3 and 4 receiving the delamanid paediatric formulation. The test result was scored by the investigator and either a parent or subject score. The frequency counts for subject with each score were summarized at visits that palatability is assessed (Day 1, Day10 and ET).

Statistical Methods

Determination of Sample Size:

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

Subject Samples:

- Enrolled Sample: comprised all subjects who signed informed consent to enrol into the current trial and without screen failure.
- Safety Sample: comprised the subjects who had received any amount of trial medication in Trial 242-12-232, regardless of any protocol deviation or violation.
- PK Sample: consisted of the safety sample having a valid PK parameter.

The following delamanid PK parameters were determined using noncompartmental analysis:

- Peak (maximal) concentration of drug in plasma (Cmax), time of peak concentration of drug (tmax), area under the plasma concentration-time curve from time 0 to 24 hours (AUC0-24h) on Day 1 and Day 10
- Accumulation ratio Day 10/Day 1 for AUC0-24h
- Apparent terminal phase elimination half-life (t1/2z) and apparent total clearance

Delamanid plasma concentrations across age groups will be analysed using a population pharmacokinetics (POPPK) modelling approach, which will be reported separately.

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

- The following PK parameters were determined for DM-6705 using noncompartmental analysis: Cmax, tmax, AUC0-24h on Day 1 and Day 10 and t1/2z.

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

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

Results

Recruitment / Number analysed

Study Population

A total of 44 subjects were screened for this trial. The trial included 37 males and females ages birth to 17 years, inclusive, who were receiving OBR for confirmed or presumptive MDR-TB were enrolled in 4 sequential age groups. Group 1 (ages 12 - 17 years, inclusive), Group 2 (ages 6 - 11 years, inclusive), Group 3 (ages 3 - 5 years, inclusive) and Group 4 (ages birth - 2 years, inclusive) each were planned to include a minimum of 12 subjects.

Thirty-seven subjects inclusive of all age and dose groups completed this trial.

Baseline data

Overall, the subjects enrolled were predominantly Asian (25 of 37 [67.6%]). The total number of male and female subjects were approximately equal (18 of 37 subjects were male [48.6%] and 19 of 37 subjects were female [51.4%]). The mean ages of Group 1, 2, 3 and 4 were 15.29, 9.42, 4.28, and 1.64 years, respectively. The mean weight of Group 1, 2, 3, and 4 were 39.0, 24.9, 14.2, 9.8 kg, respectively.

Bioanalytical Results

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

Efficacy results

There are no efficacy results.

Assessor's comments:

A total of 2 subjects had 2 major protocol deviations that pertained to entry criteria. No subject was discontinued due to a protocol deviation and none of the protocol deviations were determined to have an impact on the study analyses.

This study was designed to assess the PK safety and tolerability of delamanid in the paediatric population. There were no efficacy analyses and thus no conclusions on the treatment effect of delamanid use in children can be made.

Pharmacokinetic results

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

Figure 1 Median Delamanid Plasma Concentrations Following Delamanid Administration on Day 1 to Pediatric Subjects with MDR-TB Ages 17 Years and Younger

