5 December 2013
EMA/55567/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Deltyba

International non-proprietary name: delamanid

Procedure No.: EMEA/H/C/002552

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

E	Adverse event
FB	Acid-fast bacilli
PTT	Activated partial thromboplastin time
UC	Area under the concentration-time curve
ID	Twice daily
DISC	Clinical Data Interchange Standards Consortium
FU	Colony forming units
HMP	Committee for Medicinal Products for Human Use
L	Total body clearance of drug from plasma
max	Maximum drug concentration
LT	Dose-limiting toxicity
M	Drug metabolite
OTS	Directly observed therapy, short course
SMB	Data safety monitoring board
ST	Drug susceptibility testing
	Ethambutol
BA	Early bactericidal activity
CG	Electrocardiogram
ID	Emerging infectious disease
MA	European Medicine Evaluation Agency
SR	Erythrocyte sedimentation rate
U	European Union
	Isoniazid
AART	Highly active antiretroviral treatment
IV	Human immunodeficiency virus
C_{50}	Concentration of drug producing 50% inhibition
C_{90}	Concentration of drug producing 90% inhibition
MP	Investigational medicinal product
IDR TB	Multi-drug-resistant tuberculosis
ledDRA	Medical Dictionary for Regulatory Activities
IGIT	Mycobacteria growth indicator tube (MGIT®)
IIC	Minimum inhibitory concentration
. tb	*Mycobacterium tuberculosis*
BR	Optimized background regimen
PDC	Otsuka Pharmaceutical Development & Commercialization
O	By mouth
K	Pharmacokinetics
Tc	Corrected QT interval
TcB	Individually corrected QT interval using Bazett's formula
TcF	Individually corrected QT interval using Fridericia's formula
TcI	Individually corrected QT interval
	Rifampicin (also known as rifampin)
	Streptomycin
AE	Serious adverse event
½	Half-life
½, z	Terminal-phase elimination half-life
nax	Time to maximum concentration
B	Tuberculosis
EAE	Treatment-emergent adverse event
ID	Three times daily
K	United Kingdom
S	United States
/HO	World Health Organization
	Pyrazinamide

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Otsuka Novel Products GmbH submitted on 25 November 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Delamanid, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 April 2011.

The applicant applied for the following indication: "Delamanid is indicated for the treatment of multidrug-resistant tuberculosis (MDR-TB) in combination with an optimised background regimen (OBR) according to WHO guidelines in adult patients.

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

(R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole (Delamanid) was designated as an orphan medicinal product EU/3/07/524 on 1 February 2008.

Delamanid was designated as an orphan medicinal product in the following indication: "Treatment of tuberculosis".

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Deltyba as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation

The legal basis for this application refers to:

New active substance (Article 8(3) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/275/11 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/275/11 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's requests for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claims:

- Delamanid falls within the category of "medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000
- Delamanid also falls within Article 2(1) of EC No 507/2006 "medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases"

The CHMP considered that the eligibility criteria for a conditional marketing as laid down in Article 2 of Regulation (EC) No 507/2006 were fulfilled.

New active Substance status

The applicant requested the active substance delamanid contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

Protocol Assistance

The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ian Hudson Co-Rapporteur: Walter Janssens

- The application was received by the EMA on 25 November 2011.
- The procedure started on 21 December 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 March 2012.
- During the meeting on 19 April 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 April 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 September 2012.
- The summary report of the GCP inspection carried out at the investigational sites 002 (Latvia) and 008 (Peru) between March and April 2012 was received on 7 June 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 November 2012.

- During the November 2012 PRAC meeting the RMP Advice and assessment overview was adopted on 28 November 2012.
- During the CHMP meeting on 13 December 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 February 2013.
- The Rapporteur's joint Assessment Report was circulated to all CHMP members on 26 February 2013.
- During a meeting of a SAG on 6 March 2013, experts were convened to address questions raised by the CHMP.
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of outstanding issues to be sent to the applicant.
- The Rapporteur's joint Assessment Report was circulated to all CHMP members on 4 April 2013.
- During the CHMP meeting on 23 April 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP and a 3rd List of outstanding issues was agreed by the CHMP on 25 April 2013.
- The Rapporteur's joint Assessment Report was circulated to all CHMP members on 11 July 2013.
- During the July 2013 PRAC meeting the RMP Advice and assessment overview was adopted on 11 July 2013.
- During the meeting on 25 July 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Delamanid.

1.3. Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Ondrej Šlanar

- The applicant submitted written notice to the EMA on 9 August 2013 to request a re-examination of Deltyba CHMP opinion of 25 July 2013.
- During its meeting on 19 September 2013, the CHMP appointed Daniela Melchiorri as Rapporteur and Ondrej Šlanar as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 27 September 2013 (Appendix 2 of Final Opinion). The re-examination procedure started on 29 September 2013.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 24 October 2013. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 27 October 2013.
- During a meeting of the Scientific Advisory Group (SAG) in Anti-infectives on 15 November 2013, experts were convened to consider the grounds for re-examination.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s detailed grounds for re-examination to all CHMP members on 18 November 2013.
- During the CHMP meeting on 18 November 2013, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.

- During the meeting on 21 November 2013, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation.
- The CHMP opinion, the CHMP assessment report and the translation timetable were re-adopted via written procedure on 5 December 2013.

2. Scientific discussion

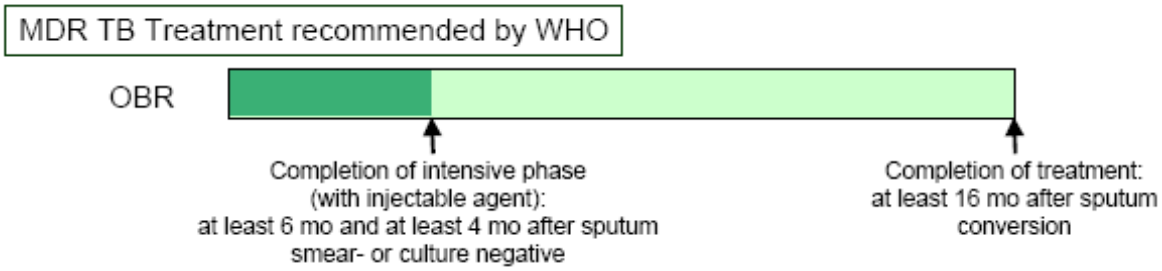
2.1. Introduction

Problem statement

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampicin. Approximately 500,000 cases of MDR-TB occur globally every year which corresponds to approximately 5% of the world's annual burden of tuberculosis. In Europe, Japan and the United States, MDR-TB is an orphan indication. Within the member states of the European Union, a total of 1715 laboratory-confirmed cases of MDR-TB were reported in 2007, including 300 in central European countries and 1415 in Eastern European countries with the largest burden in Romania (754 cases) and Lithuania (754 cases). In the United States there were 13,767 TB cases in 2006 but ~ 1% (< 150) cases were MDR-TB.

MDR-TB is associated with a considerable mortality rate and poses a significant public health threat. The mortality rate is more than 10% in national treatment programs and has been estimated to be as high as 32% worldwide. Individuals infected with drug-resistant strains who are unable to receive adequate treatment present a considerable public health risk and are capable of spreading primary MDR-TB infection.

The current treatment recommendations are based on direct susceptibility testing results to select active agents and on an overall regimen as shown in the diagram.



Nevertheless, the failure rate for MDR-TB treatment is high. In a recent meta-analysis of studies, which included 4959 patients with MDR-TB from 21 countries over a period of more than three decades, successful outcome (cure or completion of treatment) was reported for only 62% (range: 39-77%) of patients; an unsuccessful outcome was reported for 38% (range: 23-61%) of patients and death for 11% (range: 0-32%) of patients[1]. In a recent study in Latvia in which MDR-TB patients (N=167) were treated under WHO guidelines, 77% of subjects experienced a conversion of sputum culture (over a

[1] Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug resistant tuberculosis: a systemic review and meta-analysis. PLoS One.2009 Sep 9:4 (9):e6914

median duration of 60 days), 23% of patients remained sputum culture positive and 8% died[2]. Similar findings were reported from a study in Peru of 66 patients with MDR-TB who received second-line therapy as recommended by the WHO. Of these 66, 83% achieved probable cure and 8% died while receiving therapy[3].

The increasing global burden of MDR-TB and the public health risk have created an urgent need for anti-TB agents with novel modes of action and with activity against multiple drug-resistant strains of *M. tuberculosis*. Worldwide, MDR-TB has become a major barrier to achieving successful control of TB because therapy is less effective, associated with more adverse events and more costly and complex (e.g. takes much longer and involves injectable agents) compared with standard first-line therapy. The critical need in drug resistant TB is further amplified by reports of extensively drug-resistant TB (XDR-TB), which currently represents approximately 7-10% of MDR-TB isolates. In addition to rifampicin and isoniazid, XDR-TB strains are resistant to any fluoroquinolone and to at least one injectable second-line drug (capreomycin, kanamycin and amikacin) so that treatment options are very limited.

About the product

Delamanid (formerly OPC-67683) is a nitro-dihydro-imidazo-oxazole derivative that was discovered by Otsuka in a screen for inhibitors of mycolic acid biosynthesis. Delamanid is practically insoluble in aqueous solution of pH ≥ 4 but it is soluble to some extent in organic solvents and in aqueous solutions at lower pH.

The antibacterial activity of delamanid is specific for *Mycobacteria*. Against *M. tuberculosis* MIC values are typically in the range 0.006 to 0.012 µg/mL and there is no cross-resistance with any of the currently used anti-TB drugs. Delamanid has been developed solely for oral treatment of MDR-TB in conjunction with other active agents.

The (revised) proposed indication and posology from the applicant was as follows.

4.1 Therapeutic indications

{Delamanid Otsuka} is indicated for the treatment of pulmonary infections due to multidrug-resistant *Mycobacterium tuberculosis* as part of an appropriate combination regimen (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Delamanid should be administered by physicians experienced in the treatment of pulmonary tuberculosis.

Posology

The recommended daily dose for adults is 100 mg twice daily, taken with food, for 24 weeks.

Delamanid must always be administered as part of an appropriate combination regimen for the treatment of multidrug-resistant tuberculosis (MDR-TB) according to WHO guidelines (see sections 4.4 and 5.1).

Treatment with an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to WHO guidelines.

[2] Tymothy H. Holtz, Maya Sterberg, Steve Kammerer et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: Predictors and relationship to treatment outcome. Ann Intern Med 2006; 144: 650-659

[3] Mitnick C, Bayona j, Palacios E et al. Community-based therapy for multidrug resistant tuberculosis in Lima, Peru. N Engl J Med 2003; 348:119-128

Elderly patients (> 65 years of age)
No data are available in the elderly.

Renal impairment
No dose adjustment is considered necessary in patients with mild or moderate renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is considered necessary in patients with mild hepatic impairment. Delamanid is not recommended in patients with moderate to severe hepatic impairment (see sections 4.4 and 5.2).

Paediatric population
The safety and efficacy of delamanid in children and adolescents below 18 years has not yet been established. No data are available.

Method of administration
For oral use.
Delamanid should be taken with food.

The development programme / Compliance with CHMP Guidance / Scientific Advice

The applicant conducted a Phase 2 study in which delamanid (either 100 mg or 200 mg BID) was compared to placebo when each was added to optimized background regimen (OBR) over 8 weeks. After reaching week 8 (Day 56) subjects stopped delamanid/placebo and continued OBR with sampling to Day 84. Subjects were then invited to participate in an uncontrolled follow-on study in which they received delamanid 100 mg BID (with option to receive 200 mg BID after week 2) for a total of 26 weeks.

With regard to compliance with the TB guideline, the applicant approached clinical development along the lines suggested but only compared delamanid with placebo over 8 weeks.

There is an ongoing Phase 3 study 242-09-213 with an estimated date of submission in 2015. The study evaluates the efficacy of delamanid 100 mg twice daily (BID) for 2 months followed by 200 mg once daily (QD) for 4 months in combination with an optimized background regimen (OBR) versus placebo + OBR during the 6-month intensive phase of MDR TB treatment. This is a multicentre, randomized, double-blind, stratified, placebo-controlled study conducted globally in 2 parallel groups at approximately 15 sites qualified to treat MDR TB. In addition, a sub-study comprises HIV-positive patients on antiretrovirals (ARVs).

2.2. Quality aspects

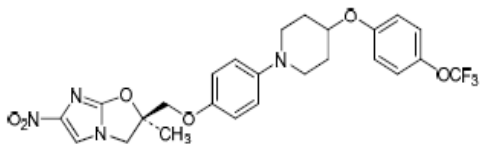
2.2.1. Introduction

The finished product is presented as a film-coated tablet containing 50 mg of delamanid as the active substance. Other ingredients are: hypromellose phthalate, povidone, all-rac-*α*-Tocopherol, microcrystalline cellulose, lactose monohydrate, sodium starch glycollate, carmellose calcium, colloidal hydrated silica, magnesium stearate and a film coating mixture (consisting of hypromellose, macrogol 8000, titanium dioxide, talc and iron oxide yellow).

The product is available in alu/alu blisters and amber glass bottles as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The chemical name (IUPAC) of delamanid is (2R)-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy] piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-b][1,3]oxazole and it has the following structural formula:



Delamanid consists of white to pale yellow crystals or crystalline powder. It is practically insoluble in water, slightly soluble in methanol, sparingly soluble in benzyl alcohol and acetonitrile, soluble in acetone, and freely soluble in tetrahydrofuran. It is not hygroscopic.

Having an asymmetric carbon at the C-2 position of the 2,3-dihydroimidazo[2,1-b]oxazole ring, it is an optically active compound; the R-enantiomer is used. The enantiomeric purity of delamanid is controlled routinely by chiral HPLC. No polymorphs or solvates have been found.

The chemical structure of delamanid has been verified using elemental and spectroscopic analysis (MS, UV, IR, 1H-NMR and 13C-NMR).

Information on the active substance was provided in an Active Substance Master File (ASMF).

Manufacture

The active substance is manufactured in three main steps, including final recrystallization. Well defined starting materials with acceptable specifications are used for the active substance synthesis. Critical process parameters have been defined. In-process controls are in place at all critical steps of the synthetic process. Specifications and control methods for starting materials, reagents and intermediate products have been presented.

During development the manufacturing process has been modified and optimised to improve quality of the active substance, increase yield and decrease environmental impact.

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the AMSF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance, identity (IR, UV), assay (HPLC), impurities (HPLC), optical purity (S-isomer; HPLC), loss on drying, residual solvents (GC), heavy metals, melting point and residue on ignition.

Each specification parameter was sufficiently justified. Analytical methods used have been adequately described and non-compendial methods appropriately validated.

Batch analysis data are provided for 32 batches produced with the proposed synthetic route four of them are of commercial size. The batch analysis data show that the active substance can be manufactured reproducibly. The results are within the specifications and consistent from batch to batch.

Sufficient information is provided on potential impurities and residual solvents. Levels of impurities found in the batches of the active substance are toxicologically justified and well below specification limits. One genotoxic impurity, which is a reagent in the synthesis, is specified in the active substance. The limit was established based on the Threshold of Toxicological Concern (TTC). Batch results are consistently below detection limit; therefore, skip testing for this impurity is considered acceptable.

Stability

Three pilot scale batches of the active substance packed in double LDPE bags and fibre drums were put on stability testing as per ICH conditions: under long term conditions (30°C/65%RH) for up to 36 months and accelerated (40°C/75%RH) for 6 months. The stability data show no apparent degradation and very little variability.

All the results conformed to the specifications for all parameters tested (appearance, identification, optical rotation, melting point, impurities, optical purity, loss on drying and assay). The analytical methods were the same as for release and were stability indicating.

Photostability testing following the ICH guideline Q1B was performed on 1 batch and confirmed that delamanid is not light sensitive.

No changes in the tested parameters were observed for delamanid stored under stressed conditions at 50°C (closed amber glass bottle), 25°C/90% RH (open glass bottle) and 40°C/75% RH (open glass bottle) for 3 months.

The stability results indicate that the drug substance manufacturer by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Delamanid is practically insoluble in water and its solubility increases only slightly under a lower pH (under 4). Therefore, a complex approach to this oral solid dosage form development was necessary.

From early development stages, formulation development was focused on dissolution enhancement. Several approaches were investigated; finally a technology showing higher solubility and higher bioavailability compared to tablets produced with active substance in crystal form was selected. Delamanid 50 mg tablets with this powder blend have been used throughout the clinical studies since the latter stage of phase I studies. The clinical and intended commercial tablets are exactly the same formula.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards and/or EC directive. 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 drug substance has been established during preliminary stability studies.

A Quality by Design (QbD) approach was applied during development, a risk analysis was conducted to identify the critical points in the manufacturing process and to establish a proven acceptable range (PAR) for each process parameter.

Critical quality attributes (CQA) were identified for the product, based on the quality target product profile (QTTP). The process parameters in the selected process have been investigated and optimized based on the design of experiments (DoE) result targeting the crystallinity as one of the proposed CQAs.

Critical parameters to the performance of the product are controlled by a dissolution method which was proved to be of sufficient discriminatory power. The manufacturing process for the powder blend is considered a key process as the dissolution performance of delamanid tablets is highly dependent on the powder blend characteristics. To establish proven acceptable ranges (PARs) for this process, a two-tier DoE with factorial design was performed to evaluate the influence of several process variables on CQAs. Cross interaction evaluation indicated that none of the combinations impacted the CQA significantly. In a second step the DoE was repeated with three of the dominating process variables in order to confirm the acceptable operating range around a centre point. Appropriate in-process controls have been put in place.

PARs which will be applied in routine production were defined and confirmed for other processes.

For the compression step, a design of experiments was set up and the results indicated the critical parameter with respect to the CQAs. A statistical evaluation is performed to identify the design space and PAR for the critical parameter with respect to the CQAs and a PAR was established which is narrower than the design space.

The film coating process was successfully scaled up and optimised. From a quality point of view, this step was deemed as low risk and not further investigated during manufacturing process development.

A discussion was provided on the impact of the batch size on the different manufacturing steps in order to identify the up- or downscaling strategy in the future.

The finished product contains hypromellose phthalate (HPMCP) as a component of the tablet formulation. There are two potentially toxic substances which may be derived from HPMCP. Sufficient toxicology and batch analysis data those substances were submitted and strict limits were introduced in the finished product specification. As the amounts in the batch analysis were well below the established limits, the presence of hypromellose phthalate in the finished product is considered acceptable.

The primary packaging is an aluminium/aluminium blister or an amber glass bottle (type III) with polypropylene child resistant closure, polyester insert and desiccant canister(s). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

Lactose monohydrate, used as an excipient, is the only material of animal origin which is used in the product. Appropriate declaration confirming compliance with the TSE guideline has been provided by the lactose manufacturer. Lactose is produced from milk obtained from healthy animals under the same conditions as milk intended for human consumption and that it has been prepared without the use of ruminant material other than calf rennet in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agent Via Human and veterinary medicinal products.

Magnesium stearate is of vegetable origin.

Manufacture of the product

The manufacturing process is divided into 4 main steps: preparation of powder blend, blending, compression, film coating.

The active substance is dispersed in polymer matrix, which is an intermediate in the finished product manufacturing process.

For the tablet manufacture, tablets are prepared using the powder blend and are mixed with the remaining excipients, in the last manufacturing step, the tablets are film-coated.

Critical steps of the manufacturing process were identified. Based on the critical quality attributes (CQAs) identified for the product, process parameters for the critical steps were evaluated and the proven acceptable ranges (PARs) were established during the development. The proposed CQAs have been incorporated either in the in-process control or the QC release testing. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs. The manufacturing process both for the intermediate and for bulk film-coated tablets is validated with three consecutive batches of commercial scale. Validation data demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form. The product is tested for appearance, identification of delamanid and tocopherol (HPLC), identification of iron oxide yellow (Ph.Eur.), impurities (HPLC), assay of delamanid (HPLC), assay of tocopherol (HPLC), uniformity of dosage units (HPLC), two specific phthalates-related substances (HPLC), dissolution and microbial purity.

The acceptance criteria for all specification parameters are justified by batch results and comply with relevant CHMP/ICH guidelines. The degradation products are discussed and specified in the finished product as appropriate.

All test methods for the finished product control are sufficiently described and appropriately validated.

Batch analysis results were provided for 3 batches of production scale. Results of clinical batches, manufactured at pilot or smaller scale, are provided as supportive data. All results comply with specifications.

Stability of the product

Stability studies were conducted on 3 production-scale batches of tablets packaged in the commercial package, glass bottles and aluminum/aluminum foil blisters. The long-term stability study is on-going (25°C/60%RH) and 24 months data are provided; results of completed accelerated studies (40°C/75%RH, 6 months) are available in the dossier.

Stability studies were also conducted on production-scale batches of bulk tablets packaged in double polyethylene bags/aluminum bag. Additionally, stability study was conducted on delamanid powder blend intermediate.

In addition, photostability testing was conducted with one batch of exposed delamanid tablets and freeze-thaw cycling studies were completed with tablets packaged in aluminium/aluminium blister packs, glass bottles and bulk packaging. The photostability results show no signs of photodegradation; freeze-thaw samples show no degradation or trends in any of the tested parameters.

The parameters tested include description, identification, impurities/degradation products, dissolution, delamanid assay, tocopherol assay and microbial testing (long-term testing only). For information purpose, additional testing is performed for water content, disintegration, hardness, crystallinity and optical purity. These tests will not be repeated in post-approval stability studies.

The stability samples were tested using the same analytical methods as for release; the methods are stability indicating.

Overall, no significant changes were observed in any studies throughout the period tested to date. The overall stability results obtained are similar between the different packaging materials.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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 the clinic.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However no design space was claimed for the manufacturing process of the finished product.

The use of HPMCP as a component of the tablet formulation has been justified and the proposed control strategy for the specific phthalates-related substances is acceptable and justified from toxicological point of view.

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.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP

The pivotal toxicology and the majority of the safety pharmacology studies conducted by the applicant were reported to be GLP compliant. The safety studies that were not conducted to GLP were conducted to an appropriate scientific standard.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacological mode of action of delamanid involves inhibition of the synthesis of the mycobacterial cell wall components, methoxy-mycolic and keto-mycolic acid. This is observed at lower IC_{50} values than that of isoniazid (INH). However, unlike INH, delamanid does not inhibit α-mycolic acid biosynthesis. The mode of action has been investigated in *M. bovis* BCG only. The genome sequence of *M. bovis* is > 99.95% identical to that of *M. tuberculosis.* Moreover, delamanid shows the same level of activity against *M. tuberculosis* and the other sub-species of the *M. tuberculosis* complex including *M. bovis* BCG. Taken together these data suggest that the mechanism of action in *M. bovis* and *M. tuberculosis* should be identical. The precise mechanism of action is unknown; however, there is evidence to suggest that delamanid requires metabolic activation by *M. bovis* BCG in order for the anti-TB activity to be exerted and that this activation is possibly mediated via the deazaflavin-dependent nitroreductase (Rv3547) and F420 coenzyme system.

M. tuberculosis is genetically diverse and different strain lineages of *M. tuberculosis* are associated with different geographic regions. Phenotypic differences between clinical isolates exist. In the *in vitro* studies a broad range of strains were investigated and the choice of the strains requires further justification in terms of the relevance to the European region. Delamanid is highly active against both sensitive and resistant strains of *M. tuberculosis*, with MIC values of 0.006 to 0.012 µg/mL compared to 0.05 to > 100 µg/mL observed for reference compounds. Delamanid is active against hypoxic-induced dormant *M bovis* BCG assessed using an anaerobic culture system. Delamanid exhibited dose-dependent bactericidal activity at concentrations ≥ 0.4 µg/mL. In contrast, INH had no effect on hypoxic-induced dormant *M bovis* BCG at concentrations up to 10 µg/mL. Elimination of dormant bacilli which may serve as a reservoir is important in reducing the duration of the treatment time. Delamanid is active against intracellular *M tuberculosis* and *M bovis* BCG, which is of importance since *M. tuberculosis* can survive as an intracellular pathogen in host macrophages, leading to prolonged or recurrent infections.

The 8 identified delamanid metabolites show a poor anti-mycobacterial effect (MIC > 6.25 µg/ml) when compared to delamanid (MIC 0.006-0.012 µg/ml) against 10 *M. tuberculosis strains*. The 3 delamanid metabolites (R)-DM-6701, (R)-DM-6702 and (R)-DM-6703 showed poor activity against standard anaerobic and aerobic strains, although more than delamanid itself.

The *in vitro* frequency of spontaneous resistance to delamanid is high and is almost equal to those for reference compounds, INH and PA-824. Values for moxifloxacin and rifampicin were substantially lower. Comparison to other agents has not been included. Mutation in one of the five coenzyme F420 genes fgd, Rv3547, fbiA, fbiB, fbiC is suggested as the mechanism for resistance against delamanid. These

seem to be the same enzymes and co-factors as suggested to be responsible for the activation of delamanid. Since these enzymes and co-factors are seemingly non-essential *in vitro*, as a result, a variety of mutations can give rise to resistance.

In vivo efficacy of delamanid has been investigated in animal models through investigation of lung, spleen and liver colony-forming unit counts.

- In mice significant decreases in pulmonary viable bacteria count vs. vehicle control were observed with delamanid ≥ 0.313 mg/kg/day ($p < 0.01$). Using regression analysis, the effective dose of delamanid (corresponding to the therapeutic dose of rifampicin 3.5 mg/kg/day) was 0.52 mg/kg/day.
- In immunodeficient BALB/c nude or immunocompetent BALB/c mice delamanid showed significant dose-dependent activity at ≥ 0.625 mg/kg/day, measured as reduction of viable bacteria count in lung, liver and spleen. Some activity was observed in both studies at 0.313 mg/kg/day. No clear distinction was seen between normal and nude mice.
- In a mouse model of TB using *M. tuberculosis* MDR strains the survival time during an 8-month period following treatment was superior in delamanid-treated mice vs. reference compounds.
- Studies in guinea pigs also supported in-vivo activity of delamanid.

  It is concluded that studies in mice suggest that once or twice daily treatment with delamanid provides comparable exposures (AUC) and demonstrates comparable efficacy. There was no difference in delamanid activity in normal and immunodeficient mice and delamanid was effective against infection with either MDR-TB or drug-susceptible strains. In a mouse model, early bactericidal activity (EBA) values for delamanid were similar to those for INH and more potent than EBA values for rifampicin.

Secondary pharmacodynamic studies

At the end of the evaluation procedure, the applicant provided a secondary pharmacology study, conducted according to the request of the Agency. The effects of delamanid on a series of receptors, enzymes and ion channels will however be further assessed in post-authorisation phase.

Safety pharmacology programme

A series of safety pharmacology studies have been provided which evaluate the effects of delamanid and its metabolites on the central nervous, cardiovascular, respiratory and renal systems.

No treatment related effects on the central nervous system were noted at plasma levels that were ~18.5-fold higher than that proposed clinically (following 100 mg BID). In addition, no treatment-related effects on respiratory rate were observed at exposures that were 3.2-fold higher than the maximum proposed C_{max} in humans.

During a series of safety pharmacology studies performed to investigate the effects on the cardiovascular system, some degree of hERG channel inhibition was observed with delamanid (35.4% at 1.6 µg/mL); no effect on action potential duration was observed during a guinea pig papillary muscle assay (at up to 1.6 µg/mL) and delamanid had no effect on QT interval *in vivo* following single oral administration in the dog, where plasma levels of delamanid were ≤3.2-fold higher than those observed in man. However, QT/QTc prolongation was observed following repeated administration in the dog and in man.

The applicant has suggested that the observed QT prolongation *in vivo* might be due to metabolites of delamanid as the exposures to the plasma metabolites were higher upon repeated administration. The

effects of the human metabolites (R)-DM 6701 (=DM-6704), (R)-DM-6702 (=DM-6705), (R)-DM-6703 (=DM-6706), (S)-DM-6717, (S)-DM-6718, (4RS, 5S)-DM-6720, (4R, 5S)-DM-6721, and (4S, 5S)-DM-6722 were investigated in subsequent studies using HEK-293 or CHO-K1 cells stably expressing the hERG channel. Inhibition of the hERG channel current was observed with (R)-DM 6701 (≥0.5 µg/mL), (R)-DM-6702 (≥ 0.15 µg/mL) and (4RS, 5S)-DM-6720 (0.5 µg/mL) and the most pronounced effects on hERG channel inhibition were observed with the predominant metabolite (R)-DM-6702 (IC_{50} 0.04 µg/mL).

Although delamanid and the metabolites (R)-DM-6701, (R)-DM-6702 and (4RS, 5S) DM 6720 could collectively contribute to the observed QT prolongation *in vivo*; given the time course and the exposures of the metabolites in man, it is likely that the (R)-DM-6702 (DM-6705) is a significant contributor to the observed effect.

Pharmacodynamic drug interactions

For a description of pharmacodynamic drug interactions, refer to the "clinical aspects" section of this report.

2.3.3. Pharmacokinetics

A series of method validation, absorption, distribution, metabolism, excretion and pharmacokinetic drug interaction studies have been conducted. With the exception of the pharmacokinetic drug interaction studies, the package is considered to be adequate.

In fed animals, the absolute oral bioavailability for the jet milled formulation was estimated to be 42.2%, 34.9% and 61.3% in the mouse, rat and dog, respectively. C_{max} and AUC for delamanid generally increased in a less than dose proportional manner and there was some evidence of accumulation on repeated-dosing in the rat and dog. In the dog, food intake caused an appreciable increase in the systemic exposures following oral administration of delamanid. However the "food effect" was less pronounced with the solid dispersion formulation and therefore supports the selection of this formulation for use in humans.

In vitro protein binding of delamanid and the metabolites (R)-DM-6701, (R)-DM-6702, and (R)-DM-6703 to mouse, rat, rabbit, dog, and human sera was high (≥ 97.4%). Distribution of delamanid and/or its metabolites into the lung was observed in both the mouse and the rat. In the rat, following oral administration of radiolabeled-delamanid, drug-related radioactivity was widely distributed and the highest tissue:plasma ratio was observed in the liver and the adrenal gland, which correlates with the route of elimination and/or the target organ toxicity observed. The radioactivity retention in the eyes of pigmented rats was longer than that observed in non-pigmented animals, which suggests an association of delamanid and/or its metabolites with melanin. Following repeated dosing for 21 days, accumulation of drug-related material was observed and the ratio of radioactivity in the tissues on Day 21 to that observed on Day 1 was highest in the testis.

Following single oral administration of ^{14}C-delamanid to pregnant rats, delamanid-related radioactivity crosses the placenta in rats, whereby the concentrations of radioactivity in fetal tissues were greater than or equal to those observed in maternal blood at ≥24 hours post-dose. The fetus:plasma ratios were >1 at 48 and 72 hours post-dose.

There is some evidence of accumulation of radioactivity within the amniotic fluid and the fetus over time and this most likely contributes to the reproductive toxicity observed in the rat. Drug-related material

also distributed into the milk of lactating rats; hence, breast-feeding should be discontinued upon treatment with delamanid.

Overall, the transformation of delamanid is thought to be mediated primarily by plasma albumin and to a lesser extent, the enzymes CYP3A4, CYP1A1, CYP2D6 and CYP2E1. There is evidence to suggest that the proposed mechanism for the metabolism of delamanid to DM-6705 involves a reaction between the amino groups in albumin and the 5-C of the 6-nitro-2,3-dihydroimidazo [2,1-b] oxazole moiety of delamanid.

Following single and repeated oral administration to the mouse, rat, rabbit and dog, the plasma levels of the metabolites were consistently lower than that of the parent, with the exception of the metabolite DM-6717 in rabbit plasma. Delamanid and (R)-DM-6702 were identified as the predominant analytes in the mouse, rat and dog (plasma, tissues, urine and/or feces). In the mouse, rat, rabbit and dog, the enantiomeric ratio of delamanid [and the metabolites (R)-DM-6701, (R)-DM-6702 and (R)-DM-6703] was ≥ 99.8% as the R-enantiomer, suggesting that there was no enantiomeric conversion. The metabolites identified following the administration of delamanid (100 or 200 mg BID) in man [(R)-DM-6701, (R)-DM-6702, (R)-DM-6703, DM-6717, DM-6718, DM6720, DM-6721, DM-6722] have all been identified in at least one or more of the species evaluated.

The question though as to whether all human metabolites have been adequately assessed from a toxicological perspective remains unanswered. Hence, this necessitates a new mass balance study to investigate and profile potential reactive metabolites.

The potential for pharmacokinetic drug interactions at the level of P-glycoprotein (P-gp) have been evaluated. *In vitro*, delamanid at 5 µM was not a substrate or an inhibitor for P-gp mediated transport and it is noted that the concentration of delamanid was approximately 15-fold lower than the estimated concentration of 74.8 µM in the intestinal lumen (following administration of 100 mg). Hence, an effect at the level of gut cannot be ruled out. Additional studies to evaluate the effects of delamanid and (R)-DM-6702 at a series of transporter systems were conducted. The results of these in vitro transporter-based studies will be further scrutinised in post-authorisation phase.. The results provided thus far suggest that at the concentrations tested (3 to 10µM), the potential for delamanid and (R)-DM-6702 to inhibit BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, OCT1 and BSEP is low.

Overall, the potential for delamanid to cause pharmacokinetic interactions via inhibition or induction of the CYP enzymes investigated thus far is considered to be low. In accordance with the Guideline on Drug Interactions, the potential to induce CYP2B6 will also be evaluated. Factors that might potentially affect metabolism by plasma albumin (which could in turn increase the levels of delamanid and thus increase the risk of CYP inhibition or transporter-mediated drug-drug interactions) have not yet been identified. However, no clinically relevant changes in the plasma concentrations of delamanid and DM-6705 occurred in MDR-TB patients with hypoalbuminaemia when compared to those with albumin levels within the normal range.

A drug-drug interaction study with Rifater, which contained rifampin, an inducer of CYP3A4, indicated that the concentrations of delamanid decreased by about 50%; hence there is a need to prohibit co-administration of delamanid with strong inducers of CYP3A4 (contra-indication added to Section 4.3 of the SmPC).

2.3.4. Toxicology

Single and repeat dose toxicity

The applicant has presented a series of single and repeated-dose studies in the rat, rabbit and dog whereby delamanid was administered via the oral route for up to 39 weeks. The studies performed are considered appropriate for the proposed clinical duration of 6 months. The systemic exposures for delamanid at the no-effect levels from the 26-week rat study are 4.3 to 16.7-fold higher than the proposed clinical C_{max} which is acceptable. The exposure margins (C_{max} and AUC) based on the no-effect levels from studies in the dog ranged from 0.48 to 1. It is evident that the no-effect levels for the pivotal toxicity studies in the dog were primarily based upon the QT prolongation observed. QT prolongation has been reported in man and some precautions have been included in the SmPC.

In the rat, alterations in red blood cell parameters (decreased hematocrit and red blood cell count and increased reticulocyte ratio) were observed at exposures in excess of those proposed clinically. Interestingly, abnormal values for hematocrit, hemoglobin and red blood cell count were observed during the clinical studies; however, the observed changes from baseline were generally comparable between treatment groups.

In vivo studies demonstrated a pronounced inhibitory effect of delamanid on blood coagulation, whereby parameters such as PT and APTT were prolonged (mouse, rat, rabbit, but no effects reported in the dog) and the plasma levels of several clotting factors, including factors, II, VII, IX and X, were reduced following administration of delamanid (rabbit). Although measurements did not show a profound impact of delamanid on endogenous vitamin K levels, these studies demonstrated that supplementation with vitamin K_1 could counteract inhibitory effects on coagulation following delamanid administration. An *in vitro* study conducted with rabbit liver microsomes demonstrated significant inhibition of vitamin K_1 epoxide reductase, a model of endogenous vitamin K_1 formation, by delamanid metabolite DM-6717. The data presented thus far therefore suggest that the metabolite DM-6717 has a key role in the interference with vitamin K-dependent coagulation and it is important to note that the exposures to DM-6717 observed at the effective doses were substantially higher than that observed in man. The role of other metabolites of delamanid in these processes has not been entirely elucidated. Although a definitive effect on clotting has not been reported in man, these findings have been summarised in Section 5.3 of the proposed SmPC.

In the dog, histopathological findings were noted in the liver at ≥ proposed clinical exposures and these findings were not associated with any signs of necrosis. There is clinical evidence to suggest that treatment with delamanid may occasionally cause hepatic damage. Hence, liver disorders have been included as an important potential risk in the risk management plan. In the same species, foamy macrophages were observed in the lymphoid follicles of various organs during the definitive 13-week and the 39-week studies. The incidence and/or degree increased in a dose dependent manner, the finding was shown to be partially reversible and the clinical relevance of these findings is unknown. These findings have been included within section 5.3 of the proposed SmPC.

Genotoxicity

The applicant has conducted a series of *in vitro* and *in vivo* genotoxicity studies with delamanid and the metabolites (R)-DM-6701, (R)-DM-6702, (R)-DM-6703 and DM-6718. Delamanid and its metabolites were non-mutagenic and the data therefore suggest that administration of delamanid will not pose a genotoxic risk to humans. Moreover, in the mouse and rat, repeated oral administration of delamanid for up to 104 weeks did not appear to be carcinogenic.

Carcinogenicity

In the mouse and rat, repeated oral administration of delamanid for up to 104 weeks did not appear to be carcinogenic.

Examination of the rat carcinogenicity study and some of the non-pivotal studies conducted in the rat, rabbit and dog revealed histopathological changes in the adrenal tissues (such as cortical cell hypertrophy, swelling and necrosis of the zona glomerulosa and focal infiltration of the mononuclear cells). These findings occurred at exposures in excess of those proposed clinically and were not observed during the pivotal repeat-dose studies. Moreover, any observed change in adrenocortical function in man (elevation of cortisol levels) was associated with tuberculosis disease and not with delamanid therapy. Hence the observed findings within the adrenal tissues were not considered to be clinically relevant.

Reproduction Toxicity

The applicant conducted a series of reproductive toxicity studies in the rat and rabbit to evaluate the effects of delamanid on fertility and embryofetal development. Delamanid had no effect on male or female fertility (rat) at up to 300 mg/kg/day. In the rat, delamanid was not teratogenic at exposures (AUC) that were ~16.7-fold higher than those proposed clinically.

Embryofetal development studies were also performed with metabolites (R)-DM-6702 and (S)-DM-6718 on the basis that these metabolites represented >20% of drug-related exposure. Following repeated administration of the metabolite (R)-DM-6702, fetal anomalies (oedema) and variations including (thymic remnant in the neck and bipartite ossification of the thoracic vertebral body) were noted at exposures that were 3.6 fold higher than proposed clinically. Following repeated administration with (S)-DM-6718, general oedema of the fetus was noted at exposures that were similar to that proposed in man. In the rabbit, delamanid was not teratogenic at the doses evaluated; however, a slight increase in the incidence of resorptions was noted at 10 mg/kg/day. Although it is feasible that the observed finding may be due to the observed toxicity in the dam (reduced body weight gain), the NOAEL for the effects on the dam and for maintenance of pregnancy is considered to be 5 mg/kg/day. The package of reproductive toxicology studies has addressed all of the identified disproportionate metabolites to date. However, the applicant should consider the impact of any significant unidentified human metabolites on the ability to predict the potential to cause reproductive toxicity.

Local Tolerance

Delamanid did not appear to have any ocular irritant effects and was a non-irritant to skin in New Zealand White rabbits

Other toxicity studies

Data from the whole tissue distribution studies indicate drug-related material is retained within the pigmented eye and that delamanid binds to melanin. There were no clear ophthalmic findings in the repeated dose studies apart from some sporadic occurrences of retinal rosettes at exposures that were 16.7-fold higher than that proposed clinically (pivotal 4 week rat study only). It is noted that these

findings were not observed in the definitive 26-week rat study, or in the repeated-dose studies in the dog. Moreover, the applicant has provided *in vitro* data which demonstrate that delamanid is not phototoxic at concentrations that are well in excess of those proposed clinically (0.41 µg/mL). Taken together the data suggest that proposed dose of delamanid does not pose a risk of phototoxicity.

The Safety Working Party (SWP) has recently considered the issue of phthalates in medicinal products. In order to address concerns with respect to the lack of data concerning the toxicity (particularly the genotoxicity and the reproductive toxicity) of hypromellose phthalate (HPMCP), the applicant has supplied data to demonstrate that the proposed dose of the excipient, hypromellose phthalate (HPMCP) does not pose a safety risk to man. The applicant provided data where HPMCP was administered as the placebo control. Repeated dose studies in the mouse (up to 100 weeks), rat (26-week) and dog (39-week) demonstrated no test-article (HPMPC) related effects at corresponding human equivalent doses (HEDs) of~6, 12 and 4-fold higher. Older studies in the published domain (Kitagawa *et al.,* 1973) have identified 6000 mg/kg/day as the NOAEL for HPMCP in the rat following repeated administration for six months. Based on the results from a bacterial reverse mutation test and a bone marrow micronucleus test and an in vivo/in vitro unscheduled DNA synthesis (USD) test in rat hepatocytes, the applicant considered HPMCP not to be genotoxic. Further data have meanwhile become available, based on a study conducted according to ICH S2 (R1) Guideline (data to be assessed in post-authorisation phase).

The applicant has provided data to demonstrate that HPMCP should not have an effect on fertility and early embryonic development. In addition, data from the literature (published in 1972) have shown that sternal deformities occurred in animals treated with HPMCP during embryofetal development studies in the mouse and rat. Similar findings were noted in controls at a slightly lower incidence which made the data difficult to interpret. Moreover, close examination of the publication revealed that in the rat, there was an increase in the incidence of a supernumerary rib and this appeared to be significant at 20 and 200 mg/kg/day. However, it was demonstrated that HPMCP had no effect on the parameters evaluated during the embryofetal development studies conducted in the rat and the rabbit (when compared to that observed with historical controls). The doses of HPMCP evaluated in the rat (900 mg/kg) were substantially higher than that proposed clinical dose; hence, the proposed levels of HPMCP are considered to be qualified from a reproductive toxicity point of view.

In view of the content of HPMCP in Delamanid tablets as well as the use of process solvent during the manufacturing process the applicant was asked to discuss the potential for formation of specific phthalates asimpurities, and ensure that the amounts within the final product have been adequately qualified. The applicant has evaluated the content of the specific phthalate impurities within the proposed medicinal product. The applicant has confirmed that one specific impurity was not detected within the medicinal product (on release or during the stability studies).

The applicant has analysed samples of placebo used for the definitive toxicity studies (such as the 26-week rat study, the 39-week dog study and the early embryonic development study), where no toxicity findings were observed. The corresponding human equivalent doses for the rat and dog are 2 and 6-fold higher than the maximum proposed dose of one of the impurities. The applicant has also presented some of the control data from the genotoxicity and reproductive toxicity studies conducted and the results provided suggest that the proposed dose of the impurity does not pose a risk to humans.

It is evident that the level of the specific impurity in the drug product is fairly low and is lower than the doses shown to have no potential to cause general toxicity, genotoxicity or reproductive toxicity in the non-clinical species evaluated. In addition a second potential impurity is not detected. The applicant has agreed to implement limits for these specific phthalates as requested.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1: Summary of main study results

Substance (INN / Invented Name): OPC-67683					
2.3.5.1.1. CAS-number (if available): 681492-22-8					
PBT screening		2.3.5.1.2. Result			2.3.5.1.3. **Conclusion**
2.3.5.1.4. *Bioaccumulation potential*- log K_{ow}	OECD 117	3.69			Not a potential PBT
PBT-assessment					
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default	4.0	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Water solubility	OECD 105	<0.017 mg/L			Very low water solubility
Adsorption-Desorption	OECD 106	K_{oc} for sludges = 1927 - 2371 L/kg K_d for sludges = 676 - 770 L/kg			K_{oc} > 10000 L/kg threshold (N) K_d > 3700 L/kg threshold (N)
Ready Biodegradability Test	OECD 301B	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	River: $DT_{50,\ water}$ = 1.9 days $DT_{50,\ whole\ system}$ = 5.2 days % shifting to sediment = 44.7 (d0) to 12.9 (d14) Pond: $DT_{50,\ water}$ = 1.5 days $DT_{50,\ whole\ system}$ = 5.3 days % shifting to sediment = 37.1 (d0) to 8.9 (d14)			Sediment toxicity study triggered. No metabolite shifting >10% to the sediment
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
2.3.5.1.5. Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	⩾0.3 (green algae) ⩾0.42 (cyano bacteria)	µg/L µg/L	*Pseudo-kirchneriella subcapitata* *Anabaena flos-aquae*
Daphnia sp. Reproduction Test	OECD 211	NOEC	⩾0.59	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	⩾0.71	µg/L	*Brachydanio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC15	⩾1000	mg/L	Limit test
Phase IIb Studies					

Bioaccumulation	OECD 305	BCF	565	L/kg	%lipids: 2.4% BCF lipids= 24,431
Sediment dwelling organism	OECD 218	NOEC measured NOEC standard sediment (corrected for carbon content)	⩾100 ⩾417	mg/kg	*Chironomus riparius*

The log K_{ow} for delamanid exceeds 3, this indicates a capacity for bioaccumulation and a bioaccumulation study was performed in Phase II Tier B. The PEC $_{surfacewater}$ value (4.0 µg/L) was above the action limit of 0.01 µg/L, therefore, a Phase II environmental fate and effect analysis was performed.