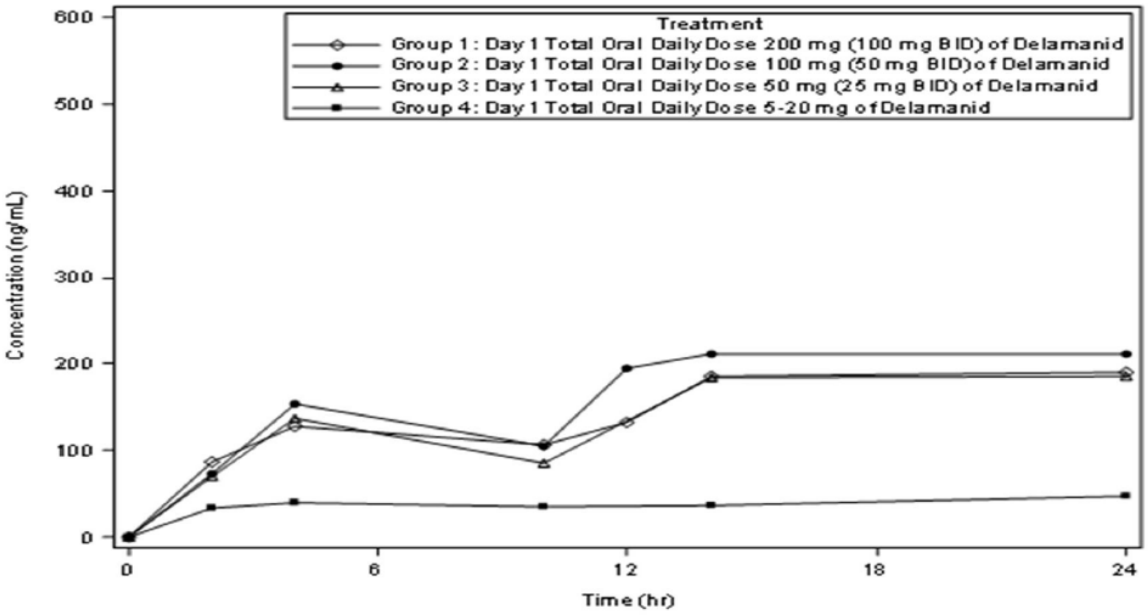
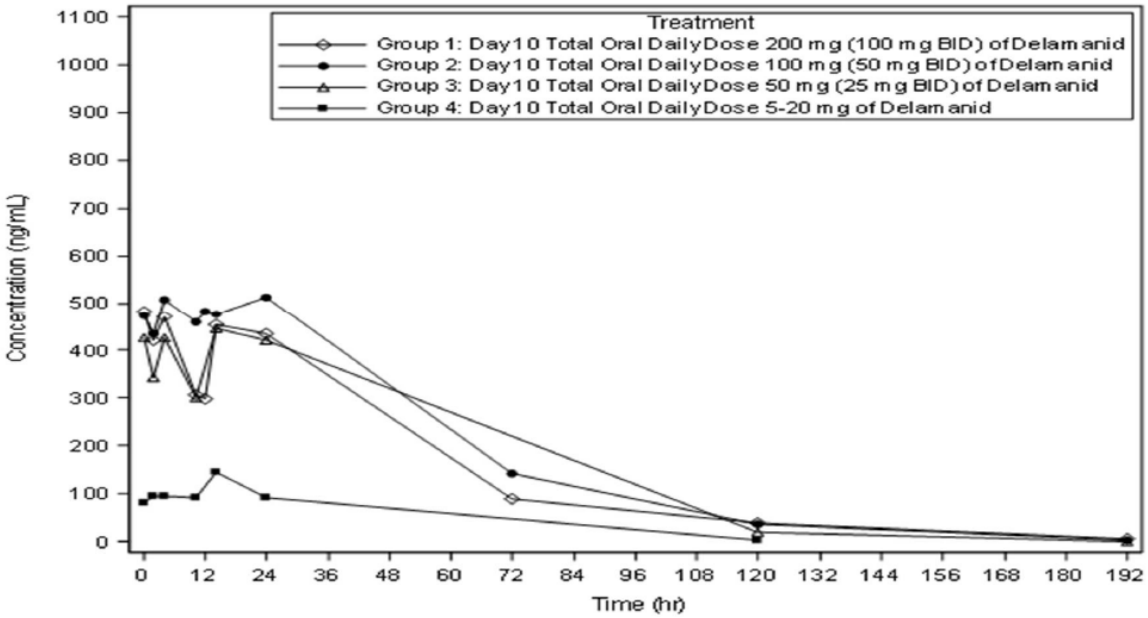


Figure 2 Median Delamanid Plasma Concentrations Following Delamanid Administration on Day 10 to Pediatric Subjects with MDR-TB Ages 17 Years and Younger



DM-6705 PK Profiles:

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

Figure 3: Median DM-6705 Plasma Concentrations Following Delamanid administration on Day 1 to Paediatric Subjects with MDR-TB Ages 17 Years and younger

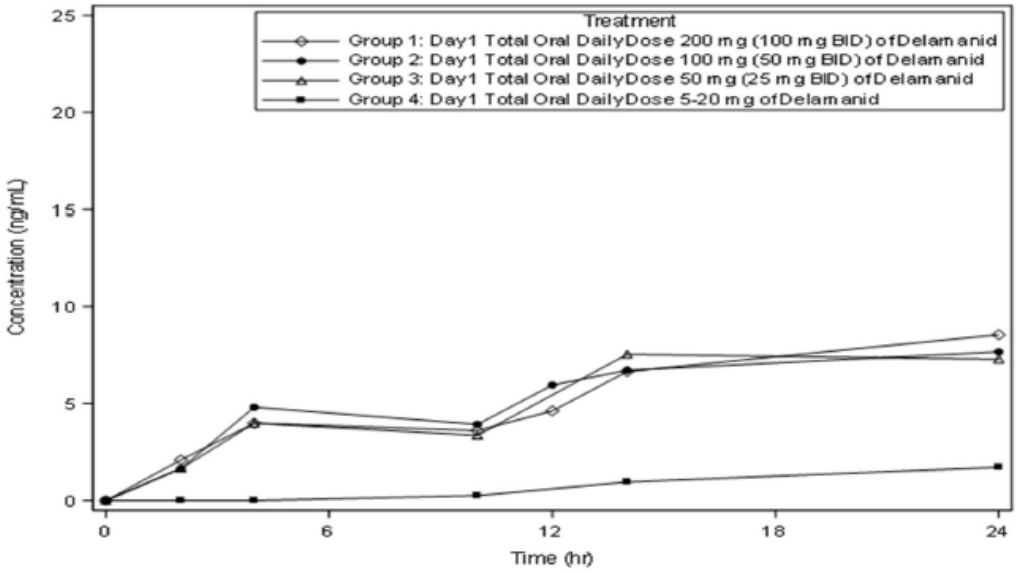
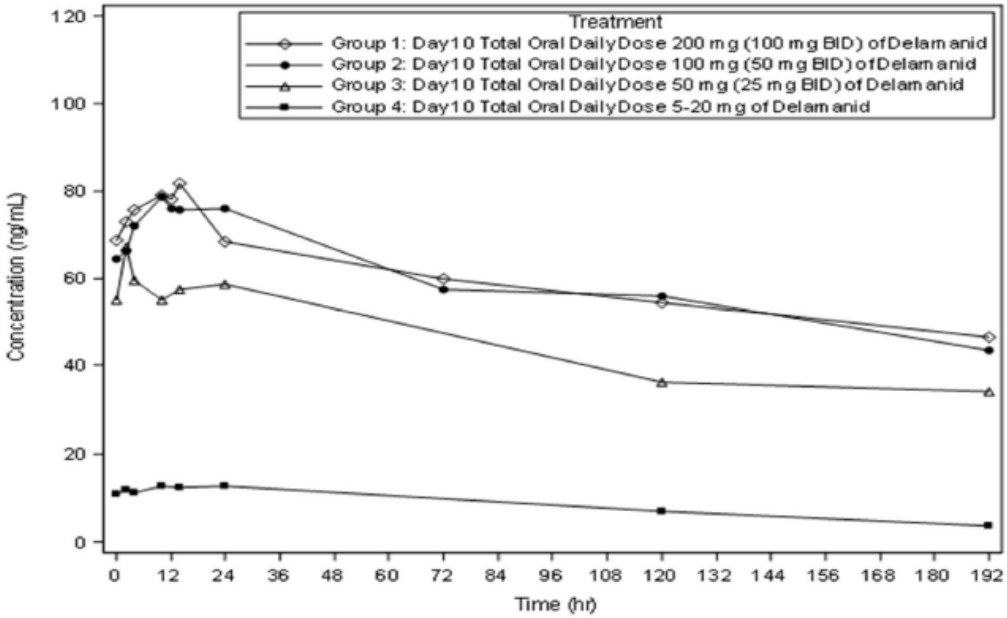


Figure 4 Median DM-6705 Plasma Concentrations Following Delamanid Administration on Day 10 to Pediatric Subjects with MDR-TB Ages 17 Years and Younger



Delamanid PK Parameters:

A summary of delamanid pharmacokinetic parameters following delamanid administration on Day 1 and Day 10 are presented in Table 1 and Table 2, respectively.

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

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

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

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

ND = No data.

DM-6705 Pharmacokinetic parameters:

A summary of DM-6705 pharmacokinetic parameters following delamanid administration on Day 1 and Day 10 are presented in Table 3 and Table 4, respectively.

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

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

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

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

In Groups 1 to 4, the median delamanid Cmax 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 Cmax and the AUC0-24h ranges were reasonably similar for Groups 1 to 3 but were much lower for Group 4.

The MAH notes that the ratio of AUC0-24h on Day 10 of DM-6705 to delamanid appears to decrease with decreasing age, indicating that either the formation of DM-6705 is decreasing or its elimination is increasing or a combination of the two scenarios. The median terminal elimination half-life of DM-6705 was 237.3 hours in Group 1 and 128.2 hours for Group 4, indicating a more rapid elimination with decreasing age.