Delamanid is not readily biodegradable and has no significant adverse effects on aquatic organisms up to and even slightly above the limit of water solubility.

An aerobic transformation study in aquatic sediment systems was performed. Dissipation of delamanid from the water phases was rapid, due to degradation and adsorption to the sediment layer. Over 10% of delamanid shifted to sediment, which triggered the requirement for a sediment toxicity study. All metabolites detected in the sediment remained below 4.9% of the applied radioactivity. DT_{90} values were in excess of 3 days.

It is evident that the maximum concentrations of delamanid evaluated during the aquatic studies were limited by the very low solubility of the compound, which resulted in PEC:PNEC ratios that were artificially high. However, it is agreed that the risk to the aquatic compartment is likely to be low and no additional studies are required.

The sediment toxicity study was conducted in accordance to OECD 218. No toxicity was observed and a NOEC of ≥ 100 mg/kg dry sediment was established. In accordance with the Questions and answers document on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010) the results from the toxicity tests should have been recalculated into standard sediment with an organic carbon content of 10%, according to the following equation:

$$NOEC_{\text{standard sediment}} = NOEC_{\text{measured}} \times \frac{f_{\text{OC, standard sediment}}}{f_{\text{OC, measured}}}$$

The artificial sediment used in the toxicity study has an organic carbon content of 2.4%. The NOEC standard sediment is thus ≥ 417mg/kg. The PEC sediment should also have been corrected for carbon content. However, in any case the PEC:PNEC ratio does not indicate any risk to sediment organisms.

A bioaccumulation study was performed according to OECD 305. Only one concentration could be tested due to its very low solubility, which is considered acceptable. The bioconcentration potential of delamanid is considered to be low. In conclusion, the applicant has conducted a series of studies to investigate the potential for ecotoxicity. Although some of the studies performed in order to evaluate the effects on the aquatic systems were limited by the solubility of delamanid, the data presented suggest that delamanid will not constitute a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The non-clinical data reveal no specific hazard for humans based on conventional studies for genotoxicity and carcinogenic potential, but in rabbit reproductive studies, embryofetal toxicity was observed at maternally toxic dosages. Delamanid /metabolites have shown to be excreted into breast milk.

The metabolic profile observed in animals was qualitatively similar across the evaluated non-clinical species. It was also clarified that the human metabolites identified to date have been sufficiently evaluated during the toxicology studies. Nevertheless, there are remaining uncertainties regarding the metabolites profile in humans, as the anomaly of the results of the mass balance study in humans has not been adequately addressed.

Delamanid and/or its metabolites have the potential to affect cardiac repolarisation via blockade of hERG potassium channels. Also, repeat-dose toxicity studies in rabbits revealed an inhibitory effect of delamanid and/or its metabolites on vitamin K-dependent blood clotting.

Prior to opinion, the applicant provided results from a secondary pharmacovigilance study to evaluate whether delamanid and /or its metabolites have any clinically relevant effects on secondary targets. These results will be assessed following marketing authorisation. Finally, the applicant considered hypromellose phthalate not to be genotoxic. However, in accordance with ICH S2(R1) Guideline, an additional study will be submitted.

In this context, at the end of the evaluation phase, an additional study was submitted in accordance with ICH-S2(R1) Guideline . Results from this study will be assessed during post-authorisation.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical profile of delamanid has been sufficiently characterised. Nevertheless, some data remain outstanding. As such, the CHMP considers the following measures to address the non-clinical issues:

- On the basis of the outcome of a new mass balance study, additional non-clinical studies in appropriate animal models may need to be conducted if disproportional metabolites are identified.
- Additional data are necessary to investigate the following:
    - The potential for delamanid to interact with secondary pharmacological targets
    - The potential for delamanid and its principal metabolite to act as substrates for a series of transporters
    - The potential for delamanid to induce CYP2B6
    - The potential for the excipient HPMCP to cause genotoxicity using with the aid of an *in vitro*/*in vivo* rat liver unscheduled DNA synthesis (UDS) study

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. A routine GCP inspection for trial 242-07-204 was carried out during the marketing authorisation application

procedure. No specific concerns, invalidating this study, were identified.

The applicant 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**

Trial/[Ref.]	Type of Trial	Dosage Regime	Number of Treated Subjects	Subjects
Phase 1 Trials - *Spray dried tablets (SD)*				
242-06-001 Module 5.3.3.1	Multiple dose dose escalation	100, 200, 400 mg single dose; 10 days multiple dosing	24 (18 delamanid, 6 placebo)	Healthy subjects
242-05-001 Module 5.3.3.1	Single dose dose escalation	50, 100, 200, 400 mg single dose	56 (42 delamanid, 14 placebo)	Healthy subjects
242-05-101 Module 5.3.3.1	Multiple dose, dose escalatioin	100, 200, 400 mg single dose; 200, 400 mg 10 days multiple dose	104 (78 delamanid, 26 placebo)	Healthy subjects
242-06-202 Module 5.3.3.4	Drug interaction (ethambutol and Rifater)	200 mg, 15 days multiple dose	55 (36 delamanid, 19 placebo)	Healthy subjects
242-07-209 Module 5.3.3.4	Drug interaction (tenofovir, efavirenz, and ritonavir/ loprinavir)	100 mg BID, 14 days multiple dose	89 (53 delamanid, 5 efavirenz only, 18 tenofovir only, 14 Kaletra only)	Healthy subjects
242-08-211 Module 5.3.3.1	Multiple dose PK: 1X, 2X and 3X daily	300 mg QD, 150 mg BID, 100 mg TID	36 delamanid	Healthy subjects
242-08-212 Module 5.3.3.4	Drug interaction efavirenz	100 mg single dose,	30 15 delamanid, 15 efavirenz	Healthy subjects
242-08-801 Module 5.3.3.1	Single dose, food interaction	100, 200, 400 mg	48 36 delamanid, 12 placebo	Healthy subjects
242-08-802	Multiple dose	200 mg and 400 mg,	32	Healthy subjects

Module 5.3.3.1		BID: single day and for 10 days	24 delamanid, 8 placebo	
[14C]-delamanid capsules				
242-06-102 Module 5.3.4.1	ADME SD	100 mg capsule containing [^{14}C]-delamanid (3.76 MBq/mg)	6	Healthy subjects
Jet milled tablets (JM)				
242-04-101 Module 5.3.3.1	Multiple dose	100 and 400 mg single dose; 10 days multiple dose	52 (36 delamanid, 16 placebo)	Healthy subjects
242-03-101 Module 5.3.1.1	First in man single dose, ascending dose	5, 15, 50, 100, 200, 300 mg single dose (fasted); 200 mg single dose (high fat); 200 mg, single dose (fasted)	56 (42 delamanid, 6 placebo);	Healthy subjects
Total Delamanid Phase 1 – (EU[a]/Non-EU)			***162/422***	
Phase 2 Trials				
242-06-101 Module 5.3.3.2	EBA	Delamanid tablet (SD) PO, fed 100, 200, 300, 400 mg QD Rifafour tablet PO QD (dose determined by body weight)	54	Uncomplicated, smear-positive, pulmonary TB
242-07-204 Module 5.3.5.1	Pivotal Trial	Delamanid tablet (SD) PO, fed 100 and 200 mg, BID + OBR Placebo + OBR	481	MDR-TB patients
242-07-208 Module 5.3.5.2	Open-label Phase 2	6-month, open-label, fed ,100 or 200 mg, BID + OBR	213	MDR-TB patients
242-08-210 Module 5.3.5.3	Open-label Phase 2	6-month, open-label, fed 6 month 250 to 400 mg BID + OBR	10	Refractory MDR-TB patients
242-10-116 Module 5.3.5.4	Observational	long-term, follow-up	126 (interim)	Patients from 204, 208 and 210
Jet milled tablets (JM)				
242-05-102 Module	Pilot EBA trial	Delamanid tablet (JM) 400 mg PO, QD (fed)	24	Uncomplicated, smear-positive, pulmonary TB

	Isoniazid 300 mg tablet PO, QD	
Total Delamanid Phase 2 – (EU[a]/Non-EU)		***81/465***
Total Delamanid all studies - EU[a]/non-EU		**243/887**

[a] Trials including EU patients were 242-04-101, 242-05 101, 242-06-102, 242-03-101, 242-07-204 (+ non-EU), 242-07-208 (+non-EU), and 242-08-210.
JM=jet milled; SD=spray dried; OBR=Optimal background regimen; PO = oral administration; ADME = Absorption, distribution, metabolism, excretion; EBA = early bactericidal activity; QD = once daily; BID = twice daily; TID = 3 times a day.

2.4.2. Pharmacokinetics

The first two studies in man concerned administrations of the jet-milled formulation (242-03-101 and 242-04-101). These studies indicated unsatisfactory absorption. All subsequent studies employed a solid dispersion formulation except for use of a gelatin capsule in the mass balance study. Almost all of the data were obtained by dosing with multiples of the 50 mg commercial film-coated tablets.

Table 3

242-05-001 [Japan]	2.4.2.1.1. DB, PC, SD ascending: 50, 100, 200, 400 mg fasted; 200, 400 mg fed; 400 mg fed high-fat	2.4.2.1.2. 6 M
2.4.2.1.3. 242-05-101 [UK]	SD: 100, 200, 400 mg fasted; 200, 400 mg fed; 400 mg fed high-fat	48 M / 8 F
	MD once daily for 10 days: 100, 200, 400 mg fed	24 M / 24 F
242-06-001 [Japan]	DB, PC under fed conditions: SD 100 mg, 200 mg, 400 mg then MD once daily for 10 days	24 M
242-06-102 [UK]	^{14}C- OPC-67683 gelatin capsule PO, 100 mg SD in fed state	6 M
242-08-801-01 [China**]**	DB, PC, SD 100, 200 and 400 mg fasting and 400 mg high fat meal	48 M
242-08-802-01 **[**China**]**	DB, PC, 100 or 200 mg twice daily for 10 days in fed state	32 M

242-08-211 [US]	Open-label under fed conditions for 10 days: 300 mg once daily, 150 mg twice daily, 100 mg three times daily	21 M / 15 F
Drug interaction trials, healthy subjects		
242-06-202 [US]	DB, MD, PC 200 mg/day with ethambutol (1100 mg) and 6 tablets Rifater (total dose 720 mg rifampin/300 mg isoniazid/1800 mg pyrazinamide) + pyridoxine 25 mg	27 M / 17 F
242-07-209 [US]	Pilot, open-label, MD 100 mg twice daily under fed conditions for 14 days. OPC-67683 twice daily +/- efavirenz 600 mg once daily (arm suspended) OPC-67683 twice daily +/- tenofovir 300 mg once daily OPC-67683 twice daily +/- Kaletra 400/100 mg twice daily	48 M / 41 F
242-08-212 [US]	OPC-67683 twice daily + efavirenz 600 mg once daily	20 M+F

Pharmacokinetic data were also obtained from one of the two Phase 2 studies of Early Bactericidal Activity (EBA) that used the solid dispersion formulation (**242-06-101**) and from subjects with MDR-TB enrolled into the Phase 2 studies of safety and efficacy (**242-07-204 and 242-07-208**).

Measurements of plasma delamanid and its three primary metabolites (DM-6704, DM-6705 and DM-6706) as well as 5 other metabolites (DM-6717, 6718, 6720-6722) were performed using a specific and sensitive HPLC-MS/MS method. This was linear over the range 1-500 ng/mL for plasma delamanid concentrations and 1-100 ng/mL for concentrations of the metabolites. Urinary concentrations were not determined due to low excretion demonstrated by chromatography and liquid scintillation counts in the mass balance study.

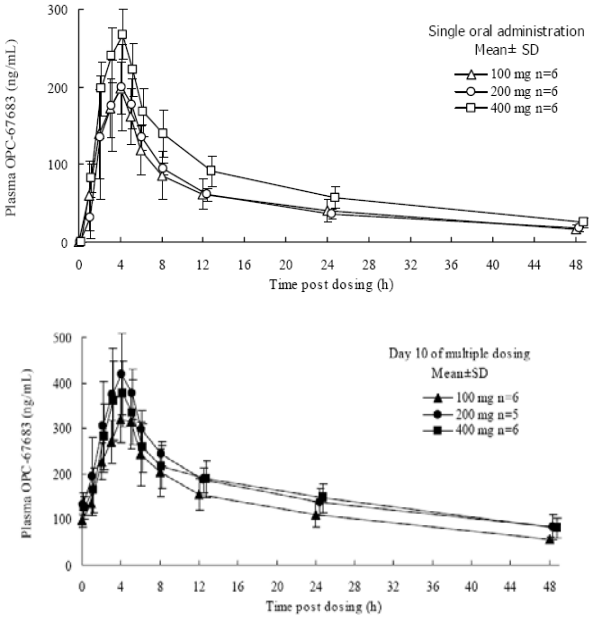
Absorption

The absolute oral bioavailability of delamanid in man has not been determined. Assuming delamanid is not excreted unchanged in humans (based on lack of biliary excretion in non-clinical studies), the delamanid recovered in the faeces after an oral dose in humans would represent non-absorbed drug. On this basis, the observation that 52.9% to 74.8% of the dose was recovered as unchanged delamanid in faeces in the human mass-balance study suggests that 25% to 47% of the delamanid dose is orally absorbed in the fed state.

A less than dose-proportional increase in plasma exposure to delamanid (and its primary metabolites; see below) was observed across the single and multiple dose studies whether administered in fed or fasting states. In 242-05-001 using single ascending doses of 50-400 mg almost no differences in Cmax or AUC0-∞ were seen between the 50 mg group and the 100 mg group. Although the Cmax and AUC0-∞ at 100, 200 and 400 mg increased with dose escalation, increases were less than dose-proportional.

Administration of single and multiple doses of delamanid after standard meals to Japanese male subjects in study 242-06-001 did not show linearity for Cmax or AUC. Mean C24h values indicated that delamanid had almost reached a steady state on day 10 in all dosage groups. The estimated accumulation ratios of C24h on Day 10 were 2.92 (±0.60), 3.82 (±0.40) and 2.63 (±0.50) for 100, 200 and 400 mg daily doses.

Figure 1



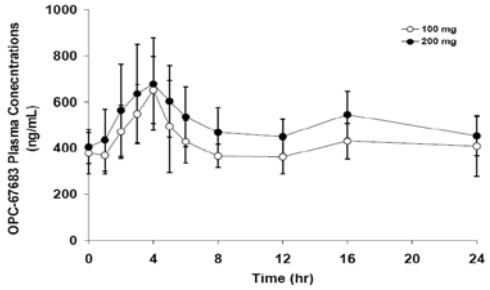
Additional data on single and multiple doses were obtained in two studies in Chinese subjects (242-08-801-01 and 08-802-01). Following administration of single doses of 100, 200 and 400 mg to fasted male subjects the Cmax and AUC∞ increased with increasing dose but in a less than dose-proportional fashion. After multiple dosing after standard meals Cmax, AUC0-12 and AUC0-24 increased with dose but in a less than dose-proportional fashion. Steady-state was reached after 8 days of dosing. The accumulation ratios and Day 10 plasma profiles are shown below.

Table 4

Accumulation Ratios of Cmax and AUC0-12, AUC0-24 and C24 for OPC-67683 Following Administration 200 mg (100 mg BID) and 400 mg (200 mg BID) OPC-67683 After a Standard Meal in Healthy Subjects

Analyte	Parameters	200 mg (100mg BID) (n=12)	400 mg (200 mg BID (n=12)
OPC-67683	C_{max} (ng/mL)	2.78± 0.43	2.31 ± 0.52
	AUC_{0-12} (h• ng/mL)	3.40 ± 0.44	3.30 ± 0.73
	AUC_{0-24} (h• ng/mL)	2.99 ± 0.54	2.85 ± 0.52
	$R_{10,ac}$ (C_{12}) (ng/mL)	4.63 ± 0.886	4.74 ± 1.07
	$R_{10,ac}$ (C_{24}) (ng/mL)	2.78 ± 0.922	3.09 ± 0.899

Figure 2



In the UK study 242-05-101 delamanid was quantifiable in plasma until at least 72 h after single doses and up to at least 144 h after the last dose on day 10. After single doses the mean Cmax, AUCt, AUC24h and AUC∞ increased with dose in a sub-proportional manner while median Tmax and mean t½, z estimates remained largely unchanged with increasing dose. Following repeated dosing for 10 days both Cmax and AUC24h increased from Day 1 in males and females, which was consistent with the decrease in clearance (CL/F) estimates. However, Vz/F did not consistently follow this trend. The predicted accumulation ratio estimates ranged between 2.2 and 3.3. Mean Cmax showed less than the predicted accumulation (between 1.5 and 2.3) whereas AUC24h and C24h showed ~ 1.8-3.2-fold and 2.6-4.8-fold accumulation, respectively. There were no consistent differences in accumulation between males and females.

Tables 5 & 6

Table 3 PK Parameters: OPC-67683. Summary Statistics by Dose of OPC-67683 (Fasted Male Subjects; n=6). Part A: Single Dose Phase, PK Population

Dose of OPC-67683 [Ratio]*	Arithmetic Mean		
	C_{max} (ng/mL) (CV%) [Ratio]*	AUC_t (ng.h/mL) (CV%) [Ratio]*	AUC_∞ (ng.h/mL) (CV%) [Ratio]*
100 mg	49.10 (35.1)	669.7 (36.6)	715.4 (35.9)
[1]	[1]	[1]	[1]
200 mg	60.05 (32.9)	1040 (36.4)	1100 (35.4)
[2]	[1.2]	[1.6]	[1.5]
400 mg	117.5 (28.7)	2038 (39.9)	2086 (38.5)
[4]	[2.4]	[3.0]	[2.9]

Table 63 PK Parameters: OPC-67683. Summary Statistics by Dose of OPC-67683 (Male and Female Fed Subjects; n=6). Part B: Multiple Dose Phase, PK Population

Dose of OPC-67683	Day of Dosing*	Arithmetic Mean			
		Males		Females	
		C_{max} (ng/mL) (CV%)	AUC_{24h} (ng.h/mL) (CV%)	C_{max} (ng/mL) (CV%)	AUC_{24h} (ng.h/mL) (CV%)
100 mg	Day 1	146.5 (33.5)	1542 (33.4)	133.7 (10.5)	1130 (21.8)
	Day 10	212.7 (14.5)	2621 (18.7)	194.7 (17.1)	2373 (5.2)
200 mg	Day 1	181.1 (26.7)	1851 (22.9)	182.1 (18.1)	1934 (20.8)
	Day 10	255.0 (18.3)	3259 (20.3)	292.8 (25.9)	4075 (19.5)
400 mg	Day 1	275.7 (28.3)	2806 (31.8)	215.6 (32.0)	1888 (29.1)
	Day 10#	421.8 (26.0)	5851 (41.8)	450.9 (18.6)	5525 (21.4)

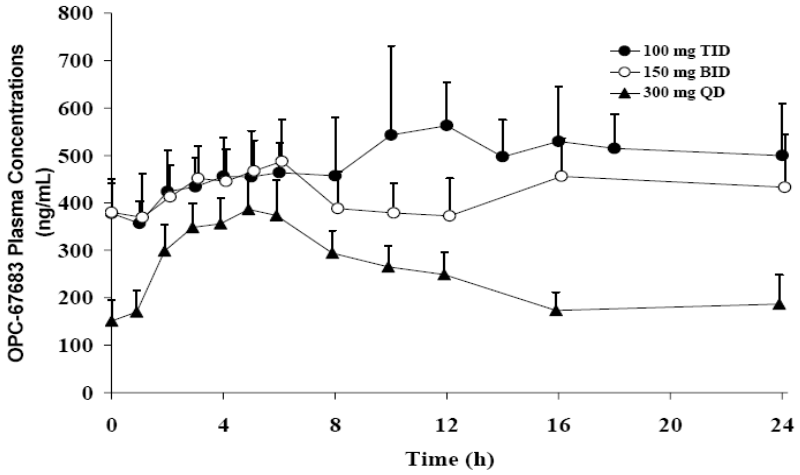
Study 242-08-211 provided an important comparison of three dosing regimens administered for 10 days in the fed state to healthy subjects in the US. Steady state was reached by Day 10 for each regimen in most of the subjects based on mean ± SD Day 8-10 trough plasma concentrations**.** On Day 10 delamanid plasma concentrations were slightly higher (~ 1.16- and 1.18-fold) after 100 mg TID compared to 150 mg BID based on mean steady state AUC0-24 and Cmax values, respectively. Both the BID and TID regimens gave significantly higher (1.93- to 2.23-fold) exposure than 300 mg QD dosing based on steady-state AUC0-24h values on Day 10.

The pre-dose (morning trough) mean ± SD plasma concentrations on Days 8, 9 and 10 after QD, BID and TID dosing regimens were comparable. However, the Day 11 (PK sampling day) mean trough concentrations were 14% to 32% higher for all the regimens, which was unexplained.

Table 7

Table 9.2.3.3.1-1	Mean (SD) Steady state OPC-67683 Plasma Pharmacokinetic Parameters Following Different Multiple-Oral Dose Regimens of OPC-67683, for a Total of 300 mg, in Healthy Subjects		
Parameters	**100 mg TID (n=9)**	**150 mg BID (n=10)**	**300 mg QD (n=9)**
C_{max} (ng/mL)	606 (168)	512 (80.9)	412 (50.6)
t_{max} (h)[a]	11.92 (10.00- 12.00)	5.00 (1.00 - 6.00)	5.00 (2.03 - 6.00)
$C_{ss,min}$	349 (49.3)	333 (68.2)	146 (41.3)
AUC_{τ} (h·ng/mL)	-	4970 (765)	5930 (1020)[b]
AUC_{0-24h} (h·ng/mL)	11800 (2080)	10200 (1570)	5840 (992)
CL_{ss}/F (mL/h/kg)	-	396 (75.4)	729 (121)

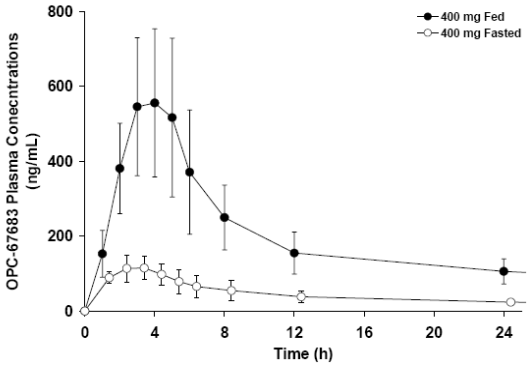
Figure 3



Mean (SD) OPC-67683 Concentration-time Profiles on Day 10 Following Multiple-dose Oral Administration of 300 mg/day OPC-67683 Following a Standard Meal to Healthy Subjects

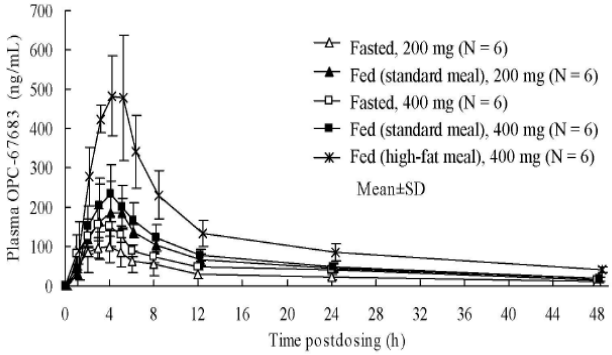
In the 400 mg SD study in Chinese male subjects (242-08-801-01) there was a marked effect on dosing after a high fat meal with a > 4-fold increase on AUC vs. the fasting state (1960 vs. 9150 h.ng/ml).

Figure 4



Similarly, in 242-05-001 after single doses the Cmax and AUC∞ were highest after a high-fat meal, followed by administration after a standard meal vs. dosing in the fasted state.

Figure 5



Following a 200 mg dose with a standard meal the mean AUC∞, AUCt and Cmax were 2.9-, 3.0- and 3.4-fold greater, respectively, vs. fasted conditions. The converse pattern applied to mean clearance and volume of distribution. Median tmax was slightly longer but there was no consistent difference in mean apparent t½,z for standard meal vs. fasted conditions.

Tables 8 & 9

Table 11 PK Parameters: OPC-67683. Summary Statistics by Food Status (Male Subjects; n=6). Part A: Single Dose Phase, PK Population

Food Status	Dose of OPC-67683	Arithmetic Mean		
		C_{max} (ng/mL) (CV%)	AUC_t (ng.h/mL) (CV%)	AUC_∞ (ng.h/mL) (CV%)
Fasted	200 mg	60.05 (32.9)	1040 (36.4)	1100 (35.4)
Standard meal	200 mg	205.4 (25.6)	3082 (33.6)	3153 (33.5)
Fasted	400 mg	117.5 (28.7)	2038 (39.9)	2086 (38.5)
Standard meal	400 mg	250.6 (14.2)	4250 (9.7)	4304 (9.5)
High fat meal	400 mg	384.5 (14.7)	7141 (31.9)	7250 (31.3)

Table 12 PK Parameters: OPC-67683. Summary Statistics by Food Status (Male Subjects; n=6). Part A: Single Dose Phase, PK Population

Food Status	Dose of OPC-67683	Median (Min,Max)	Arithmetic Mean (SD)	Arithmetic Mean (CV%)			
		t_{max} (h)	$t_{½,z}$ (h)	CL/F (L/h)	CL/F/BW (L/h/kg)	Vz/F (L)	Vz/F/BW (L/kg)
Fasted	200 mg	2.50 (1.00,4.00)	26.55 (4.61)	206.0 (41.9)	2.676 (41.5)	7542 (27.8)	97.80 (28.3)
Standard meal	200 mg	4.00 (3.00,5.00)	31.55 (11.53)	68.72 (28.9)	0.1833 (19.3)	3007 (33.0)	35.92 (30.6)
Fasted	400 mg	2.50 (1.00,4.00)	25.53 (6.70)	211.6 (30.6)	2.623 (20.5)	8134 (53.9)	97.61 (36.5)
Standard meal	400 mg	3.00 (2.00,5.00)	21.48 (2.75)	93.60 (9.20)	1.326 (11.1)	2896 (14.5)	40.92 (13.5)
High fat meal	400 mg	3.50 (1.00,5.00)	33.74 (4.65)	59.28 (27.0)	0.7901 (34.9)	2841 (25.9)	37.67 (32.8)

Distribution

Delamanid was bound extensively (> 99.5%) to total human serum proteins *in vitro* with no saturation of binding capacity at 5 µg/mL. Binding occurred preferably (≥ 97.3%) to albumin and human lipoproteins (VLDL, LDL and HDL) and to a lesser and more variable extent to human α1-acid glycoprotein (68.7% to 87.9%) and γ-globulin (77.6% to 97.1%). The metabolites DM-6704, DM-6705 and DM-6706 also bound extensively (99.60%, 99.70% and 99.21%, respectively) to human serum proteins. In the mass balance study the whole blood to plasma ratio of radioactivity was consistent and indicated negligible binding of delamanid to whole blood components.

Across the studies the derived estimates suggested a large V/F for delamanid that increased with dose in relation to the non-dose-proportional behaviour of the drug (i.e. decrease in F with dose). For example, the V/F in healthy subjects was 1100 and 1800 L after 100 mg and 200 mg BID dosing, respectively. Estimates of the apparent volume of distribution during the terminal phase (Vz/F) and of Vz/F adjusted for body weight (Vz/F/BW) ranged from 936.5 to 16100 L and from 15.48 to 163.2 L/kg, respectively.

Transporter studies

Delamanid was shown not to be a substrate for P-gp transport.

Delamanid and DM-6705, believed to be principally responsible for QTc interval prolongation, are being assessed as substrates for transporters relevant to absorption (including gastro-intestinal secretion), and to hepatic uptake and biliary excretion, considering no renal excretion is involved. Substrate studies were conducted on transport by P-gp for DM-6705, and on transport by BCRP, OATP1B1, OATP1B3 and OCT1 for delamanid and DM-6705.

Delamanid does not inhibit P-gp transport at 5 µM (this was the maximum concentration tested due to solubility issues), but this is approximately 15-fold lower than the estimated concentration of 74.8 µM in the intestinal lumen after 100 mg and therefore an effect in the gut cannot be ruled out. It is theoretically conceivable that the concentrations in the gut could be much higher than the concentrations of delamanid tested in the in vitro study.

Transporter inhibition studies were conducted with delamanid and four metabolites (DM-6704, DM-6705, DM-6718 and DM-6720) based on total percent circulating amount of delamanid entities and their potential for QTc interval prolongation. The results suggest that there is a low potential for inhibition of BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT2, OCT1 and BSEP but the maximum concentrations tested were relatively low.

The applicant will further address the margins between IC_{50} values and hepatic inlet concentrations.

Elimination

In study 242-05-101, concentrations of delamanid decreased in a biphasic manner in the majority of profiles. Across the studies the data suggested that delamanid is eliminated from plasma with a t1/2 of 30 to 38 hours whereas the t1/2 for the metabolites ranges from 121 to 322 hours. In the mass balance study, peak delamanid concentrations occurred at ~ 4-8 h. Concentrations continued to be quantifiable until 96 h after dosing and up to 144 h in one subject. The terminal half-life was nearly 32 h while the apparent clearance (CL/F) was high.

Table 10

Parameter	Units	Mean	SD
Cmax(obs)	ng/mL	49.143	18.260
Tmax(obs)	h	5.00*	3.00*, 8.00*
AUC(0-∞)	ng.h/mL	926.4	441.5
T½el	h	31.94	9.56
Kel	1/h	0.02399	0.009491
CL/F	L/h	117.400	33.560
Vd/F	L	5346	2208

After 192 h (end of collection period), urinary excretion accounted for just over 3% of the radioactivity dose and was still continuing. Faecal elimination accounted for almost 90% of the administered radioactivity within 96 h. Mean total recovery of radioactivity in urine and faeces amounted to 92.4% of the administered dose. Unchanged delamanid was the major radiolabeled compound in faeces (52.9% to 74.8% of the dose). Besides unabsorbed delamanid, DM-6705, DM-6718 and DM-6704 were also recovered in faeces. Delamanid was not detected in urine in the mass balance study. Also, after 10 days of 100 to 400 mg QD dosing in another study, less than 1% of the dose was recovered in urine as DM-6705 and DM-6720; unchanged delamanid was not found in urine.

Metabolism

Delamanid is an optically active compound (R-form) with an asymmetric carbon at the C-2 position of the 2,3-dihydroimidazo [2,1-b]oxazole ring. The potential for in-vivo inter-conversion to occur was addressed during 242-04-101 using the jet-milled formulation in which R-/S-enantiomer analysis of Day 10 samples revealed that plasma contained 100% R-enantiomer for parent and each analyzed metabolite (DM-6704, DM-6705 and DM-6706). Therefore, delamanid does not undergo chiral inter-conversion *in vivo*.

The pharmacokinetics of 8 identified metabolites of delamanid was described in several Phase 1 studies. The applicant concluded that delamanid metabolism in humans is generally comparable to that in animal species with some qualitative differences. It was considered that single dose mass balance studies in animals and humans and short-term urine excretion profiles only partially describe the metabolism and

excretion profile of delamanid. The applicant proposed that the more relevant analyses concern the concentrations and proportions of delamanid and its metabolites found after 6 months of dosing in MDR-TB patients in 204/208, as described in the next section.

Delamanid is proposed to undergo primary metabolism to DM-6705 mainly in plasma, which the applicant ascribes to an effect of human serum albumin (HSA). This assertion was supported by the observation that intrinsic clearance of delamanid in plasma (0.224 µL/min/mg of HSA) was similar to that in albumin (0.223 µL/min/mg). Delamanid is stated to be immediately and rapidly metabolized into DM-6705 in plasma by albumin, with a disappearance/formation half-life (at 37°C) of 0.64 hours. Metabolism of delamanid to DM-6705 is believed to result from reaction of the amino groups in albumin with the 5-C of 6-nitro-2,3-dihydroimidazo[2,1-b]oxazole moiety of delamanid. Since the metabolites are missing the nitro group of delamanid, they are not further metabolized by HSA.

Delamanid was minimally metabolised in human liver microsomes and 9000 g supernatant (S9) fractions while the three metabolites (DM-6704, DM-6705 and DM-6706) were stable in human plasma. *In vitro*, delamanid was metabolised by CYP3A4 and CYP1A1 in the presence of NADH and NADPH. CYP1A1 involvement was not confirmed in S9 fractions or human hepatocytes. The applicant concluded that only CYP3A4 makes a contribution to the metabolism of delamanid. The predominance of albumin vs. CYP3A4 involvement in the metabolism of delamanid is proposed to be supported by the moderate effect of potent CYP inducers and inhibitors on delamanid plasma exposure (see *Interactions*).

As shown in the Figure below, DM-6705 is proposed to be metabolized via 3 routes - two involve hydrolysis (to DM-6704 and DM-6706) while the third route involves CYP3A4 oxidation to form DM-6720. Further biotransformation of DM-6704 and DM-6720 also occurs via CYP3A4. DM-6704 is further transformed into DM-6721 and DM-6722 to finally form DM-6717, while DM-6720 is further transformed into DM-6718.

Figure 6

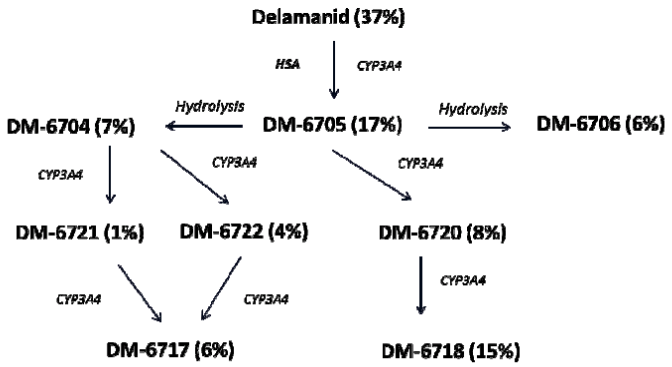


Figure 3.1-1 **Human Steady-State Plasma Exposure (AUC) after Delamanid 100 mg BID in MDR-TB Patients (Percent of Total Drug Related Exposure)**

Although the applicant has stressed the importance of the steady-state PK data in patients with MDR-TB over single dose studies in healthy subjects, there remains some difficulty reconciling the proposed metabolic pathway for delamanid with the findings of the human mass balance study (single dose 100 mg capsule; fed state). In this study delamanid in plasma accounted for 45.6% of the total radioactivity (TR) at Tmax (4 h post-dose) but only 3.42% of TR AUCinf.

Radioactivity remained well above the LLOQ at 192 h. The t1/2 of delamanid and TR were 32 and 180 hours, respectively, reflecting the presence of metabolites with longer t1/2 values than delamanid itself.

The study report states that *none of these 8 known metabolites therefore accounts for the majority of the circulating radioactivity.*

It is of concern that > 90% of circulating radioactivity has not been accounted for. Circulating metabolites present in high concentrations relative to parent drug or relative to total radioactivity are of concern for their potential to cause drug-drug interactions. A quantitative assessment of the contribution of individual metabolites is needed because so little of the total radioactivity AUC is explained. On this basis, the applicant's proposed metabolic pathway is not correct and is incomplete since it points to the presence of other compounds being present that predominate over the 8 characterised metabolites in the early phases of dosing.

As for delamanid, the metabolites show marked increases in exposure with multiple dosing and some also show this with food. Most seem to show less than dose-proportional kinetics and have elimination half-lives much longer than that of delamanid.

Pharmacokinetics in target population

In the Phase 2 study **242-07-204,** delamanid was administered for 8 weeks at 100 or 200 mg twice daily with standard meals (550 kcal, 25% from fat) in addition to OBR to subjects with MDR-TB. Full PK profiles were obtained up to 24 h post-dose on each of days 1, 14, 28 and 56.

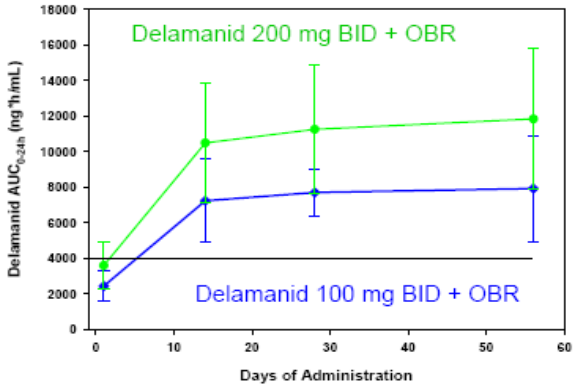
Tmax occurred at ~4 h after each dose. On Day 56 mean (% CV) values for Cmax were 414 (39.9) and 611 (35.6) ng/mL while mean AUC0-24h values were 7,925 (37.5) and 11,837 (33.6) h.ng/mL with 100 mg and 200 mg BID dosing, respectively. Hence AUC0-24h was 50% higher after the 200 mg vs. 100 mg BID dose. CL/F on Day 28 and 56 was higher in the 200 mg BID dose group (e.g. on day 56 values were 0.597 L/h/kg vs. 0.801 L/h/kg). Plasma concentrations of delamanid reached 90% (steady state) of the Day 56 values by Day 14 and AUC0-24h on Day 56 was 3.4- to 3.5-fold that on Day 1. After cessation of dosing, delamanid t1/2 was 38 h and median plasma concentrations were zero on Day 84.

Table 11

Table 10.2.2.2.1-1 Mean (%CV) Delamanid Pharmacokinetic Parameters in Patients With MDR TB

Study Day	PK Parameter	Delamanid 100 mg BID + OBR (n = 143 to 151)	Delamanid 200 mg BID + OBR (n = 144 to 154)
Day 1	C_{max1} (ng/mL)	135 (40.7)	187 (39.7)
	C_{max2} (ng/mL)	151 (40.1)	228 (40.2)
	C_{0h} (ng/mL)	0.00 (ND)	0.00 (ND)
	AUC_{0-24h} (h·ng/mL)	2441 (36.1)	3598 (36.5)
Day 14	C_{max1} (ng/mL)	369 (37.1)	547 (36.5)
	C_{max2} (ng/mL)	361 (35.3)	513 (34.7)
	C_{0h} (ng/mL)	283 (37.4)	414 (37.7)
	AUC_{0-24h} (h·ng/mL)	7234 (32.4)	10490 (32.2)
	CL/F (L/h/kg)	0.602 (47.8)	0.825 (45.1)
	R_{ac}(AUC)	3.14 (30.7)	3.13 (34.0)
Day 28	C_{max1} (ng/mL)	404 (35.7)	599 (37.0)
	C_{max2} (ng/mL)	381 (33.5)	560 (35.0)
	C_{0h} (ng/mL)	306 (40.5)	453 (37.2)
	AUC_{0-24h} (h·ng/mL)	7700 (30.2)	11251 (32.2)
	CL/F (L/h/kg)	0.546 (36.5)	0.764 (40.8)
	R_{ac}(AUC)	3.35 (37.1)	3.33 (33.6)
Day 56	C_{max1} (ng/mL)	414 (39.9)	611 (35.6)
	C_{max2} (ng/mL)	400 (40.5)	588 (36.2)
	C_{0h} (ng/mL)	304 (42.2)	460 (36.6)
	AUC_{0-24h} (h·ng/mL)	7925 (37.5)	11837 (33.6)
	CL/F (L/h/kg)	0.597 (73.6)	0.801 (93.6)
	R_{ac}(AUC)	3.41 (34.9)	3.52 (39.1)
	$t_{1/2}$ (h)	37.8 (34.3)	38.3 (37.5)

Figure 7



Formation of the three primary metabolites (DM-6704, 6705 and 6706) was slow. Each showed flat daily concentration-time profiles without a clear Cmax with a slow increase over time through Day 56. On Day 56, delamanid represented 41% of total drug-related AUC0-24h (parent and metabolites) in plasma. Metabolites exceeding 10% of total drug-related exposure (AUC) were DM-6705 (17% to 18%) and DM-6718 (12% to 13%).

In the 6-month open label Phase 2 study **242-07-208** all subjects commenced 100 mg BID with an option to receive 200 mg BID after an initial 2-week period. Dosing was to be with food but subjects were not hospitalised after week 2, so meals were not standardised. Due to the variable PK sampling times (median [CV%] 2 [112%] h post-dose), descriptive statistics are indicative only.

Over the 26 weeks and from Day 14 onwards median plasma delamanid concentrations ranged from 342-408 ng/mL and from 284-540 ng/mL at 100 mg BID and 200 mg BID doses, respectively. Metabolite plasma concentrations reached or exceeded 90% (steady state) of the Week 26 values by Week 6 for DM-6704, DM-6705 and DM-6706, by Week 10 for DM-6720 and by Week 14 for the others.

Table 12

Table 2.7.2.4.1-18 Delamanid and Metabolites Plasma Concentrations Over Time in Trial 242-07-208

Analyte	DLM Dose[a] (mg BID + OBR)	Delamanid Concentration[b] (ng/mL) (Median [CV%])						
		Week 2	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26
DLM	100	340 (44.0)	408 (38.8)	373 (30.9)	419 (42.1)	381 (44.0)	387 (49.2)	401 (45.3)
	200	295 (36.1)	476 (42.6)	473 (29.1)	604 (37.7)	481 (38.5)	425 (51.5)	453 (42.9)
DM-6704	100	30.6 (61.1)	49.1 (57.4)	52.4 (49.4)	63.1 (58.4)	57.6 (68.6)	58.5 (55.9)	55.2 (63.6)
	200	42.6 (56.2)	74.9 (44.2)	104 (41.0)	85.7 (50.6)	88.7 (60.9)	76.9 (55.1)	87.0 (63.2)
DM-6705	100	100 (46.4)	165 (36.6)	195 (34.0)	192 (40.9)	208 (42.4)	213 (47.3)	196 (54.4)
	200	51.7 (40.0)	153 (34.7)	168 (39.6)	180 (40.3)	169 (42.7)	152 (46.6)	149 (49.9)
DM-6706	100	30.3 (43.4)	53.7 (34.9)	57.5 (30.2)	60.9 (38.7)	59.8 (42.7)	59.5 (40.1)	57.9 (49.6)
	200	36.1 (45.3)	74.5 (41.2)	84.0 (37.8)	86.2 (46.7)	89.2 (47.5)	89.9 (34.5)	87.1 (42.8)
DM-6717	100	4.55 (104.8)	29.4 (51.9)	33.1 (55.3)	51.1 (52.9)	48.6 (56.9)	51.9 (65.1)	53.9 (74.4)
	200	6.91 (83.9)	35.9 (58.3)	49.4 (41.1)	69.0 (52.5)	56.8 (60.4)	80.9 (64.9)	69.6 (61.1)
DM-6718	100	19.9 (77.6)	84.2 (50.1)	104 (45.7)	120 (42.6)	118 (45.9)	129 (48.6)	123 (57.6)
	200	27.2 (79.9)	85.3 (46.6)	114 (26.8)	137 (48.4)	144 (41.1)	152 (45.5)	146 (40.9)
DM-6720	100	22.2 (51.4)	58.3 (39.4)	62.2 (39.3)	68.7 (39.4)	67.4 (39.1)	70.0 (44.6)	75.0 (50.5)
	200	19.2 (55.4)	57.6 (36.4)	73.6 (20.9)	88.9 (34.3)	86.4 (30.6)	87.3 (32.9)	89.4 (35.6)
DM-6721	100	2.45 (63.6)	4.79 (48.5)	4.94 (49.4)	5.79 (52.7)	5.74 (59.8)	6.11 (61.5)	6.12 (65.2)
	200	2.70 (65.4)	6.98 (49.3)	8.13 (59.9)	10.0 (59.6)	10.1 (63.1)	9.87 (58.9)	9.61 (72.7)
DM-6722	100	18.0 (65.8)	28.5 (54.1)	25.8 (42.4)	29.9 (49.5)	31.0 (60.5)	33.2 (56.8)	32.5 (62.5)
	200	17.9 (63.7)	41.5 (51.8)	50.9 (59.6)	55.7 (64.1)	55.0 (64.5)	50.8 (55.3)	59.5 (86.6)

The Phase 2 population PK model (i.e. built using data from 242-07-204 and 208) reported that for a typical MDR-TB subject (55 kg male, plasma albumin > 3.4 mg/dL), the PK parameters of delamanid (apparent clearance, inter-compartment clearance, central and peripheral volume) were , respectively: CL/F = 39.3 L/hr (95%CI: 37.5 - 41.1 L/hr), Q/F = 106 L/hr (95%CI: 92.3 - 120 L/hr), V2/F = 624 L (95%CI: 573 - 675 L), and V3/F = 930 L (95%CI: 843 - 1020 L). In a typical subject on delamanid 100 mg or 200 mg BID, steady state was reached at about 1.5 weeks with a Rac (AUC24h) of approximately 3.1 to 3.5.