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

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

Assessor's comments:

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

The dosing regimen for Group 4 was determined by modelling PK data from the previous three groups and it was thus expected that the delamanid doses used would have a higher predicted bioavailability for children in this age cohort. However, the current data suggest that a higher delamanid dose is needed in the youngest children.

There is a trend for more rapid elimination with decreasing age, but the effect of food on absorption and plasma exposure might be a significant factor for lower delamanid exposure in this age group. Although there were no efficacy nor PK/PD analyses performed in this study, the dose administered in

the youngest cohort could potentially result in sub-optimal exposures, with a reduction in cures rates in young children and might encourage the development of microbiological resistance. A discussion of the effect of food on delamanid exposure in young infants, should be considered for inclusion in the SmPC when the MAH submits their application to extend the indication to children.

These data are proposed to update the model used to predict the dose in young children. This is acceptable, however, further data may have to be generated to confirm if the updated dosing regimen has similar exposure and safety profile to older children and adults, to support the extrapolation of efficacy from adults.

The data support further paediatric development but at this stage, do not fully determine the benefit: risk of delamanid in the paediatric population.

Safety results

- All 37 subjects (100%) enrolled in the trial received all doses of IMP for 10 days. Overall safety results for this open-label, multiple-dose, and age de-escalating trial of 37 subjects showed:
- No subject had a fatal outcome during the trial and no subject discontinued the trial.
- Overall a total of 126 TEAEs were reported by 31 of 37 subjects (83.8%).
- The most frequently reported TEAEs were vomiting (9 of 37 subjects [24.3%]) followed by hyperuricaemia (5 of 37 subjects [13.5%]), nausea (5 of 37 subjects [13.5%]), and toothache (5 of 37 subjects [13.5%]).
- All 12 subjects (100.0%) aged 0 to 2 years experienced ≥ 1 TEAE during the trial followed by 9 of 12 subjects (75.0%) aged 3 to 5 years, 5 of 6 subjects (83.3%) aged 6 to 11 years, and 5 of 7 subjects (71.4%) aged 12 to 17. There was no clinically meaningful difference of TEAE incidences across all age groups.
- Most TEAEs were mild or moderate in intensity except for the TEAE of lower respiratory tract infection, which was considered to be severe in intensity.
- Two subjects (5.4%) each had a SAE; for one subject the SAE was hepatitis A (aged 3to 5 years) and for the other subject the SAE was lower respiratory tract infection (aged 0 - 2 years). Both SAEs were not related to IMP.
- Of 37, 9 subjects (24.3%) subjects experienced ≥ 1 TEAE that was related to the IMP; the most frequently reporting terms were diarrhoea (2 subjects [5.4%]) and ECG QT prolongation (2 subjects [5.4%]).
- All IMP-related TEAEs were mild or moderate in severity.
- There were no IMP-related TEAEs experienced by subjects aged 12 to 17 years and 3 subjects each from all other age groups reported IMP-related TEAEs. There were no clinically meaningful differences between the age groups.
- Overall, eosinophilia (2 of 37 subjects (5.4%]; 1 subject aged 3 - 5 and 1 subject aged 0 - 2) and neutropenia (1 of 37 subjects (2.7%]; 1 subject aged 3 - 5) were the TEAEs reported for blood and lymphatic system disorders. One incidence of eosinophilia and neutropenia were assessed as IMP-related TEAEs.

- Concurrent elevation of transaminases (≥ 3 × ULN) and bilirubin levels (≥ 2 × ULN) was experienced by 1 subject (2.7%) with diagnosed hepatitis A.
- No subject had an abnormal physical examination finding that was considered to be clinically significant.
- Potentially clinically significant abnormalities in vital signs only included changes ≥ 5% in body weight for 8 subjects across all age groups. A decrease ≥ 5% in body weight was only reported for 1 of 37 subjects (2.7%). An increase of ≥ 5% in body weight was reported for 7 of 37 subjects (18.9%) which can be considered as a benefit for the purpose of this trial.
- Overall, 2 of 12 subjects (16.7%) aged 3 to 5 years experienced TEAEs related to ECGs; 1 subject experienced PR prolongation, QT prolongation, and presence of U wave and the other subject experienced QT prolongation. These incidences were reported as IMP-related TEAEs.
- No clinically relevant differences were noted for clinical laboratory results, ECGs, vital signs, physical findings, or other observations relating to safety parameters a13.