Delamanid exposure was not affected by age, mild renal impairment or drug resistance status (MDR-TB vs. XDR-TB). Delamanid clearance was independent of weight, and exposure-related PK parameters were independent of gender. Only hypo-albuminaemia tended to coincide with higher delamanid CL/F, and possibly more likely a lower F. This is believed to be possibly related to confounding pre-existing physiological conditions (e.g. disease status, malabsorption) in these patients. Among the extrinsic factors, delamanid exposure was not affected by OBR treatment or other concomitant medications.

Actual differences in delamanid exposure across regions may reflect intrinsic ethnic differences, including body composition, as well as food differences. Intra-subject variability (i.e. estimated from proportional residual variability) was moderate (27% to 39%) and appeared to be highest in 208, reflecting primarily outpatient conditions and therefore more variable food intakes. The regional differences were on average within the range of the 50% difference in exposure observed between the delamanid 100 and 200 mg BID doses, both of which were well tolerated. In addition, *post hoc* simulations at the 100 mg BID dose across regions in both in-patients and out-patients indicated that delamanid AUC in the European population exceeded 3,500-5500 ng*h/mL in 100% of the population.

The relative bioavailability of the evening dose was 45% (95% CI: 37% to 52%) higher than the morning dose and 19% (95% CI: 16% to 21%) higher in the non-hospitalised vs. hospitalised setting possibly due to differences in food composition/amount associated with these different settings.

For 100 mg BID with standard meals the Phase 2 POP-PK model predicted the lowest plasma AUC0-24h = 6395 h*ng/mL during steady-state for a female, non-Asian, hospitalized patient and the highest plasma exposure AUC0-24h =11465 h*ng/mL for a North-East Asian male out-patient with MDR-TB under OBR therapy. Corresponding estimates for 200 mg BID were 9129 h*ng/mL for female non-Asian hospitalized patients and 16306 h*ng/mL for a North-East Asian female out-patient with MD-TB under OBR therapy.

Special populations

In the dataset used to derive the Phase 2 population PK model there were 60 (14.8%) subjects with mild (CrCLN < 80 mL/min/[1.73 m2]) and 4 with moderate renal impairment (CrCLN < 50 mL/min/[1.73 m2]). There was no impact of mild to moderate renal impairment on delamanid and DM-6705 exposures. DM-6705 plasma concentrations in patients with mild to moderate renal impairment on Day 56 in study 204 indicated a trend towards slightly higher DM-6705 plasma exposure in patients with mild renal impairment that remained well within the variability in exposure. The DM-6705 exposure in patients with moderate renal impairment after delamanid 100 mg BID remained well within that observed after delamanid 200 mg BID.

No hepatic impaired subjects were enrolled but 9 had ALT > 56 U/L, 41 had AST > 40 U/L, 3 had AST > 80 U/L and 7 had total bilirubin > 1 mg/dL. Hepatic impairment may have an influence on DM-6705 exposure but the applicant concluded from the DDI study with Kaletra (see below) that a major loss of CYP3A4 activity would not result in concentrations > those observed with 200 mg BID in 204/208. In trials 204/208 a trend towards slightly lower DM-6705 concentrations in hypoalbuminaemic patients

was observed. The lack of data on patients with severe hepatic impairment has been reflected in the proposed Product Information.

Pharmacokinetic interaction studies

See *Distribution* for details of completed transporter studies and *Metabolism* for what is known and/or proposed to be the mode of biotransformation of delamanid and its metabolites.

When delamanid was co-administered with P-gp inhibitors cyclosporin A or verapamil HCl to rats the Cmax was unchanged but the AUC was slightly increased. The slight increase in AUC was not considered to be caused by inhibition of P-gp since Cmax was not affected and delamanid was not shown to be transported by P-gp in a study with human MDR1-expressing cell monolayers.

Factors that may influence metabolism by albumin are yet unknown. In study 204 no patient had hyperalbuminaemia and 30.6% had hypoalbuminaemia. No clinically relevant changes in delamanid and DM-6705 plasma concentrations occurred in MDR-TB patients with hypoalbuminaemia vs. those with normal albumin levels. The applicant does not expect interactions to occur via interference with metabolism by albumin.

Regarding interactions at the level of cytochrome P450 isoenzymes:

- Delamanid did not induce human CYP1A2, CYP2C9 and CYP3A4/5 and mRNA levels in fresh primary cultures of hepatocytes at 0.1, 1 and 10 µmol/L. At 100 µmol/L there was little possibility for mechanism-based inhibition by delamanid on the CYP isoforms tested (CYP1A1/2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 [testosterone, midazolam]).
- DM-6704 inhibited CYP2B6, CYP2C8/9 and CYP2C19 activities with IC50 values ranging from 25.2 to 89.4 µmol/L.
- DM-6705 inhibited CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP3A4 (nifedipine oxidation) and CYP3A4 (testosterone 6β-hydroxylation) activities with IC50 values ranging from 18.3 to 87.5 µmol/L.
- DM-6706 inhibited CYP2B6, CYP2C8/9, and CYP2C19 activities with IC50 values ranging from 32.8 to 90.6 µmol/L.
- DM-6720 inhibited CYP2A6, CYP2B6, CYP3A4 (testosterone 6 β-hydroxylation) with IC50 values ranging from 10.9 to 42.3 µmol/L.
- DM-6718 had little inhibitory potency against CYPs (IC50 > 100 µmol/L).

Based on the steady-state Cmax after delamanid 200 mg BID in humans and the Ki values, the calculated I/Ki values for the metabolites (DM-6704, DM-6705, DM-6706, DM-6718, and DM-6720) indicate that the likelihood for inhibition potential is remote (I/Ki < 0.1). No inhibition was observed with delamanid so no IC50 or Ki was determined. These *in-vitro* results indicated that enzyme inhibition *in vivo* with specific probe substrates can be excluded for delamanid and the metabolites that were tested.

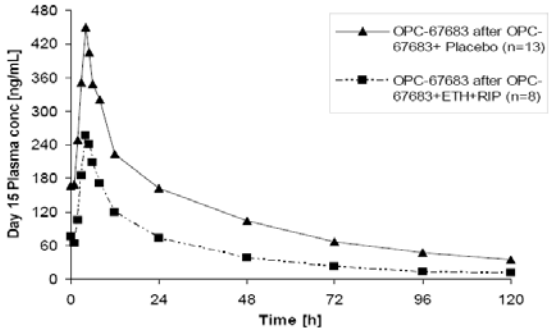
The worst case scenario for *CYP3A4 induction* was assessed in a 15 day study with Rifater (isoniazid/rifampicin/pyrazinamide) + ethambutol (242-06-202). Ethambutol and Rifater were administered before and delamanid after a standard breakfast. Subjects were genotyped for CYP2C9, CYP 2C19 and N-acetyltransferase-2 (NAT-2).

Co-administration with Rifater reduced plasma exposure to delamanid by 47% and also decreased steady state plasma concentrations of DM-6704, DM-6705, DM-6706, DM-6717, DM-6721 and DM-6722 from 15 to 45%.

Table 13

Table 9.2.3.1.2-1	Mean (SD) Steady State OPC-67683 Plasma Pharmacokinetic Parameters Following Multiple-dose Oral Administration of Either OPC-67683, Ethambutol and Rifater or OPC-67683 and Placebo to Healthy Subjects	
Parameter	**OPC-67683+ Placebo (N = 13)**	**OPC-67683+ Ethambutol+ Rifater (N = 8)**
C_{max} (ng/mL)	476 (119)	270 (38.9)
t_{max} (h)[a]	4.00 (4.00-8.00)	4.06 (4.00-5.00)
AUC_τ (h·ng/mL)	5950 (1440)	3110 (706)
CL_{ss}/F (mL/h/kg)	483 (93.4)	938 (137)
$t_{1/2,z}$ (h)[b]	41.1 (6.05)[c]	32.4 (12.1)[b]

Figure 8



By applying the same ratios to the Day 56 plasma levels observed in patients with MDR-TB in study 204 the applicant concluded that co-administration of delamanid with a strong inducer of CYP3A4 would not result in a significant effect on safety or efficacy. It is not really expected that rifampicin and its analogues would be used for the treatment of MDR-TB. However, the value of the data is more related to its predictive capacity for co-administration with other strong inducers. On this basis, there is sufficient concern at this stage and in light of lack of information to prohibit co-administration of strong inducers of CYP3A4 with delamanid (noted as a contra-indication, section 4.3 of proposed SmPC).

The metabolite/parent AUC ratios with and without Rifater + EMB showed that the ratio was unchanged for DM-6704 (suggestive of mainly decreased absorption) but modestly increased for DM-6705 (0.26 vs. 0.19) and DM-6720 (0.058 vs. 0.028) (suggestive of the presence of induced metabolism). Hence, in addition to an effect on CYP3A4 metabolism decreased absorption possibly due to the number of tablets (15) taken, may have occurred.

Co-administration with delamanid significantly increased steady state plasma concentrations of ethambutol by approximately 25%. The individual ethambutol PK profiles and the slightly more pronounced change in Cmax than in AUC suggested slightly improved absorption rather than decreased elimination of ethambutol. Ethambutol bioavailability has been shown to be absorption-dependent, as antacids are known to decrease ethambutol bioavailability.

The underlying reasons are unclear considering the limited information on ethambutol metabolism and considering that delamanid and related metabolites do not show CYP isoform inhibition. This minor change in exposure was considered not to be relevant.

- The report states that co-administration with delamanid did not significantly alter steady state plasma concentrations of rifampicin. The GMRs were 1.07 (90% CI 0.69, 1.67) for AUCt and 1.14 (0.78, 1.68) for Cmax. The tables of 25-desactyl rifampicin data show slightly higher plasma levels on dosing with delamanid but no formal analysis was planned.
- When PK data for subjects with a given NAT-2 genotype were compared, co-administration with delamanid did not appear to alter isoniazid PK.
- Co-administration with delamanid did not significantly alter steady state plasma concentrations of pyrazinamide. The GMRs (90% CI) were 1.07 (0.89, 1.30) for AUCt and 1.04 (0.88, 1.24) for Cmax.

The worst case scenario for *CYP3A4 inhibition* was assessed in the 14-day DDI study with lopinavir/ritonavir (Kaletra). In 242-07-209 delamanid steady state was reached by Day 14 regardless of co-administered anti-HIV agents based on pre-dose plasma concentrations but none of the metabolites had reached steady state on this day.

Table 14

Table 9.2.3.2.1-1 Mean (SD) OPC-67683 Pharmacokinetic Parameters Following Administration of 100 mg OPC-67683 BID, alone or with 300 mg Tenofovir QD or 400/100 mg Kaletra BID (lopinavir/ritonavir) to Healthy Subjects

PK Parameter	100 mg OPC-67683 BID (n=11)	100 mg OPC-67683 BID + 300 mg Tenofovir QD (n=13)	100 mg OPC-67683 BID + 400/100 mg Kaletra BID (n=12)
C_{max} (ng/mL)	617 ± 135	518 ± 114	734 ± 196
t_{max} (hr)[a]	4.00 (4.00 - 4.00)	4.00 (3.00 - 8.05)	4.00 (3.00 - 5.00)
AUC_τ (ng·h/mL)	4700 ± 733	4510 ± 770	5830 ± 1660
$CL_{ss/F}$ (mL/h/kg)	293 ± 76.2	313 ± 68.0	240 ± 44.0
Ratio of Mean C_{max} Values[b] (90% CI)	NA	0.844 (0.714 - 0.989)	1.177 (0.997 - 1.390)
Ratio of Mean AUC_τ Values[b] (90% CI)	NA	0.958 (0.835 - 1.099)	1.216 (1.057 - 1.399)

NA=Not applicable.
[a]Median (minimum - maximum).
[b]Geometric mean ratio of OPC-67683 + co-treatment to OPC-67683.

- Kaletra slightly increased delamanid steady-state AUC (ratio 1.22). Marginally higher steady-state exposure of DM-6704 (ratio 1.75) and DM-6705 (ratio 1.28) was observed, while no effect occurred on DM-6720 (ratio 1.03) exposure. The limited impact of ritonavir was deemed compatible with the predominant contribution of HSA to delamanid metabolism and formation of DM-6705 and alternative routes (hydrolysis) in the biotransformation of DM-6705 into DM-6704 and DM-6706. The more pronounced increase in DM-6704 was consistent with its persistent formation through hydrolysis and is indicative of CYP3A4 being solely responsible for its disappearance.
- The applicant further assessed the impact of CYP3A4 inhibition by applying the effect factors to the Day 56 data obtained from patients in study 204 and concluded that there was no need for dose adjustment when delamanid is given with strong inhibitors of CYP3A4. However, the effect on DM6705 and the risk of QTc prolongation is considered to be a concern that merits a warning in the proposed Product information.
- Plasma concentrations were unaffected (DM-6704 and 6706) or lower (DM-6705) on co-administration with tenofovir (a CYP1A2 inhibitor).
- Plasma concentrations of tenofovir, ritonavir and lopinavir were considered to be not greatly affected by co-administration with delamanid over 14 days. Tenofovir GMC ratios (90% CI) were 0.89 (0.77, 1.04) for Cmax and 0.91 (0.78, 1.07) for AUCt, lopinavir ratios were 1.05 (0.88, 1.25)

and 1.04 (0.86, 1.24) and ritonavir ratios were 0.96 (0.66, 1.4) and 1.03 (0.77, 1.37), respectively.

In 242-08-212 subjects received either efavirenz 600 mg QD for 10 days (at 20.00 h and 2 h post-food) or delamanid 100 mg BID without (7 days) and then with (10 days) efavirenz 600 mg QD. Delamanid was given at 08.00 and 18.00 within 30 minutes of a standard meal.

Efavirenz exposure was described as being comparable when given alone or with delamanid (Cmax GMR 0.94 [0.75, 1.17]; AUCt GMR 0.94 [0.72, 1.23]. Trough concentrations were also comparable although there was a greater spread of values on co-administration. One subject per group with 3 to 4 times higher efavirenz exposure had *6/*6 and *6/*15 alleles, which are predictive for considerably reduced CYP2B6 enzyme activity. In addition, the 11 subjects with *1/*6 alleles tended to show higher efavirenz exposure vs. those genotyped as *1/*1 alleles. Comparisons within each CYP2B6* genotype did not reveal any overt difference in exposure on co-administration.

Delamanid plasma exposure was comparable when given alone or with efavirenz and steady state was reached after 7 days of administration. The GMRs were 0.995 (0.93, 1.07) for Cmax and 0.97 (0.91, 1.03) for AUCt. Trough levels were slightly lower on co-administration but with a similar spread. Plasma concentrations of the three primary metabolites were higher on co-administration, especially for DM-6705 and 6706.

2.4.3. Pharmacodynamics

Mechanism of action

Delamanid is an inhibitor of mycolic acid biosynthesis. It is described as a pro-drug that undergoes reductive metabolism by *M. tuberculosis* to produce an active free radical. Specifically, it was reported to exert anti-TB activity in *M. bovis* through bioreductive activation of an aromatic nitro group that is possibly mediated via the F420 coenzyme system. These enzymes have been reported in other mycobacteria including *M. tuberculosis* and *M. africanum* with near 100% homology.

Delamanid inhibited methoxy-mycolic and keto-mycolic acid synthesis in M. bovis BCG with IC50 values of 0.036 and 0.021 µg/mL but the IC50 for α-mycolic acid was > 0.25 µg/mL. While isoniazid also inhibits mycolic acid synthesis it has been reported to inhibit mainly the enoyl-ACP reductase InhA-NDA complex. Since the in-vitro activity of delamanid was unaffected by mechanisms conferring resistance to isoniazid it has been deduced that the precise mechanism of mycolic acid synthesis inhibition differs between the two agents.

Primary pharmacology

In-vitro susceptibility testing of *Mycobacteria* mostly employed agar dilution with 14 days incubation at 37^0C. The agar proportion method generally gave MICs up to 4-fold lower than the agar dilution method. There was an inoculum effect (higher MICs of delamanid) detected at > 10^7 cfu/ml. Higher MICs of delamanid were also observed at pH >7 vs. pH 6-7. A comparison of MICs determined using agar dilution against *M. tuberculosis* showed the following for delamanid in comparison (on a wt/wt basis only) with primary anti-TB agents.

Table 15

	delamanid	RFP	INH	EB	SM
M.tuberculosis H37Ra	0.006	0.05	0.1	1.56	1.56
H37Rv	0.012	0.78	0.1	1.56	1.56
H37Rv RFP-r	0.006	>100	0.1	1.56	0.78
H37Rv INH-r	0.012	0.39	>100	3.13	0.78
H37Rv EB-r	0.012	0.2	0.2	50	0.78
H37Rv SM-r	0.012	0.78	0.1	3.13	>100
H37Rv PZA-r	0.012	0.78	0.2	1.56	1.56
Aoyama B	0.024	0.1	0.05	3.13	1.56
Erdman	0.012	0.39	0.1	1.56	1.56
Kurono	0.012	0.39	0.1	3.13	0.78
TU-26	0.012	>100	12.5	12.5	6.25

(Otsuka Study No. 019064)

Using the agar dilution method the MICs of delamanid for 67 clinical isolates of *M. tuberculosis* ranged from 0.006 to 0.024 µg/mL. The in-vitro activity of delamanid was unaffected in the presence of mechanisms conferring resistance to one or more other anti-TB agents. For example, against 24 *M. tuberculosis* MICs of delamanid determined using the agar proportion method ranged from ≤ 0.00625 to 0.0125 µg/mL regardless of whether strains were classified as drug-sensitive, MDR or XDR.

The in-vitro activity of delamanid against 17 non-tuberculous *Mycobacterium* strains (all ATCC) determined by the agar (7H11) dilution method showed that:

- Delamanid MIC against *M. kansasii, M. shimoidei, M. xenopi* and *M. marinum* was 0.024 µg/mL.
- For *M. avium, M. intracellulare, M. kansasii ATCC 12478, M. scrofulaceum, M. malmoense, M. simiae* and *M. ulcerans* the MICs were in the range 0.5 -1.56 µg/mL
- MICs were > 100 µg/mL against *M. smegmatis, M. aurum, M. szulgai, M. fortuitum* and *M. chelonae*
- Against *M. africanum* ATCC 25420 the MIC delamanid was comparable to *M. tuberculosis*.
- For single strains of sub-species of the MTB-complex including *M. pinnipedii* (ATCC BAA-688), *M. microti* (ATCC19422 & 11152), *M. caprae* (ATCC BAA-824) and *M. bovis* (ATCC BAA-935) the delamanid MICs were similar to those for *M. tuberculosis*.

The MICs of the primary metabolites of delamanid (DM-6704, 6705 and 6706) against 10 *M. tuberculosis* strains, including some resistant to currently used anti-TB drugs, was determined using the agar dilution method. These metabolites showed poor activity with MICs that ranged from 6.25 to 50 µg/mL. For the other five metabolites (i.e. DM-6717, 6718, 6720, 6721 and 6722) all MICs were ≥ 12.5 µg/mL. Against a range of non-Mycobacterial species the MIC of delamanid was > 100 µg/mL. MICs of DM-6704, DM-6705 and 6706 were 12.5 - > 100 µg/mL, 6.25 to > 100 µg/mL and 50 to > 100 µg/mL, respectively.

Delamanid showed no antagonistic activity with ethambutol, isoniazid, rifampicin and streptomycin. Combination with these agents was classified as synergistic or partially synergistic for 88.9%, 44.4%, 92.6% and 25.9%, respectively, of all tested strains.

Against *M. bovis* BCG Tokyo under aerobic conditions and in liquid culture with incubation at 37°C delamanid showed bactericidal effects after 3 and 7 days at 0.016, 0.080 and 0.40 µg/mL but not at 0.0032 µg/mL. At 0.016 µg/mL delamanid gave a 3-log reduction in CFU on day 3 and a 4-log reduction in CFU on day 7. Also, delamanid showed bactericidal activity [IC90 0.215 µg/mL, 95% CI 0.178 to

0.261 µg/mL] against intracellular *M. tuberculosis* (H37Rv strain) and against the same strain in primary human macrophages. Against dormant *M. bovis* BCG Tokyo delamanid exhibited dose-dependent bactericidal activity that was significant at concentrations ≥ 0.4 µg/mL.

Regarding clinical isolates, initially the applicant did not conduct any susceptibility testing against delamanid at baseline in study 204. There is an ongoing effort to retrieve, identify and perform susceptibility testing for as many baseline isolates as possible form study 204. There are inadequate data available during the procedure to support setting of breakpoints by EUCAST.

In "*delamanid-resistant*" *M. bovis* BCG Tokyo (i.e. with much higher than usual MICs), mutations were identified in coenzyme F420 genes *fgd*, *Rv3547*, *fbiA*, *fbiB* and *fbiC*, based on HPLC elution profiles and DNA sequencing. When delamanid-resistant *M. bovis* BCG Tokyo strains were complemented with wild-type genes *fgd*, *Rv3547*, *fbiA*, *fbiB*, *fbiC* or both *fbiA* and *fbiB* susceptibility was restored (MICs 0.006 to 0.024 µg/mL). These results suggest that mutation in one of the 5 coenzyme F420 genes is the mechanism for resistance of *M. bovis* BCG against delamanid.

Investigation of clinical isolates of *M. tuberculosis* that were "resistant" to delamanid (i.e. growth on solid media containing delamanid at 200 ng/mL) showed that the mechanism of resistance was exclusively due to lack of conversion of delamanid to the desnitro-imidazooxazole form by the bacilli. Specifically, clinical isolates from study 208 that showed high MICs of delamanid have been found to contain functional mutations of any of the 5 genes (*Rv3547, FGD, FbiA, FbiB* and *FbiC*), resulting in the inability of the bacilli to convert delamanid to the desnitroimidazooxazole. Four (2 from EU) out of 213 (49 from EU) patients had isolates that were confirmed to develop delamanid resistance during the 6-months' treatment period. All of these patients were on effective mono-therapy with delamanid or with only the addition of a weak, bacteriostatic drug to which the patient's isolate was susceptible.

The spontaneous resistant rate in H37Rv for delamanid is 6.44 x 10-6 – 4.19 x 10-5, which is very similar to that of isoniazid: 1.74 x 10-5 – 3.13 x 10-5. Therefore, based on the experience with isoniazid, the applicant expects that the rate of emergence of resistance to delamanid will be high unless it is paired with a potent bactericidal drug or multiple bacteriostatic or weakly bactericidal drugs.

Secondary pharmacology

In stably transfected HEK293 cells delamanid (0.03 to 3 µmol/L) showed increasing inhibition potential (19.6% to 35.4%) without evidence of a dose-response and hence no IC50 was reported. DM-6705 showed the highest inhibitory potential (IC50 of 0.0822 µmol/L) followed by DM-6704 (IC50 of 1.60 µmol/L), while DM-6706 showed no significant effect on hERG at 3 µmol/L.

In Chinese hamster ovary (CHO) K1 cells stably expressing hERG channel the inhibition rate for delamanid at 1 µmol/L (0.5 µg/mL) was 7.9% vs. the DMSO vehicle control. It was considered that any of delamanid (no IC50), DM-6704 (IC50 1.6 µM), DM-6705 (IC50 0.082 µM) and DM-6720 (IC50 1 µM) could possibly contribute to QTc prolongation. Their steady-state Cmax total plasma concentrations in patients with MDR-TB in 204/208 were 0.33, 0.15 and 0.13 µmol/L after 100 mg BID and 0.50, 0.20 and 0.18 after 200 mg BID. The inhibition rates for DM-6704, 6720 and 6705 at 1 µmol/L vs. control were 23.7%, 54.9% and 90.6%, respectively. The other 5 metabolites did not affect hERG current at 1 µmol/L.

A clinical TQT study was not performed but ECG data were obtained in Phase 2 studies. In the Phase 2 study of 8 weeks delamanid vs. placebo (**242-07-204**), ECGs were measured at baseline and at each PK sampling time (except for pre-dose) on the PK visit days and QTcF and QTcB values were generated. Progressive increase in QTc intervals over time occurred during delamanid treatment with higher values

for QTcF vs. QTcB. For the PK/PD analysis only the records where both QTc and PK data were available were used. The applicant conducted a full dataset analysis and a restricted dataset analysis after exclusion of all the data collected in two sites in Peru (sites 15 and 16). Day 56 Cmax values were used to compute predictions for QTc change from baseline.

The predicted placebo-adjusted ΔQTcF values were higher than the corresponding predicted placebo-adjusted ΔQTcB values. The highest placebo-adjusted ΔQTcF value was predicted for DM-6705 Cmax. The PK/PD analysis for change in QTc from baseline (ΔQTcF and ΔQTcB) for delamanid, DM-6704, DM-6705 and DM-6720 indicated that the linear models for delamanid and DM-6704 overestimated the effect at high concentrations, while for DM-6705 and DM-6720 the regression lines went through the observed points. DM-6705 concentrations were identified as a surrogate marker for QTc prolongation since plasma levels predicted the highest change in QTcF at Cmax. The highest DM-6705 concentrations were observed on Day 56 and the QTc prolongation reversed after drug was discontinued on this day.

Figures 9 & 10

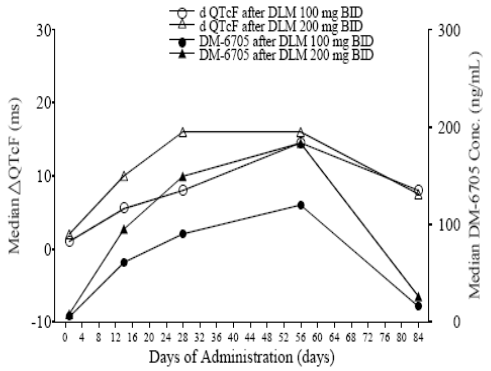


Figure 2.7.2.2.3.2.1-1 Median QTcF Change From Baseline and Plasma DM-6705 Concentration Versus Time

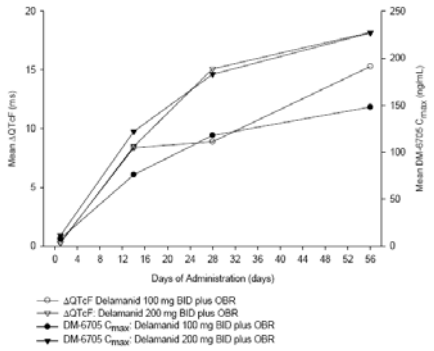


Figure 10.4.2-2 Mean QTcF Change From Baseline and Plasma DM-6705 Cmax Versus Time

Based on the full dataset during delamanid administration for 2 months, the highest mean placebo-adjusted ΔQTcF [upper 95% CI] values were 14.2 ms [15.4 ms] for a DM-6705 Cmax of 151 ng/mL (delamanid 100 mg BID) and 22.0 ms [23.8 ms] for a DM-6705 Cmax of 233 ng/mL (200 mg BID).

The time course of QTcF and ΔQTcF and PK (delamanid, DM-6704, DM-6705 and DM-6720) in **242-07-208** indicated that DM-6705 and QTcF values were essentially unchanged from Week 10 onwards. The mean change from baseline was 3.0 to 6.1 ms for delamanid 100 mg BID from Week 2 to Week 26 compared to 9.4 to 13.9 ms in the 200 mg BID group.

Further analysis of QTc data from study 204 revealed a strong association between hypoalbuminaemia and prolongation of the QtC interval. There was no correlation found between serum albumin and QTc in the placebo groups.

Patients on treatment with delamanid (+OBR) who had low albumin (< 3.4 mg/dL) significantly more often experienced ΔQTcF > 60 ms as compared to patients on delamanid with normal albumin; this difference was not observed in patients on placebo. At each time point of the study, the median ΔQTcF was higher in patients on delamanid treatment who had a low albumin level at baseline. When the frequency of patients with ΔQTcF above 60 ms was stratified by albumin and ΔQTcF at each visit, it was also apparent that patients with low albumin who were treated with delamanid more often experienced pronounced QTc prolongation. Based on the performed sub-analysis, there seems to be a 6- to 8-fold higher risk for a patient with a baseline albumin level <3.4 mg/dL to develop ΔQTcF exceeding 60 ms; the same elevation of the risk is seen if Day 56 albumin levels are used as the cut-off.

Over time, the mean ΔQTcF observed in patients with a low baseline albumin level treated with delamanid ranges between 20 ms and 25 ms as compared to 15 ms to 20 ms in patients with albumin >3.4 mg/dL.

The underlying mechanism for the observed association between hypoalbuminaemia and QTc prolongation in patients treated with delamanid is not clearly understood; the fraction of unbound drug (or metabolite), the severity of the disease or other yet unknown factors may be contributing.

2.4.4. Discussion on clinical pharmacology

Taking into account the unresolved matter of the inadequate metabolic profiling in the human mass-balance study, there are remaining uncertainties regarding delamanid and metabolite PK, and hence the risk for drug-drug interactions to occur, as well as the implications for the total effect on QTc. This uncertainty will be further addressed in a new mass balance study to investigate and to profile potential reactive metabolites.

Further on, sparse sampling in ongoing phase 3 trial (213) is not adequate to document the metabolic fate of delamanid or the potential for DDIs affecting plasma concentrations of delamanid to occur. Hence, detailed characterisation of patient plasma profiles to further assist in exploring circulating delamanid-associated molecules is imperative.

Regarding the potential effects of hepatic insufficiency on the fate of delamanid, more data are required on patients with MDR-TB and hepatic impairment during the course of study 213. Likewise, the applicant should obtain more data by allowing enrolment of patients with renal insufficiency into study 213.

Delamanid has a relatively low genetic barrier to resistance and it is truly essential that it is co-administered with other agents predicted to be active. Study 213 should include collection of full delamanid susceptibility data for baseline isolates from all patients. Additional susceptibility test data (with MIC determination) from EU reference laboratories to document the rate of resistance in circulating isolates, including those from EU countries is further required.

Finally, the data regarding the relationship between hypo-albuminaemia and risk of QTc prolongation is important to communicate to healthcare professionals.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers the following measures to address the issues related to pharmacology:

- A new human mass balance study should be carried out to investigate and profile potential reactive metabolites. The major elimination pathways of delamanid should be clarified and enzymes/transport proteins involved in major in vivo pathways should be identified in vitro. If there are reactive metabolites of likely safety importance, the major formation and elimination pathways of these metabolites, and the main enzymes/transporters involved should be identified.
- The applicant should address the margins between IC_{50} values and hepatic inlet concentrations
- For ongoing study 213, the sponsor was asked to assess the feasibility of a protocol revision evaluated

  to include collection of full delamanid susceptibility data for baseline isolates from all patients and to provide the data in the Study Report for the planned interim analysis;

  to monitor both PK and ECG data at frequent intervals in patients with mild to moderate hepatic or renal insufficiency, subject to the feasibility of modifying the protocol and the agreement by competent authorities for including these populations.
- The applicant should provide further details of the European drug susceptibility testing system once these are known, including a timetable for the provision of results.

2.5. Clinical efficacy

2.5.1. Dose response studies

Subjects enrolled into the two EBA studies had fully susceptible *M. tuberculosis*. Both studies employed once daily dosing of delamanid but only the second used the solid dispersion formulation as follows:

Table 16

Protocol No. [Location]	**2.5.1.1.1. Design and Endpoints**	**2.5.1.1.2. Treatment regimen**	**2.5.1.1.3. Number of Subjects (Males / Females)**
2.5.1.1.4. 242-06-101 [South Africa]	Open-label, randomised, dose-response, controlled trial to assess the safety, efficacy and PK of delamanid. Subjects with uncomplicated, smear positive, pulmonary tuberculosis were eligible for enrolment. The primary efficacy variable was EBA determined from sputa.	tablet (**selected powder blend formulation**) orally for 14 days at daily doses of 100 mg, 200 mg, 300 mg and 400 mg. Rifafour tablet (a combination tablet of H, R, Z and E) was administered 10 days over a 14-day treatment period. Dose was determined by body weight.	54 33 M / 21 F

Delamanid was administered once daily after a standard breakfast for 14 days. Rifafour e-275 tablets were administered once daily in the fasting state (2-5 tablets per day according to body weight).

The primary efficacy analysis focused on the Early Slopes, the Late Slopes and AUClog10 bacteria vs. time (AUC0-14). The 200 mg delamanid dose achieved a mean change point in regression slope after 5.8 days, followed by the 300 mg dose with a mean change point at 6.8 days. The 400 mg group reached

a mean change point after 7.8 days and the 100 mg group after 8.4 days. The mean AUC0-14 of log10 bacterial counts was highest for the 300 mg group (8.485) followed by 200 mg (7.672), 400 mg (2.703) and 100 mg (2.576). Similar findings applied to the ITT population.

All delamanid treatment groups had a greater negative slope (decline in log10 CFU/mL) in their respective earlier phase (prior to the regression split point being reached) than in the later phase. The largest average decrease in log10 CFU/mL (mean Early Slope of -0.15) was observed with 200 mg, for which the mean Late Slope was -0.09. The exploratory p-values showed no significant difference in either Early or Late Slope across treatment groups.

The actual counts were very variable at baseline with no trend in change from baseline values with dose.

Table 17

Table 11.4-2 Actual Bacterial Counts (PP population)

	OPC-67683 Treatment Groups				Standard Therapy N = 6
	100 mg N = 12	200 mg N = 12	300 mg N = 12	400 mg N = 12	
Actual:					
Baseline					
n	10	10	10	10	5
Mean	16,871.00	16,997.00	8,405.70	21,844.00	5,380.80
SD	12,495.04	31,272.90	8,158.42	47,544.60	5,919.09
CV%	74.1	184.0	97.1	217.7	110.0
Median	14,787.50	7,712.50	7,836.25	6,478.70	3,930.00
Min to Max	1,785.0 to 41,625.0	300.5 to 104,000.0	634.5 to 29,250.0	840.0 to 155,750.0	351.5 to 15,275.0
Endpoint					
n	10	10	10	10	5
Mean	14,397.80	1,579.00	7,824.25	5,805.40	662.43
SD	20,177.16	1,816.40	15,671.34	7,651.00	1,250.91
CV%	140.1	115.0	200.3	131.8	188.8
Median	7,275.0	1,017.7	1,587.5	2,607.5	118.0
Min to Max	108.0 to 68,500.0	43.9 to 5,750.0	0.93 to 51,000.0	499.0 to 20,850.0	0.16 to 2,895.0
Endpoint Change from Baseline					
n	10	10	10	10	5
Mean	-2,473.20	-15,418.00	-581.44	-16,038.60	-4,718.36
SD	19,561.23	29,877.50	8,653.40	43,033.70	6,472.90
Median	-3,375.0	-5,187.5	-2,612.7	-2,329.2	-3,698.0
Min to Max	-39,105.0 to 39,875.0	-98,250.0 to 882.5	-7,836.5 to 21,750.0	-136,250.0 to 12,767.5	-15,157.0 to 1,345.0
Log:					
Endpoint Change from Baseline					
n	10	10	10	10	5
Mean	-0.292	-0.976	-0.891	-0.318	-1.672
SD	0.701	0.656	1.296	0.485	1.836
Median	-0.156	-0.880	-0.696	-0.441	-1.229
Min to Max	-1.65 to 0.64	-1.93 to 0.20	-3.77 to 0.54	-0.90 to 0.41	-4.57 to 0.27

The delamanid treatment groups had lower EBA (0-2) and Slope (0-14) values vs. standard therapy. The mean Baseline Time to Culture Positivity for the delamanid groups ranged from 4.0 days (100 mg) to 4.5 days (400 mg) vs. 5.0 days with standard therapy. The mean Endpoint Time to Culture Positivity for the delamanid groups ranged from 4.2 days (100 mg) to 5.7 days (200 mg) vs. 7.3 days for standard therapy.

Overall, the applicant concluded that in the 14-day treatment period a decline of ≥ 0.9 log10CFU/mL sputum occurred i.e. with an average EBA disappearance rate of 0.040 ± 0.056 log10CFU/mL sputum/day.

No relationship between EBA and dose was observed but the applicant concluded there was an association between AUC24h and maximum change in log10CFU/mL in sputum on Day 14.

Figure 11

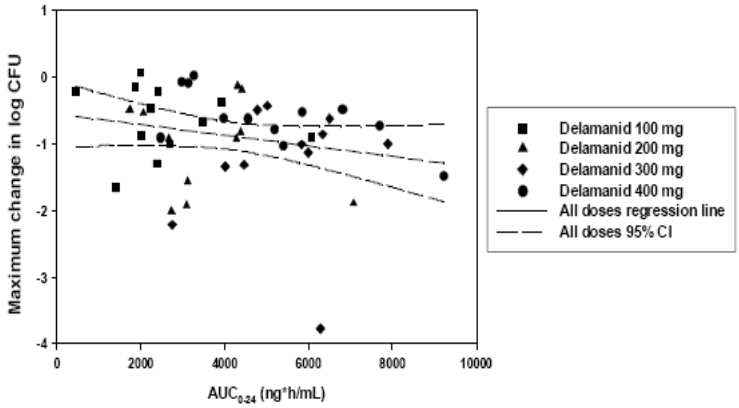


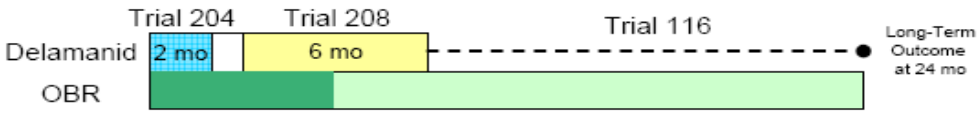
Figure 2.7.2.2.3.1.1-1 Relationship Between AUC24h and Maximum Fall in Log10 CFU/mL on Day 14

The ROC analysis revealed that an AUC24h of 3500 ng.h/mL at steady state (Day 14) was an appropriate cut-off for CFU count reduction. Modelling from a Phase I study of QD, BID and TID dosing showed that >85% of subjects on 100 mg BID and >95% on 200 mg BID would achieve an AUC of at least 4000 ng.h/mL. Based on these clinical findings and available non-clinical data the dose regimens 100 mg and 200 mg BID were selected for development.

In the Phase 2 studies in MDR-TB (242-07-204 and 208) over 95% of subjects treated with 100 mg BID for up to 6 months had delamanid steady-state exposure that exceeded an AUC24h of 3500 ng.h/mL.

2.5.2. Main studies

- The **pivotal study** in this application is the **Phase 2** study **242-07-204**, which compared delamanid 100 mg or 200 mg BID with placebo over 8 weeks only.
- The same study had a follow-on open-label phase designated as study **242-07-208** from which the complete data were provided during the procedure. Participation was voluntary.
- There was a further follow-on study (**242-10-116**) to capture long term outcome at 24 months. The complete data were provided during the procedure. Participation was voluntary and was independent of participation in 208 or having documented MDR-TB at baseline.



- Study **242-08-210** was conducted in 30 subjects with MDR TB refractory to OBR after 9 months.
- There is an ongoing **Phase 3** study (**242-09-213**), expected to report initially (SCC at 6 months) in 2014.

Study 242-07-204:

A Multi-center, Randomized, Double-blind, Placebo-controlled Phase 2 Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of Multiple Doses of OPC−67683 in Patients with Pulmonary Sputum Culture-Positive, Multidrug-resistant Tuberculosis

Methods

Study Participants

The critical inclusion criteria were as follows:

Table 18

Table 5.2.1-1	Inclusion Criteria
1.	Patients able to provide written, informed consent prior to all trial-related procedures.
2.	Male or female patients, 18 to 64 years of age, inclusive.
3.	Patient with either mycobacterial culture of sputum positive for growth of MTB or sputum smear positive for AFB within 60 days from the time of sputum collection for the respective culture or smear until the expected date of enrollment (defined as the date the ICF was signed and screening began).
4.	Patients with TB caused by isolates of MTB complex confirmed to be resistant to treatment with isoniazid and rifampicin, or with positive rapid test for rifampicin resistance on direct sputum positive for AFB or on culture positive for growth of MTB within 60 days prior to the expected date of enrollment, performed on sputum samples described above in criterion number 3.
5.	Patients with findings on chest radiograph consistent with TB.
6.	Patients able to produce sputum for mycobacterial culture.
7.	Female patients of childbearing potential must have a negative urine pregnancy test and agree to use a highly effective method of birth control (for example, 2 of the following precautions: tubal ligation, vaginal diaphragm, intrauterine device, oral contraceptives, contraceptive implant, combined hormonal patch, combined injectable contraceptive or depot-medroxyprogesterone acetate) throughout the participation in the trial and for 22 weeks after last dose (to cover duration of ovulation).
8.	Male patients must agree to use an adequate method of contraception (double barrier) throughout the participation in the trial and for 30 weeks after last dose (to cover duration of spermatogenesis).

The study excluded subjects with ECG abnormalities or laboratory tests indicating renal or hepatic dysfunction. HIV-infected subjects were enrolled if they were not on or requiring ART according to the guidance operative at the time the study was initiated.

Treatments

The study comprised three periods:

Pre-treatment Period (Days −12 to −1) for screening and establishing baseline culture status

Treatment Period (Days 1 to 56) for BID administration of delamanid or placebo plus OBR
Post-treatment Period (Days 57 to 84) for OBR to all subjects

All subjects were hospitalised for the duration of the Treatment Period. At the discretion of the investigator, subjects could be discharged from the hospital on Day 57.

Subjects were randomised to one of the following treatments in a 1:1:1 ratio:

Delamanid 100 mg BID + OBR

Delamanid 200 mg BID + OBR

Placebo + OBR

Treatment allocation was stratified by extent of pulmonary TB (i.e. cavitation) so that an equal number of subjects with cavities visible on chest radiograph were allocated to each treatment group.

Delamanid 50 mg tablets (lot numbers 07F91A050A, 07F91A050B, 07F91A050C) and matching placebo tablets were administered under fed conditions in the morning and evening within 30 minutes of the start of a meal (minimum of 550 calories with at least 25% from fat). The OBR for each subject was selected by the site's lead investigator, who could change the OBR as necessary based on tolerability or DST results at any time during the study. The OBR was to be selected in accordance with the WHO Guidelines for the Programmatic Management of Drug-resistant TB. If a subject's organism was resistant to a higher number of second-line anti-TB medications or the subject had problems tolerating some of the second-line medications the OBR could consist of < 4 medications. Note that moxifloxacin was not allowed in any OBR in this study due to the QTc effects.

After completion of 56 days of delamanid + OBR all subjects were to continue treatment with OBR alone.

Objectives

The primary objective was to evaluate the safety, efficacy and PK of 2 doses of delamanid (100 mg BID and 200 mg BID) administered orally for 56 consecutive days + OBR vs. placebo + OBR to subjects with pulmonary, sputum-culture-positive MDR-TB.