Assessor's comments:

Most paediatric patients in this study reported adverse events (AE's). However, none of the AEs led to discontinuation of delamanid or to a fatal outcome during the trial. Only 2 patients had TEAEs classed as serious: 1 subject in Group 3 and 1 subject in Group 4 each had 1 serious TEAE.

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

No other TEAEs of special interest were identified during the study. Any changes from baseline for clinical laboratory test parameters were not clinically significant across the age groups. All of the AE's reported are similar to those in adults and are currently listed in the SmPC. No new safety concern has been identified that warrants an update to the SmPC and PIL or additional risk management measures.

Palatability results

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.

2.3.3. **Discussion on clinical aspects**

This was a phase 1, multicentre, open-label, uncontrolled, multiple-dose, and age de-escalation trial of delamanid administered for 10 days with 8 days of safety follow-up and PK sampling. The trial enrolled 37 paediatric MDR-TB subjects from Philippines and South Africa. Four different dosses of delamanid were administered to the subjects in 4 different age groups: Group 1 (ages 12 - 17 years, inclusive), Group 2 (ages 6 - 11 years, inclusive), Group 3 (ages 3 - 5 years, inclusive), and Group 4 (ages 0 - 2 years, inclusive). Subjects in Groups 1 and 2 received the adult formulation and subjects in Groups 3 and 4 received the paediatric formulation cross the age groups.

The objectives of this trial were to determine PK of delamanid and its metabolites in combination with OBR, safety, and tolerability of delamanid in combination with OBR, and palatability of DPF. In Groups 1 to 4, the median delamanid Cmax on Day 10 was 557, 573, 500, and 179 ng/mL, respectively; the median AUC0-24h on Day 10 was 9790, 12000, 9290 ng*h/mL, and 2740, respectively. The Cmax and the AUC0-24h ranges were reasonably similar for Groups 1 to 3 but were much lower for Group 4. The median weight-normalized oral clearance on Day 10 for delamanid was 8.92, 6.11, 6.68, and 8.34 for Groups 1 to 4, respectively.

Since the dosing regimens were different for each group as well as subject to body weights, to compare the exposures across the groups, the weight normalized oral clearance, was calculated for each regimen. A visual check of the numbers indicated that when normalized, the median oral clearance normalized to subject body weight (CL/F/BW) ranged between 6.11 to 8.92 for all Groups, except for the two subjects (# 43 and # 45) in Group 4 (5 mg QD), whose CL/F/BW was about twice the value of the other groups, (i.e., 17.8). This could be due to either impaired absorption (F) or increased intrinsic clearance. It is unlikely to be due to increased intrinsic clearance as this would have been indicated by a systematic increase in oral clearance across the groups, which was not observed. The impaired absorption could be due to either the dosage strength or the amount/type of food ingested along with the dose. The dosage strength of 5 mg in Group 4 appears unlikely as a factor in explaining the lower exposure, as the subjects receiving 10 mg BID (5 mg × 2 BID) and 5 mg BID had CL/F/BW values within the range seen in other groups. Since the absorption of delamanid is affected by food it is very possible that subjects in Group 4, being the youngest in the trial, consumed both a lower total amount of food as well as relatively, a lower amount of fat with delamanid administration. Overall, this indicates that the delamanid oral clearance in the paediatric subjects was within a narrow range and the lower exposures observed in Group 4 can be overcome by administering higher doses of delamanid.

For comparison to the adult data, following 100 mg BID delamanid administration in adults with MDR-TB, on Day 14, the median Cmax was 371 ng/ml and the AUC0-24h was 6811 ng*h/ml22 which are lower than that observed in Groups 1 to 3 paediatric subjects. The median clearance on Day 14 was 0.602 L/h/kg which is equal to 10.03 mL/min/kg, a value somewhat higher that the clearance observed in the paediatric subjects. It appears that the ratio of AUC0-24h on Day 10 of DM-6705 to delamanid decreased with decreasing age, indicating that either the formation of DM-6705 is decreasing or its elimination is increasing or a combination of the two scenarios. The median terminal elimination half-life of DM-6705 is 237.3 hours in Group 1 and 128.2 hours for Group 4, indicating a more rapid elimination with decreasing age.