Outcomes/endpoints

The primary efficacy endpoint was the proportion of the subset of MITT subjects (sputum culture positive for MDR-TB at baseline) that achieved SCC using the MGIT system by Day 57. The time to SCC was based on the collection of the first sputum specimen with MGIT culture negative for growth of MTB that was followed by at least one additional sputum specimen with no MTB growth in MGIT at least 27 days after the first negative specimen and not followed by any sputum specimens with MGIT growth of MTB at any point during the remainder of the 84 day study period.

Morning sputum specimens were to be collected on Day −1, Day 1 and Days 8, 15, 22, 29, 36, 43, 50 and on the day after stopping delamanid/placebo (57) for culture using the MGIT system and solid media. Spot sputum sampling was to be conducted prior to the morning meal whenever possible on Days 63, 70, 77 and 84 during the Post-treatment Period. Induction of sputum was used as needed. The Company states that standardised mycobacterial methods were used (as per CLSI) but the "comprehensive laboratory manual" was not included in the dossier.

Secondary efficacy endpoints included analyses of SCC based on solid culture media and other measures of anti-mycobacterial effect.

Sample size

Relying largely on microbiological data using solid culture media, it was estimated that adding delamanid would result in 60% of subjects achieving SCC after 56 days of treatment compared with 40% on OBR alone. Based on this effect size, a study with 120 fully evaluable subjects per treatment arm would have 80% power to detect this 20% treatment difference at type I error = 0.025 (2-sided) using a 2-sample Chi-square test. The study finally randomised a total of 481 subjects to insure that at least 360 subjects would have full data available for the primary efficacy analysis.

Randomisation

This was accomplished by IWRS and was stratified by cavitations on chest radiograph. The randomisation ratio was maintained for the study as a whole, but not necessarily within each site.

Blinding (masking)

A double blind design was maintained. The DSMB and an independent unblinded DSMB support statistician were unblinded to study treatment as needed in order to adequately assess safety issues.

Statistical methods

Analysis populations were defined as:

Intent-to-Treat (ITT) - all randomised who received a dose of IMP

Modified Intent-to-treat (MITT) - all subjects who had sputum cultures positive for MDR-TB at baseline (Day −1 and/or Day 1) using the MGIT system based on results of local laboratories

Per Protocol (PP) - the subset of the MITT population that adhered to the protocol up to Day 84

Primary efficacy analysis

The primary efficacy analysis sought to ascertain whether delamanid at either dose tested was superior to placebo when given with OBR during early treatment based on proportions in the MITT population with SCC at Day 57. The study was not powered to compare the two delamanid regimens. In this primary analysis the proportions with SCC in each of the delamanid groups vs. placebo group were compared using the CMH test by randomisation strata (cavitation/no cavitation).

Results

Recruitment

Study 242-07-204 was initiated in May 2008 and enrolled 481 subjects across 17 sites in 9 countries. The numbers enrolled by site are shown below; note the predominance of site 001 in Manila (150/481), which was the only SE Asia regional site.

Table 19

Table 3.53-1 Geographical Location of Sites and Numbers of Patients Enrolled			
Site number	**Location**	**Region**	**Number of patients enrolled**
1	Makati City, Philippines	SE Asia	150
2	Riga, Latvia	Europe/Med	68
3	Tartu, Estonia	Europe/Med	7
4	Tallinn, Estonia	Europe/Med	5
5	Seoul, S. Korea	NE Asia	8
6	Seoul, S. Korea	NE Asia	8
7	Seoul, S. Korea	NE Asia	5
8	Lima, Peru	Americas	64
9	Beijing, China	NE Asia	23
10	Shanghai, China	NE Asia	39
11	Osaka, Japan	NE Asia	5
12	Tokyo, Japan	NE Asia	7
13	San Antonia, USA	Americas	2
15	Lima, Peru	Americas	35
16	Lima, Peru	Americas	32
17	Cairo, Egypt	Europe/Med	12
18	Geyongsangnam-do, S Korea	NE Asia	11
		TOTAL	**481**

Participant flow

Of the 481 subjects enrolled 90% (434/481) completed 242-07-04. Percentages that discontinued were evenly distributed across groups. The most common reason for discontinuation was subject withdrawal of consent. The majority of subjects were analysed for efficacy using the MGIT system (402/481, 83.6%) and/or using solid culture media (347/481, 72.1%).

Table 20

Table 8.1-1 Patient Disposition					
Patients	**Delamanid 100 mg BID + OBR (N = 161) n (%)**	**Delamanid 200 mg BID + OBR (N = 160) n (%)**	**Total Delamanid BID + OBR (N = 321) n (%)**	**Placebo + OBR (N = 160) n (%)**	**Total (N = 481) n (%)**
Screened	--	--	--	--	612[a]
Randomized	161 (100.0)	160 (100.0)	321 (100.0)	160 (100.0)	481 (100.0)
Treated	161 (100.0)	160 (100.0)	321 (100.0)	160 (100.0)	481 (100.0)
Completed	143 (88.8)	146 (91.3)	289 (90.0)	145 (90.6)	434 (90.2)
Discontinued:	18 (11.2)	14 (8.8)	32 (10.0)	15 (9.4)	47 (9.8)
AE	4 (2.5)	6 (3.8)	10 (3.1)	4 (2.5)	14 (2.9)
Lost to follow up	0 (0.0)	1 (0.6)	1 (0.3)	2 (1.3)	3 (0.6)
Patient met withdrawal criteria	1 (0.6)	0 (0.0)	1 (0.3)	2 (1.3)	3 (0.6)
Patient withdrawn by investigator	0 (0.0)	4 (2.5)	4 (1.2)	1 (0.6)	5 (1.0)
Patient withdrew consent	13 (8.1)	2 (1.3)	15 (4.7)	5 (3.1)	20 (4.2)
Protocol deviation	0 (0.0)	1 (0.6)	1 (0.3)	1 (0.6)	2 (0.4)
Analyzed for safety[b]	161 (100.0)	160 (100.0)	321 (100.0)	160 (100.0)	481 (100.0)
Analyzed for efficacy by MGIT system[c]	141 (87.6)	136 (85.0)	277 (86.3)	125 (78.1)	402 (83.6)
Analyzed for efficacy by solid culture media[d]	119 (73.9)	115 (71.9)	234 (72.9)	113 (70.6)	347 (72.1)

AE = adverse event; BID = twice daily; IMP = investigational medicinal product; MDR TB = multidrug-resistant tuberculosis; MGIT = Mycobacterial Growth Indicator Tubes; OBR = optimized background treatment regimen.

[a] The actual number of patients screened for the trial was 611. One patient failed screening procedures; this patient was given a new screening number and was rescreened, but was inadvertently counted as 2 patients (S0036 and S0042) in the database.

[b] Patients who received any amount of IMP.

[c] Patients who were randomized and had a positive sputum culture for MDR TB at baseline (Day −1/1) using the MGIT system.

[d] Patients who were randomized and had a positive sputum culture for MDR TB at baseline (Day −1/1) using solid culture media.

Conduct of the study

A particular issue regarding microbiology data was the report of false positive results in MGIT at sites 001 (66 patients) and 009 (16 patients). Only cultures from these sites that were definitively identified as MTB were reported as such in the database. Site 009 was placed on temporary hold due to GCP compliance issues and it was later decided that no further subjects should be enrolled. Some microbiology data from this site were considered questionable due to the GCP compliance issues, so a sensitivity analysis of the primary efficacy endpoint was performed without the microbiology data from Site 009.

Baseline data

The treatment groups were well balanced in terms of baseline characteristics. About two thirds were male, ~ one quarter was of Hispanic/Latino ethnicity and just over half were described as Asian. The age range was from 18-63 years.

All subjects had an abnormal chest radiograph consistent with the diagnosis of TB at baseline. More than two-thirds had cavitation and 24% had bilateral cavitation. Rates of signs and symptoms were comparable between treatment groups except for haemoptysis, which was reported by 32.9% and 37.5% in the delamanid groups vs. 46.9% in the placebo group.

Overall, 433/481 (90.0%) had received prior treatment for TB for at least 30 days, including 243/481 (50.5%) who had been treated with a first-line regimen only. At randomization major changes to treatment mostly involved drugs being added rather than stopped. The highest proportion of patients had no change in regimen content with respect to injectables, fluoroquinolones or pyrazinamide (range 40.3 - 60.4% in each OBR class). During the study, the majority (51%) of patients had no change to their OBR with respect to these drug groups (72% for injectables; 83.8% for fluoroquinolones; 38.8% for pyrazinamide).

Overall, 63.6% of Day 1 sputum specimens were positive for MTB complex using both MGIT and solid culture media, 15.8% were negative in both, 17.3% were positive using MGIT and negative using solid culture media while 3.1% were negative using MGIT and positive using solid culture media. Isolates were not speciated within the MTB complex.

Day 1 susceptibility test results were available for MTB isolated from 399/481 subjects enrolled. It was later clarified that susceptibility testing was only performed for isolates from MGIT and not from solid culture. It was established that testing susceptibility to delamanid was not performed at baseline in this study but it remains possible that some data could be provided assuming that the strains have been deposited in the applicant's NJ repository. There were 27/399 isolates susceptible to isoniazid and/or rifampicin, with 5 missing results for each drug. Rates for other first and second line agents varied. In both ITT and MITT populations and using MGIT and solid culture data a higher proportion of placebo subjects had XDR-TB (e.g. MITT rates were 22% for placebo vs. 17% and 13% in the delamanid groups; p-values slightly less than 0.05).

Numbers analysed

A total of 402/481 (83.6%) subjects qualified for the MITT population defined as subjects who had a positive sputum culture for MDR-TB at baseline using the MGIT system. The PP data set based on the MGIT system included 69.9% (336/481) subjects. Among 145 patients who were excluded from the PP population 79 were excluded due to their baseline culture status, while the remainder was excluded due to major protocol deviations. A total of 347/481 (72.1%) of subjects from the MITT population were analysed for efficacy using solid culture media. The PP data set based on solid culture media included 60.7% (292/481) of subjects.

Outcomes and estimation

SCC rates by MGIT up to Day 57 were statistically significantly higher in the two groups treated with delamanid (100 mg BID 45.4%; 200 mg BID 41.9%) vs. placebo [p = 0.0083 and 0.0393, respectively]). For subjects with cavitation the proportions achieving SCC were also statistically significantly higher for delamanid vs. placebo. For subjects without cavitation the differences were not significant for either delamanid group vs. placebo or overall for delamanid vs. placebo.

Table 21; Figure 12 &13

Table 9.3.1-1 Proportion of Patients Achieving Sputum Culture Conversion at Day 57 Using the MGIT System - Modified Intent-to-treat Population

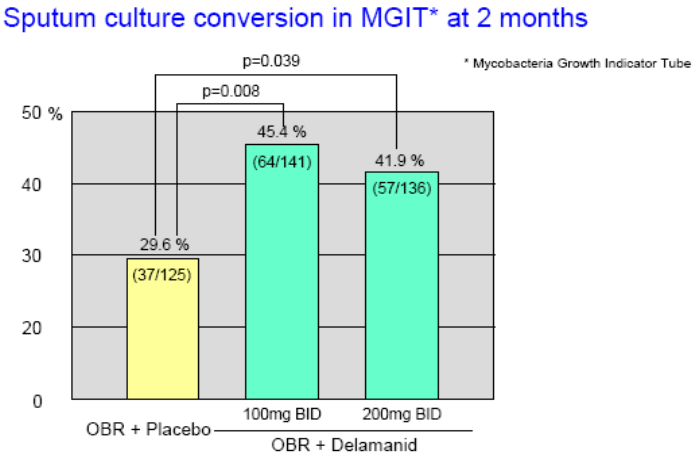
Cavitation at Baseline	Delamanid		Placebo + OBR	Treatment Comparison[a]	Risk Ratio Mean (95% CI)	P-value[b]	Dose Response[c] P-value
	100 mg BID + OBR (N = 141) n (%)	200 mg BID + OBR (N = 136) n (%)	(N = 125) n (%)				
Absent	n = 41 18 (43.9)	n = 41 15 (36.6)	n = 38 12 (31.6)	Delamanid 100 mg BID vs PLC Delamanid 200 mg BID vs PLC	1.390 (0.777, 2.488) 1.159 (0.625, 2.148)	0.2625 0.6414	0.6629
Present	n = 100 46 (46.0)	n = 95 42 (44.2)	n = 87 25 (28.7)	Delamanid 100 mg BID vs PLC Delamanid 200 mg BID vs PLC	1.601 (1.080, 2.372) 1.539 (1.031, 2.297)	0.0155 0.0311	0.0368
Total	N = 141 64 (45.4)	N = 136 57 (41.9)	N = 125 37 (29.6)	Delamanid 100 mg BID vs PLC Delamanid 200 mg BID vs PLC	1.534 (1.107, 2.124) 1.416 (1.012, 1.980)	0.0083 0.0393	0.0468

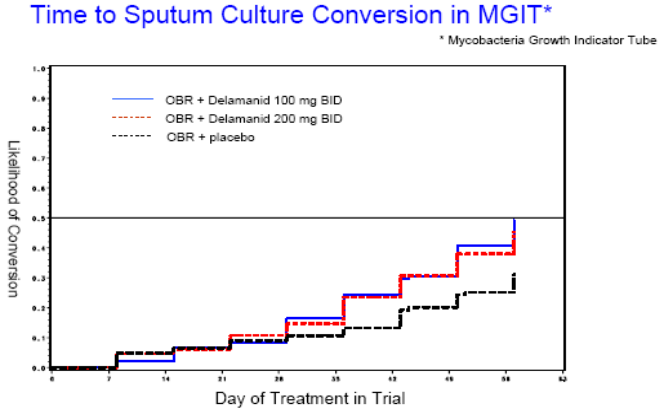
BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; MGIT = Mycobacterial Growth Indicator Tube system; OBR = optimized background treatment regimen; PLC = placebo.

[a] CMH test stratified by randomization strata (cavitation). Treatment comparison groups include OBR for all groups.

[b] P-values based on the comparison of proportions between groups.

[c] Cochran-Armitage test performed for dose response with the treatment group ordered as placebo + OBR, delamanid 100 mg BID + OBR, and delamanid 200 mg BID + OBR.





Number of Patients Not Achieving Sputum Culture Conversion by Week:

Week	0	1	2	3	4	5	6	7	8
Delamanid 100 mg BID + OBR	141	134	125	122	110	98	91	76	65
Delamanid 200 mg BID + OBR	136	127	123	114	109	96	86	77	67
Placebo + OBR	125	117	113	110	106	102	95	89	81

For SCC rates based on solid culture media data, statistically significantly higher proportions in the delamanid groups achieved SCC regardless of cavitation.

Table 22

Table 9.3.1-2 Proportion of Patients Achieving Sputum Culture Conversion at Day 57 Using Solid Culture Media - Modified Intent-to-treat Population

Cavitation at Baseline	Delamanid		Placebo + OBR	Treatment Comparison[a]	Risk Ratio Mean (95% CI)	P-value[b]	Dose Response[c] P-value
	100 mg BID + OBR (N = 119) n (%)	200 mg BID + OBR (N = 115) n (%)	(N = 113) n (%)				
Absent	n = 34	n = 32	n = 32	Delamanid 100 mg BID vs PLC	1.882 (1.048,3.382)	0.0257	
	20 (58.8)	22 (68.8)	10 (31.3)	Delamanid 200 mg BID vs PLC	2.200 (1.251,3.869)	0.0029	0.0027
Present	n = 85	n = 83	n = 81	Delamanid 100 mg BID vs PLC	1.497 (1.041,2.153)	0.0259	
	44 (51.8)	53 (63.9)	28 (34.6)	Delamanid 200 mg BID vs PLC	1.847 (1.314,2.597)	0.0002	0.0002
Total	N = 119	N = 115	N = 113	Delamanid 100 mg BID vs PLC	1.599 (1.175,2.177)	0.0021	
	64 (53.8)	75 (65.2)	38 (33.6)	Delamanid 200 mg BID vs PLC	1.939 (1.449,2.595)	<0.0001	<0.0001

BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; OBR = optimized background treatment regimen; PLC = placebo.

[a] CMH test stratified by randomization strata (cavitation). Treatment comparison groups include OBR for all groups.

[b] P-values based on the comparison of proportions between groups.

[c] Cochran-Armitage test performed for dose response with the treatment group ordered as placebo + OBR, delamanid 100 mg BID + OBR, and delamanid 200 mg BID + OBR.

Analysis of sensitivity data sets (LOCF, OC and PP) for both the MGIT system and solid culture media results supported the results from the MITT data sets.

Other MGIT system data

At all post-baseline visits the time to culture positivity was longer for both of the delamanid groups vs. placebo. Differences were not statistically significant at Day 57 using the LOCF data set but were statistically significant at Days 36 and 43 for both delamanid groups vs. placebo. The results for the two delamanid groups were comparable.

In the MITT population the LS mean of AUC of change from baseline in time to culture positivity (mean, SE) was 13.4, 13.1 and 11.1 in the delamanid 100 mg and 200 mg BID groups vs. placebo. The omnibus Kruskal-Wallis test was not statistically significant but the pair wise comparisons (delamanid 100 mg or 200 mg BID vs. placebo) showed p-values of 0.0246 and 0.0529, respectively.

The analysis of sputum culture negativity at Day 57 without consideration of subsequent culture results in the MITT population showed numerically but not statistically higher rates for delamanid vs. placebo, regardless of the presence of cavitation. In addition, the proportion with sputum culture negativity at Day 57 and Day 84 without respect to interim culture results was numerically but not statistically higher for delamanid vs. placebo.

Table 23

Table 9.4.4-1 Proportion of Patients With Sputum Culture Negative at Day 57 Using the MGIT System Without Respect to Subsequent Culture Results - Modified Intent-to-treat Population

Cavitation at Baseline	Delamanid		Placebo + OBR	Treatment Comparison[a]	Risk Ratio Mean (95% CI)	P-value[b]	Dose Response[c] P-value
	100 mg BID + OBR (N = 141) n (%)	200 mg BID + OBR (N = 136) n (%)	(N = 125) n (%)				
Absent	n = 41	n = 41	n = 38	Delamanid 100 mg BID vs PLC	1.274 (0.797, 2.037)	0.3076	0.4274
	22 (53.7)	21 (51.2)	16 (42.1)	Delamanid 200 mg BID vs PLC	1.216 (0.754, 1.961)	0.4203	
Present	n = 100	n = 95	n = 87	Delamanid 100 mg BID vs PLC	1.272 (0.953, 1.697)	0.0976	0.2450
	57 (57.0)	51 (53.7)	39 (44.8)	Delamanid 200 mg BID vs PLC	1.198 (0.888, 1.614)	0.2339	
Total	N = 141	N = 136	N = 125	Delamanid 100 mg BID vs PLC	1.272 (0.995, 1.627)	0.0518	0.1591
	79 (56.0)	72 (52.9)	55 (44.0)	Delamanid 200 mg BID vs PLC	1.203 (0.934, 1.550)	0.1506	

BID = twice daily; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; MGIT = Mycobacterial Growth Indicator Tube system; OBR = optimized background treatment regimen; PLC = placebo.

Since baseline susceptibility was perfomed only for the MGIT isolates the applicant was only able to analyse outcomes by number of predicted active drugs in the OBR for these cases. In addition the

analysis was confined to those taking any of an injectable agent (INJ), a fluoroquinolone (FQ), pyrazinamide (PZA) or ethambutol (EMB). The numbers who were infected with a sensitive strain and received a given drug was approximately 25% for PZA, 19% for INJs, 68% for FQs and 29% for EMB.

- SCC rates among those with strains sensitive to PZA and received it were 62.9%, 51.5% and 23.5% in the DLM 100 mg BID, 200 mg BID and Placebo arms, respectively.
- For INJs the corresponding SCC rates were 71.4%, 44.8% and 25.0% in the DLM 100 mg BID, 200 mg BID and Placebo arms, respectively.
- For FQs the corresponding rates were 51.5%, 40.4% and 32.9% in the DLM 100 mg BID, 200 mg BID and Placebo arms, respectively.
- For EMB the corresponding rates were 52.5%, 40.9% and 26.5% in the DLM 100 mg BID, 200 mg BID and Placebo arms, respectively.

The applicant observed that:

- Across arms the highest proportion received 1 type of active drug (38.8%), followed by no drug (28.4%) and 2 types of drugs (24.1%), with relatively few (8.7%) having received 3 active drugs.
- The proportions achieving SCC at 2 months were higher for each of the delamanid groups vs. placebo for the patients who received no active drug, 2 types and 3 types of active drugs in the OBR.
- For the patients who received 1 type of active drug (predominantly a fluoroquinolone) the 2 months SCC proportions were similar for each of the 3 treatment arms.

Since this analysis is confined to INJ, PRZ or FQs these patients could have been receiving other agents to which their strain was susceptible so the 114 in the analysis that did not receive an agent from the 3 classes that was predicted to be active cannot be assumed to have received delamanid monotherapy. The SCC rates in the delamanid 100 mg BID group increased considerably when 2 or 3 types of agents were included in the OBR but it was not possible to discern such a clear trend for the 200 mg BID group or placebo group.

Other solid media culture data

The proportion of MITT subjects with sputum culture negative at Day 57 without respect to subsequent culture results was statistically significantly higher for delamanid vs. placebo. A statistically significant dose response across the 3 treatment groups was observed ($p = 0.0007$). In the presence of cavitation the difference between delamanid and placebo did not reach statistical significance. The proportion of subjects with sputum culture negative for growth at Day 57 and Day 84 without respect to interim culture results was statistically significantly higher for delamanid vs. placebo.

Table 24

Table 9.4.6-1 Proportion of Patients With Sputum Culture Negative at Day 57 Using the Solid Culture Media Without Respect to Subsequent Culture Results - Modified Intent-to-treat Population							
Cavitation at Baseline	Delamanid		Placebo + OBR (N = 113) n (%)	Treatment Comparison[a]	Risk Ratio Mean (95% CI)	P-value[b]	Dose Response[c] P-value
	100 mg BID + OBR (N = 119) n (%)	200 mg BID + OBR (N = 115) n (%)					
Absent	n = 34 24 (70.6)	n = 32 24 (75.0)	n = 32 14 (43.8)	Delamanid 100 mg BID vs PLC Delamanid 200 mg BID vs PLC	1.613 (1.030, 2.527) 1.714 (1.103, 2.664)	0.0287 0.0116	0.0095
Present	n = 85 54 (63.5)	n = 83 58 (69.9)	n = 81 42 (51.9)	Delamanid 100 mg BID vs PLC Delamanid 200 mg BID vs PLC	1.225 (0.940, 1.596) 1.348 (1.046, 1.736)	0.1289 0.0183	0.0176
Total	N = 119 78 (65.5)	N = 115 82 (71.3)	N = 113 56 (49.6)	Delamanid 100 mg BID vs PLC Delamanid 200 mg BID vs PLC	1.323 (1.053, 1.661) 1.438 (1.155, 1.791)	0.0141 0.0008	0.0007

MGIT and solid culture media data

The benefit ratios (i.e. that subjects treated with either dose of delamanid BID would achieve SCC more rapidly than subjects treated with placebo; see table) calculated by the applicant showed that:

- With the MGIT system, the likelihood of achieving final SCC by Day 57 was 73% and 59% higher for the delamanid 100 mg and 200 mg groups, respectively, vs. placebo. Results were statistically significantly higher for both doses of delamanid vs. placebo for subjects with cavitation at baseline.
- The benefit ratios were higher with solid culture media (probability of final SCC by Day 57 was 85% and 130% higher for the delamanid 100 mg and 200 mg BID groups, respectively, vs. placebo). Also, results were statistically significantly higher for both doses of delamanid vs. placebo for subjects without cavitation at baseline and for 200 mg BID vs. placebo for subjects with cavitation at baseline.
- Results of the sensitivity analyses (LOCF, OC, and PP data sets) were consistent with those of the MITT data set using both the MGIT system and solid culture media.

Table 25

Table 9.4.11-1 Benefit Ratios for Patients Achieving Sputum Culture Conversion, Modified Intent-to-treat Population				
Comparison	MGIT System		Solid Culture Media	
	Hazard Ratio[a], Mean (95% CI)	p-value[b]	Hazard Ratio[a], Mean (95% CI)	p-value[b]
Delamanid 100 mg BID + OBR vs placebo + OBR	1.727 (1.152, 2.591)	0.0056	1.846 (1.235, 2.759)	0.0016
Delamanid 200 mg BID + OBR vs placebo + OBR	1.585 (1.048, 2.399)	0.0232	2.301 (1.555, 3.405)	< 0.0001

BID = twice daily; CI = confidence interval; MGIT = Mycobacterial Growth Indicator Tube; OBR = optimized background treatment regimen.

[a] Hazard ratio (ie, benefit ratio) computed with SAS PROC PHREG for comparisons with placebo.

[b] P-value was derived from log-rank test with SAS PROC LIFETEST for comparisons with placebo.

XDR-TB

Both the MGIT and solid culture method showed that a higher proportion in the placebo + OBR group had XDR-TB vs. either of the delamanid groups. The numbers in some of the cells in the table below are very small. Nevertheless, a lower percentage of patients with XDR-TB achieved SCC compared with patients who had MDR-TB while SCC was achieved in a greater percentage of patients in both delamanid groups compared to the placebo group regardless of whether patients had XDR-TB or MDR-TB. The treatment effect was greater in the XDR-TB subset based on solid culture and, for 200 mg BID, also for MGIT data.

Table 26

Table 3.49-2 Proportion of Patients with MDR-TB and XDR-TB Achieving SCC						
Test Method/ Treatment Group	SCC achieved					
	MDR only		XDR only		All	
	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)
MGIT						
100 mg	57 (48.7)	60 (51.3)	20 (83.3)	4 (16.7)	77 (54.6)	64 (45.4)
200 mg	66 (55.9)	52 (44.1)	13 (72.2)	5 (27.8)	79 (58.1)	57 (41.9)
Placebo	63 (64.3)	35 (35.7)	25 (92.6)	2 (7.4)	88 (70.4)	37 (29.6)
Solid Media						
100 mg	42 (42.9)	56 (57.1)	13 (61.9)	8 (38.1)	55 (46.2)	64 (53.8)
200 mg	30 (31.3)	66 (68.8)	10 (52.6)	9 (47.4)	40 (34.8)	75 (65.2)
Placebo	51 (60.0)	34 (40.0)	24 (85.7)	4 (14.3)	75 (66.4)	38 (33.6)

Exploratory Multiple Logistic Regression analysis of SCC

A multiple logistic regression analysis that combined all potential independent predictive factors for SCC into one model was conducted for the MGIT and solid culture media datasets in the MITT population.

- A longer time to culture positivity **using MGIT at baseline** correlated with a higher likelihood of SCC at Day 57 (p = 0.0003). Moderate previous treatment was associated with an approximate 3-fold higher likelihood of SCC at Day 57 than limited previous treatment (p = 0.0193).
- Baseline resistance to fluoroquinolone agents and at least one of the injectable anti-TB agents was associated with a 4.5-fold decreased likelihood of SCC at Day 57 (p = 0.0019).
- The odds of achieving SCC within 57 days decreased by 2.5% for each year age increase (p = 0.0181).
- A longer time to positivity in MGIT at baseline showed that for the **solid culture** MITT population, lower bacterial load was also associated with a higher likelihood of SCC at Day 57 (p < 0.0001).
- The use of a later generation fluoroquinolone increased the likelihood of SCC (p = 0.0594).
- Baseline resistance to fluoroquinolone agents and injectable anti-TB agents was associated with an approximate 4-fold decreased likelihood of SCC at Day 57 (p = 0.0106).

In the subgroup analyses by regions (the Americas, European/Mediterranean, NE and SE Asia):

- Using the MGIT data higher proportions treated with delamanid achieved SCC vs. placebo except in NE Asia and in SE Asia in the delamanid 200 mg BID group.
- Using solid culture media, higher proportions treated with delamanid achieved SCC vs. placebo in all of the regions.

In the subgroup analyses by ethnicity (Hispanic or Latino vs. not Hispanic or Latino):

- Using the MGIT data proportions of Hispanic or Latino subjects achieving SCC were 12/39 (30.8% 100 mg BID), 18/38 (47.4% 200 mg BID) and 7/39 (17.9% placebo). The difference was statistically significant for 200 mg BID vs. placebo (p = 0.0067). The corresponding rates for non-Hispanic or non-Latino subjects were 52/101 (51.5%), 39/98 (39.8%) and 30/86 (34.9%) with statistical significance for 100 mg BID (p = 0.0235).

- Using solid culture media data proportions of Hispanic or Latino subjects achieving SCC were 14/38 (36.8%), 20/34 (58.8%) and 8/37 (21.6%), respectively, with statistical significance for 200 mg BID vs. placebo (p = 0.0016). The proportions of non-Hispanic or non-Latino subjects achieving SCC were 49/80 (61.3%), 55/81 (67.9%) and 30/76 (39.5%) with statistical significance for 100 mg (p = 0.0071) and 200 mg BID (p = 0.0004) groups vs. placebo.

Effects of anti-TB medications on SCC outcome in the MITT

- Use of a later generation fluoroquinolone demonstrated an increased likelihood that subjects would achieve SCC at Day 57 using MGIT with a trend toward statistical significance.

Table 27

Table 9.5.2-1 Multiple Logistic Regression Analysis of Sputum Culture Conversion - Modified Intent-to-treat Population

Parameter for Comparison	MGIT System		Solid Culture Media	
	Odds Ratio[a] Mean (95% CI)	P-Value	Odds Ratio[a] Mean (95% CI)	P-Value
Delamanid 100 mg BID + OBR vs placebo + OBR	1.770 (1.008, 3.110)	0.0470	2.281 (1.224, 4.249)	0.0094
Delamanid 200 mg BID + OBR vs placebo + OBR	1.364 (0.772, 2.409)	0.2853	4.059 (2.145, 7.683)	< 0.0001
Unilateral cavitation vs no cavitation	1.106 (0.644, 1.902)	0.7146	1.086 (0.583, 2.023)	0.7939
Bilateral cavitation vs no cavitation	0.843 (0.444, 1.600)	0.6009	0.527 (0.255, 1.088)	0.0834
Resistance to injectables only vs sensitive to injectables and/or quinolones	0.978 (0.558, 1.713)	0.9376	1.129 (0.568, 2.242)	0.7296
Resistance to quinolones only vs sensitive to injectables and/or quinolones	2.086 (0.240, 18.093)	0.5048	0.203 (0.013, 3.188)	0.2563
Resistance to both injectables and quinolones vs sensitive to injectables and/or quinolones	0.222 (0.086, 0.574)	0.0019	0.244 (0.083, 0.720)	0.0106
Moderate vs limited previous treatment	3.043 (1.198, 7.729)	0.0193	--	--
Extensive vs limited previous treatment	0.946 (0.492, 1.818)	0.8670	--	--
Previous exposure: second-line vs first-line	--	--	1.472 (0.766, 2.828)	0.2459
Previous exposure: third-line vs first-line	--	--	0.395 (0.118, 1.315)	0.1299
Region America vs North East Asia	0.651 (0.270, 1.572)	0.3403	0.300 (0.107, 0.837)	0.0215
Region European/Mediterranean vs North East Asia	1.549 (0.604, 3.970)	0.3625	0.858 (0.224, 3.287)	0.8226
Region South East Asia vs North East Asia	1.993 (0.830, 4.789)	0.1230	3.286 (0.943, 11.457)	0.0618
Time to positivity at baseline	1.089 (1.040, 1.140)	0.0003	1.143 (1.073, 1.217)	< 0.0001
Pyrazinamide: Yes vs No	1.809 (0.937, 3.490)	0.0772	--	--
Late generation fluoroquinolones	--	--	2.373 (0.966, 5.821)	0.0594
Age (years):	0.975 (0.955, 0.996)	0.0181	--	--

Effects of previous treatment history on SCC

- The odds of SCC occurring in subjects who had previous exposure to third line anti-TB medications were approximately 4 times lower than those exposed only to first-line anti-TB medications (odds ratio = 0.26; p < 0.0039).
- Previous exposure to second-line anti-TB medications did not prove to be an independent predictor of SCC in this analysis. The results using solid culture media were similar to those using MGIT.
- The MGIT data showed that the odds of SCC occurring in subjects who had moderate previous treatment with anti-TB medications were ~ 2.5 times those with limited previous treatment.

Additional analyses of the effects of region and ethnicity (see logistic regression above)

There was no benefit for delamanid in NE Asia based on MGIT while rates for solid culture in this region were 52% and 58% for delamanid vs. 40% for placebo. The MGIT data showed a benefit for 100 mg BID vs. 200 mg BID only in SE Asia (single site in Manila; 150 total enrolled) yet the solid culture media data showed a comparable benefit for both doses.

Figure 14

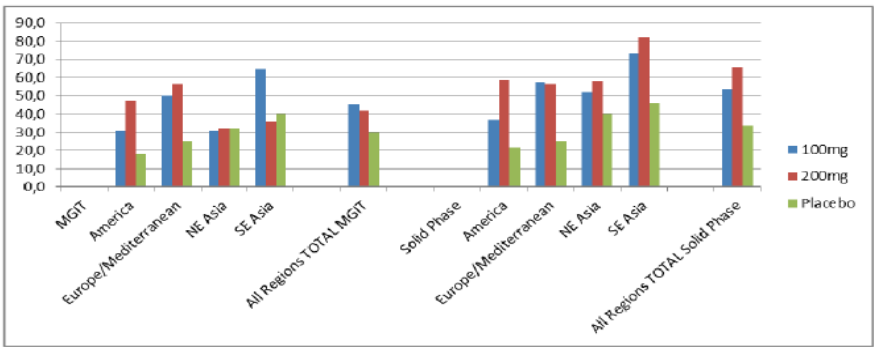


Figure 3.56-1 **Bar Charts of the Proportion of Patients Achieving SCC Assessed using the MGIT System and Solid Media by geographical region**

- The overall number of patients contributing to the solid phase assessment of response was 347, which is 55 (14%) less than in the MGIT assessment (402 patients) and 36/55 were entirely in the single Philippines centre comprising the SE Asia region (150 total patients enrolled).
- The MGIT SCC for 100 mg BID group in NE Asia (31.0%) is similar to that for the Americas (30.8%).
- The MGIT SCC for 200 mg BID group in NE Asia (32.1%) is similar to that for SE Asia (36.2%)
- The SCC for the placebo group in NE Asia (32.0%) lies within the middle of the range of SCC results for the placebo groups across all regions (17.9% - 40.0%).

The applicant concluded that the similar responses for all 3 treatment groups in the NE Asia region are possibly just coincidence rather than indicative that the NE Asia region was either different or anomalous. Sites in NE Asia tended to be more tertiary referral than primary or even secondary care facilities. In keeping with this the proportion of patients in each region with XDR-TB using the MGIT system ranged from America 6.9%, European/Mediterranean 17.4%, SE Asia 0%, and NE Asia 59.8% and results were similar using solid media. Thus, the NE Asia population contained a disproportionate number of XDR-TB cases and had the highest rate of previous third-line anti-TB therapy than in any other region. In contrast, in the single SE Asia site, where 100 mg BID seemed better than either 200 mg BID or placebo based on MGIT, there was no XDR-TB.

The applicant concluded that the NE Asia population was least likely to benefit substantially from the addition of delamanid as a single bactericidal treatment agent, which may explain why MGIT results showed no clear benefit in NE Asia, while this finding was not the case using the less sensitive solid media for assessing SCC. Finally, there was no indication from the population PK data that drug exposure to delamanid (as indicated by AUC0-24) in the NE Asia population of patients was suboptimal; if anything it may have been somewhat greater among patients in this region than in other regions.

Analysis of SCC with dose and according to plasma exposure data (PK/PD analysis)

The proportions with SCC using the MGIT system increased from 29.60% at zero mg/kg (placebo) to 48.04% at 2 to 3.5 mg/kg but dropped to 38.64% for doses ≥ 3.5 mg/kg, and no statistically significant dose response was observed.

Figure 15

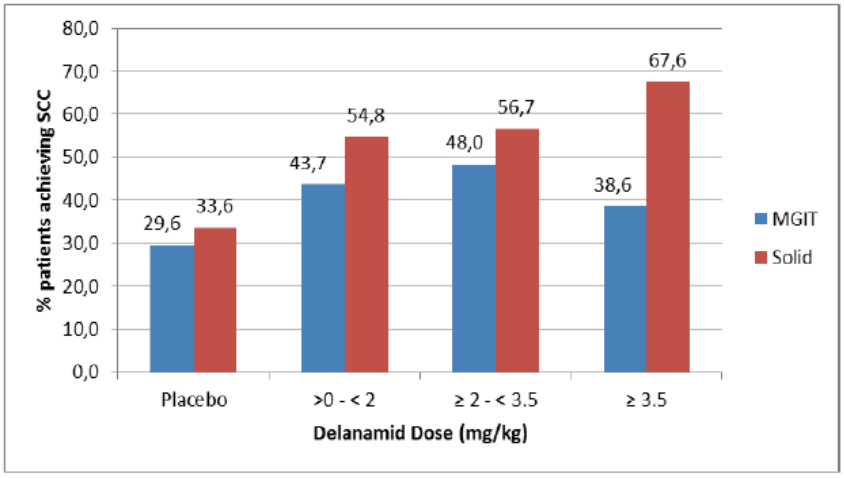


Figure 3.57-1 **Proportion of Patients Achieving SCC by Delamanid Dose Determined by MGIT and Solid Media.**

When subdividing this analysis by region, the MGIT SCC rates for each delamanid mg/kg subgroup were higher vs. placebo in the USA and the European Mediterranean region but the effect of delamanid vs. placebo was not consistent in NE or SE Asia (note that numbers per cell are often very small).

Figure 16

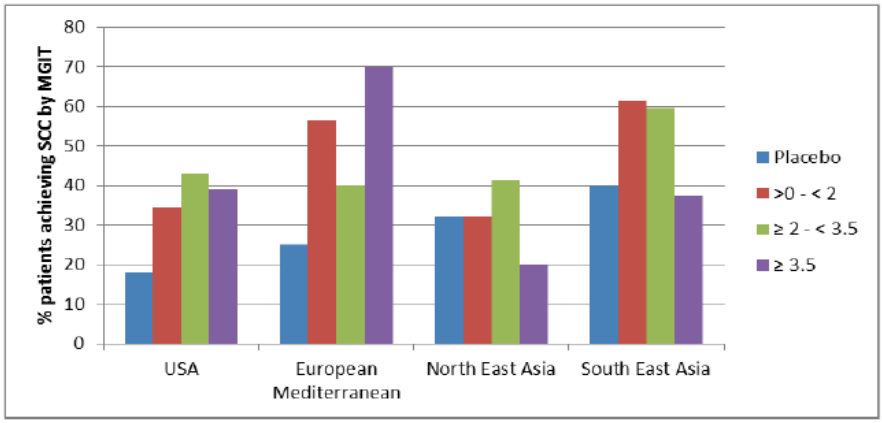


Figure 3.57-2 **Proportion of Patients Achieving SCC by Region and Delamanid Dose determined by MGIT**

The solid media SCC rate increased from 29.6% at 0 mg/kg (i.e. placebo) to 67.6% in the sub-group that received ≥ 3.5 mg/kg delamanid. The data were more consistent than the MGIT data in showing higher SCC rates by mg/kg subgroup vs. placebo.

Figure 17

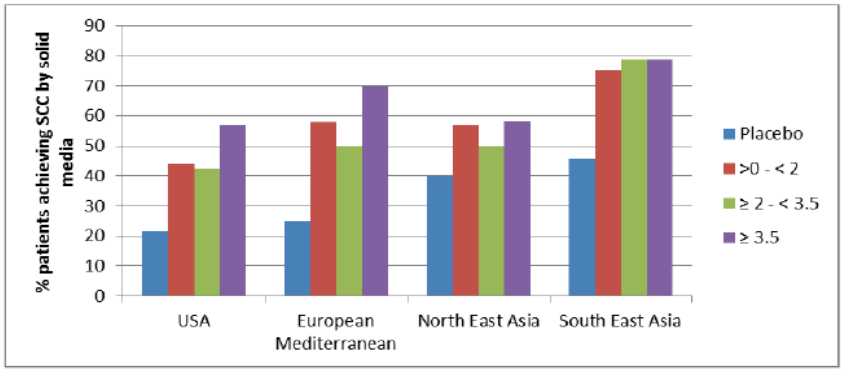


Figure 3.57-3 **Proportion of Patients achieving SCC by Region and delamanid Dose determined by Solid Media**

The analysis of SCC as a function of delamanid exposure, expressed as average AUC24h over the 56-day treatment period, suggested that SCC increased up to an inflection point (AUC24h) of 3000 ng.h/mL and a plateau above 5000 ng.h/mL.

Additional PK/PD analyses of study 204 data during the procedure attempted to further support the proposed dose regimen. Bactericidal efficacy was presented for each patient by the dichotomous primary outcome variable sputum culture conversion SCC (yes/no; based on the MGIT-MITT population) and by patient's slope for time-to-positivity (TTP; MGIT), indicative for bacterial load reduction per day.

Figure 18 & 19

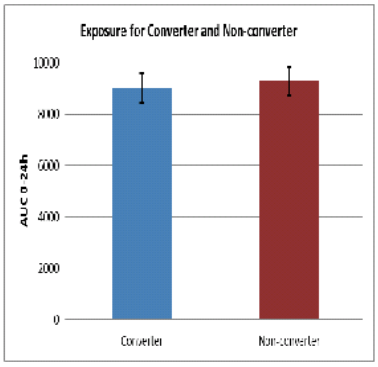


Figure 2-2 **AUC [95% CI] for Converters and Non-converters**

Mean exposure [95% CI] of converter: $AUC_{0\text{-}24h}$ = 9001.35 h*ng/mL [95% CI: 8441.83-9560.87]

Mean exposure [95% CI] of non-converter: $AUC_{0\text{-}24h}$ = 9281.27 h*ng/mL [95% CI: 8751.76-9810.78]

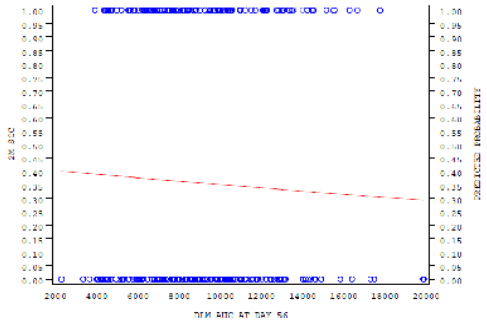


Figure 2-1 **Logistic regression plot for AUC0-24h vs. Probability for Conversion in Trial 204**

The applicant concluded that although 200 mg BID resulted in an approximately 50% higher exposure (mean AUC0-24h [CV %I] = 11837 [33.6 %]) than 100 mg BID (mean AUC0-24h [CV %I] = 7925 [37.5 [%]), the efficacy end-point (SCC; MGIT) showed comparable results for both delamanid doses. Exposure measured at month 2 appeared to be above the potential threshold for maximum efficacy as increased exposure did not result in increased efficacy.

The applicant also looked at time-to-positivity (TTP) by AUC. The mean TTP increased over 2 months in all 3 treatment groups, indicating a reduced bacterial load. The time to sputum mycobacterial culture growth in the MGIT assay at Day 56 (LOCF) showed a mean increase from baseline of 22.1 days for 100 mg delamanid, 22.4 days for 200 mg delamanid and 19.3 days placebo; the differences compared to placebo were not statistically significant at Day 56 (100 mg delamanid, p=0.0786; 200 mg delamanid, p=0.0583).

Figure 20

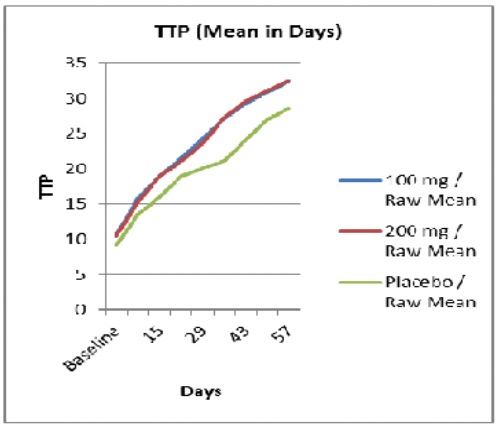


Figure 3-1 **TTP for 100 mg, 200 mg and Placebo**

The mean slope for the 100 mg (mean slope = 0.265/day) and 200 mg (mean slope = 0.253/day) were higher than the slope for placebo (mean slope = 0.203/day) (p-values were 0.0153 for 100 mg vs. placebo and 0.0417 for 200 mg vs. placebo, ANCOVA, cavitation and baseline TPP as covariates). The analysis of delamanid slopes as a function of AUC0-24h at the end of 2-month therapy did not reveal any

association between both parameters for the combined groups (R2=0.002) nor for any of both delamanid treatment groups separately (R2=0.009 for 100 mg and R2=0.001 and 200 mg. This finding suggests that during steady state conditions for 100 and 200 mg BID delamanid, patients were above the exposure threshold for maximum efficacy evaluated as increase in TTP per day.

An assessment of the threshold was performed using data from the EBA study in which 100 mg, 200 mg, 300 mg and 400 mg QD were administered after standard breakfasts for 14 days to newly diagnosed TB patients. EBA was not statistically different between delamanid doses and exposure was less than dose proportional. EBA assessed as a function of AUC0-24h from all patients was weakly correlated with EBA at Day 14 (i.e. a higher AUC0-24h was associated with greater decrease in log-CFU counts). This association no longer held when only patients with an AUC0-24h above 3500 h*ng/mL were considered. The applicant concluded that the threshold of AUC0-24h for maximum bactericidal efficacy was between 3500 and 5500 h*ng/mL.

Study 242-07-208 (and follow-up study 242-10-116)

A Phase 2, Multi-center, Uncontrolled, Open-label Trial to Evaluate Safety, Tolerability, and Efficacy of Orally Administered OPC-67683 as 100 mg BID with Optional Titration to 200 mg BID for up to Six Months Exposure in Patients with Pulmonary Multi-drug Resistant Tuberculosis (208)

Registry for Data Collection to Determine Final Treatment Outcomes of Multidrug Resistant Tuberculosis Patients Previously Enrolled in Otsuka Trials Assessing Treatment with OPC-67683 (116)

In study 242-07-208 subjects were to be enrolled no earlier than day 84 of study 204 and no later than 30 days after day 84 or 30-90 days after site initiation for study 208. The final dataset for the **integrated analysis of 242-07-08 and 242-10-116** reported on 87.5% (421/481) of the patients initially randomised into 204 (not all had confirmed MDR-TB at baseline). Of these 421 patients 53.4% were from Asia and 66% were men. The median age was 34 years (range 18-63) and 56 (13.3%) had confirmed XDR-TB.

From the total 481 randomised into 204 there were 213 patients who chose to enter study 208 and 268 patients who did not enter study 208. Observational data were collected in study 116 from 421 patients, comprising 192/213 who entered study 208 and 229/268 who did not enter study 208.

Throughout 204/208 there were:

- 38 patients who received ONLY 100 mg BID and were followed through 116
- 22 who received ONLY 200 mg BID and were followed through 116
- 73 who did NOT receive delamanid in either study and were followed through 116

but it seems that not all of these had MDR-TB at baseline in 204. All other patients who chose to participate in 208 received a different dose of delamanid for at least some period of time vs. the dose they were randomised to receive in 204. Also, patients entered 208 at different time points relative to their participation in 204 - 54.5% within 2 months but 37.6% after a gap of more than 4 months.

Figure 21

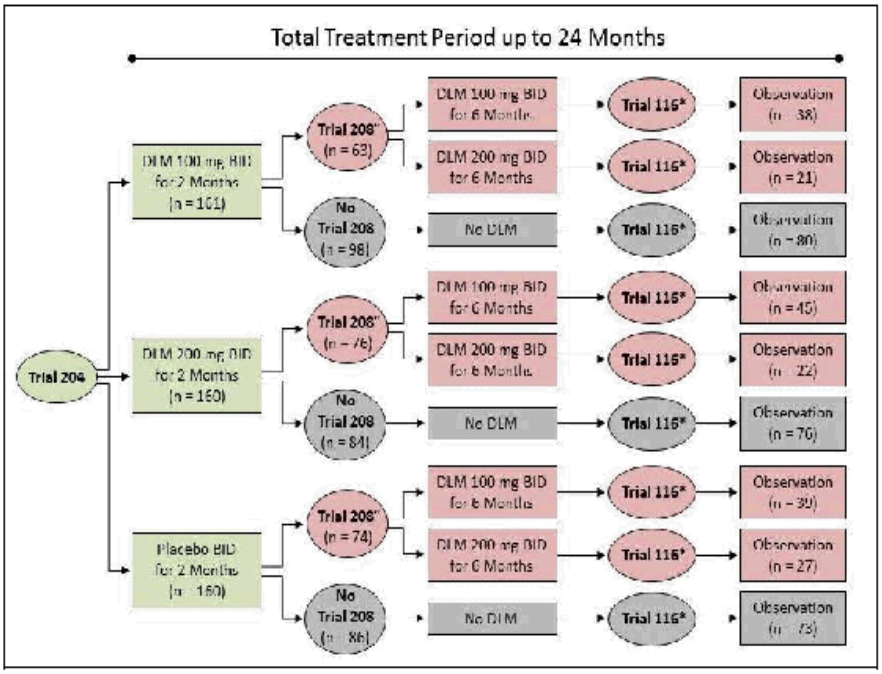


Figure 3.3-2 **Flow of MDR-TB Patients through Trial 204, Trial 208, and Trial 116 over 24 months for the Integrated Efficacy Analysis of Delamanid Treatment**

The analysis of sustained effect was based on the mITT population (i.e. sputum culture positive for MDR-TB at baseline) and on the solid culture data (rather than the MGIT data). In this analysis the applicant combined all data for delamanid (i.e. regardless of the dose[s] used).

Additionally, the applicant assessed sustained SCC after 8, 6, 2 or 0 months of treatment with delamanid. For this the results for groups of patients receiving 8 or 6 months were combined into one group for analysis of delamanid treatment ≥ 6 months (n = 192 patients). The remaining 229 patients who received 2 months of delamanid (156 patients) at either dose or placebo (73 patients) and who received no further treatment with delamanid during the remainder of MDR-TB treatment were combined into one group for analysis of delamanid treatment ≤ 2 months. The total of 192 treated for at least 6 months and 229 treated for < 2 months is 421, which implies the analysis was not confined to the proven MDR-TB population (402 by MGIT and 347 by solid culture).

For time to sustained SCC over the full treatment period, the Kaplan–Meier curve of the delamanid treatment ≥ 6 months group had a substantial increase above the curve for the delamanid treatment ≤ 2 months group starting at 3 months (Day 84).

Figure 22

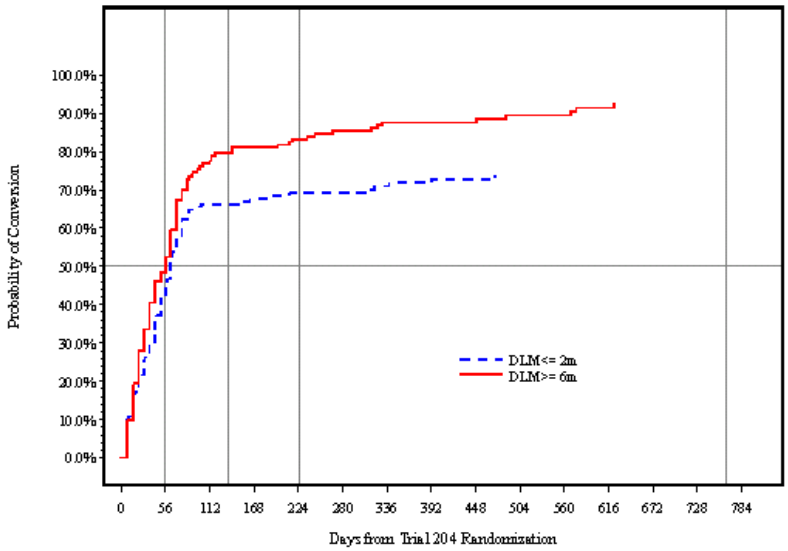


Figure 3.3-3 Survival Analysis of Days to sustained Sputum-Culture Conversion based on sputum culture results on solid media [a]

[a]The time point at which the Kaplan-Meir curves stop for each treatment group represent the time after which no further SCC is achieved for patients in the corresponding treatment group.

Both curves reached a relative plateau at approximately 11 months. Although a large proportion of patients were treated for a total of 24 months, the Kaplan-Meir curves stop after approximately 20 months for the delamanid treatment ≥ 6 months group and 16 months for the delamanid treatment ≤ 2 months due to the fact that no additional patients achieved SCC beyond those time points.

The applicant concluded that the results from this survival analysis demonstrate that patients treated with delamanid ≥ 6 months experienced accelerated SCC that was sustained throughout the treatment period and that overall a higher proportion of these patients achieved sustained SCC compared to those treated with delamanid ≤ 2 months (including those who never received delamanid).

As shown in the table below (which is confined to the 301 with MDR-TB on solid culture at 204 baseline who chose to be followed; note that the XDR-TB group is a subset of the MDR-TB) by the end of treatment 90.9% (130/143) in the delamanid ≥ 6 months group achieved sustained SCC compared to 70.9% (112/158) in the delamanid ≤ 2 months group. Among the patients in the delamanid ≤ 2 months group, out of 48 who had no treatment with delamanid at any time, 37 (77.1%) achieved sustained SCC. This compares with 75 out of 110 (68.2%) of those who received delamanid for a maximum of 2 months.

Table 28

Table 3.3-2	Proportion of MDR-TB Patients and the Sub-set of XDR-TB Patients with Positive Sputum Cultures at Baseline Achieving Sustained Sputum Culture Conversion by Duration of Delamanid Treatment			
Duration of Delamanid Exposure	**MDR-TB**		**XDR-TB**	
	Patients (N = 301)	**Sustained SCC n (%)**	**Patients (N = 56)**	**Sustained SCC n (%)**
≥ 6 Months	143	130 (90.9)	40	31 (77.5)
≤ 2 Months	158	112 (70.9)	12	5 (41.7)
TOTAL	301	242 (80.4)	52	36 (69.2)

MDR-TB = Multi-drug resistant tuberculosis; XDR-TB = extensively drug-resistant tuberculosis; N = total number of patients, n = number of patients, SCC = sputum culture conversion.

In the subset of XDR-TB patients in the delamanid ≥ 6 months group, 77.5% (31/40) achieved sustained SCC compared to 41.7% (5/12) patients in the delamanid ≤ 2 months group.

The full ITT population of 421 patients who agreed to participate in 116 was assessed for final treatment outcomes. The outcomes were determined by clinicians managing the patients' care and were based on a given patient's clinical status, including sputum culture status, at the end of treatment. Definitions for the outcomes were based on those outlined in the WHO guidelines and were subsequently grouped as favourable or unfavourable.

Table 29

Table 3.3-3	Final outcomes (with ITT population) after 24 Months of Treatment for MDR-TB Patients Randomized in Trial 204 (ITT Population) and Followed in Trial 116 by Duration of Treatment with Delamanid added to an Optimized Background Regimen per WHO Recommendations				
Duration of Delamanid Exposure	**Total ITT Patients N**	**24-Month Outcomes**			
		Favorable[a] n (%)	**95% Confidence Interval**	**Death n (%)**	**95% Confidence Interval**
≥ 6 Months	192	143 (74.5%)	67.7 - 80.5	2 (1.0%)	0.1 – 3.7
≤ 2 Months	229	126 (55.0%)	48.3 - 61.6	19 (8.3%)	5.1 - 12.7
TOTAL	421	269 (63.9%)	59.1 - 68.5	21(5.0%)	3.1 - 7.5
No delamanid[b]	73	42 (57.5)		6 (8.2%)	

N = total number of patients; n = number of patients; ITT = intention-to-treat; MDR-TB = multidrug-resistant tuberculosis.

[a] As per WHO's definition for treatment success, the favourable outcomes category was comprised of patients who met the criteria for cured or treatment completed.

[b] Patients in "No delamanid" group are a subset of the "≤ 2 Months" group.

Favourable outcomes were significantly increased in patients in the delamanid ≥ 6 months group vs. ≤ 2 months group and mortality was also reduced (2 vs. 19). Also, 42/73 (57.5%) patients who received no treatment with delamanid during the 24-month treatment period had a favourable outcome and 6/73 (8.2%) died.

The applicant considered that the 73 that did not receive delamanid can serve as a control group for the overall analysis. This group, which is anyway a subset of the 229 in the ≤ 2 months group, showed a comparable favourable response rate vs. the total treated for no more than 8 weeks.

The applicant proposed that the fact that substantial numbers received more than one dose of delamanid throughout 204/208 is addressed by the results of 204 at week 8 that relate to only one assigned dose.

The applicant also concludes that the results are conservative since a much greater proportion in the delamanid ≥ 6 months group had XDR-TB vs. the ≤ 2 months group (22.9% vs. 5.2%). In the smaller subset with XDR-TB the results are shown below.

Table 30

Table 3.3-4	Final outcomes (with ITT population) after 24 Months of Treatment for XDR-TB Patients Randomized in Trial 204 (ITT Population) and Followed in Trial 116 by Duration of Treatment with Delamanid added to an Optimised Background Regimen per WHO Recommendations				
Duration of Delamanid Exposure	**Total ITT Patients N**	**24-Month Outcomes**			
		Favorable[a] n (%)	**95% Confidence Interval**	**Death n (%)**	**95% Confidence Interval**
≥ 6 Months	44	27 (61.4)	45.5 – 75.6	0 (0.0)	-
≤ 2 Months	12	6 (50.0)	21.1 – 78.9	3 (25.0)	5.5 – 57.2
TOTAL	56	33 (58.9)	45.0 – 71.9	3 (5.4)	1.1 – 14.9

N = total number of patients; n = number of patients; ITT = intention-to-treat; XDR-TB = extensively drug-resistant tuberculosis.

[a] As per WHO's definition for treatment succes, the favourable outcomes category was comprised of patients who met the criteria for cured or treatment completed.

The applicant also provided several additional analyses in an attempt to support a lack of bias resulting from the lack of randomisation of subjects into study 208 and the fact that follow-up in study 116 was according to subject volition.

However, CHMP questioned the reliability of these further analyses. It is not possible to agree that the results of 208 and 116 are without potential bias. Even if the data from 208 and 116 were to be accepted they fail to support a recommendation for 100 mg BID delamanid. The available datasets actually do not support any clear conclusion regarding the dose, they only point strongly to the insufficiency of 8 weeks delamanid.

To further explain the problem over and above the fact that 208 was not a randomised study, that the dose used was decided by the physicians for individual patients and the comparison between delamanid and placebo was limited to 8 weeks, it should be noted that of the patients randomised into 204:

- 44% did continue to 208
- 28% did not have the possibility to continue (delayed start up 23% + site did not participate 5%)
- 28% could have enrolled in 208 but did not either because they withdrew during 204 (10%) or completed 204 and chose not to continue to 208 (18%)

This large proportion (28%; including 18% who completed 204) of patients who could have continued into study 208 but did not, creates the possibility that the sample continuing into 208 is subject to selection bias. One way of assessing whether the sample in 208 could be biased would be to compare those patients who did continue with those who did not.

From the group originally randomised to delamanid, it was observed that at the end of study 204 (after 2 months) for the ITT population the SCC rate based on PI favourable outcome was 85/126 (67.5%) in those who went into 208 vs. 91/156 (58.3%) in those who did not. For the mITT population SCC rates at the end of 204 for those randomised to delamanid were 71/107 (66.4%) for those who went into to 208 and only 68/127 (53.5%) for those who did not. These observations pointed to concern that the 208 population is subject to selection bias and that the bias favours delamanid in that response rates in the group that continued into 208 are likely to be biased upwards. All the subsequent presentations, including those of death rates, were considered to be flawed and difficult to interpret because of the **potential for selection bias** (see also: "Ancillary analyses").

Study 242-09-213 was designed to confirm and extend the results observed in 204 and is ongoing. Results for the co-primary endpoints of proportion with SCC and time to SCC over 6 months will be available within the first quarter of 2014. Top line results on 30 month outcomes and the final report will be available in 2016.

The study compares:

- OBR for 18-24 months with placebo for the first 6 months
- Delamanid 100 mg BID for 2 months + 200 mg QD for 4 months plus OBR for 18-24 months

Follow-up will continue for 30 months after randomization (i.e. 6-12 months post OBR). The study includes a comparison of the SCC rates at 8 weeks (one of the co-primary endpoints) and will allow for comparisons of time to SCC and declines in time to positivity in the MGIT system.

The study also examines 3 other aspects:

- Approximately, 40 HIV positive patients on ART will be enrolled in sites in South Africa and there is a modified protocol describing special procedures required for these patients, including additional blood draws, analysis of genetic polymorphisms potentially affecting the metabolism of anti-retroviral drugs and a requirement for hospitalization for at least the first 10 weeks.
- Moxifloxacin will be allowed provided that the patients are hospitalized for the first 10 weeks
- The study will otherwise be conducted as an out-patient study unless local practice or patient condition requires this

There are 18 sites with 5 in Europe. Six participated in Otsuka clinical studies before and 12 are new (in India, South Africa and Moldova).

Study 242-208-210 is an open-label dose escalation study (range 250 mg -400 mg BID delamanid added to OBR) in sputum culture positive MDR-TB patients refractory to treatment with OBR. Study is ongoing and a total of 30 patients are envisaged for enrolment.

Ancillary analyses (trials 204/208 – 116)

Updated mortality data

In a supplementary analysis, as requested by the CHMP following the oral explanation, the applicant focused on updated mortality data. Information had been collected on a total of 37 deaths among 464 patients for whom vital status was known. All deaths except 2 occurred prior to day 771 and the analysis concentrated on 14 deaths in the placebo group and 21 deaths in the delamanid group (35 deaths in the ITT population) as well as on 32 deaths that occurred in the mITT-MGIT population.

Mortality data were shown for 4 groups according to the actual treatment received:

- Those who only ever received 100 mg BID throughout 204 and 208 (100/100 group)
- Those who received 200 mg BID throughout 204 and 208 except during the initial 2 weeks of 208 (200/200 group)
- Those who did not enter 208 but received up to 8 weeks delamanid (2M delamanid [DLM] group)
- Those who never received delamanid (No DLM group)

Figure 23

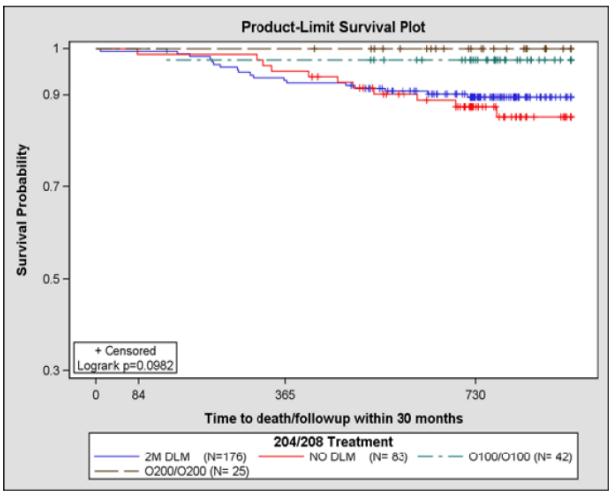


Figure 1.1-2 **Kaplan Meier Survival Plots for Time to Death Within 30 Months for Four 204/208 Treatment Groups**

Table 31

Table 1.1-3 **Analysis of Mortality Rate and Time to Mortality for Four 204/208 Treatment Groups**

Trial 204/208 Treatment	N	Mortality Rate				Time to Mortality	
		Died (%)	Alive (%)	Relative Risk	p-value CMH	Hazard Ratio	p-value Log Rank
200/200	25	0 (0)	25 (100)	*	*	0	0.0680
100/100	42	1 (2.4)	41 (97.6)	0.18	0.0522	0.17	0.0550
2M DLM	176	18 (10.2)	158 (89.8)	0.77	0.4720	0.77	0.4958
No DLM	83	11 (13.3)	72 (86.7)				

Source: SCE-STAT-14.3.2

Notes: No deaths occurred in the 200/200 group so a relative risk cannot be calculated. Relative Risks have the No DLM as the Reference Group

To further explain this subset analysis it is pertinent to recall that there were **213** patients enrolled into 204 who continued in study 208 (44% of the 481 randomised) and **192** of these were followed up in study 116. However, considerable proportions of those who entered 208 received a *different dose* of delamanid vs. the dose assigned in 204. This is why the numbers in the 100/100 and 200/200 groups are small relative to the total initially randomised to delamanid that participated in both 204 and 208.

These results show the value of a period of delamanid administration greater than two months to achieve a significant treatment effect and mortality reduction. The 2 M DLM group shows a more limited treatment effect with a 23% reduction in mortality relative to the No DLM group. Though consistent with a treatment benefit for delamanid this is not statistically significant.

Nevertheless, caution is needed when viewing these data. It should be recalled that the proportion with XDR-TB at baseline in study 204 was highest in the total patients randomised to placebo (27% vs. 13% and 17% in the delamanid groups). Also, in the following table for 299 patients as described in the table heading there is a higher failure rate for those who received delamanid but a much higher default rate in the OBR only group. These observations point to a conclusion that those did not enter 208 (a substantial proportion of whom chose not to enter rather than being at sites where participation became impractical) were also more likely to default from OBR. This fact adds to the questionable validity of the overall comparisons that have been made according to “actual treatment” received.

Table 32

Table 3.1.2-4	Final Outcomes for 299 Patients in the OBR Only, Delayed Delamanid and Immediate Delamanid Treatment Groups; Including Vital Status for Patients not Participating in Study 116.		
Treatment outcome	**Immediate and Delayed delamanid, combined (N=213)**	**OBR Only (N=86)**	**All Patients (N=299)**
Favorable	143 (67.1)	42 (48.8)	185 (61.9)
Unfavorable	70 (32.9)	44 (51.2)	114 (38.2)
Died	6 (2.8)	12 (14.0)	18 (6.2)
Lost to follow up or unknown	13 (6.1)	3 (3.5)	16 (5.4)
Died, lost to follow up, or unknown	19 (8.9)	15 (17.4)	34 (11.4)
Failed	32 (15.0)	7 (8.1)	39 (13.0)
Defaulted	15 (7.0)	18 (20.9)	11 (3.7)
Alive, not in Study 116	4 (1.9)	4 (4.7)	8 (2.7)

The results for the three randomisation groups (100 mg BID, 200 mg BID and Placebo) were as follows:

Table 33

Table 1.1-5	Analysis of Mortality Rate and Time to Mortality for Original Randomization Groups in Trial 242-07-204 with 30 Months Follow Up						
Treatment Group	**Mortality Rate**					**Time to Mortality**	
	N	**Died (%)**	**Alive (%)**	**Relative Risk**	**p-value CMH**	**Hazard Ratio**	**p-value Log Rank**
100 BID	155	13 (8.4)	142 (91.6)	0.91	0.7993	0.92	0.8184
200 BID	157	8 (5.1)	149 (94.9)	0.55	0.1603	0.55	0.1673
Placebo	152	14 (9.2)	138 (90.8)	-	-	-	-

Each of the three randomisation groups reported in the table included those who did and did not enter study 208. The death rates in the initial delamanid groups and in the initial placebo group cannot be related to any treatment effect of delamanid due to the mixture of actual regimens that each group received in accordance with participation or no participation in 208. Hence, it is no surprise that there is little appreciable difference in death rates between the three initial randomised groups.

As shown below the combination of achieving SCC by 2 months and longer duration of delamanid treatment yielded the lowest risk of mortality.

Table 34

Table 1.1-7 Distribution of 464 Patients With Known Mortality Status by 2-Month SCC and Participation in Trial 242-07-208								
Trial 204 Group	N	2-Month SCC n (%)		Participation in Trial 208 n (%)		Death by Subset n (%)	Death by 2-M SCC n (%)	Deaths by Trial 204 Group
100 BID	155	YES	71 (45.8)	YES	33 (46.5)	0	2 (2.8)	14 (9.0)
				NO	38 (53.5)	2 (5.3)		
		NO	84 (54.2)	YES	31 (36.9)	2 (6.5)	12 (14.3)	
				NO	53 (63.1)	10 (18.9)		
200 BID	157	YES	71 (45.2)	YES	37 (52.1)	0	3 (4.2)	8 (5.1)
				NO	34 (47.9)	3 (8.8)		
		NO	86 (54.8)	YES	35 (40.7)	1 (2.9)	5 (5.8)	
				NO	51 (59.3)	4 (7.8)		
Placebo	152	YES	50 (32.9)	YES	25 (50.0)	0	1 (2.0)	15 (9.9)
				NO	25 (50.0)	1 (4.0)		
		NO	102 (67.1)	YES	44 (43.1)	3 (6.8)	14 (13.7)	
				NO	58 (56.9)	11 (19.0)		
Total	464				464	37		

The highest mortality rates occurred among patients who neither achieved 2-month SCC nor participated in 208. Among those patients failing to achieve 2-month SCC, the 100 mg BID group has the lowest proportion (36.9%) of patients participating in 208 and the placebo group has the highest proportion (43.1%). This may explain in part why the mortality rate in the 100 mg BID group is not significantly lower than the placebo group.

The association of 2-month SCC and mortality for the Otsuka 204 patients was assessed for 386/402 patients in the mITT MGIT population (96.0%) with known vital status. Among the patients achieving 2-month SCC, 2.7% died during MDR-TB treatment or during the average 2 years of follow up after treatment, compared with 11.9% of those who did not achieve 2-month SCC. The relative risk of death for patients who did not convert is 4.5.

Table 35

Table 1.1-14 Mortality Within 4 Years After Randomization in Trial 204 by 2-Month Sputum Culture Conversion Status for 386 Patients With Baseline Sputum Cultures Positive by MGIT Regardless of Assignment to Delamanid or Placebo			
2-Month Sputum Conversion	Vital Status		Total
	Alive	Dead	
No	207 (88.1)	28 (11.9%)	235
Yes	147 (97.4%)	4 (2.7%)	151
Total	354	32	386

The association of 2-month SCC and mortality was adjusted for covariates indicative of more severe disease in bivariate models to see if the magnitude of effect of 2-month SCC was changed. Participation in the open-label extension trial was also included as a covariate to ensure that it had no impact on the strength of the association of 2-month conversion and mortality.

Table 36

Table 1.1-15 Bivariate Analysis of the Association of 2-Month Sputum Culture Conversion Status for Factors Associated With Poor Treatment Outcomes for 386 MGIT mITT MDR-TB Patients in Trial 242-07-204			
Covariate	**2-Month Conversion Odds Ratio**	**95% Confidence Interval**	**P-value**
None	0.201	0.069 to 0.586	0.003
Extent of cavitation on x-ray	0.202	0.069 to 0.589	0.003
Degree of positivity on microscopy[a]	0.212	0.072 to 0.624	0.005
Extent of Drug Resistance[b] (MDR, Pre-XDR, XDR)	0.234	0.079 to 0.691	0.009
Duration of previous treatment	0.203	0.070 to 0.595	0.004
Extent of previous treatment	0.203	0.070 to 0.591	0.004
Patient age at randomization	0.198	0.068 to 0.578	0.003
Region (Europe/Med, NE Asia, SE Asia, Americas)	0.201	0.069 to 0.590	0.004
Sex of patient	0.202	0.069 to 0.589	0.003
Participation in Trial 208	0.211	0.072 to 0.619	0.006

The MGIT result at week 8 and sustained SCC cannot be assessed since sustained SCC was captured in 116 using solid culture data only. In the population positive at baseline in 204 by solid culture and with a PI outcome in study 116, an association between the month 2 result and final outcome is apparent particularly for those with SCC at week 8. However, more than half of those without SCC at 2 months went on to a favourable outcome and just under half did not.

It is important to take into account this table since the applicant's proposal is essentially that the comparison with placebo over only 8 weeks in 204 predicts a long-term benefit. In reality the available data cannot be used to confirm this supposition because of the variable management of patients after week 8 that would be reasonably expected to affect outcomes.

Table 37

SCC at 2 months		**116 - PI Favorable Outcome**		**Total**
		Yes	**No**	
Yes	**n (%)**	**115 (73.7)**	**41 (26.3)**	**156**
No	**n (%)**	**83 (57.2)**	**62 (42.8)**	**145**
Total	**n (%)**	**198**	**103**	**301**

To further explore the possible treatment effect of delamanid in the reduction of mortality, 5 of the actual treatment groups were analysed. All of these analyses show a reduction in mortality associated with the treatment of MDR-TB with delamanid. In all cases the relative risk of death for the delamanid group is presented relative to the placebo group.

Table 38

Table 1.1-17 Treatment Effect of Delamanid in the Reduction of Mortality in Eight Different Comparisons				
Type of Comparison	**Delamanid Treatment**	**Comparator**	**Relative Risk of Death**	**95% CI**
Randomized Groups	100 mg BID	Group Randomized to Placebo	0.91	0.43-1.95
	200 mg BID		0.55	0.23-1.30
	Pooled DLM		0.73	0.38-1.40
Actual Treatment	100/100	Randomized to Placebo and not Participating in Trial 208	0.18	0.02-1.35
	200/200		*	*
	2-Month DLM		0.77	0.38-1.56
	All delamanid		0.48	0.24-0.93
	Randomized Delamanid		0.51	0.26-1.01

* There were no deaths among the 25 patients in the 200/200 group so a Relative Risk cannot be calculated

Dose selection: 100 mg BID

The table below describes 301 patients with positive solid culture at baseline for MDR-TB who chose to be followed up in 116 and provides their 24 month outcomes based on the WHO classification.

These are presumed to be the same 301 patients shown in Table 28 (see above), comprising as a subset, 56 with XDR-TB.

Table 39

Trial 204 Rx group	**Trial 208 Participation**	**2.5.2.1.1. Total Patients N=301**	**2-month SCC N=156/301 (%)**	**2.5.2.1.2. Favorable Outcomes* N=301**	
				Yes (%)	**No (%)**
100-BID	100-BID	25	14 (56.0)	16 (64.0)	9 (36.0)
	200-BID	17	10 (58.8)	14 (82.4)	3 (17.6)
	No	58	28 (48.3)	24 (41.4)	34 (58.6)
200-BID	100-BID	34	25 (73.5)	30 (88.2)	4 (11.8)
	200-BID	19	14 (73.7)	15 (78.9)	4 (21.1)
	No	52	32 (61.5)	32 (61.5)	20 (38.5)
Placebo	100-BID	29	9 (31.0)	23 (79.3)	6 (20.7)
	200-BID	19	6 (31.6)	15 (78.9)	4 (21.1)
	No	48	18 (37.5)	29 (60.4)	19 (39.6)

These data show that:

- In the group that received ONLY 100 mg BID in trials 204/208, 16/25 (64.0%) had a favourable outcome compared to 29/48 (60.4%) of those who received NO delamanid. 32 weeks of delamanid 100 mg BID gave the same outcomes as only 8 weeks of 200 mg BID followed by OBR only (32/52; 61.5%).

- In the group that received ONLY 26 weeks of delamanid 100 mg BID in trial 208 (i.e. had placebo in 204) 23/29 (79.3%) had a favourable outcome. 9/29 in this group had already achieved SCC in 204 (i.e. on OBR without delamanid).

Summary of main study

The following table summarises the efficacy results from the main study 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 40: Summary of Efficacy for trial 204

Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2 Trial to Evaluate the Safety, Efficacy and Pharmacokinetics of Multiple Doses of OPC−67683 in Patients with Pulmonary Sputum Culture-Positive, Multidrug-resistant Tuberculosis			
Study identifier	242-07-204		
Design	Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2 Trial		
	Duration of main phase:		The first patient was randomized on 14 May 2008 and the last patient (N=481) was randomized on 31 March 2010. The last patient randomized completed the last visit in the trial on 22 June 2010.
Hypothesis	Superiority in the proportion achieving sputum culture conversion within 8 weeks among the group treated with delamanid (OPC-67683) at either of two doses, compared with the proportion achieving sputum culture conversion within 8 weeks in the placebo group.		
Treatments groups	Delamanid 100 mg BID		Delamanid 100 mg twice-daily, administered as two 50 mg delamanid tablets plus two placebo tablets, added to an optimized background regimen (OBR) for multidrug-resistant tuberculosis (MDR-TB)for 8 weeks; 161 randomized
	Delamanid 200 mg BID		Delamanid 200 mg twice-daily, administered as four 50 mg delamanid tablets, added to a OBR for MDR-TB for 8 weeks; 160 randomized
	Placebo		Matching placebo twice-daily, administered as four placebo tablets, added to OBR for MDR-TB for 8 weeks; 160 randomized
Endpoints and definitions	Primary endpoint	Sputum Culture Conversion using the MGIT® system (SCC-MGIT)	Sputum culture conversion (SCC) is defined as a negative sputum culture confirmed by a second negative sputum culture at least 28 days later with all weekly intervening cultures non-positive and all subsequent cultures after the confirmatory culture also non-positive.
	Secondary	Sputum Culture Conversion using solid media (SCC-SOLID)	SCC is defined as a negative sputum culture confirmed by a second negative sputum culture at least 28 days later with all weekly intervening cultures non-positive and all subsequent cultures after the confirmatory culture also non-positive.
	Secondary	Time to SCC in the MGIT system	Time in days from randomization to the first of the negative MGIT sputum cultures defining SCC.
	Secondary	Time to SCC on solid media	Time in days from randomization to the first of the negative solid media sputum cultures defining SCC.

Database lock	October 28, 2010			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	A modified Intent to Treat (mITT) population was used for analysis of efficacy. Patients were included in the mITT population if they had a positive culture in the MGIT® system confirmed to be MDR-TB on Day -1 and/or Day 1. The full mITT population was 402 patients, 141 patients in the delamanid 100 mg twice daily group, 136 in the delamanid 200 mg twice daily group and 125 in the placebo group			
Descriptive statistics and estimate variability	Treatment group	Delamanid 100 mg twice daily	Delamanid 200 mg twice daily	Placebo
	Number of mITT patients	141	136	125
	Primary endpoint: SCC-MGIT within 8 weeks and Risk ratio comparing delamanid group to placebo group	SCC = 45.4% Risk Ratio=1.534	SCC = 41.9% Risk Ratio=1.416	SCC = 29.6% not applicable
	95% confidence interval on Risk Ratio comparing delamanid group to placebo	1.107-2.124	1.012-1.980	not applicable
	Secondary endpoint SCC-SOLID within 8 weeks and Risk ratio comparing delamanid group to placebo group	SCC = 53.8% Risk Ratio=1.599	SCC = 65.2% Risk Ratio=1.939	SCC = 33.6% not applicable
	95% confidence interval on Risk Ratio comparing delamanid group to placebo	1.175-2.177	1.449-2.595	not applicable
	Secondary Endpoint Time to SCC-MGIT comparing hazard ratio for delamanid group to placebo	hazard ratio=1.727	hazard ratio=1.585	not applicable
	95% confidence interval on hazard ratio	1.152 - 2.591	1.048 - 2.399	not applicable
	Secondary Endpoint Time to SCC on solid media comparing hazard ratio for delamanid group to placebo	hazard ratio=1.846	hazard ratio=2.301	not applicable
	95% confidence interval on hazard ratio	1.235 - 2.759	1.555 - 3.405	not applicable

Effect estimate per comparison	Primary endpoint SCC-MGIT	Comparison groups	delamanid 100 mg twice daily vs. placebo delamanid 200 mg twice daily vs. placebo
		Cochran-Mantel-Haenszel test stratified by cavitation	delamanid 100 mg twice daily vs. placebo p=0.0083 delamanid 200 mg twice daily vs. placebo p=0.0393
	Secondary endpoint SCC-SOLID	Comparison groups	delamanid 100 mg twice daily vs. placebo delamanid 200 mg twice daily vs. placebo
		Cochran-Mantel-Haenszel test stratified by cavitation	delamanid 100 mg twice daily vs. placebo p=0.0021 delamanid 200 mg twice daily vs. placebo p<0.0001
	Secondary Endpoint Time to SCC-MGIT	Comparison groups	delamanid 100 mg twice daily vs. placebo delamanid 200 mg twice daily vs. placebo
		Stratified Log-Rank Test	delamanid 100 mg twice daily vs. placebo: p=0.0056 delamanid 200 mg twice daily vs. placebo p=0.0232
	Secondary Endpoint Time to SCC-SOLID	Comparison groups	delamanid 100 mg twice daily vs. placebo delamanid 200 mg twice daily vs. placebo
		Stratified Log-Rank Test	delamanid 100 mg twice daily vs. placebo: p=0.0016 delamanid 200 mg twice daily vs. placebo p=<0.0001

2.5.3. Discussion on clinical efficacy

The integrated analysis of the combined set of data does not provide sufficient evidence of meaningful benefits for MDR-TB patients from treatment with delamanid 100-mg BID for 6 months added to an OBR compared to those treated with OBR alone.

The applicant provided two *Position Papers* – one to support the *Combined analysis* across 204/208/116 (the critical results are shown above) and one (reflected in the PK/PD analysis) to support the dose of *100 mg BID delamanid over 6 months* (see the PK/PD section).

Based on the data provided, the integrated analysis and the two *Position Papers,* the following observations are made:

Design and conduct of clinical studies

The main trial in the submission for conditional marketing authorisation is study 204, which was a double-blind, placebo controlled trial to evaluate efficacy (in terms of sputum culture conversion, SCC) and safety of delamanid given for 2 months of treatment. Patients could then (after at least 4 weeks off delamanid and taking OBR only; the gap between 204/208 exceeded 2 months in 45% of patients)

participate in an open label extension trial (study 208), designed to the safety and efficacy of delamanid during 6 months of treatment. All subjects (< 50% of the number randomised into study 204) who entered in trial 208 (i.e. whether or not they received delamanid in 204; which was not known when entering 208) initially received delamanid for two weeks at 100 mg BID after which the physicians could increase the dose to 200 mg BID. Hence, the randomization allocation of trial 204 (100 mg BID or 200 mg BID or placebo) was not respected and the two treatment groups created were not comparable with respect to prognostic factors. The submission also reported outcomes (vital status and solid culture status) from patients who elected to be followed in trial 116. This was an observational study designed to capture additional data and final treatment outcome for patients who participated in trial 204 whether or not they participated in trial 208.

The single pivotal study with a primary analysis at week 8 is insufficient. To support the indication claimed by the applicant there should have been a comparison of delamanid vs. placebo over a continuous 6-month treatment period. Patients themselves selected to be treated in study 208 and only 213 out of 481 randomised into 204 chose to enter. Some of the initial 481 patients never had the chance to enter 208 because this extension study could not be initiated at some sites in time to allow their participation. Patients who had achieved SCC in 204 were more likely to enter 208 than those who did not. Outcomes at the end of trial 208 are therefore subject to unknown bias and therefore cannot be interpreted. It is also not possible to interpret with confidence the solid culture or mortality data collected in trial 116.

Regarding the delamanid dose regimen, many of the analyses presented to attempt to address the deficiencies of the trial designs were based on pooling of the dose groups. The lack of an adequate comparison with placebo cannot be addressed by comparing outcomes in 116 or vital status between the very small numbers that actually received a single dose level of delamanid (i.e. only 100 mg or 200 mg BID throughout 204/208) or did not receive any delamanid throughout (i.e. placebo in 204 and declined to enter 208).

Comparisons between 100 mg and 200 mg BID are also subject to bias, as in trial 208 the dose was selected, not randomised. This would be expected to bias against the higher dose as patients would only be up-titrated if they were felt to “need” the higher dose i.e. those treated with 200 mg BID in 208 may represent a population in a poorer general state. Despite this there were several trends in the data to suggest that 200 mg BID, at least for the initial 8 weeks, followed by 16 weeks at either dose might be the better regimen.

Efficacy data and additional analyses

Despite the concerns regarding interpretation of the data, the small number of patients who only received one of 100 mg BID, 200 mg BID or no delamanid at any time, raise several concerns. For example, the solid culture data collected in trial 116 show no difference between the applicant’s proposed dose of 100 mg BID for 24 weeks and the group that never received delamanid.

Added to these problems is the heterogeneity of the study population. In the MITT population 17% and 13% in the two delamanid groups had XDR-TB vs. 22% in the placebo group and the outcomes by sub-group clearly showed lower SCC rates in the XDR-TB patients regardless of the treatment given. This baseline imbalance in XDR-TB has potential to make the overall benefit of delamanid vs. placebo in the study (i.e. for all mITT patients) look better than it really was.

Regional enrolment and outcomes also illustrated the difficulties of interpreting the overall findings when the population included MDR and XDR-TB. The answer clarified that a single site in SE Asia contributed 150 patients to study 204. Not unexpectedly, removal of this site (~ one third of patients) from the analysis resulted in loss of statistical significance for SCC rates between delamanid 100 mg BID

groups and placebo based on the primary (MGIT) analysis.

The MGIT SCC rate with 100 mg BID was considerably higher at this single SE Asia site, where there was no XDR-TB, compared to other sites (e.g. vs. NE Asia where plasma exposures were comparable with SE Asia but there were more XDR-TB cases). Also, the solid culture SCC rates at the SE Asia site were highest compared to other regions for both delamanid dose levels. As such, the overall efficacy for delamanid 100 mg BID and overall in 204 appears to have been driven to some considerable extent by the results from the single site in SE Asia that enrolled 150 out of 481 patients. In accordance with the CHMP guidance regarding provision of a single pivotal study, these findings add to the doubts regarding the robustness of study 204.

In the applicant's separate *Position Paper* to further support selection of 100 mg BID the PK/PD analysis attempts to identify a threshold delamanid exposure associated with efficacy. From this, the applicant has concluded that exposure to delamanid in study 204 was above the threshold for maximum efficacy as no association between a further increase in plasma exposure and increase in efficacy was observed. Hence, as long as exposure comparable to that in trial 204 is achieved, other factors such as morphological conditions of the host (cavitation), concomitant OBR therapy and corresponding susceptibility or duration of MDR-TB would have to be considered to explain individual differences in efficacy.

The CHMP however remains critical of this conclusion. The analysis of SCC vs. AUC and TTP vs. AUC is based on only 8 weeks treatment. Whether or not patients achieved SCC based on MGIT was not solely due to delamanid. Also, the study population was heterogeneous in terms of MDR/XDR (with a slightly higher proportion with XDR-TB in the placebo group that may be at least partly responsible for the TTP results).

These issues weaken the discriminative capacity of the analysis to confirm a lack of association between dose (based on AUC at steady state) and MGIT SCC. Such an analysis cannot supplant and/or overturn the few actual data that can be gleaned regarding the comparison of 100 mg vs. 200 mg BID. The attempt to establish a threshold AUC correlating with maximal efficacy from the EBA study data is also not considered reliable.

Additional expert consultation

The advice of an Ad-Hoc Expert Group was sought on the following aspects:

Efficacy & Drug Resistance

1. Expert opinion was sought on the fact if comparison of delamanid vs. placebo over 8 weeks suffices to predict the treatment effect of 6 months therapy?

The group was not confident that this is indeed possible. The experts were concerned that the data to Week 8 included too much heterogeneity. Indeed, in their view, the data are clearly subject to influence according to region/site. Treatment groups were imbalanced in the proportion of patients with XDRTB. Open-label data from 208/116 do not further add in confirming the treatment effect.

2. Do the data adequately support the proposed posology for 100 mg BID for 6 months? If not, can an alternative dose regimen and/or duration be suggested as more appropriate?

The experts agreed that although there is some evidence of efficacy obtained with a 100 mg bid regimen, there is also some indication that a 200 mg bid could be more appropriate, but with the caveat of potential concern about QTc prolongation and drug interactions. It could however be advantageous to explore other dosages (e.g. in between 100-200 mg), taking account of the appropriate precautions.

3. It was asked if the experts consider that the ongoing Phase 3 trial is adequate to confirm the proposed posology?

The experts noted that in trial 213, the dosage schedule differs from the one used in the presently submitted 8 –weeks controlled trial 204. The group considered that possibly 200 mg OD for 4 months could be an acceptable dose (as proposed), whilst large uncertainties remain regarding the optimal treatment dose for the first 2 months: should it be 100 mg BID or an initial higher dose? Ultimately, a right balance needs to be struck between the higher probability in achieving reliable SCC across the range of MDR/XDR-TB and risk of extensive QTc prolongation. Also, retaining a contra-indication in using moxifloxacin as part of the OBR seems to deviate from reality of clinical practice. Hence, drug interactions between delamanid and fluoroquinolones (including moxifoxacin) should be adequately addressed (note: moxifloxacin will be allowed in trial 213, protocol amendment).