The safety results exhibited during this trial are consistent across all age groups. The TEAEs observed in this 10-day trial were consistent with the current safety profile of delamanid. There were no trends in the incidences of TEAEs across the age groups. Overall, the most frequently reported TEAEs occurred in the MedDRA SOCs of gastrointestinal disorders (17 of 37 subjects [45.9%]) and Infections and Infestations (15 of 37 subjects [40.5%]). Overall, the most frequently reported TEAE was 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%]). Poor dental hygienic conditions were observed during this 10-day trial in subjects aged 12 to 17 years, 6 to 11 years, and 3 to 5 years. The assessment of ECGs, vital signs, and clinical laboratory tests did not show any consistent differences across the age groups. Overall, elevated uric acid (8.3%), elevated AST (3.1%), elevated ALT (2.9%), elevated total bilirubin (2.9%), elevated cholesterol (2.7%), and elevated prothrombin time (2.9%) were the only reported clinically significant laboratory test abnormalities. One subject (2.7%) aged 3 to 5 years reported elevated levels of transaminases and total bilirubin and with diagnosed hepatitis A.

New onset changes > 450 msec (40.5%) in QTcB, new onset changes > 450 msec (8.1%) in QTcF, new abnormal rhythm (81.0%), and new conduction abnormalities (62.1%) were the most frequently reported clinically significant abnormalities or changes in ECG results. There were no new onset changes > 500 msec in QTcB or QTcF. Decrease of ≥ 5% of body weight (2.7%) and increase of ≥ 5% of body weight (18.9%) were the potentially clinically significant abnormalities reported for vital signs. There were no clinically relevant differences in the mean changes from baseline for the various vital sign parameters across the age groups. The majority of the subjects aged 0 to 5 years liked the palatability of the DPF.

Summary

Delamanid exposures were higher in the MDR-TB paediatric population, except Group 4, compared to adult data. Exposures of delamanid metabolite DM-6705 were lower in the paediatric population, compared to adults with MDR-TB. The terminal half-life of DM-6705 decreased with decreasing age. Delamanid demonstrated an acceptable safety profile in the paediatric population studied during this 10-day trial and no new safety concerns were identified. Delamanid paediatric formulation was palatable in children aged from birth to 5 years.

The Trial 242-11-232 involved children aged 0-17 years , a patient population for which the treatment with Deltyba is not yet approved in the EU. The MAH states that the results of the trial are of significant importance for the future application of the approval of delamanid paediatric MDR-TB indication, however, do not require an immediate change of the current SmPC for Deltyba. This is acceptable.

Further MS comments were received regarding PK data, which are endorsed by the Rapporteur:

No conclusions can be drawn on the basis of the current PK analyses. The sampling times were too sparse to have reliable results with noncompartmental analysis. With that none of the PK parameters the Company is showing (Cmax, tmax, AUC0-24h on Day 1 and Day 10 and t1/2z) is reliable. This is also very clear from the values of Tmax shown in tables 1 (Delamanid Day 1) and 2 (Delamanid Day10) on page 13 of the assessment report: with Tmax values of 23-96 hours in group 3 (table 1) or 13-75 hours in group 4 (table 2) with BID dosing. These Tmax values do not correspond with the currently proposed dose regimen.

Given the sampling schedule, popPK analysis makes more sense. PopPK analysis is planned, but this will be reported separately, after completion of the follow-up study 233.

3. Rapporteur's overall conclusion and recommendation

This study provides preliminary PK, safety and tolerability data for delamanid administration in children. However, no conclusions can be made based on the current PK analyses. These data can be used to support further paediatric development of this product. At this stage of paediatric development, they do not fully determine the benefit: risk of delamanid in the paediatric population. Therefore, no update to the product information is required.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Not applicable.

4. Additional clarification requested

Not applicable.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non-clinical study

Product Name: Deltyba Active substance: Delamanid

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

Clinical studies

Product Name: Deltyba Active substance: Delamanid

Study title	Study number	Date of completion	Date of submission of final study report
Phase 1, 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	242-12-245 (PIP: Study 3 OTS-BIOE)	25 Oct 2014	02 Mar 2016
Phase 1, Open-Label, Multiple-Dose, Age De-escalation Trial to Assess the Pharmacokinetics, Safety and Tolerability of Delamanid (OPC 67683) in Paediatric Multidrug-Resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Anti-Tuberculosis Drugs.	242-12-232 (PIP: Study 4 OTS-PAED-TB)	28 Dec 2017	22 Jun 2018
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 Anti-tuberculosis Drugs over a 6-Month Treatment Period	242-12-233 (PIP: Study 5 OTS-PAED-TBEXTENSION)	30 Nov 2019	To be confirmed.