Although, the ongoing phase 3 trial will not adequately confirm the currently proposed posology (100 mg BID), the ultimate contribution of the proposed trial on the overall B/R balance of delamanid, will ultimately depend on the strength of its findings.

4. The experts were asked to consider if the results obtained at 8 weeks can be widely extrapolated across MDR patients taking into account the regional variations observed and the SCC rates for XDR-TB?

An overall recommendation could not be made on this. MDRTB and XDRTB represent a spectrum of TB with various resistances. A section of this spectrum is likely to benefit but this will be based on microbiological evidence and clinical judgment.

5. It was requested to comment on how the prescribing information might be amended to minimise the potential risk that use of delamanid along with other poorly effective agents could select for resistant organisms?

The group stressed that where available treatments are very limited, every effort should be made to combine with other agents showing evidence of an effect against the resistant pathogen, and the decision to use should be according to expert advice. The risk for the patient and the public health implication due to potential emergence of resistance should be part of the consideration.

Additional efficacy data proposed by the applicant as a specific obligation in the context of a conditional MA

Ongoing study 213 will further try to confirm the efficacy of delamanid in MDR/XDR-TB patients.

The study compares OBR for 18-24 months with either placebo or delamanid for the first 6 months.

The dose regimen of delamanid is 100 mg BID for 8 weeks followed by 200 mg QD to complete a total of 6 months.

However, the CHMP has doubts whether indeed this constitutes the optimal dose regimen to provide best chance of achieving reliable SCC across the range of MDR/XDR-TB patients.

2.5.4. Conclusions on the clinical efficacy

There are several issues regarding the design and conduct of 204 that raise serious doubts regarding the robustness of the data to demonstrate the treatment benefit of delamanid at either dose vs. placebo and to support the applicant's proposed delamanid dose regimen.

In particular:

a) The duration of comparison between delamanid and placebo is too short to be able to discern the benefit of adding delamanid at either 100 mg or 200 mg BID to an optimised background regimen for 6 months. Study 242-07-208 cannot repair this major deficiency since it does not allow for an assessment of SCC rates vs. placebo over the applicant's proposed duration of use of delamanid (6 months). In addition, the data obtained in both 208 and 116 do not allow for a robust assessment of sustained SCC and must be viewed with much caution since patients self-selected to enter study 208 and to be followed in trial 116.

b) There are inadequate data to identify the dose of delamanid that should be used. The data obtained in 208 and 116 cannot provide a reliable conclusion regarding the most appropriate dose regimen as doses used in study 208 were selected and not randomised. It is also of concern that the magnitude of benefit of delamanid 100 mg BID vs. placebo based on MGIT SCC rates at week 8 was substantially driven by the result for this dose at a single site that enrolled 150/481 patients where no patient had XDR-TB.

There is a critical need to substantiate the efficacy of delamanid at a final proposed dose regimen with an adequate comparison vs. placebo over 6 months.

2.6. Clinical safety

The most informative data come from the comparison with placebo over 8 weeks in 242-07-204 while 242-07-208 provided information on longer-term exposure to delamanid without a control group.

Patient exposure

In **242-07-204**, 91% (437/481) of subjects were treated for at least 56 days.

Three studies were completed after the initial application was submitted: 242-07-208, 242-08-210 and 242-10-116; all were ongoing at submission. In total, since 2004 there have been 887 individuals exposed to delamanid.

Table 41

Table 3.64-2 Number of Individuals Exposed in Delamanid Trials Worldwide by Population	
Population	**Number of Subjects**
All exposed (total)	887
Patients with MDR-TB[a]	395
Patients with uncomplicated drug-susceptible TB[b]	60
Healthy subjects[c]	422
Patients with MDR-TB refractory to treatment (OBR)[d]	10

Adverse events

In **242-07-204** > 90% of subjects per treatment group had at least one TEAE.

Table 42

Table 11.2-1	Summary of Adverse Events - Intent-to-treat Population				
Parameter	**Delamanid 100 mg BID + OBR n (%)[a]**	**Delamanid 200 mg BID + OBR n (%)[a]**	**Total Delamanid BID + OBR n (%)[a]**	**Placebo + OBR n (%)[a]**	**Total n (%)[a]**
Patients treated	161	160	321	160	481
Patient days of IMP exposure	8360	8425	16785	8536	25321
Patients with AEs	147 (91.3)	151 (94.4)	298 (92.8)	151 (94.4)	449 (93.3)
AEs	1798	2013	3811	1825	5636
Patients with TEAEs	145 (90.1)	149 (93.1)	294 (91.6)	149 (93.1)	443 (92.1)
TEAEs	1230	1471	2701	1343	4044
Patients with SAEs	16 (9.9)	20 (12.5)	36 (11.2)	14 (8.8)	50 (10.4)
Patients with severe TEAEs	9 (5.6)	10 (6.3)	19 (5.9)	8 (5.0)	27 (5.6)
Patients discontinued due to TEAEs	4 (2.5)	6 (3.8)	10 (3.1)	4 (2.5)	14 (2.9)

In trial 204, women treated with either dose of delamanid had a higher incidence of TEAEs by SOC vs. men (overall 95.4% vs. 89.7%) and a similar pattern was observed in the placebo group (98.0% vs. 91.0%). The increased incidence of TEAEs for women vs. men was apparent for the majority of SOCs although rates among women in the delamanid BID groups were not higher than rates among women in the placebo group except Investigations and Renal and Urinary Disorders. In the Renal and Urinary Disorders SOC no specific PT contributed to the observed difference. In the Investigations SOC, the difference was due to ECG QT prolonged (13.0% vs. 8.2%), which reflected the overall effect of delamanid in this respect.

To explore whether the difference in incidence of TEAEs by gender may be related to body weight and delamanid exposure the applicant provided plots for delamanid AUCss by gender. Separate plots for each delamanid dose group showed a similar pattern. Women showed a slightly higher exposure at steady state, possibly related to their slightly lower body weight vs. men.

The incidence of TEAEs reported in the SE Asian region in delamanid and placebo groups was 100%, which was higher than for other regions combined (88% delamanid BID and 89.6% placebo).

Although the applicant dismissed the possibility that the gender difference in TEAE rates reflected delamanid exposures it is stated that the difference in incidence by region may partially be explained by a slightly higher delamanid exposure in the SE Asian population. The Population PK data also showed slightly higher delamanid exposure in SE Asia in the 100 mg BID and 200 mg BID groups vs. other regions combined. However, the predicted delamanid exposure at steady state based on the average body weight in men and women by region showed very similar delamanid exposures despite the slightly lower body weight observed in women.

In 242-07-208 there were no new clinically important TEAEs relative to those reported in 204 and no meaningful increases in the incidence of any TEAEs vs. 204. In particular, the incidence of TEAEs of QT interval prolongation did not increase in study 208 vs. either delamanid treatment group in trial 204.

From the listing it seems that 0-2 TEAEs of any one type were considered to be severe in intensity and for the majority there were no TEAEs considered severe.

The table summarises the most commonly reported AEs by treatment group in 204 and pooled for delamanid doses in 208

Table 43

Table 3.64-8 Treatment-Emergent Adverse Events With an Incidence of ≥ 5% in Any Treatment Group - MDR-TB Patients, Safety Population				
System Organ Class and MedDRA Preferred Term[a]	Number (%) of Patients[b]			
	Trial 204			Trial 208
	Delamanid 100 mg BID + OBR (N = 161)	Delamanid 200 mg BID + OBR (N = 160)	Placebo + OBR (N = 160)	All Delamanid[c] (N = 213)
Patients reporting any TEAE[d]	145 (90.1)	149 (93.1)	149 (93.1)	200 (93.9)
Blood and Lymphatic System Disorders				
Reticulocytosis	19 (11.8)	20 (12.5)	17 (10.6)	0
Anaemia	18 (11.2)	10 (6.3)	14 (8.8)	7 (3.3)
Eosinophilia	7 (4.3)	11 (6.9)	15 (9.4)	3 (1.4)
Cardiac Disorders				
Palpitations	13 (8.1)	20 (12.5)	10 (6.3)	18 (8.5)
Ear and Labyrinth Disorders				
Tinnitus	16 (9.9)	22 (13.8)	12 (7.5)	21 (9.9)
Eye disorders				
Vision blurred	12 (7.5)	15 (9.4)	9 (5.6)	6 (2.8)
Gastrointestinal Disorders				
Nausea	58 (36.0)	65 (40.6)	53 (33.1)	35 (16.4)
Vomiting	48 (29.8)	58 (36.3)	44 (27.5)	29 (13.6)
Abdominal pain upper	41 (25.5)	36 (22.5)	38 (23.8)	25 (11.7)
Diarrhoea	20 (12.4)	12 (7.5)	22 (13.8)	21 (9.9)
Abdominal pain	16 (9.9)	12 (7.5)	11 (6.9)	9 (4.2)
Abdominal discomfort	10 (6.2)	14 (8.8)	7 (4.4)	6 (2.8)
Gastritis	8 (5.0)	14 (8.8)	16 (10.0)	18 (8.5)
Dyspepsia	6 (3.7)	14 (8.8)	6 (3.8)	13 (6.1)
Abdominal pain lower	4 (2.5)	11 (6.9)	7 (4.4)	8 (3.8)
Abdominal distension	5 (3.1)	9 (5.6)	5 (3.1)	3 (1.4)
Constipation	6 (3.7)	8 (5.0)	8 (5.0)	6 (2.8)
Toothache	6 (3.7)	7 (4.4)	11 (6.9)	14 (6.6)
General Disorders and Administration Site Conditions				
Asthenia	20 (12.4)	27 (16.9)	20 (12.5)	7 (3.3)
*Chest pain	16 (9.9)	14 (8.8)	7 (4.4)	18 (8.5)
Malaise	12 (7.5)	16 (10.0)	12 (7.5)	5 (2.3)

Table 3.64-8 Treatment-Emergent Adverse Events With an Incidence of ≥ 5% in Any Treatment Group - MDR-TB Patients, Safety Population				
System Organ Class and MedDRA Preferred Term[a]	Number (%) of Patients[b]			
	Trial 204			Trial 208
	Delamanid 100 mg BID + OBR (N = 161)	Delamanid 200 mg BID + OBR (N = 160)	Placebo + OBR (N = 160)	All Delamanid[c] (N = 213)
Hypoaesthesia	12 (7.5)	7 (4.4)	8 (5.0)	2 (0.9)
Dysgeusia	6 (3.7)	10 (6.3)	11 (6.9)	5 (2.3)
Psychiatric Disorders				
Insomnia	42 (26.1)	52 (32.5)	42 (26.3)	50 (23.5)
Anxiety	9 (5.6)	12 (7.5)	5 (3.1)	13 (6.1)
Depression	4 (2.5)	13 (8.1)	5 (3.1)	8 (3.8)
Psychotic disorder	6 (3.7)	8 (5.0)	4 (2.5)	0
Restlessness	8 (5.0)	5 (3.1)	4 (2.5)	5 (2.3)
Respiratory, Thoracic, and Mediastinal Disorders				
Haemoptysis	19 (11.8)	15 (9.4)	17 (10.6)	12 (5.6)
Rales	12 (7.5)	11 (6.9)	16 (10.0)	1 (0.5)
Cough	8 (5.0)	8 (5.0)	7 (4.4)	10 (4.7)
Oropharyngeal pain	5 (3.1)	9 (5.6)	6 (3.8)	4 (1.9)
Throat irritation	5 (3.1)	8 (5.0)	0	10 (4.7)
Dyspnoea	3 (1.9)	8 (5.0)	5 (3.1)	6 (2.8)
Skin and subcutaneous tissue disorders				
Pruritus	15 (9.3)	15 (9.4)	20 (12.5)	18 (8.5)
Hyperhidrosis	9 (5.6)	17 (10.6)	8 (5.0)	5 (2.3)
Rash papular	9 (5.6)	8 (5.0)	7 (4.4)	13 (6.1)
Rash	8 (5.0)	3 (1.9)	10 (6.3)	10 (4.7)
Pyrexia	9 (5.6)	18 (11.3)	18 (11.3)	9 (4.2)
Injection site pain	13 (8.1)	12 (7.5)	23 (14.4)	6 (2.8)
Hepatobiliary Disorders				
Hyperbilirubinaemia	1 (0.6)	1 (0.6)	2 (1.3)	11 (5.2)
Infections and Infestations				
Nasopharyngitis	4 (2.5)	5 (3.1)	6 (3.8)	24 (11.3)
Lung infection	2 (1.2)	4 (2.5)	5 (3.1)	10 (4.7)
Upper respiratory tract infection	2 (1.2)	4 (2.5)	2 (1.3)	16 (7.5)
Investigations				
*Electrocardiogram QT interval prolonged	16 (9.9)	21 (13.1)	6 (3.8)	6 (2.8)
Blood cortisol increased	4 (2.5)	5 (3.1)	1 (0.6)	13 (6.1)
Metabolism and Nutrition Disorders				
Decreased appetite	24 (14.9)	37 (23.1)	25 (15.6)	14 (6.6)
Hyperuricaemia	31 (19.3)	38 (23.8)	35 (21.9)	14 (6.6)
Hypokalaemia	20 (12.4)	31 (19.4)	24 (15.0)	12 (5.6)
Musculoskeletal and connective tissue disorders				
Arthralgia	32 (19.9)	43 (26.9)	47 (29.4)	29 (13.6)
Myalgia	15 (9.3)	21 (13.1)	26 (16.3)	17 (8.0)
Back pain	12 (7.5)	16 (10.0)	19 (11.9)	13 (6.1)
Musculoskeletal pain	9 (5.6)	8 (5.0)	10 (6.3)	4 (1.9)
Pain in extremity	6 (3.7)	8 (5.0)	7 (4.4)	4 (1.9)
Neck pain	1 (0.6)	11 (6.9)	9 (5.6)	4 (1.9)
Nervous System Disorders				
Dizziness	48 (29.8)	49 (30.6)	49 (30.6)	22 (10.3)
Headache	38 (23.6)	41 (25.6)	30 (18.8)	54 (25.4)
Paraesthesia	17 (10.6)	20 (12.5)	12 (7.5)	13 (6.1)
Tremor	19 (11.8)	16 (10.0)	13 (8.1)	9 (4.2)
Somnolence	11 (6.8)	9 (5.6)	15 (9.4)	18 (8.5)

In study 204, TEAEs for which the total rate for delamanid was higher by > 5 percentage points vs. placebo included nausea, vomiting, headache and prolonged ECG QT (37/321, 11.5% vs. 6/160, 3.8%). For all of these events, the rates were also higher in the delamanid 200 mg vs. 100 mg BID group.

More subjects in the delamanid 100 mg and 200 mg BID groups (26/159, 16.4% and 22/158, 13.9%, respectively) had a ≥ 5% decrease in body weight compared with placebo (10/157, 6.4%).

The table shows TEAEs in 204 that occurred at a rate higher by 3 percentage points for delamanid (either dose) vs. placebo.

Table 44

Table 11.3-1	Most Frequently Reported Treatment-emergent Adverse Events by 3% or Greater Incidence in the Total Delamanid BID + OBR Group and Greater Than Placebo + OBR - Intent-to-treat Population				
System Organ Class and MedDRA Preferred Term	**Delamanid 100 mg BID + OBR (N = 161) n (%)[a]**	**Delamanid 200 mg BID + OBR (N = 160) n (%)[a]**	**Total Delamanid BID + OBR (N = 321) n (%)[a]**	**Placebo + OBR (N = 160) n (%)[a]**	**Total (N = 481) n (%)[a]**
Patients with any TEAE[b]	145 (90.1)	149 (93.1)	294 (91.6)	149 (93.1)	443 (92.1)
Blood and Lymphatic System Disorders					
Reticulocytosis	19 (11.8)	20 (12.5)	39 (12.1)	17 (10.6)	56 (11.6)
Cardiac Disorders					
Palpitations	13 (8.1)	20 (12.5)	33 (10.3)	10 (6.3)	43 (8.9)
Ear and Labyrinth Disorders					
Tinnitus	16 (9.9)	22 (13.8)	38 (11.8)	12 (7.5)	50 (10.4)
Eye Disorders					
Vision blurred	12 (7.5)	15 (9.4)	27 (8.4)	9 (5.6)	36 (7.5)
Gastrointestinal Disorders					
Abdominal discomfort	7 (4.3)	8 (5.0)	15 (4.7)	5 (3.1)	20 (4.2)
Abdominal distension	5 (3.1)	9 (5.6)	14 (4.4)	5 (3.1)	19 (4.0)
Abdominal pain	16 (9.9)	12 (7.5)	28 (8.7)	11 (6.9)	39 (8.1)
Abdominal pain lower	4 (2.5)	11 (6.9)	15 (4.7)	7 (4.4)	22 (4.6)
Abdominal pain upper	41 (25.5)	36 (22.5)	77 (24.0)	38 (23.8)	115 (23.9)
Dyspepsia	6 (3.7)	14 (8.8)	20 (6.2)	6 (3.8)	26 (5.4)
Nausea	58 (36.0)	65 (40.6)	123 (38.3)	53 (33.1)	176 (36.6)
Stomach discomfort	3 (1.9)	7 (4.4)	10 (3.1)	3 (1.9)	13 (2.7)
Vomiting	48 (29.8)	58 (36.3)	106 (33.0)	44 (27.5)	150 (31.2)
General Disorders and Administration Site Conditions					
Asthenia	20 (12.4)	27 (16.9)	47 (14.6)	20 (12.5)	67 (13.9)
Chest pain	16 (9.9)	13 (8.1)	29 (9.0)	7 (4.4)	36 (7.5)
Malaise	12 (7.5)	16 (10.0)	28 (8.7)	12 (7.5)	40 (8.3)
Investigations					
Breath sounds abnormal	7 (4.3)	5 (3.1)	12 (3.7)	5 (3.1)	17 (3.5)
Electrocardiogram QT prolonged	16 (9.9)	21 (13.1)	37 (11.5)	6 (3.8)	43 (8.9)
Metabolism and Nutrition Disorders					
Anorexia	23 (14.3)	34 (21.3)	57 (17.8)	24 (15.0)	81 (16.8)
Hypokalaemia	20 (12.4)	31 (19.4)	51 (15.9)	24 (15.0)	75 (15.6)
Nervous System Disorders					
Headache	36 (22.4)	41 (25.6)	77 (24.0)	30 (18.8)	107 (22.2)
Hypoaesthesia	12 (7.5)	7 (4.4)	19 (5.9)	8 (5.0)	27 (5.6)
Paraesthesia	17 (10.6)	20 (12.5)	37 (11.5)	12 (7.5)	49 (10.2)
Tremor	19 (11.8)	16 (10.0)	35 (10.9)	13 (8.1)	48 (10.0)
Psychiatric Disorders					
Anxiety	9 (5.6)	12 (7.5)	21 (6.5)	5 (3.1)	26 (5.4)
Depression	4 (2.5)	13 (8.1)	17 (5.3)	5 (3.1)	22 (4.6)
Insomnia	42 (26.1)	51 (31.9)	93 (29.0)	42 (26.3)	135 (28.1)
Psychotic disorder	6 (3.7)	8 (5.0)	14 (4.4)	4 (2.5)	18 (3.7)
Restlessness	8 (5.0)	5 (3.1)	13 (4.0)	4 (2.5)	17 (3.5)
Respiratory, Thoracic, and Mediastinal Disorders					
Cough	8 (5.0)	8 (5.0)	16 (5.0)	7 (4.4)	23 (4.8)
Dyspnoea	3 (1.9)	8 (5.0)	11 (3.4)	5 (3.1)	16 (3.3)
Oropharyngeal pain	5 (3.1)	9 (5.6)	14 (4.4)	6 (3.8)	20 (4.2)
Throat irritation	5 (3.1)	8 (5.0)	13 (4.0)	0 (0.0)	13 (2.7)
Skin and Subcutaneous Tissue Disorders					
Hyperhidrosis	9 (5.6)	17 (10.6)	26 (8.1)	8 (5.0)	34 (7.1)

Within study 204, the rates for TEAEs considered drug-related were also mostly comparable between groups except for prolonged QT (23/321; 7.2%, total delamanid vs. 2/160; 1.3%, placebo).

Table 45

Table 11.4-1	Most Common Treatment-emergent Adverse Events Considered by the Investigator as Potentially Causally Related to the Investigational Medicinal Product by 3% or Greater Incidence in Any Treatment Group - Intent-to-treat Population				
System Organ Class and MedDRA Preferred Term	Delamanid 100 mg BID + OBR (N = 161) n (%)[a]	Delamanid 200 mg BID + OBR (N = 160) n (%)[a]	Total Delamanid BID + OBR (N = 321) n (%)[a]	Placebo + OBR (N = 160) n (%)[a]	Total (N = 481) n (%)[a]
Patients with any potentially IMP-related TEAE[b]	62 (38.5)	65 (40.6)	127 (39.6)	57 (35.6)	184 (38.3)
Cardiac Disorders					
Palpitations	2 (1.2)	8 (5.0)	10 (3.1)	4 (2.5)	14 (2.9)
Gastrointestinal Disorders					
Nausea	6 (3.7)	7 (4.4)	13 (4.0)	6 (3.8)	19 (4.0)
Vomiting	10 (6.2)	5 (3.1)	15 (4.7)	2 (1.3)	17 (3.5)
Investigations					
Electrocardiogram QT Prolonged	10 (6.2)	13 (8.1)	23 (7.2)	2 (1.3)	25 (5.2)
Metabolism and Nutrition Disorders					
Anorexia	1 (0.6)	3 (1.9)	4 (1.2)	5 (3.1)	9 (1.9)
Hypokalaemia	6 (3.7)	2 (1.3)	8 (2.5)	3 (1.9)	11 (2.3)
Nervous System Disorders					
Dizziness	4 (2.5)	7 (4.4)	11 (3.4)	6 (3.8)	17 (3.5)
Headache	3 (1.9)	5 (3.1)	8 (2.5)	5 (3.1)	13 (2.7)
Somnolence	7 (4.3)	4 (2.5)	11 (3.4)	6 (3.8)	17 (3.5)
Psychiatric Disorders					
Insomnia	13 (8.1)	19 (11.9)	32 (10.0)	9 (5.6)	41 (8.5)

The primary ECG analysis (time-matched change in QTcF from Day −1 to Day 56) showed that delamanid was associated with a progressive increase in QTcF. The upper CIs increased from 11 ms (100 mg BID) and 14 ms (200 mg BID) at Day 14 to 12 and 17 ms at Day 28 and 16 and 19 ms at Day 56.

The greatest magnitude of effect at Day 56 was 13 ms (10 to 16 ms) change for delamanid 100 mg BID vs. placebo and 16 ms (12 to 19 ms) change for 200 mg BID vs. placebo, indicating a QTc dose relationship.

Figure 24

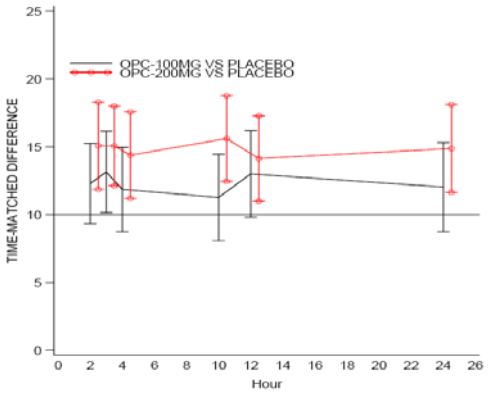


Figure 11.13.1.1-1 Time-matched Difference in QTcF Interval at Day 56

Using the time-averaged method for QTcF, delamanid showed a dose-response relationship with a progressive increase from Day 1 to Day 56 with a 12 ms (10 to 15 ms) mean change at the 100 mg BID dose level and a 15 ms (12 to 17 ms) mean change at the 200 mg BID dose level.

At Day 56, there were also imbalances between total delamanid and placebo groups for the incidences of categorical changes in QTcB and QTcF. No subject had a new onset QTcF > 500 ms but 5/321 (1.5%) in the delamanid group (all 200 mg BID) had a new onset QTcF > 480 ms versus 1/160 (0.6%) on

placebo. Rates for new onset QTcF > 450 ms were 47/321 (14.6%) vs. 10/160 (6.2%), respectively. Also, 11/321 (3.4%) in the total delamanid group had a change in QTcF of > 60 ms versus 0% on placebo while 30 to 60 ms changes from baseline occurred in 129/321 (40.1%) and 25/160 (15.6%). The analysis using the restricted dataset gave the same pattern of findings with no important differences vs. the original ECG analysis dataset.

TEAEs of QT/QTc prolongation in individual subjects were reported for 16/161 (9.9%) in the delamanid 100 mg BID group, 21/160 (13.1%) in the 200 mg BID group and 6/160 (3.8%) for placebo. Other reported ECG-related TEAEs in subjects treated with delamanid were ECG ST segment depression (3 subjects), ECG ST segment abnormal (1 subject) and ECG abnormal T wave (1 subject). The time point analysis showed a slight drop in HR ranging on Day 56 from −3.5 to −6.7 ms in the delamanid 100 mg BID group and −3.3 to −5.9 ms in the 200 mg BID group. No signal of any effect on PR duration or QRS duration was demonstrated.

Overall, there were 43 patients with QTc interval outlier events of > 60 ms change from baseline at any time in 204 (29 patients), 208 (13 patients) and 210 (1 patient); all were in the delamanid treatment groups. In 204, 13 were in the 100 mg BID group and 16 in the 200 mg BID group with 7 and 6 in respective dose groups in 208 and one subject in 210 who received 300 mg BID. All 29 subjects with QTcF increase > 60 ms in 204 were taking a fluoroquinolone; 9/29 patients were taking levofloxacin and 20/29 were taking ofloxacin. No patient on placebo with or without low potassium had a QTcF > 60 ms change from baseline.

There were 11out of 43 subjects with QTc change > 60 ms who also had a serum potassium ≤ 3.1 mEq/L. However, based on readings taken as close together as possible there was no clear correlation between timing of low potassium and QTc prolongation except for a very few patients. Hence, delamanid was associated with QTc prolongation regardless of serum potassium.

Review of Cardiac TEAEs and SMQ terms showed that palpitation was the most frequently reported TEAE. There was no consistent pattern in time to onset or duration of palpitation and most patients reported pre-existing conditions and/or were taking concomitant medications that possibly had a causal role in the event. There were more TEAEs of ECG QT prolonged reported in the delamanid treatment groups vs. placebo but there were no cases of Torsades de pointes or serious ventricular arrhythmias.

Table 46

Table 3.66-1	Cardiac Disorders and QT Prolongation SMQ Treatment-Emergent Adverse Events[d] - Multidrug resistant Tuberculosis Patients, Safety Population: Trial 204 and Trial 208				
SOC MedDRA PT[a]	Number (%) of Patients[b]				
	Trial 204			Trial 208	
	Delamanid 100 mg BID + OBR (N = 161)	Delamanid 200 mg BID + OBR (N = 160)	Placebo + OBR (N = 160)	Delamanid 100 mg BID + OBR (N = 137)	Delamanid 200 mg BID + OBR (N = 76)
Cardiac Disorders	18 (11.2)	25 (15.6)	17 (10.6)	22 (16.1)	0
Palpitations	13 (8.1)	20 (12.5)	10 (6.3)	18 (13.1)	0
Supraventricular extrasystoles	1 (0.6)	2 (1.3)	1 (0.6)	0	0
Atrioventricular block first degree	2 (1.2)	0	1 (0.6)	1 (0.7)	0
Sinus tachycardia	0	2 (1.3)	2 (1.3)	0	0
Tachycardia	1 (0.6)	1 (0.6)	3 (1.9)	0	0
Ventricular extrasystoles	0	2 (1.3)	2 (1.3)	0	0
Conduction disorder	1 (0.6)	0	0	0	0
Sinus bradycardia	1 (0.6)	0	0	0	0
Angina pectoris	0	0	0	1 (0.7)	0
Bundle branch block left	0	0	1 (0.6)	0	0
Extrasystoles	0	0	0	1 (0.7)	0
Right ventricular failure	0	0	0	1 (0.7)	0
QT Prolongation SMQ Terms					
Investigations					
ECG QT Prolonged	16 (9.9)	21 (13.1)	6 (3.8)	4 (2.9)	2 (2.6)
Nervous System Disorders					
Sycope	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.7)	0 (0.0)

The incidence for other Cardiac Disorders TEAEs in trial 204 was < 2% for any TEAE including supraventricular extrasystoles, AV block first degree, sinus tachycardia, tachycardia, ventricular extrasystoles, conduction disorder, sinus bradycardia, and bundle branch block left. The onset of these events ranged from Day 7 to Day 63 and the duration from 1 day to 62 days. One TEAE of bundle branch block started on Day 28 and was continuing. The events were assessed by the investigator as mild severity and not related, except the events of AV block. No TEAEs of AV block or bundle branch block were reported in patients with TEAEs of QT prolongation

In trial 208, 16.1% (22/137) reported TEAEs mapped to the Cardiac Disorders SOC and all events occurred with 100 mg BID: 13.1% palpitations and <1% each for first degree AV block, angina pectoris, extrasystoles and right ventricular failure. ECG QT prolonged was reported in 2.9% (4/137) in the 100 mg BID group and 2.6% (2/76) in the 200 mg group. There was one TEAE of syncope reported in the 100 mg BID group. Most events were assessed by the investigator as mild severity and not related.

In trial 210, the doses used were 250 mg, 300 mg, 350 mg and 400 mg BID in combination with OBR administered for 28 weeks in patients with refractory MDR-TB (no SCC after 9 months of treatment with second-line anti-TB drugs). Of the 10 enrolled, one patient on 300 mg BID group experienced an acute MI and QT prolonged while one in the 250 mg BID group reported syncope on Day 224.

Serious adverse event / deaths / other significant events

Deaths

The single death in study 242-07-204 occurred in a 50-year-old Asian female with MDR TB that had been treated several times previously. On Day 1 she had a potassium level of 3.2 mEq/L, which dropped to 1.9 mEq/L on Day 7, when she had worsening anaemia, sinus tachycardia and QTcB prolongation (from Day

-1 468 ms to 541 ms; this decreased to 397 ms on Day 8 after the hypokalaemia had been treated). The plasma concentration of DM-6705 was 20.3 ng/ml on Day 6, when delamanid was stopped. On Day 7 she developed respiratory failure, was intubated in ICU but on the next day had two cardiac arrests and died.

The single death in study 242-07-208 involved a 25-year-old Asian male with a 3-year history of treatment for TB who received delamanid 100 mg BID. He died of right ventricular failure on Day 72, 63 days after discontinuation of delamanid on Day 9 (he had also received 200 mg BID for 8 weeks in study 204). He had evidence of right ventricular hypertrophy at study 204 screening and all subsequent ECGs but this was not seen on the screening ECG for study 208. On Day 9 of study 208 he had SAEs of right ventricular failure and increased hepatic transaminase, with severe drug-induced liver injury and mild increased blood uric acid. Delamanid was stopped. The elevated blood uric acid resolved by Day 19 and the elevated hepatic transaminase, drug induced liver injury and hyperbilirubinaemia resolved by Day 27. On Day 34 he had severe respiratory failure and he died on Day 72. The investigator considered the right ventricular failure, drug-induced liver injury, increased hepatic transaminase, and hyperbilirubinaemia all possibly related to delamanid.

One additional death occurred in trial 210 on Day 78 following discontinuation of delamanid on Day 64. This 46-year-old male patient died due to acute non-Q wave myocardial infarction (Day 63), coronary artery disease, worsening MDR-TB and alcohol abuse. Delamanid, as well as other anti-TB medications, were discontinued. The plasma concentration of DM-6705 on Day 64 was 121 ng/mL with QTcF of 415 ms, which was not an increase from baseline.

There were another 21 deaths in the registry study 116, for which cause of death was not recorded. These subjects were not taking delamanid. The median time from last dose of delamanid to death was 231.5 days, with a range from 3 days to 705 days.

Six of the 24 total patients who died did not receive delamanid. Among 18 that did receive any delamanid, 6 cases had actually achieved SCC in 204 or in 208 without a documented reversion. In all except 3 instances death occurred at > 100 days after the last dose of delamanid. The other three had intervals of 3 days (case in 204), 15 days and 63 days.

During the procedure, information was collected on a total of 37 deaths by means of study 116 as well as review of TB program records at sites where 204 was conducted. These data were analysed in support of efficacy and are described in the previous section.

Severe adverse events

Overall, 74 patients in 204/208 reported SAEs. No new clinically relevant SAEs were reported in 208 vs. 204. QT interval prolongation was reported as an SAE for 2 patients. Most SAEs in 208 occurred 4 months or longer after starting treatment with delamanid. Those occurring in > 1 patient are shown in the table.

Table 47

Table 3.64-9	Serious Adverse Events Reported by More Than 1 Patient in Any Treatment Group - Multidrug-resistant Tuberculosis Patients, Safety Population			
System Organ Class and MedDRA Preferred Term[a]	Number (%) of Patients[b]			
	Trial 204			Trial 208
	Delamanid 100 mg BID + OBR (N = 161)	Delamanid 200 mg BID + OBR (N = 160)	Placebo + OBR (N = 160)	All Delamanid[c] (N = 213)
Patients with any SAE	16 (9.9)	20 (12.5)	14 (8.8)	25 (11.7)
Blood and Lymphatic System Disorders				
Anaemia	3 (1.9)	2 (1.3)	1 (0.6)	0
Thrombocytopenia	1 (0.6)	1 (0.6)	0	0
Hepatobiliary Disorders				
Hepatitis	1 (0.6)	1 (0.6)	1 (0.6)	0
Hyperbilirubinaemia	0	0	0	3 (1.4)
Infections and Infestations				
Tuberculosis	0	0	0	3 (1.4)
Investigations				
Electrocardiogram QT prolonged	7 (4.3)	9 (5.6)	3 (1.9)	2 (0.9)
Metabolism and Nutrition Disorders				
Hypokalaemia	0	2 (1.3)	0	0
Psychiatric Disorders				
Agitation	1 (0.6)	1 (0.6)	0	0
Psychotic disorder	2 (1.2)	2 (1.3)	3 (1.9)	0
Respiratory, Thoracic, and Mediastinal Disorders				
Haemoptysis	3 (1.9)	1 (0.6)	2 (1.3)	2 (1.6)
Pneumothorax	1 (0.6)	0	1 (0.6)	0

In **242-07-204** the overall incidence of SAEs was slightly higher for the pooled dose delamanid group (36/321, 11.2%) vs. placebo (14/160, 8.8%). Rates for individual SAEs were mostly comparable except for prolonged ECG QT (16/321, 5.0% vs. 3/160, 1.9%). Prolonged QT was considered by the investigator as possibly related for 9/16 of those treated with delamanid. Rates were 7/161 (4.3%; 5 related) for 100 mg BID and 9/160 (5.6%; 4 related) for 200 mg BID. None of the three SAEs of this type on placebo were considered related and no event was accompanied by clinical symptoms. SAEs of hypokalaemia were reported for 2 subjects in the delamanid 200 mg BID group but were not considered to be related by the investigator.

One 32-year-old Asian subject became pregnant after receiving 200 mg BID in study 204 and 100 mg BID in study 208. She conceived approximately 34 days after the last dose of delamanid. At 33 weeks gestation she experienced pre-term labour that did not progress and at nearly 39 weeks she delivered a healthy male by Caesarean section.

Laboratory findings

In 242-07-04 clinically significant abnormal chemistry values were most frequently observed for uric acid, potassium, sodium and albumin. Hyperuricaemia was the only parameter for which the proportion of subjects with clinically significant abnormal values was higher for the total delamanid group (26.1% vs. 22.9% for placebo).

TEAEs related to serum chemistry abnormalities were reported at comparable rates for delamanid and placebo groups. The most frequently reported was hypokalaemia (15.9% vs. 15.0%). Hypokalaemia was also the most frequently reported potentially drug-related chemistry abnormality (2.5% [8/321] delamanid and 1.9% [3/160] placebo). SAEs of hypokalaemia were reported for 2 subjects.

Elevated serum cortisol may be seen in progressive TB due to disturbance of the peripheral metabolism of cortisol leading to increased cortisol production. The proportion with ≥ 26 µg/dL was higher in the

delamanid groups (58/161, 36.0% and 78/160, 48.8%) vs. placebo (47/160, 29.4%). In addition, about half of the subjects had a single elevation that met clinically significant criteria including 28/58 (48%) subjects in the 100 mg BID group, 38/78 (49%) in the 200 mg BID group and 26/47 (55%) in the placebo group. The onset of clinically significant serum cortisol values varied across treatment groups. Among those with clinically significant serum cortisol levels, 42/58 (72%) in the 100 mg BID group, 52/78 (67%) in the 200 mg group and 30/47 (64%) in the placebo group had cavitations on the baseline chest radiograph. Also, 13/58 (22%), 11/78 (14%) and 7/47 (15%) with elevated cortisol in respective groups had XDR-TB.

Clinically significant abnormal haematology values were most frequently observed for aPTT, absolute eosinophils, haematocrit, haemoglobin, MCV, absolute neutrophils, platelet count, RBC count, reticulocyte count and WBC count. Higher proportions in the total delamanid group had clinically significant abnormal values for haematocrit (13.4% vs. 11.3% placebo), haemoglobin (25.9% vs. 22.5%), MCV (28.3% vs. 26.9%), platelet count (15.9% vs. 13.8%) and RBC count (27.4% vs. 26.3%). Clinically significant abnormal values for aPTT were observed less frequently with delamanid (44/321, 13.7% vs. 26/160, 16.3% for placebo) but the converse applied to abnormal values for PT (11/263, 4.2% vs. 2/138, 1.4%). No apparent safety signal of effect of delamanid on PT or aPTT was observed. One SAE of thrombocytopenia and a case of leucopenia were considered possibly related to delamanid and treatment was discontinued for both subjects.

Haematuria was the most frequently reported TEAE related to urinalysis but was reported for a lower percentage in the total delamanid group vs. placebo (2.5% vs. 3.1%). Other than haematuria for one subject none of the TEAEs related to urinalysis abnormalities were considered by the investigator to be potentially drug-related, none was serious and none resulted in discontinuation.

Regarding the potential for hepatotoxicity, the Asian male who died in study 208, having also received delamanid in 204, is described above. The cause of the liver injury was felt to be most likely liver hypoxia secondary to right ventricular failure. He did not have elevated bilirubin by laboratory evaluation, although he was reported by the investigator to have a TEAE of hyperbilirubinaemia. The investigator assessed the events as cardiac failure and hepatic injury, possibly related to the investigational medicinal product (IMP). The assessment was based on the observation that the patient had a relatively good Karnofsky score (80%) prior to the event, the OBR drugs were not new to the patient, the LFTs improved after IMP discontinuation, the secondary lung infection had not worsened appreciably at the time of the event, and the IV fluid given to improve liver function was not large enough to cause cardiac decompensation (there was global cardiac failure, which was refractory to diuretic and other treatment). Based on the Hy's Law criteria the patient did have AST 20 x ULN and ALT of 10 x ULN at 3 days after elevation was first noted and the day before values were clearly rapidly declining.

The three other possibly related TEAEs of abnormal hepatic function in 208 came from a single site in China. None of the patients met biochemical criteria consistent with Hy's Law and none had isolated elevated bilirubin or a transaminase that was > 3 x ULN. Briefly, these cases concerned:

- A 31-year-old female on delamanid 100 mg BID had an ALT level > 1 x ULN, an AST level > 2 x ULN and a normal total bilirubin level (0.3 mg/dL). The abnormalities occurred at Week 26, were mild and were noted to have resolved at the follow-up visit (Day 225; but actual values not available).
- A 41-year-old male on delamanid 200 mg BID had normal ALT, AST and bilirubin levels without any other evidence of abnormal hepatic function in the patient profile. On Day 45, not closely associated with any scheduled laboratory investigations, he was reported to have the TEAE of abnormal hepatic function possibly related to the study drug, which was considered mild and no change in study drug was made. The TEAE was said to have resolved 9-days later. The sponsor

does not know the basis of the TEAE report and it is not supported by any laboratory values in the database.

- A 24-year-old male had mild elevations of transaminases (> 1 x ULN) at Day 7 of 208, which was Day 84 of his participation in 204. He received 200 mg BID and had an ALT level > 2 x ULN, an AST level > 1 x ULN, and a bilirubin level minimally elevated at 1.3 mg/dL at Day 70. The event was mild, possibly related to study drug and no change in study medication was made. The patient withdrew on Day 78.

One additional patient did meet the criteria for Hy's law but the event was not considered to be related to delamanid. This case was reported in 208 following closure of the database for the interim report for the dossier filing. The patient was an 18-year-old male who received delamanid 200 mg BID during 204 and had no TEAEs related to liver abnormality. At Day 99 in 208, when he was also taking 200 mg BID, he had an acute hepatitis event (AST/ALT 40 x ULN and bilirubin 6.6 x ULN). Viral hepatitis A, B and C were ruled out by appropriate testing. The patient was taken off all medications including delamanid and the event subsided. The investigator deemed the event due to pyrazinamide, a frequent cause of elevated transaminases and bilirubin in TB patients that has been associated with liver failure and death.

Immunological events

Thus far there seem to be very few TEAEs reported as "hypersensitivity" in the database and very few other TEAEs that could potentially represent allergic reactions to treatment.

Safety related to drug-drug interactions and other interactions

There is a risk of co-administration of delamanid with other agents that can prolong QTc. This is an important fact to be communicated to healthcare professionals.

Discontinuation due to adverse events

In study 204 the percentages that discontinued treatment (delamanid or placebo) due to TEAEs were comparable (10/321, 3.1% and 4/160, 2.5%). No TEAE resulting in discontinuation was reported for more than one subject with the exception of psychotic disorder (in 3 subjects; 2 at 200 mg BID and one placebo).

In study 208 7/213 (3.3%) discontinued delamanid because of TEAEs. These included SAEs of right ventricular failure, QT prolongation and oral malignancy.

In study 210 two of 30 discontinued due to TEAEs of atrial fibrillation and progressive TB.

Post marketing experience

None

2.6.1. Discussion on clinical safety

The total safety database for this new anti-mycobacterial agent is relatively limited in terms of total numbers exposed.

The predominant concern regarding use of delamanid is the effect on QTc, which did show evidence of increased magnitude with dose. However, there does not seem to be a clear relationship between this effect and rates of TEAEs and there were only 2 deaths in the 204/208 combined datasets.

It is important to note that moxifloxacin was not allowed in clinical studies. All 29 patients with QTcF increase > 60 ms in trial 204 were prescribed a fluoroquinolone; nine out of 29 patients were taking levofloxacin and 20 out of 29 were taking ofloxacin. This is important since it is expected that fluoroquinolones would be standard (rather than exception) as part of an adequate regimen to treat MDR-TB.

The details of the TEAEs that resulted in the higher reporting rates for the SOCs cardiac, investigations and psychiatric disorders in SE Asia showed, among other things, that QTc prolongation accounted for the difference in the cardiac and investigations SOC. The relationship between occurrence of these TEAEs and delamanid plasma levels was examined and suggests a trend to a positive correlation. However, it is difficult to draw any definitive conclusions in light of the apparent geographical variability in AEs reporting that confounds the assessment of reporting rates vs. plasma exposures.

Another concern is the potential for delamanid to be associated with an increased risk of hepatotoxicity. This cannot be dismissed on current evidence and would require further characterisation of this risk.

2.6.2. Conclusions on the clinical safety

The total safety database for Delamanid is relatively limited in terms of total numbers exposed, but overall re-assuring.

Electrocardiogram QTc interval prolongation has been identified as the most prominent safety concern of treatment with delamanid. This is an important fact, since co-prescription with fluoroquinolones is to be expected as part of an adequate regimen to treat MDR-TB.

Another concern constitutes the potential for delamanid to be associated with an increased risk of hepatotoxicity.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The RMP (v2.2) is acceptable with minor revisions required for the next update:

- Section 2.2 should be amended to include hyperglycaemia as an event to be kept under review and reported on through PSURs
- Elements for summary tables in the EPAR and elements for a public summary should be provided

This advice is based on the following content of the Risk Management Plan **(Table 48)**:

- **Safety concerns**

Important identified risks	• QT interval prolongation • Paresthesia • Tremor • Anxiety
Important potential risks	• Tinnitus • Blurred vision • Hypokalemia • Depression • Insomnia • Drug resistance • Blood cortisol level increase • Drug use during pregnancy • Drug use during breastfeeding • Nausea • Vomiting • Liver disorders
missing information	• Drug use in paediatric patients • Drug use in elderly patients • Drug use in patients with HIV) • Drug use in patients with severe renal impairment • Drug use in patients with severe hepatic impairment • Drug-drug interactions

- **Pharmacovigilance plans**

Table 2.2-1 Safety Concerns and Planned PV Actions	
Safety concern	**Planned actions**
Important identified risks	
QT interval prolongation	Routine PV Multivariate analysis to characterize the factors that affect QT interval prolongation from treatment with delamanid and clarify the potential role of hypoalbuminaemia. Analysis of ECGs in Trial 242-09-213 Registry as a part of Responsible Access Program
Paresthesia	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Tremor	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Anxiety	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Important potential risks	
Tinnitus	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Blurred vision	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program

Hypokalemia	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Depression	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Insomnia	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Blood cortisol increased	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Drug resistance	Routine PV Trial 242-07-204 MIC determinations for all isolates that can be recovered and determination of the sub-species within the Mycobacterium tuberculosis complex Trial 242-09-213 including the interim CSR Registry as a part of Responsible Access Program Setup a network of laboratories offering DST to delamanid and integration of DST into the European system for TB drug resistance surveillance
Drug use during pregnancy	Routine PV Registry as a part of Responsible Access Program

Safety concern	Planned actions
Drug use during breast feeding	Routine PV Registry as a part of Responsible Access Program
Nausea	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Vomiting	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program
Liver disorders	Routine PV Trial 242-09-213 Registry as a part of Responsible Access Program

missing information	
Drug use in paediatric patients	Pediatric Investigational Plan
Drug use in elderly patients	Routine PV Registry as a part of Responsible Access Program
Drug use in patients with HIV	Routine PV including Additional data analysis from the Trial 242-09-213 (HIV subpopulation) Registry as a part of Responsible Access Program
Drug use in patients with severe renal impairment	Routine PV including close monitoring Registry as a part of Responsible Access Program
Drug use in patients with severe hepatic impairment	Routine PV including close monitoring Registry as a part of Responsible Access Program
Drug-drug interactions	Routine PV including close monitoring Trial 242-09-213 Registry as a part of Responsible Access Program

- **Risk minimisation measures**

Table 3.1-1 Summary of Planned Actions		
Safety concern	**Routine risk minimisation activities sufficient?**	**If yes, provide description of routine activity and justification**
Important identified risks		
QT interval prolongation	No	
Paraesthesia	Yes	Listed as Undesirable effects in the proposed SmPC (section 4.8)
Tremor	Yes	Listed as Undesirable effects in the proposed SmPC (section 4.8)
Anxiety	Yes	Listed as Undesirable effects in the proposed SmPC (section 4.8)
Important potential risks		
Tinnitus	Yes	Considering the nature of the risk and a limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid.
Blurred vision	Yes	Considering the nature of the risk and a limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid.
Hypokalemia	Yes	Hypokalemia in general is a risk factor for QT prolongation and is mentioned as such in special warnings and precautions for use in the proposed SmPC (QT prolongation: section 4.4)

Safety concern	Routine risk minimisation activities sufficient?	If yes, provide description of routine activity and justification
Depression	Yes	Considering the nature of the risk and a limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid.
Insomnia	Yes	Considering the nature of the risk and a limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid.
Drug resistance	No	
Blood cortisol level increase	Yes	Considering the nature of the risk and a limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid.
Drug use during pregnancy	No	The guidance for use is provided in proposed SmPC (section 4.6)
Drug use during breast- feeding	No	
Nausea	Yes	Considering the nature of the risk and a limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid
Vomiting	Yes	Considering the nature of the risk and a limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid
Liver disorders	Yes	Considering the limited strength of the signal the focus for this potential risk is on PV activities in order to get a better understanding of the nature of the risk and the relation to the use of delamanid

missing information		
Drug use in paediatric patients	Yes	The guidance for use is provided in proposed SmPC (section 4.2)
Drug use in elderly patients	Yes	Considering the low anticipated risk the focus for this item is on PV activities in order to get more information Section 4.2 of the proposed SmPC informs that no data are available for the use in elderly
Drug use in patients with HIV	Yes	Warnings are provided in section 4.4 of the proposed SmPC Interactions with anti-HIV drug are discussed in section 4.5 of the proposed SmPC.
Drug use in patients with severe renal impairment	Yes	Considering the low anticipated risk the focus for this item is on PV activities in order to get more information
Drug use in patients with severe hepatic impairment	Yes	Section 4.4 of the proposed SmPC contains a warning for use in patients in moderate to severe hepatic impairment
Drug-drug interactions	Yes	The focus for this item is on PV activities in order to get more information

The CHMP, having considered the data submitted in the application concluded that no risk minimisation activities could be appropriate taking into account the negative benefit risk balance of this medicinal product.

2.9. Significance of paediatric studies

Not applicable

2.10. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The pivotal trial for establishing efficacy and safety of delamanid in MDR-TB patients was the randomised placebo-controlled phase 2 trial 242-07-204. The demonstration of the efficacy of delamanid was based on the increase in sputum culture conversion (SCC) after 2 months of delamanid treatment given in combination with OBR.

Follow-on studies (208 and 116) aim to provide support to the sustained efficacy of delamanid.

During 8 weeks treatment with delamanid 100 mg or 200 mg twice daily in study 204, a higher proportion of subjects with pulmonary tuberculosis caused by organisms that were at least resistant to rifampicin and isoniazid achieved SCC compared to the placebo group: in 45.4% of the patients treated with delamanid 100 mg BID, 41.9% in patients treated with delamanid 200 mg BID, and 29.6% in patients treated with OBR only (MGIT media); for patients with XDR-TB these figures were 4/24 (17%), 5/18 (28%) and 2/27 (7%).

As such, the magnitude of the difference vs. placebo in the MITT population varied by dose group, MDR-TB vs. XDR-TB, presence of cavitation, region and whether the analyses were based on MGIT or solid culture media results.

The applicant's integrated analyses showed that delamanid use for ≥6 months (*any* combination of doses) yielded a sustained culture conversion in 91% of patients with MDR-TB (130/143), and in 78% (31/40) in those with XDR-TB. Of note though, among 48 MDR-TB patients who had no treatment with delamanid in 204/208 at any time, 37 (77.1%) achieved sustained SCC (on solid culture media). This compares with 75 out of 110 (68.2%) of those who received delamanid for a maximum of 2 months.

Uncertainty in the knowledge about the beneficial effects

The comparison between delamanid and placebo was restricted to 8 weeks only, which is insufficient. In principle, there should have been a comparison of delamanid vs. placebo over a continuous 6-month treatment period. In addition, the data to Week 8 are clearly subject to influence according to region/site, at least part of which reflects the rates of XDR-TB.

The open-label data from 208/116 reflect patient decisions to continue with open-label treatment, investigator decisions to change the dose and willingness of patients to be followed up for final outcomes (24 months). As such, the reliability of the additional integrated analyses is questioned. Also, the available datasets do not support any clear conclusion regarding the appropriateness of the recommended dose regimen (100 mg BID).

Actual results for the relatively small numbers who were proven to have MDR-TB at baseline in trial 204 and at any time *only* received one of the following: 100 mg BID, 200 mg BID or no delamanid, raise concerns. Indeed, in the group that received only 100 mg BID in trials 204/208, 16 out of 25 patients (64.0%) had a favourable outcome (WHO classification) compared to 29 out of 48 patients (60.4%) who received no delamanid at all.

Risks

Unfavourable effects

Delamanid is associated with prolongation of the QTc interval that is driven predominantly but not wholly by plasma levels of a major metabolite DM-6705. Currently, there remain uncertainties regarding the metabolic fate of delamanid, since the apparently anomalous results of the human mass balance study remain unexplained.

Uncertainty in the knowledge about the unfavourable effects

The total safety database, consisting of two delamanid dose groups and placebo in the first study and uncontrolled use of delamanid in the second study, is limited.

The potential for delamanid to be associated with an increased risk of hepatotoxicity is uncertain and would need further characterisation.

Benefit-risk balance

Importance of favourable and unfavourable effects

The actual benefit of delamanid cannot be established from the data provided. The efficacy in terms of sputum culture conversion of the two investigated doses (100 mg BID and 200 mg BID) was superior to placebo, but the duration of comparison was too short. The results of the follow-on studies are difficult to interpret. These data cannot address the essential deficiencies of study 204 and the available results cannot confirm the appropriateness of the applicant's proposed dose regimen for delamanid.

The main safety issue observed with delamanid relates to QT-prolongation, albeit no associated cases of ventricular tachycardia /torsades de pointes were observed. Further on, hepatotoxic potential cannot be dismissed.

Benefit-risk balance

On current evidence, the benefit-risk balance of Delamanid in treatment of pulmonary infections due to multidrug-resistant *Mycobacterium tuberculosis* as part of an appropriate combination regimen is deemed unfavourable.

Discussion on the benefit-risk balance

MDR-TB is defined as TB caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampicin. It represents a significant unmet medical need in Europe and developing countries. MDR-TB is associated with a considerable mortality rate and poses a significant public health threat. New medicinal products that can be used in combination with existing therapies are therefore much needed.

Delamanid, a nitro-dihydro-imidazo-oxazole derivative, provides a novel mechanism of action. It has been developed for clinical use against MDR strains of *M. tuberculosis*, as part of combination therapy.

Efficacy results (superiority outcome) were obtained in phase-2 pivotal trial 242-07-204. All patients were diagnosed for pulmonary, sputum culture positive MDR-TB and received an optimal background regimen (OBR). Patients were randomised into 3 groups and received 100 mg BID delamanid, 200 mg BID delamanid, or placebo, in combination with OBR (BID), and sputum culture status was assessed weekly; SCC was measured after 2 months of treatment.

Following completion of trial 242-07-204, patients were eligible for participation in the uncontrolled open-label trial 242-07-208 and received up to an additional 6 months treatment (or first-time 6 months

for patients randomised to the placebo group in trial 242-07-204) with delamanid 100 mg BID or 200 mg BID during their course of 24 months MDR-TB treatment with OBR.

The overall data are however difficult to interpret. The duration of comparison between delamanid and placebo is too short to be able to discern the benefit of adding delamanid at either 100 mg or 200 mg BID to an optimised background regimen for 6 months. Study 242-07-208 cannot repair this major deficiency since it does not allow for an assessment of SCC rates vs. placebo over the applicant's proposed duration of use of delamanid (6 months). In addition, the data obtained in both 208 and 116 do not allow for a robust assessment of sustained SCC and must be viewed with much caution since patients self-selected to enter study 208 and to be followed in trial 116.

In addition, there are inadequate data to identify the dose of delamanid that should be used. The data obtained in 208 and 116 cannot provide a reliable conclusion regarding the most appropriate dose regimen as doses used in study 208 were selected and not randomised. It is also of concern that the magnitude of benefit of delamanid 100 mg BID vs. placebo based on MGIT SCC rates at week 8 was substantially driven by the result for this dose at a single site that enrolled 150/481 patients where no patient had XDR-TB.

The adverse events profile for Delamanid has been established in a limited safety database, comprising approximately 900 individuals. Delamanid was generally well tolerated. However, potential hepatoxicity cannot be dismissed and needs further investigation. The predominant concern regarding use of delamanid is the effect on QTc. Hypoalbuminaemia (particularly below 2.8 mg/dl) is identified as a major contributing factor. Also, caution has to be applied if delamanid would be administered with quinolones to construct an adequate regimen for treating MDR-TB. Of note, moxifloxacin was contra-indicated during the phase-2 study programme.

Finally, the metabolic fate of delamanid remains largely unexplained, due to apparently anomalous results obtained in the human mass balance study.

Based on the available data, a positive benefit-risk balance of this medicinal product cannot be established, which precludes the granting of a conditional marketing authorisation.

4. Recommendations

Similarity with authorised orphan medicinal products

Not applicable

Derogation(s) from market exclusivity

Not applicable

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Delamanid in the treatment of pulmonary infections due to multidrug-resistant *Mycobacterium tuberculosis* as part of an appropriate combination regimen, the CHMP considers by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated as:

- the duration of comparison between delamanid and placebo is too short to be able to discern the benefit of adding delamanid at either 100 mg or 200 mg BID to an optimised background regimen for 6 months. Study 242-07-208 cannot repair this major deficiency since it does not allow for an

assessment of SCC rates vs. placebo over the applicant's proposed duration of use of delamanid (6 months). In addition, the data obtained in both 208 and 116 do not allow for a robust assessment of sustained SCC and must be viewed with much caution since patients self-selected to enter study 208 and to be followed in trial 116;

- there are inadequate data to identify the dose of delamanid that should be used. The data obtained in 208 and 116 cannot provide a reliable conclusion regarding the most appropriate dose regimen as doses used in study 208 were selected and not randomised. It is also of concern that the magnitude of benefit of delamanid 100 mg BID vs. placebo based on MGIT SCC rates at week 8 was substantially driven by the result for this dose at a single site that enrolled 150/481 patients where no patient had XDR-TB;

therefore the CHMP recommends the refusal of the granting of the conditional Marketing Authorisation for the above mentioned medicinal product

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

5. Re-examination of the CHMP opinion of 25 July 2013

Following the CHMP conclusion that Delamanid was not approvable for the following indication:

"Delamanid is indicated for the treatment of pulmonary infections due to multidrug-resistant *Mycobacterium tuberculosis* as part of an appropriate combination regimen (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents".

as the efficacy of the above mentioned medicinal product was not sufficiently demonstrated, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation their grounds that the adopted CHMP opinion may not have considered the data fully and also provided further information. The applicant presented the revised indication:

"Deltyba is indicated for the treatment of pulmonary infections in adults due to multidrug-resistant *Mycobacterium tuberculosis* as part of an appropriate combination regimen (see sections 4.2, 4.4 and 5.1).

Deltyba is not recommended for use in the treatment of extra pulmonary tuberculosis (e.g. central nervous system, bone), latent infection with M. tuberculosis, drug-susceptible M. tuberculosis or infections due to Mycobacterial species other than those of the M. tuberculosis complex.

Consideration should be given to official guidance on the appropriate use of antibacterial agents".

During the oral explanation held on the 18 November 2013, the applicant addressed specifically the CHMP's grounds for refusal as follows:

Ground 1

The duration of comparison between delamanid and placebo is too short to be able to discern the benefit of adding delamanid at either 100 mg or 200 mg twice daily to an optimized background regimen for 6 months. Study 208 cannot repair this major deficiency since it does not allow for an assessment of SCC rates vs. placebo over the applicant's proposed duration of use of delamanid (6 months). In addition, the data obtained in both Trials 208 and 116 do not allow for a robust assessment of sustained SCC and must be viewed with much caution since patients self-selected to enter Trial 208 and to be followed in Trial 116.

The Applicant proposes 3 lines of data supporting the sustained efficacy of delamanid in MDR-TB patients:

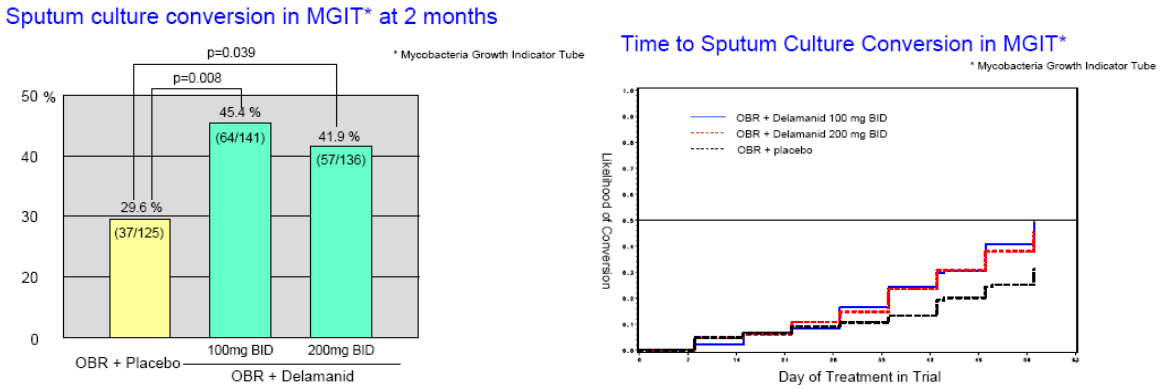
1. The data from Trial 204 to demonstrate a sustained benefit in SCC out to 3 months from the 2 months of treatment with delamanid at either dose in that trial.
2. Analysis of 2-month SCC, sustained SCC, and mortality in Trials 204, 208, and 116 to demonstrate sustained efficacy and reduced mortality.
3. The association between 2-month SCC and the longer term efficacy of MDR-TB treatment demonstrated by the Collaborative Group data.

1. ***Analysis of data from Trial 204 on efficacy of delamanid***

The primary endpoint pre-specified for the randomized, controlled Trial 204 was the proportion of patients achieving sputum culture conversion (SCC) within 2 months by measuring mycobacterial growth incubation tube (MGIT). The results were an increase relative to the placebo group in the proportion of patients achieving SCC of 45% and 42% for 100 mg BID and 200 mg BID dosing groups, respectively.

A key secondary endpoint was the time to SCC, shown with the Kaplan-Meier curve analysis. The curve for the two delamanid groups are nearly superimposed and separate from the placebo curve by day 28 (one month) and the separation continues to increase during the second month.

Figure 25: Primary and secondary analyses for Trial 204



SCC was measured by MGIT (mycobacterial growth incubation tube)

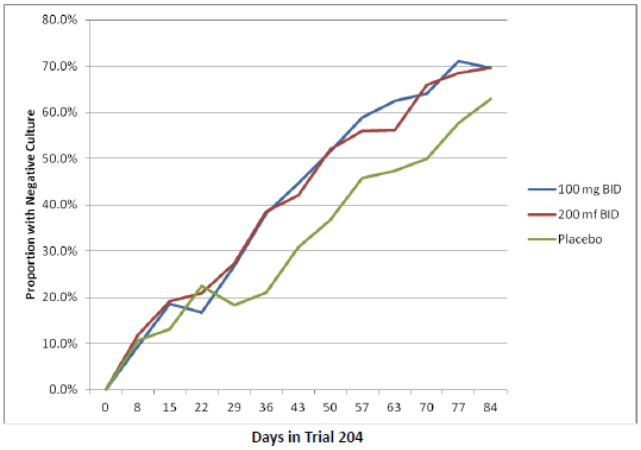
Proportion negativity at each time point

Controlled data on sputum culture status was available up to 3 months (Day 84) in Trial 204 since to meet the definition of 2-month SCC, a patient was required to have achieved a negative culture by 2 months in the trial as well as in the 4 subsequent weekly cultures.

The proportion of culture results that are negative at each time point have been used to determine sustained efficacy. This is different from conversion, since it does not require a confirmatory negative culture but the proportion negative is a useful population measure of the efficacy of treatment. Figure 26 below illustrates the proportion of all culture results that are negative at each time point.

Figure 26

Figure 3.2-5 Proportion of all culture results in the randomized, controlled Trial 204 that are negative at each time point

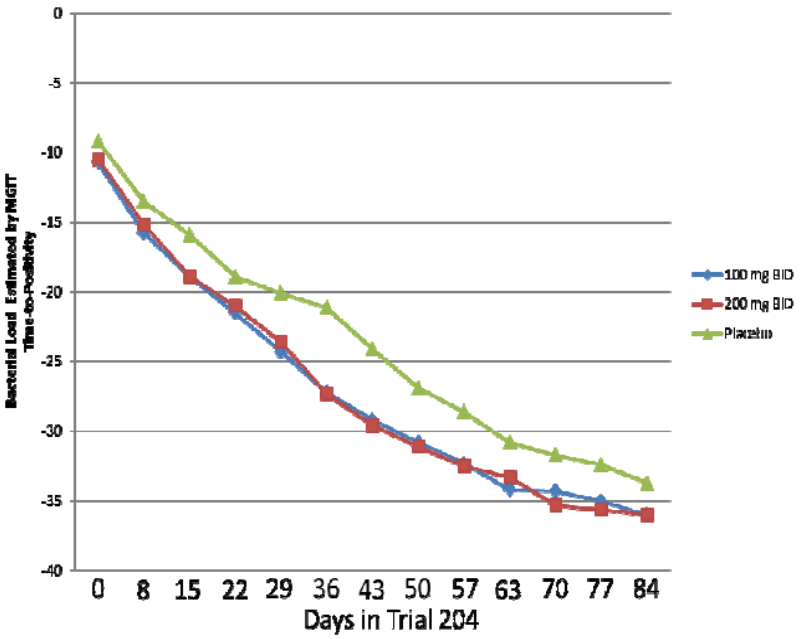


Time to culture positivity (TTP) in MGIT

For patients with positive cultures, the change in the mean TTP in the MGIT culture system can be examined. TTP is a measure of bacterial load in sputum and an increase in TTP indicates a lower bacterial load. The TTP in the delamanid groups separates from the placebo group at Day 29 and the difference between the delamanid groups and the placebo group remains statistically significant through Day 50 (Figure 27). Overall, in a regression model, the reduction in bacterial load is estimated to be 22-27% faster in the delamanid groups compared to the placebo group.

Figure 27

Figure 3.2-6 Bacterial load at each time point in Trial 204 as estimated by the mean TTP for the randomized groups in Trial 204

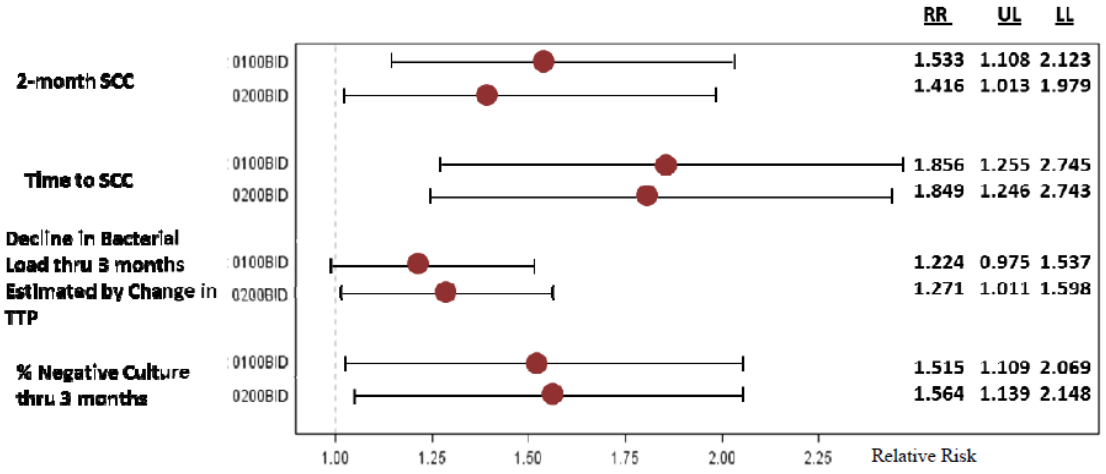


Consistency of results at 2 and 3 months

The results were consistent for the efficacy measures at 2 months and at 3 months. In all cases the efficacy measure for delamanid groups are significantly different from the placebo group. For each of the measures there is little difference between the two delamanid dose groups when compared to placebo.

Figure 28

Figure 3.2-7 Forest Plots summarizing the relative efficacy of the delamanid groups compared to the placebo group in the randomized, controlled Trial 204



N = Number of patients; RR = Risk ratio; LL = Lower Limit; UL = Upper Limit

2. Analysis of 2-month SCC, sustained SCC, and mortality in Trials 204, 208, and 116 to demonstrate sustained efficacy and reduced mortality.

Final treatment outcomes were ascertained on 421 (87.5%) patients in Trial 116 and follow-up vital status was available on 464 (96.5%) of the original Trial 204 patient population at ≥24 months after the date of randomization in that trial (Table 49):

Table 49

Table 3.2-1 Population for Analysis of Longer-term Treatment Benefit of Delamanid

	Trial 204	Trial 116	Vital status accessed
Intent-to-treat (ITT)	481	421	464
Modified ITT[a] (based on MGIT)	402	350	n/a
Modified ITT[a] (based on Solid media)	347	301	n/a

[a] Modified ITT population comprises all patients in the ITT with microbiologically confirmed MDR-TB at baseline.
n/a = not available

The applicant claims that bias is unlikely to have affected enrolment of patients completing Trial 204 into Trial 208 for the following reasons:

- Nearly all patient treatment assignments in Trial 204 were unknown to investigators and patients at the time of their potential to enroll in Trial 208, so previous treatment in Trial 204 did not influence the decision to enter Trial 208.
- The Trial 208 protocol was designed to duplicate care delivered by the high-quality treatment programs where the Trial 204 sites were located; patients not participating in Trial 208 were managed in the same manner at the same sites.

Association between 2-month SCC and mortality

Mortality is an important clinical outcome from the perspective of both efficacy and safety and is least likely to be affected by bias. In the Otsuka MDR-TB development program for delamanid, vital status at ≥24 months was determined on 464 (96.5%) of the original 481 patients randomized in Trial 204. This high level of capture of vital status serves to further attenuate concerns of bias in interpreting beneficial trends from 6 months of treatment with delamanid. As a frame of reference, overall mortality published in 2012 from the large meta-analysis of treatment data from >9,000 MDR-TB patients was 15%; ECDC reported 19.6% mortality for MDR-TB patients treated in the EU/EEA (Ahuja SD, et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. PLoS Med 2012;9(8):e1001300).

The mortality according to original Trial 204 randomization group, 2-month SCC, and Trial 208 participation is summarized in the Table below:

Table 50

Table 3.2-2 Mortality Among Otsuka MDR-TB Program Patients by Trial 204 Randomization, Group 2-month SCC and Trial 208 Participation

Trial 204 Randomization Group (treated with delamanid + OBR for 2 months or placebo + OBR)	N	Achieved 2-month SCC n (%)		Trial 208 Participation (treated with delamanid for 6 months) n (%)		Mortality by subgroup (as documented in Trial 116) n (%)
100 mg + OBR	155	Yes	71 (45.8)	Yes	33 (46.5)	0
				No	38 (53.5)	2 (5.3)
		No	84 (54.2)	Yes	31 (36.9)	2 (6.5)
				No	53 (63.1)	10 (18.9)
200 mg + OBR	157	Yes	71 (45.2)	Yes	37 (52.1)	0
				No	34 (47.9)	3 (8.8)
		No	86 (54.8)	Yes	35 (40.7)	1 (2.9)
				No	51 (59.3)	4 (7.8)
Placebo + OBR	152	Yes	50 (32.9)	Yes	25 (50.0)	0
				No	25 (50.0)	1 (4.0)
		No	102 (67.1)	Yes	44 (43.1)	3 (6.8)
				No	58 (56.9)	11 (19.0)
Total	464	-	-	-	464	37

BID = twice daily; OBR = optimized background regimen.

The key findings include:

- No deaths occurred among patients who achieved 2-month SCC as assessed with the MGIT system and then enrolled in Trial 208 (received 6 months delamanid) in each of the original 3 Trial 204 randomization groups.
- Among those who did not achieve 2-month SCC in each of the original 3 randomization groups in Trial 204, mortality for patients who enrolled in Trial 208 was consistently two thirds lower than for those who did not enroll in Trial 208 (and did not receive 6 months delamanid).
- The highest mortality was for those who did not achieve 2-month SCC in Trial 204 and then did not enroll in Trial 208 (did not receive 6 months delamanid).

Though the number of patients in each of the various sub-groups for analysis is relatively small, the mortality benefit of delamanid treatment is clear.

Association between 2-month SCC, sustained SCC, and Mortality

Treatment with delamanid led to a 50% increase in 2-month SCC. As demonstrated in Table below, patients in Trial 204 who achieved 2-month SCC and then enrolled in Trial 208 achieved the highest level of sustained SCC (98.7%) among all groups; none of these patients died during the follow-up period.

Their level of sustained SCC was higher than for those patients who achieved 2-month SCC in Trial 204 but did not enrol in Trial 208 (85.9%), suggesting an added benefit from 6 months of treatment with delamanid.

Among those who did not achieve 2-month SCC in Trial 204, those who did enroll versus those who did not enrol in Trial 208 experienced a substantially higher level of sustained SCC (81.5% versus 56.5%) and lower mortality (5.5% vs. 15.4), respectively.

Table 51

Table 3.2-3 Mortality and Sustained SCC Among Otsuka MDR-TB Program Patients by 2-month SCC status from Trial 204 and Trial 208 Participation

Achieved 2-month SCC in Trial 204 (irrespective of treatment with delamanid) n (%)		Trial 208 Participation (Treated with delamanid for 6 months) n (%)		Mortality[a] n = 464 (%)	Sustained SCC[b] n = 301 (%)
Yes	192 (41.4)	Yes	95 (49.5)	0 (0)	77/78 (98.7)
		No	97 (50.5)	6 (6.2)	67/78 (85.9)
No	272 (58.6)	Yes	110 (40.4)	6 (5.5)	53/65 (81.5)
		No	162 (59.6)	25 (15.4)	45/80 (56.3)
Total	464	-	-	37 (8.0)	242/301 (80.4)

[a] Mortality presented on total intent-to-treat population for whom vital status at ≥ 24 months post randomization was available.

[b] Sustained sputum culture conversion (SCC) presented on subset of modified intent-to-treat population as defined by culture positive status using solid media at Trial 204 baseline who consented to participate in Trial 116 (Table 3.2-1).

3. Association of 2-month SCC with Sustained SCC and Reduced Mortality from Collaborative Group Data

The 2-month SCC has long been considered a very good predictor of relapse-free survival in drug-sensitive TB and of favorable treatment outcomes, including a reduction in mortality in patients with MDR-TB. The largest meta-analysis of MDR-TB was conducted by the Collaborative Group for the WHO Stop TB Department using patient level data combined from different centers, using methods suggested by the Cochrane group (*Stewart LA, Tierney JF, Clarke M on behalf of the Cochrane Individual Patient Data Metaanalysis Methods Group 2008. Reviews of individual patient data. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic reviews of Intervention. Wiley-Blackwell; 48-58*).

An initial analysis of 9,153 patients with MDR-TB from 32 observational studies was published in 2012 (Ahuja SD et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. PLoS Med 2012;9(8):e1001300).

To evaluate the validity of the 2-month SCC as a predictor of clinical outcome in MDR-TB, 2 co-authors (Richard White, PhD and Carole Mitnick ScD) undertook a series of analyses of a subset of 2,942 patients from the original total group (9,153 TB patients) for whom baseline culture data were available. The findings are described below and the resulting conclusions have been endorsed by the authors.

Objectives: To evaluate the evidence that supports the utility and predictive value of sputum culture conversion (SCC) from growth of Mycobacterium tuberculosis to no growth after two months of intensive treatment (2-month SCC) as an endpoint in the context of MDR-TB, using individual sputum culture results that could be linked with long-term outcomes, such as mortality, assessment of treatment outcome at 24 months, using a WHO algorithm, by the PI of each cohort, assessment of treatment outcome at 24 months using a computer program implementation of the WHO algorithm, and with sustained SCC, from 2,492 patients included in the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB database.

To compare the strength of the association of SCC measured at 2 months, 3 months and 6 months to identify if there is an optimum time point for measuring SCC.

To compare the association of 2-month SCC with mortality, sustained SCC and PI assessment of MDR-TB treatment outcomes at 24 months identified in the meta-analysis with the results observed in the combined dataset from Otsuka Trials 242-07-204, 242- 07-208, and 242-09-116.

Methodology: The database for this analysis was assembled from a larger database of 9,153 patients from 32 MDR-TB treatment cohorts assembled to provide a robust evidence base for the 2011 update for the WHO Guidelines for the programmatic management of drug resistant tuberculosis.[7] The database includes patient information from 10 cohorts with agreement from the principal investigator to analyze the data in that cohort and 2,942 of these patients were included in the analysis. The Applicant claims that the meta-analysis is methodologically rigorous following methodologies outlined by the Cochrane Collaboration and meets criteria set out in EMA Points to Consider (CPMP/EWP/2330/99) on validity and use of meta-analysis data sets. In fact the meta-analysis was conducted under protocol with clear statement of objectives, study selection criteria, specification of endpoints and statistical methods; the patients dataset of 9,153 patients are representative of geographically diversity from all WHO regions; it is a meta-analysis of individual patient data from the eligible cohorts.

Number of Patients: 2,492 patients with baseline sputum cultures positive for growth of Mycobacterium tuberculosis. The analysis of association of SCC with long-term outcomes has been performed with a subset of 2,942 patients with sputum culture data available and culture positive at

baseline. The patients in this subset had demographic, geographic diversity and clinical characteristics similar to the large data set of 9,153 and that homogeneity of study results for association of SCC and mortality demonstrated qualitatively in forest plots and quantitatively (p=0.07).

Statistical Methods: Pooled estimates of the effects for each of the outcome measures were calculated using both fixed-effect and random-effect models. Data for each outcome variable were presented in 2 x 2 tables and for each of the cohorts. The crude odds ratios (OR) were then adjusted for cohort and then for cohort plus one other clinical or demographic covariate available in both the collaborative group and Otsuka Trials databases. In brief, 93 studies of MDR-TB or meta-analyses of MDR-TB cohorts were identified. Of these, 26 publications were excluded because they represented the same or overlapping cohorts and an additional 35 cohorts were excluded because the authors did not respond or could not provide the required individualized patient data. The remaining 32 cohorts included data on 9,898 patients, of whom 410 were excluded since they had XDR-TB, 208 were excluded because they had no treatment information and 127 were excluded with extra-pulmonary TB, leaving 9,153 patients for analysis.

Analysis and Results

One of the key findings of this meta-analysis was that whether SCC was measured at 2-months, 3-months or 6-months, a similarly strong association of SCC and a reduction in the odds of mortality was noted. The Odds Ratio for mortality, given SCC, was 0.20, 0.15 and 0.12 when SCC was measured at 2-months, 3-months or 6-months, respectively (Table 52). This indicates that SCC measured as early as 2 months serves as a meaningful predictor of long-term outcome, in this case mortality.

Table 52

Table 3.2-4 Association of Sputum Culture Conversion with Mortality at 2-months, 3-months, and 6-months in 2,942 Patients in the Collaborative Group Database

Time point	Odds ratio adjusted for cohort effect	95% Confidence interval
Two Months	0.20	0.12 – 0.28
Three Months	0.15	0.11 – 0.20
Six Months	0.12	0.08 – 0.16

One hypothesis for why achieving 2-month SCC is associated with a reduced likelihood of mortality is that those who achieve SCC earlier are most likely to achieve sustained SCC. In turn, those with sustained SCC are most likely to survive to the end of treatment and during follow-up.

This was observed among patients in the Collaborative Group meta-analysis (Table 53). The Odds Ratio for achieving Sustained SCC, given that the patient achieved 2-month SCC, was 12.7. The Odds Ratio for mortality, among those achieving Sustained SCC was 0.08. This means that after SCC at 2 months, there is a >12-fold chance to achieve sustained SCC and the odds of survival are 90% higher.

Table 53

The association of 2-month SCC and Long-Term Outcome: Mortality after 4 Years, PI Assessed Outcome and Sustained Conversion in the Collaborative Group database

Outcome measure	Odds Ratio (adjusted for cohort)	95% CI	p-value
2-Month SCC and mortality	0.20	0.12 - 0.28	<0.001
2-Month SCC and sustained SCC	12.70	8.92 - 18.08	<0.001
Sustained SCC and mortality	0.08	0.06 - 0.11	<0.001

These results are consistent with the biological hypothesis for the observed association of 2- month SCC and a reduction in mortality.

Overall Results from Otsuka Dataset consistent with Analysis of Collaborative Group Dataset

The results from the analysis of the overall data from the Otsuka MDR-TB program (irrespective of treatment with delamanid) were consistent with and are supported by the analysis of the Collaborative Group data. The association of 2-month SCC with mortality and sustained SCC and the association of sustained SCC and mortality are very similar (Table 54). The magnitude of effect is very similar in all cases. These three associations are consistent with the proposed hypothesis that delamanid increases the proportion achieving 2-month SCC which in turn increases the proportion achieving sustained SCC and finally that those achieving sustained SCC have a very low risk of mortality.

Table 54

Table 3.2-6 The Association of 2-month SCC with Key Long-Term Outcomes in the Collaborative Group Dataset and in the Otsuka Development Program

Outcome Measures	Odds Ratio(adjusted for cohort effects) from the Collaborative Group	Odds Ratios from the Otsuka Clinical Development Program
2-month SCC and Mortality	0.20	0.20
2-month SCC and Sustained SCC	12.70	8.41
Sustained SCC and Mortality	0.08	0.02

Summary of Longer-term benefit from 6 months of Treatment with Delamanid

In summary, the analysis of the data from patients treated with 6 months of delamanid provides support for an added longer-term benefit from the treatment.

The data have demonstrated that 2-month SCC is valid to discern the benefit of adding delamanid to OBR for 6 months.

- The data from Trial 204 demonstrate a sustained benefit in SCC out to 3 months from the 2 months of treatment with delamanid at either dose.

- Furthermore, patients who achieved 2-month SCC in Trial 204 (irrespective of receiving delamanid) and then enrolled in Trial 208 to receive 6 months of delamanid treatment had the highest level of sustained SCC (and very low mortality), especially compared to those patients who did not achieve 2-month SCC and then did not enroll in Trial 208.
- The Collaborative Group data provide independent corroboration of the Otsuka results demonstrating a strong association between 2-month SCC, sustained SCC, and improved clinical outcome.

Data supporting the sustained efficacy of delamanid from Trial 213 which is nearing the completion of enrollment and in which MDR-TB patients receive delamanid or placebo for 6 months of the treatment with OBR and are followed for 30 months will serve to confirm this longer-term benefit.

Ground 2

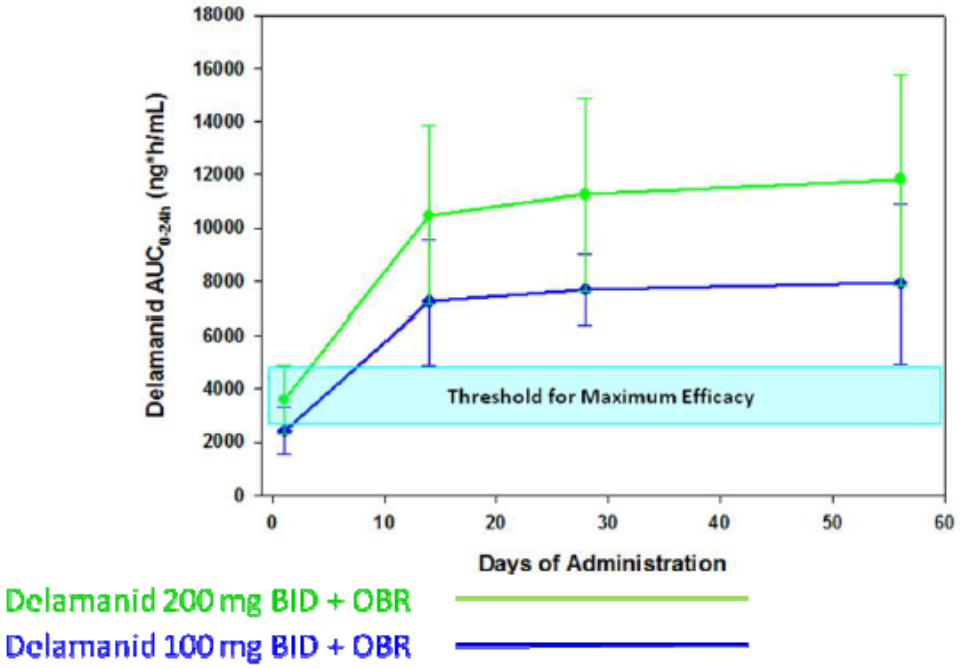
There are inadequate data to identify the dose of delamanid that should be used. The data obtained in 208 and 116 cannot provide a reliable conclusion regarding the most appropriate dose regimen as doses used in Trial 208 were selected and not randomized. It is also of concern that the magnitude of benefit of delamanid 100 mg twice daily vs. placebo based on MGIT SCC rates at week 8 was substantially driven by the result for this dose at a single site that enrolled 150/481 patients where no patient had XDR-TB

Evidence that the 100 mg delamanid twice daily dose should be used as the most effective dose was obtained from the efficacy results of the double-blind, randomized, controlled trial, Trial 204.

In Trial 204, both of the delamanid doses assessed, 100 mg and 200 mg twice daily, showed similar results for all efficacy endpoints. Furthermore, exposures from both dose regimens were above the threshold for maximum efficacy (Figure 29), as no association between increased plasma exposure and increased efficacy was observed. This indicates that saturation of delamanid's anti-bacterial efficacy was reached at the exposures obtained with either dose in the trial. Doubling of the daily dose did not increase anti-bacterial benefit to the patients and would potentially increase risk and escalate +the already high pill burden of patients on MDR-TB therapy.

Figure 29

Figure 3.3-1 **Both 100 mg and 200 mg twice daily Provide Exposures well above the Threshold range for maximum efficacy determined from Delamanid Trials**



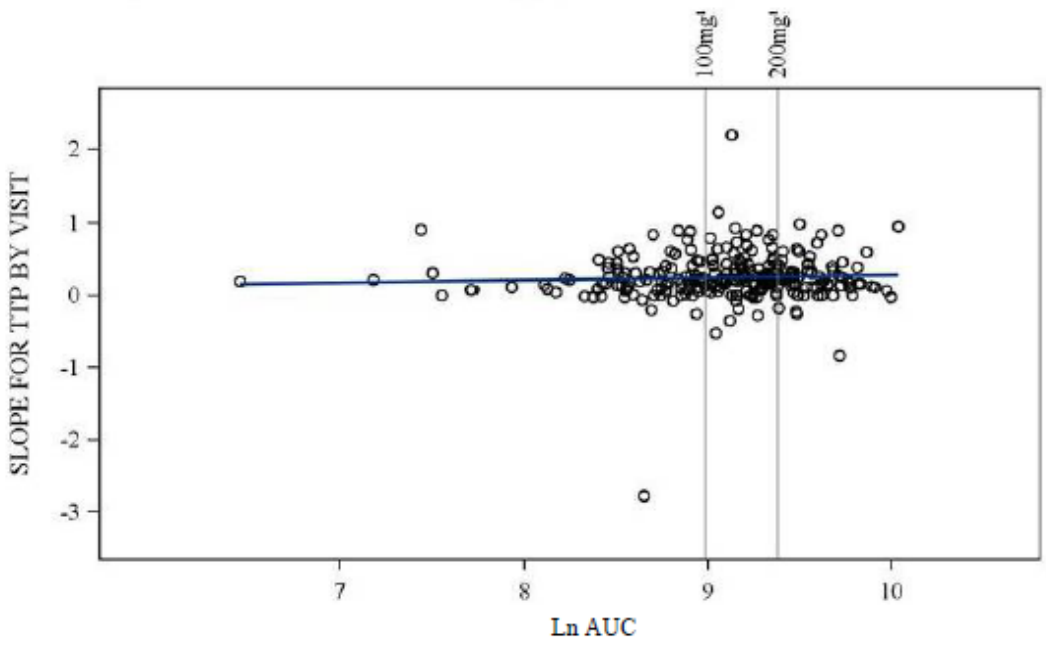
The main conclusions from Trial 204 supporting the delamanid 100 mg twice daily dose were:

- Both delamanid 100 mg twice daily + OBR treatment and 200 mg twice daily + OBR treatment for 2 months in MDR-TB patients resulted in virtually identical clinically meaningful and statistically significant increases in the primary efficacy variable, SCC at Month 2compared to placebo (29.6%): 45.4% for 100 mg (p=0.0083) and 41.9%, for 200 mg twice daily, (p=0.0393).
- Mean exposures for delamanid 100 mg BID and 200 mg BID during steady state at Day 56 were AUC0-24h = 7952 (37.5 CV%) and 11837 (33.6 CV%) ng*h/mL. Although delamanid exposure was 49% higher for 200 mg BID + OBR, the proportion of patients reaching SCC at 2 months was comparable between delamanid dose groups. These results suggest that during steady-state conditions in Trial 204 for both the 100 and 200 mg BID delamanid doses, patients' plasma exposure was above the exposure threshold for maximum efficacy when evaluated as SCC rate.
- Essentially identical results for both doses were also seen for time-to-conversion, assessed as a secondary end-point, where both were significantly better compared to placebo.
- There was no association between delamanid anti-bacterial efficacy (assessed as bacterial load reduction measured by the slope of the time to culture positivity [TTP] curve) and plasma exposure (AUC) to delamanid.

As demonstrated in Figure 30 the regression line between AUC and anti-bacterial efficacy (TTP curve slope) is horizontal indicating no association (similar efficacy for either dose), whereas a positive association would have resulted in a diagonal regression line (as the efficacy would be higher at higher exposure).

Figure 30

Figure 3.3-2 Association between efficacy (Slope for TTP by Visit) and Exposure (ln AUC at Day 56)



O - TTP slope for individual patients;
vertical lines represent the ln mean AUC for each dose group (100 mg and 200 mg)
horizontal line is the AUC vs. TTP slope regression line

Summary of Delamanid Dose Justification

The dose-response relationships were explored using the antibacterial efficacy, measured as SCC, TTP at various time points, the slope of the TTP and the time to culture conversion of the delamanid 100 and 200 mg BID doses in Trial 204. Delamanid's antibacterial efficacy from the 100 mg and 200 mg BID regimens showed virtually the same results, both being clinically meaningful and statistically superior to placebo.

With regard to delamanid exposure, although 200 mg BID resulted in an approximately 50% higher exposure (mean AUC_{0-24h} [CV %I] = 11837 [33.6 %]) than 100 mg BID (mean AUC_{0-24h} [CV %I] = 7925 [37.5 [%]), the efficacy end-points measured as SCC, TTP at various time points, as slope for TTD or time to culture conversion all show comparable results for both delamanid doses. A potential initial exposure range was identified in the EBA trial seeking to optimize the bactericidal activity in the early stage of treatment. The bactericidal activity of delamanid was assessed through daily measurements of CFU counts in sputum and expressed as the slope of log CFU change per day over the 14 days of trial duration in EBA. A threshold of AUC_{0-24h} for maximum bactericidal efficacy was determined to be between 3500 an 5500 ng*h/mL. Thereafter, in a longer-term trial utilizing a split/BID dosing to further optimize exposure, the original initial bactericidal range appeared to be validated. The threshold was further evaluated using a nonlinear mixed-effect modeling approach with delamanid exposure and TTP data, which indicated a threshold of about 6000 ng*h/mL in XDR-TB-negative patients or 7000 ng*h/mL

in XDR-TB patients. In addition, the intraquartile odds ratio analysis indicated no significant differences between delamanid 100 mg and 200 mg BID on the probability of conversion and a plateau in efficacy was reached with the exposures beyond that associated with delamanid 100 mg BID.

In summary, the delamanid exposure following the 100 mg BID regimen is well above the threshold indicated by the EBA trial, the exposure-TTP analysis, and the nonparametric logistic regression. Increased delamanid exposure, beyond that from the 100 mg BID regimen, does not result in increased efficacy. While the 200 mg BID regimen provides higher plasma concentrations and AUC_{0-24h}, it also resulted in increased incidence of adverse events as well as the QTc interval, a marker for cardiac toxicity.

Since the exposure of delamanid in trial 204 was above the threshold for maximum efficacy, it is unlikely that differences in delamanid exposure are a discriminating factor for differences in antibacterial efficacy (conversion/non-conversion or bacterial load reduction measured by TTP). As long as exposure above the threshold is achieved, other factors such as morphological conditions of the host (cavitation), concomitant OBR therapy and corresponding susceptibility or duration of MDR-TB would have to be considered to explain individual differences in efficacy.

Justification for Delamanid Treatment Duration

The proposed treatment duration with delamanid in MDR-TB therapy is 6 months. The 6-months treatment duration for delamanid is justified following analysis of durability of sputum conversion through determination of final sustained SCC. Durability of delamanid's antibacterial efficacy was assessed by comparing sustained final SCC at the end of MDR-TB therapy 20-24 months after the start of Trial 204 between patients treated with delamanid for ≥ 6 months and patients treated for ≤ 2 months. The results indicated that patients treated long-term with delamanid 100 mg BID and 200 mg BID + OBR showed notably and clinically meaningful higher rates of sustained SCC (92.3%) than delamanid 2 month or OBR only treated patients (73.4%). Furthermore, consistent with 2-month efficacy results, sustained SCC rates for 200 mg BID were not significantly higher than for delamanid 100 mg BID. These results clearly support the proposed 100 mg BID regimen administered for 6 months to MDR-TB patients. It should be noted that a total SCC of around 90% is very much in the range of bacterial clearance in other bacterial diseases like CAP.

Magnitude of Benefit of delamanid 100 mg twice daily is consistent across Region and extent of drug resistance

Consistency of Delamanid Effect Across Regions

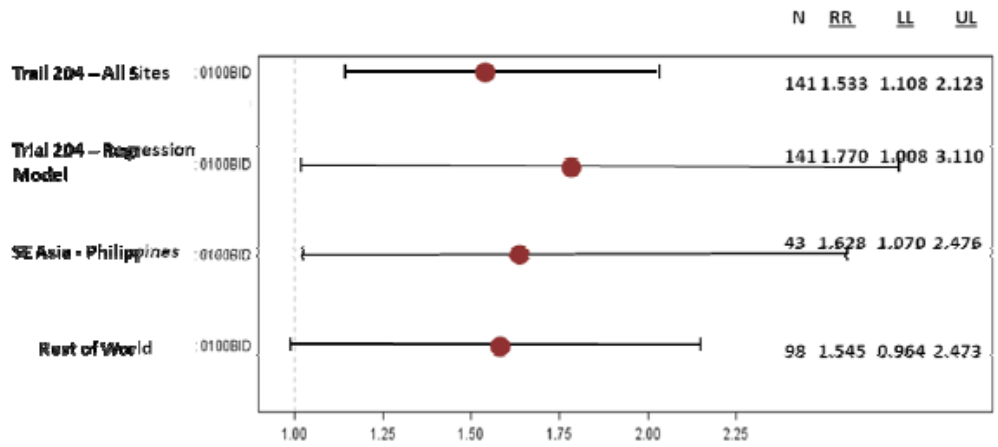
The single trial site mentioned in Ground for Refusal 2 is the Manila, Philippines site. The potential imbalances represented by the large sample size enrolled at this site were addressed using statistical methods including a pre-specified sensitivity analysis.

The pre-specified secondary analyses for Trial 204 consistently confirmed the favorable and clinically meaningful effect of treatment with delamanid + OBR compared to placebo + OBR.

Sensitivity analyses were conducted on the primary endpoint using the MGIT system and solid culture media, excluding microbiology data from each country/region; additionally, for the Manila, Philippines, by far the largest site for enrolment. The results of these analyses were consistent with those of the primary analysis (Figure 31).

Figure 31

Figure 3.3-3 Sensitivity Analysis of Efficacy of Delamanid in the Treatment of MDR-TB Shows Consistency of Effect



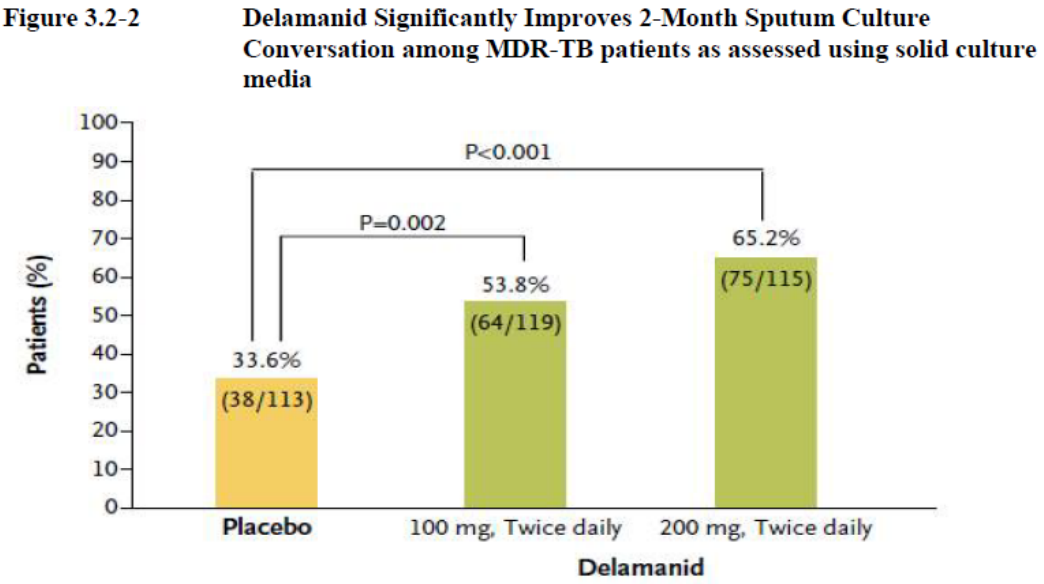
Source: Trial 204 CSR, Table 5.1

N = Number of patients; RR = Risk ratio; LL = Lower Limit; UL = Upper Limit

2-month SCC assessed using solid media

- Results from the secondary analysis of 2-month SCC assessed with the use of solid media were consistent with the results of the primary analysis (Figure 32).
- The proportions of patients with 2-month SCC in both dose groups receiving delamanid were higher compared to placebo and the differences were statistically significant (p= 0.002 for 100 mg vs. placebo and p<0.001 for 200 mg vs. placebo).

Figure 32

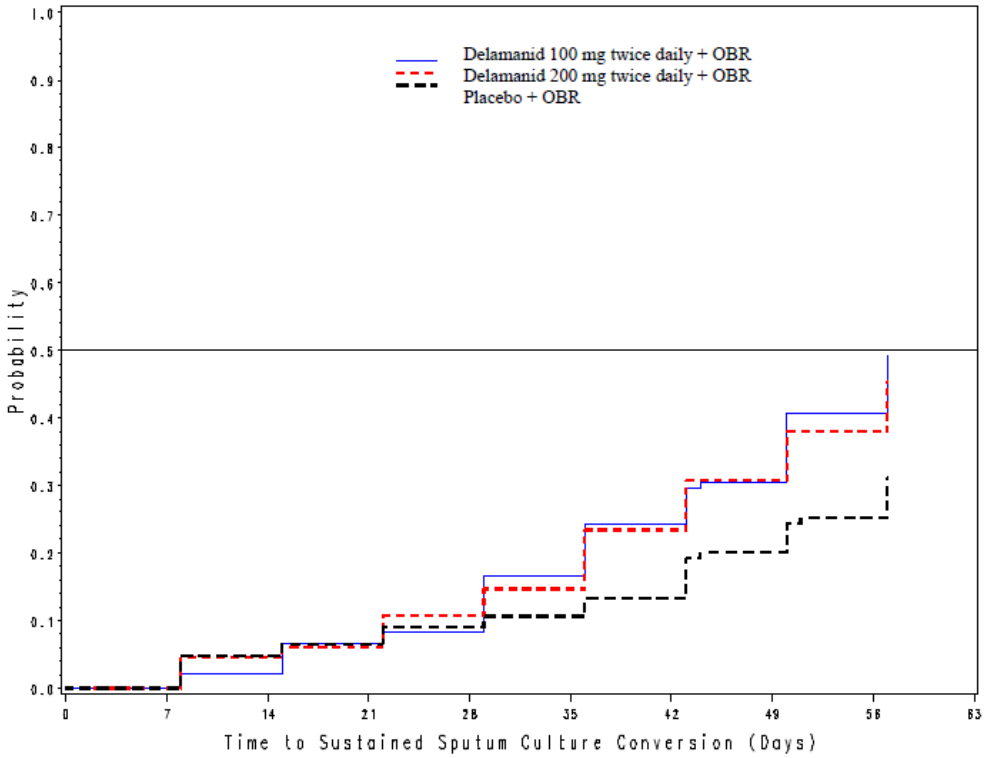


Time (in days) to achieve SCC

- An analysis of the time to achieve SCC among the 3 patient groups, demonstrated improved results for patients treated with either dose of delamanid + OBR compared to patients treated with placebo + OBR.
- In the Kaplan-Meier curve analysis for time to sustained SCC (SCC maintained out to 3 months) using the MGIT system, there was a clear separation between each delamanid + OBR treatment group and the placebo + OBR treatment group (Figure 33);
- Treatment with delamanid resulted in earlier SCC with differences apparent within 3 weeks and increasing over the 8 weeks of treatment.

Figure 33

Figure 3.2-3 Survival Analysis of Days to Sputum-Culture Conversion using MGIT System



*OBR: Optimized Background Treatment Regimen

Pre-specified sensitivity analyses

The protocol also required the analysis of 2-month SCC in 3 other populations as a sensitivity analysis and to test the robustness of the conclusions about SCC (Figure 34).

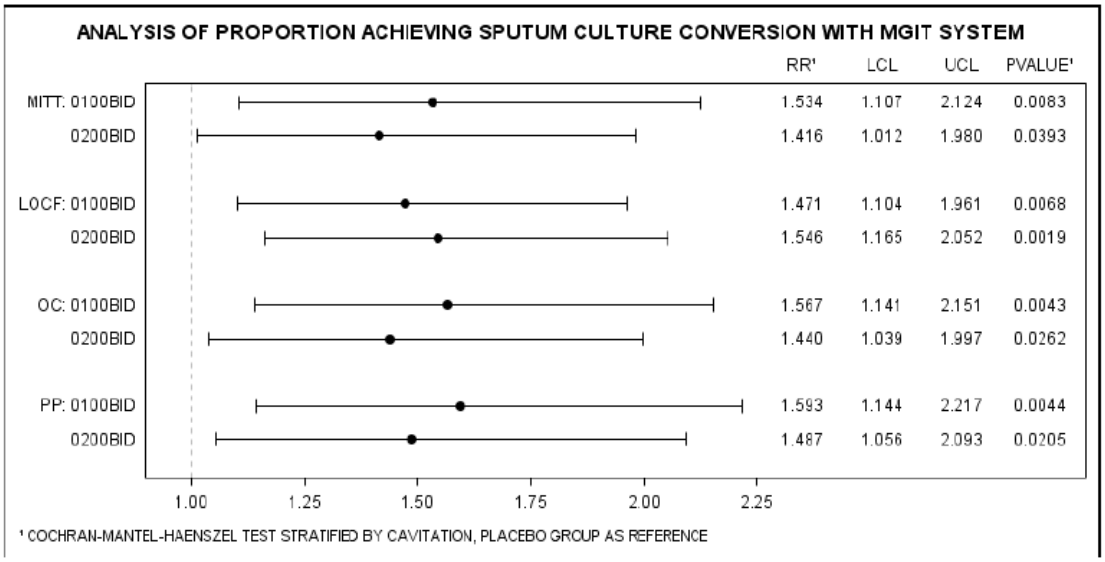
These populations were:

- LOCF - for the Last Observation Carried Forward (LOCF) analysis in the case of missing values the result for the last non-missing culture was carried forward to the end of the trial.
- OC - The Observed Cases (OC) data set is the population completing the 84-day trial, for patients with data through Day 84 and is a subset of the MITT population.
- PP - A subset of the OC population with no major protocol deviation.

In all cases, the delamanid group has a statistically higher likelihood of conversion compared to the placebo group (Figure 34).

Figure 34

Figure 3.2-4 **Sensitivity Analysis of Trial 204 Primary Efficacy Outcome of 2-month SCC (Delamanid vs. Placebo) by various Populations**



Consistency of Delamanid Effect Across Extent of Drug Resistance

Until recently, the WHO classified streptomycin as a "Group 2 injectable" among the second line drugs used to treat MDR-TB in the 2008 Guidelines. Therefore, resistance to streptomycin was included in the pre-specified analysis plan of Trial 204 to define XDR-TB. Now however, the WHO no longer classifies streptomycin as a second-line anti-TB medication for treating MDR-TB. Therefore, the data from Trial 204 were re-analyzed using both the previous and current WHO definitions of XDR-TB (with and without streptomycin). In applying this updated definition, the imbalance at baseline disappears (Table 55). Critically, the marked treatment benefit of delamanid compared to placebo is apparent in XDR-TB patients according to both definitions (Table 56).

Table 55

Table 3.3-1 **Distribution of XDR-TB patients in Trial 204 Randomization Groups based on inclusion and exclusion of streptomycin resistance to define injectable status**

Randomization group in Trial 204	Sample Size	Previous XDR Definition Including Streptomycin Resistance		Current XDR Definition Excluding Streptomycin Resistance	
		MDR N (%[a])	XDR N (%[a])	MDR N (%[a])	XDR N (%[a])
Delamanid 100 mg	141	117 (83.0)	24 (17.0)	128 (90.8)	13 (9.2)
Delamanid 200 mg	136	118 (86.8)	18 (13.2)	126 (92.6)	10 (7.4)
Placebo	125	98 (78.4)	27 (21.6)	111 (88.8)	14 (11.2)

[a] Percentage is the percent of each group achieving 2-month SCC
Source: FDATYPE B-1.1 and FDATYPE B-1.1.1

Table 56

Table 3.3-2 Conversion of XDR-TB patients in Trial 204 Randomization Groups based on inclusion and exclusion of streptomycin resistance to define injectable status				
Randomization group in Trial 204	Previous XDR Definition Including Streptomycin Resistance		Current XDR Definition Excluding Streptomycin Resistance	
	MDR % SCC	XDR % SCC	MDR % SCC	XDR % SCC
Delamanid 100 mg	51.3	16.7	47.6	23.1
Delamanid 200 mg	44.1	27.8	42.8	30.0
Placebo	28.1	7.4	33.3	0.0

Source: FDATYPE B-1.1 and FDATYPE B-1.1.1

5.2. Additional expert consultation- Report from the Ad hoc expert group meeting

Following a request from the applicant at the time of the re-examination, and supported by both rapporteurs, the CHMP convened an Ad hoc Expert Group inviting the experts (and including two representatives from patient organisations), to provide their views on the questions posed by the CHMP, taking into account the applicant's response to the grounds for refusal.

Efficacy & Drug Resistance

1. Does the SAG consider the applicant's claim that the short term efficacy results obtained in the placebo controlled trial with delamanid may be used as a proxy to predict the long-term maintenance effect of delamanid, taking into consideration the evidence published in the literature and the results of the meta-analysis which highlight the correlation between SCC results after 2 months and treatment effect at 6 months?

   According to the SAG, do the 2-month SCC results together with the evidence of the correlation existing between results at 2 month and results at 6 months provide sufficient demonstration of delamanid efficacy for use in patients with limited options?

Despite the imbalances in groups in MDRTB and XDR-TB numbers and recruitment sites in trial 204, the experts agreed that there is evidence of efficacy over an initial period of 8 weeks treatment. Based on the experience of the experts there is a significant possibility that indeed it could maintain effect in use over the later phase of treatment. However, the less than perfect evidence so far available from trials 208 and 116, cannot rule out the possibility that delamanid would behave like pyrazinamide and lose its effect over a variable period. Nevertheless, based on the fact that a confirmatory trial is awaited soon to complement the current evidence, the level of efficacy demonstrated over 8 weeks in a superiority setting could be used preliminarily as a proxy for efficacy.

2. Can the results obtained at 8 weeks be widely extrapolated across MDR patients taking into account the regional variations observed and the SCC rates for XDR-TB?

Bearing in mind the reservations about the small numbers and some imbalance in sub-groups studied, such as XDR TB cases, there is nevertheless no clear evidence that any of these groups failed to show a response.

3. Is the overall evidence provided by the applicant to support the selection of the 100mg BID dose as opposed to the 200 mg dose (for treatment over 6 months), sufficiently robust and adequate?

   If not, can the SAG suggest an alternative dose regimen and/or duration that might be more appropriate?

Data available from the trials cannot confirm 100 mg bid to be the optimal dosage. This is based particularly on mortality outcomes (in which 200 mg bid appears to outperform placebo and 100 mg bid), although it was recognized that the long term data are potentially biased as no randomization took place. The group recommends that whilst 100 mg bid might be a starting point, 200 mg bid and maybe equivalent once daily dosage (i.e. 400 mg OD) could be explored as alternatives. Most members felt that such dose should be explored in studies which may be differently designed and more discriminating than those completed so far, even from the beginning of the treatment course (thus to be employed over the whole course). At the same time it was reflected that co-administration with other medicines with an effect on QTc prolongation calls for some caution in the conduct of studies with higher doses.

4. The SAG's opinion is sought on which further data would be required post-or pre-approval in addition or as alternative to the proposed equivalence study and the ongoing Phase III study.

<u>The SAG strongly recommended the following points for attention:</u>

- to explore a higher dose usage, including once daily dose regimen (preferable from practice viewpoint)
- MGIT culture data to be maintained as long as possible through the treatment of patients
- Observational registry to be set up to collect information on sustained responses, recrudescence/ relapse (including outcome in pre-XDRTB, XDRTB) and culture sensitivity data.

5. Can the SAG comment on how the prescribing information might be amended to minimize the potential risk that use of delamanid in combination regimens could select for resistant organisms?

The advice given by the group concurs with the opinion expressed by the experts at the first SAG for delamanid (March 2013).

Where available treatments are very limited, every effort should be made to combine with other agents showing evidence of an effect against the resistant pathogen (including at least one other bactericidal medicine), and the decision to use should be according to expert advice (and based in accordance with national and international guidelines).

The risk for the patient and the public health implication due to potential emergence of resistance should be part of the consideration.

5.3. Additional information provided by the applicant

Following the Oral Explanation on 18 November 2013, the applicant provided additional clarification on the progress and timelines for phase III, pivotal trial 242-09-213:

Milestone	**Target Date**
First Patient Randomised	Sept – 2011
Last Patient Randomised	Nov – 2013

Last Patient Last Visit for 6-month Co-Primary Endpoints	May – 2014
Data Base Lock **Top-line results available for 2-month SCC proportions, 6-month Time-to-conversion analysis and safety data during the administration of DLM and Placebo.** **Results will be reported by treatment arm but the study blind for individual patients will be maintained for the 24-month follow-up period**	**Oct – 2014**
Clinical Study Report (CSR) completed for efficacy and safety data through the first six months	May – 2015
Last Patient 30-month Follow-up Visit	Jun – 2016
Final Data Base Lock including 24-month follow-up after IMP	**Oct – 2016**
Final Clinical Study Report (CSR) for Trial 213	April – 2017

5.4. Discussion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the ad hoc expert group meeting held on 15 November 2013.

Ground 1

The CHMP noted that delamanid 100mg bid versus placebo (in both arms added to OBR), proved superior in terms of achieving SCC at month 2 of therapy (figure 27) in a well-designed trial 204, including MDR-TB /XDR-TB patients. Also data provided on proportion negativity at each time point, up to 3 months (figure 28) and time-to-positivity (TTP) (figure 29) were further supportive of the short term efficacy of delamanid (100 mg bid or 200 mg bid) over placebo.

With regard to whether the proven short term measure of efficacy is predictive for long-term patient outcome, the applicant asserted that patients who achieved 2-month SCC in trial 204 (irrespective of receiving delamanid) and then enrolled in trial 208 to receive 6 months of delamanid treatment had the highest level of sustained SCC (and very low mortality), especially compared to those patients who did not achieve 2-month SCC and then did not enroll in trial 208.

CHMP remarked that enrolment in follow-on trial 208 did not further inform opinion on sustained efficacy due to recognised methodological flaws, such as open-label treatment, investigator decisions to change the dose and willingness of patients to be followed up for final outcomes (24 months). Also, there was an important time gap in rollover between trials 204 and 208 (with delamanid interruption of at least 2 months for 50% and up to 4 months for > 38 % of enrolled subjects in trial 208). As such, the reliability of the additional integrated analyses is questioned. Thus, the strength of the evidence of delamanid efficacy on long-term, is limited by the lack of a direct and sound proof of continuous benefit for at least 6 months, since study 208 is biased by the inadequate design.

However, the CHMP took into consideration that, the experts concurred that indeed two months SCC could be a proxy for long term outcome in MDR-TB. The value of 2 months SCC as important prognostic factor for outcome has been proposed in several studies, such as the one discussed by Ahuja SD *et al.* (2012).

Notwithstanding the uncertainties and limitations of data from the submitted literature references and the additional meta-analysis, the CHMP considered that, on balance, the SCC results obtained in trial 204 can be regarded as sufficient demonstration of therapeutic effect in a superiority setting. CHMP

considers the following measure necessary to address the missing longer term efficacy data in the context of a conditional MA:

"completion and submission of the final study result of the ongoing confirmatory trial examining delamanid added to optimal background regimen in licensed indication (Phase 3 trial comparing delamanid 100 mg BID for 2 months + 200 mg QD for 4 months plus OBR for 18-24 months versus OBR for 18-24 months with placebo for the first 6 months)".

Ground 2

It is appreciated that data obtained from double-blind, randomized trial 204 fully informed the selection of dosage for use of delamanid. The applicant performed various analyses to demonstrate that delamanid assessed at 100 mg and 200 mg twice daily, showed similar results for all efficacy endpoints. The applicant argues that exposures from both dose regimens were above the threshold for maximum efficacy and no association between increased plasma exposure and increased efficacy was observed. Doubling of the daily dose, therefore, would not give added benefit and could potentially increase risk for patients on MDR-TB therapy. It is also argued that the analyses of trial 204 demonstrate the consistency of the delamanid benefit compared to placebo across all regions and the extent of resistance.

The CHMP considered that doubts remain if the 100mg twice daily dosing constitutes the optimal schedule. It is re-iterated that mortality outcomes at month 24 by initial randomization pointed towards a higher effect of 200 mg bid versus placebo and 100 mg bid, noting however the caveat that the long term data are potentially biased as no randomization took place.

Also considering the recommendation obtained from the expert group, the CHMP concludes that, although the currently proposed dose schedule is acceptable within the context of conditional Marketing Authorisation, a higher dose should be appropriately studied to better define optimal exposure-response relationship and impact on emergence of bacterial resistance, whilst taking account of the safety considerations, in particular the effect on QTc interval, expected with higher plasma exposure (and in context of combination with other potentially pro-arrhythmic therapeutic agents).

In consequence, to resolve the uncertainties around exposure and antimycobacterial activity, by conducting a further study exploring the relationship between different doses with respect to 2 months SCC and longer term outcome, the CHMP considers the following measure necessary to address the missing efficacy data in the context of a conditional MA:

"a post-authorization controlled study of the efficacy, safety and pharmacokinetics of delamanid 100 mg twice daily for 2 months followed by delamanid 200 mg in a single daily dose for 4 months or delamanid 400 mg single daily dose for 6 months in adult patients with pulmonary multidrug-resistant tuberculosis to be conducted, based on a CHMP-agreed protocol".

5.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

5.6. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 58: Summary of the Safety Concerns

Important identified risks	QT interval prolongation Paraesthesia Tremor Anxiety
Important potential risks	Tinnitus Blurred vision Hypokalaemia Depression Insomnia Drug resistance Blood cortisol level increase Drug use during pregnancy Drug use during breastfeeding Nausea Vomiting Liver disorders
Missing information	Drug use in paediatric patients Drug use in elderly patients Drug use in patients with HIV) Drug use in patients with severe renal impairment Drug use in patients with severe hepatic impairment Drug-drug interactions

The CHMP agreed.

Pharmacovigilance Plan

Table 59: Summary of ongoing actions including milestones

Summary of ongoing actions including milestones			
Actions (category)	**Milestones /exposure**	**Milestones / calendar time**	**Study status**
Multivariate analysis to characterize the factors that affect QT interval prolongation from treatment with delamanid and clarify the potential role of hypoalbuminaemia.	Report final	June 2013	Ongoing
Trial 242-09-204 MIC determinations for all isolates that can be recovered and determination of the sub-species within the Mycobacterium tuberculosis complex	Report on first 141 baseline isolates Final report	June 2013 January 2014	Ongoing
Setup a network of laboratories offering DST to delamanid and integration of DST into the European system for TB drug resistance surveillance (Category 3)	Materials transfer agreement (MTA) executed with laboratories Training for implementation of the existing DST procedure at these laboratories completed Meeting to address the development of DST methodologies and integration of delamanid DST into existing European systems for TB drug resistance surveillance	September 2013 October 2013 October 2013	Ongoing
Trial 242-09-213	Interim CSR Final data	2Q 2015 2Q 2017	Ongoing
Delamanid registry: EU-wide Patient Registry Post-Marketing Authorization (Category 3)	Final data	2020	Planned
Paediatric Investigational Plan including Efficacy and Safety Studies: Trial 242-12-232 Trial 242-12--233	Final data	October 2016 October 2017	Ongoing
A Phase 1 Trial to Assess the Mass Balance and Pharmacokinetics of ^{14}C-delamanid Following Oral Administration to Healthy Subjects (Category 3)	Metabolic profiling Final data	• October 2014 • January 2015	Planned

Risk minimisation measures for delamanid

Table 60: Summary table of Risk Minimisation Measures

Table Summary of Planned Actions		
Safety concern	**Routine risk minimisation activities**	**Additional risk minimisation activities**
Important identified risks		
QT interval prolongation	Listed as Undesirable effects in the proposed SmPC (section 4.8) Special warnings and precautions for use in the proposed SmPC (QT prolongation: section 4.4) A contraindication targeted at risk minimisation for QT interval prolongation is contained in section 4.3 of the proposed SmPC	- Educational material for healthcare professionals which is part of the Responsible Access Programme, to be completed and to be implemented by the applicant.
Paraesthesia	Listed as Undesirable effects in the proposed SmPC (section 4.8)	n.a.
Tremor	Listed as Undesirable effects in the proposed SmPC (section 4.8)	n.a.
Anxiety	Listed as Undesirable effects in the proposed SmPC (section 4.8)	n.a
Important potential risks		
Tinnitus	Routine risk minimisation activities	n.a.
Blurred vision	Routine risk minimisation activities	n.a.
Hypokalemia	Hypokalemia in general is a risk factor for QT prolongation is mentioned as such in the section on Special warnings and precautions for use in the proposed SmPC (QT prolongation: section 4.4)	n.a.
Depression	Routine risk minimisation activities	n.a.
Insomnia	Routine risk minimisation activities	n.a.
Drug resistance	Sections 4.1 and 4.2 of theproposed SmPC inform that delamanid should be administered for 24 weeks of therapy for multidrug-resistant tuberculosis in combination with an optimized background regimen according to WHO guidelines. Listed in Pharmacodynamic properties in the proposed SmPC (section 5.1)	- Educational material for healthcare professionals which is part of the Responsible Access Programme, to be completed and to be implemented by the applicant.
Blood cortisol level increase	Routine risk minimisation activities	n.a.

Table Summary of Planned Actions		
Safety concern	**Routine risk minimisation activities**	**Additional risk minimisation activities**
Drug use during pregnancy	The guidance for use is provided in proposed SmPC (section 4.6)	- Educational material for healthcare professionals - Educational material to the patient which are part of the Responsible Access Programme to be completed and to be implemented by the applicant.
Drug use during breast- feeding	The guidance for use is provided in proposed SmPC (section 4.6)	- Educational material for healthcare professionals - Educational material to the patient which are part of the Responsible Access Programme to be completed and to be implemented by the applicant.
Nausea	Routine risk minimisation activities	n.a.
Vomiting	Routine risk minimisation activities	n.a.
Liver disorders	Routine risk minimisation activities	n.a.
missing information		
Drug use in paediatric patients	The guidance for use is provided in proposed SmPC (section 4.2)	n.a.
Drug use in elderly patients	Section 4.2 of the proposed SmPC informs that no data are available for the use in elderly	n.a.
Drug use in patients with HIV	Warnings are provided in section 4.4 of the proposed SmPC Interactions with anti-HIV drug are discussed in section 4.5 of the proposed SmPC.	n.a.
Drug use in patients with severe renal impairment	Section 4.2 of the proposed SmPC informs that no data are available on the use of delamanid in patients with severe renal impairment and its use its not recommended (also reflected in section 4.4)	n.a.

Table Summary of Planned Actions		
Safety concern	**Routine risk minimisation activities**	**Additional risk minimisation activities**
Drug use in patients with severe hepatic impairment	Section 4.2 of the proposed SmPC informs that no data are available on the use of delamanid in patients with severe renal impairment and its use its not recommended (also reflected in section 4.4)	n.a.
Drug-drug interactions	Routine risk minimisation	n.a.

The MAH should agree the educational material with the Member States, prior to launch.

The CHMP endorsed this advice with changes. These changes concerned the following elements of the Risk Management Plan:

The CHMP considers the following measures necessary to address issues related to safety:

To Review feasibility of amending the current protocol for 213 concerning:

- collection of full delamanid susceptibility data for baseline isolates from all patients (Ongoing)
- monitoring of PK and ECG data at frequent intervals in patients with mild to moderate hepatic or renal insufficiency (Feasibility assessment is on-going and can be provided by time of Commission Decision)

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

6. Benefit-Risk Balance

Benefits

Beneficial effects

During 8 weeks treatment with delamanid 100 mg or 200 mg twice daily in the Phase 2 study (242-07-204), a higher proportion of subjects with pulmonary tuberculosis caused by organisms that were at least resistant to rifampicin and isoniazid achieved sputum culture conversion (SCC) compared to the placebo group: in 45%, 42% and 30% in those treated with 100 mg bid, 200 mg bid and placebo, respectively; for patients with XDR-TB these figures were 4/24 (17%), 5/18 (28%) and 2/27 (7%).

As such, the magnitude of the difference vs. placebo in the MITT population varied by dose group, MDR-TB vs. XDR-TB, presence of cavitation, region and whether the analyses were based on MGIT or solid culture media results.

It is noted that delamanid for ≥6 months (any combination of doses) yielded a sustained culture conversion in 91% of patients with MDR-TB (130/143), and in 78% (31/40) in those with XDR-TB.

Delamanid showed to be significantly active over the short term period and overall data point towards its incremental value as part of an optimal treatment regimen in MDR-TB.

Uncertainty in the knowledge about the beneficial effects

The comparison between delamanid and placebo was restricted to 8 weeks only. In addition, the data to Week 8 are clearly subject to influence according to region/site, at least part of which reflects the rates of XDR-TB.

The open-label data from 208/116 reflect patient decisions to continue with open-label treatment, investigator decisions to change the dose and willingness of patients to be followed up for final outcomes. Data from studies 208/116 do not address the essential deficiencies of study 204 and the available data cannot confirm the appropriateness of the applicant's proposed dose regimen for delamanid. However, data from literature and collaborative research data provides sufficient arguments that 2-month SCC be associated with better long term clinical outcome.

Whilst awaiting results from confirmatory trials, it can be considered, based on preliminary evidence, that the addition of delamanid to the armamentarium in an area of unmet medical need will be beneficial.

Risks

Unfavourable effects

The overall safety profile of delamanid is considered acceptable despite the fact that the size of the safety database is currently limited.

Delamanid is associated with prolongation of the QTc interval that is driven predominantly but not wholly by plasma levels of a major metabolite DM-6705. However, no torsades de pointes or any other major cardiac arrhythmia have been observed. Use with other medicinal products affecting QTc interval has been addressed in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

The total safety database, consisting of two delamanid dose groups and placebo in the first study and uncontrolled use of delamanid in the second study, is limited.

There are still missing data regarding interactions with transporters, which has important implications for potential drug-drug interactions.

The potential for delamanid to be associated with an increased risk of hepatotoxicity is uncertain and requires further characterisation.

Benefit-risk balance

Importance of favourable and unfavourable effects

The efficacy in terms of sputum culture conversion of the two investigated doses (100 mg BID and 200 mg BID) was superior to placebo, but the duration of comparison was too short. The results of the

follow-on studies are difficult to interpret. These data cannot address the essential deficiencies of study 204 and the available results cannot confirm the appropriateness of the applicant's proposed dose regimen for delamanid. However, recent data from literature and collaborative research data provide sufficient arguments that 2-month SCC obtained in trial 204 be correlated with better long term clinical outcome. Uncertainty remains on the most appropriate daily dosing schedule.

The main safety issue observed with delamanid relates to QT-prolongation, albeit no associated cases of ventricular tachycardia /torsades de pointes were observed. Further on, hepatotoxic potential cannot be dismissed.

Benefit risk balance

MDR-TB is a public health problem for which only limited treatment options are available. MDR-TB patients generally require treatment with a combination of at least 5-6 "second-line" anti-TB medications for up to 24 months. The current treatment success rate for MDR-TB patients is deemed inadequate, with a sizable proportion of patients dying, failing treatment or lost to follow-up. Hence, it has been recognised that new medicinal products are urgently needed, in order to improve overall outcome in MDR-TB patients. The development programme of delamanid aims to respond to this unmet medical need.

Based on current evidence, the benefit-risk balance of Deltyba indicated for the treatment of pulmonary infections in adults due to multidrug-resistant *Mycobacterium tuberculosis* as part of an appropriate combination regimen (Deltyba is not recommended for use in the treatment of extra pulmonary tuberculosis [e.g. central nervous system, bone], latent infection with M. tuberculosis, drug-susceptible M. tuberculosis or infections due to Mycobacterial species other than those of the M. tuberculosis complex) could be deemed favourable for a limited indication only. It should be restricted 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. This position takes into account the limited evidence of efficacy to support the proposed posology.

The benefit/risk of using Delamanid is to be acceptable only under following strict conditions:

- be initiated and monitored by a physician experienced in the management of multi-drug resistant Mycobacterium tuberculosis
- an appropriate combination regimen should continue after completion of the 24-week delamanid treatment period according to WHO guidelines
- serum albumin < 2.8 mg/dL or taking medicinal products that are strong inducers of CYP3A, constitute contra-indications.

It is recommended that treatment be administered by directly observed therapy (DOT).

Further data are requested before the CHMP would consider whether those recommendations can be altered. CHMP is of the opinion that information from the planned post authorisation measures is essential to determine the full scope of safety and efficacy at chosen dosing regimen.

Discussion on the benefit-risk balance

MDR-TB is defined as TB caused by *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampicin. It represents a significant unmet medical need in Europe and developing countries. MDR-TB is associated with a considerable mortality rate and poses a significant public health threat. New medicinal products that can be used in combination with existing therapies are therefore much needed.

Delamanid, a nitro-dihydro-imidazo-oxazole derivative, provides a novel mechanism of action. It has been developed for clinical use against MDR strains of *M. tuberculosis*, as part of combination therapy.

Efficacy results (superiority outcome) were obtained in phase-2 pivotal trial 242-07-204. All patients were diagnosed for pulmonary, sputum culture positive MDR-TB and received an optimal background regimen (OBR). Patients were randomised into 3 groups and received 100 mg BID delamanid, 200 mg BID delamanid, or placebo, in combination with OBR (BID), and sputum culture status was assessed weekly; SCC was measured after 2 months of treatment.

Following completion of trial 242-07-204, patients were eligible for participation in the uncontrolled open-label trial 242-07-208 and received up to an additional 6 months treatment (or first-time 6 months for patients randomised to the placebo group in trial 242-07-204) with delamanid 100 mg BID or 200 mg BID during their course of 24 months MDR-TB treatment with OBR.

Unfortunately, study 242-07-208 does not allow for an assessment of SCC rates vs. placebo over the applicant's proposed 6 months duration of use. As such, the strength of the evidence of delamanid efficacy on long-term, is limited by the lack of a direct and sound proof of continuous benefit for at least 6 months, since study 208 is biased by the inadequate design. However, the value of 2 months SCC as important prognostic factor for longer term outcome has been proposed in several published analyses. Re-examining all submitted data, and taking account of the position expressed by the expert group, the CHMP considers that notwithstanding the uncertainties and limitations of the data and further analyses, the limited evidence provided to date could be acceptable within the context of a conditional MA, subject to forthcoming confirmatory results from the phase 3 trial, necessary to address the missing longer term efficacy data.

In re-examining the submitted data, the CHMP confirmed that doubts remain if the 100mg twice daily dosing constitutes the optimal schedule. A total daily higher dose might be more appropriate, preferably within the context of once daily administration (which facilitates DOT practice). The CHMP concludes that, although the currently proposed dose schedule is acceptable within the context of conditional Marketing Authorisation, a higher dose (as once daily administration) should be appropriately explored to better define the optimal exposure-response and impact on emergence of bacterial resistance.

The adverse events profile for Delamanid has been established in a limited safety database, comprising approximately 900 individuals. Delamanid was generally well tolerated. However, potential hepatoxicity cannot be fully dismissed. The predominant concern regarding use of delamanid is the effect on QTc. Hypoalbuminaemia (particularly below 2.8 mg/dl) is identified as a major contributing factor.

Based on the totality of available data and the view expressed by the experts during the re-examination of delamanid MAA, the CHMP concludes that a positive benefit-risk balance of this medicinal product can be established, recommending the granting of a conditional marketing authorisation. This position takes into account that further confirmatory data will become available within a specified timeframe; that delamanid fulfils an unmet medical need and that the benefit to public health of the immediate availability on the market of delamanid outweighs the risk inherent in the fact that additional data are still required.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the risk-benefit balance of Deltyba "*indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.*

Consideration should be given to official guidance on the appropriate use of antibacterial agents."

is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other Conditions and requirements of the Marketing Authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures

The MAH should agree the educational material with the Member States, prior to launch.

In each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority and implement it prior to launch.

The MAH shall ensure that all healthcare professionals involved in the prescribing, dispensing, handling or administration of Deltyba are provided with educational material.

1. The Educational material for Healthcare Providers (HCPs) shall address the following key elements:

- SmPC
- Drug- resistance
- Risk of QT interval prolongation
- Drug use during pregnancy
- Drug use during breast feeding.

2. The educational material for Patients to be provided via the HCPs to reinforce and supplement the information provided in the patient information leaflet. It shall address the following key elements:

- Drug use during pregnancy
- Drug use during breast feeding.

Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To complete a confirmatory trial examining delamanid added to optimal background regimen in licensed indication (Phase 3 trial **242-09-213**, comparing delamanid 100 mg BID for 2 months + 200 mg QD for 4 months plus OBR for 18-24 months versus OBR for 18-24 months with placebo for the first 6 months).	Submission of final report: By 2Q2017
To resolve the uncertainties around exposure and antimicobacterial activity, by conducting a further study exploring the relationship between different doses with respect to 2 months SCC and longer term outcome (to perform a controlled study of the efficacy, safety and pharmacokinetics of delamanid 100 mg twice daily for 2 months followed by delamanid 200 mg in a single daily dose for 4 months or delamanid 400 mg single daily dose for 6 months in adult patients with pulmonary multidrug-resistant tuberculosis, based on a CHMP-agreed protocol)	Submission of final report: By 4Q2018

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

Not applicable.

Divergent positions to the majority recommendation are appended to this report.

Appendix

Divergent Position

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a conditional Marketing Authorisation for Deltyba.

The reasons for divergent opinion were as follows:

Although the undersigned acknowledged that there is an unmet clinical need for new medicinal products for the treatment of multi-resistant (MDR) and extensive resistant (XDR) tuberculosis, they cannot support the approval of Deltyba in this indication MDR-TB for the following reasons.

1. The appropriate dose to be used has not been defined and there are concerns that a higher daily dose might be necessary to achieve full efficacy. The currently proposed dose might therefore result in sub-optimal cure rates and encourage the development of microbiological resistance.
2. The data package submitted showed a treatment effect over just 2 months on sputum culture conversion and it has not been established that clinical efficacy would be maintained over the proposed 6 months treatment period.

Considering these uncertainties in life threatening conditions, the undersigned do not agree with the CHMP majority opinion.

London, 5 December 2013

…….

Greg Markey (United Kingdom)

……..

Robert Hemmings (United Kingdom)

…….

Jan Mazag (Slovakia)

……..

Aikaterini Moraiti (Greece)

…….

Concepcion Prieto Yerro (Spain)

……..

Sol Ruiz (Spain)

…….

Bruno Sepodes (Portugal)

……..

Ondřej Slanař (Czech Republic)

……..

Daniel Brasseur (Belgium)

……

Nevenka Tršinar (Slovenia)

……..

Reynir Arngrímsson (Iceland)

……..

Karsten Bruins Slot (Norway)