Official Title:	**Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC 67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs over a 6-Month Treatment Period**
NCT Number:	NCT01859923
Document Date:	Protocol Version Amendment 5: 28 February 2019

Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Delamanid (OPC 67683)

REVISED CLINICAL PROTOCOL

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

Protocol No. 242-12-233
IND No. 76,728

CONFIDENTIAL – PROPRIETARY INFORMATION

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Issue Date:	09 November 2012
Amendment 1 Issue Date:	11 March 2013
Amendment 2 Issue Date:	14 October 2014
Amendment 3 Issue Date:	29 June 2015
Amendment 4 Issue Date:	04 October 2016
Amendment 5 Issue Date:	28 February 2019

Protocol Synopsis

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc. Name of Investigational Medicinal Product: Delamanid	Protocol # 242-12-233
Protocol Title:	Phase 2, Open-label, Multiple-dose Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Delamanid (OPC 67683) in Pediatric Multidrug-resistant Tuberculosis Patients on Therapy with an Optimized Background Regimen of Antituberculosis Drugs Over a 6-Month Treatment Period
Clinical Phase:	Phase 2
Treatment Indication:	Pediatric patients with multidrug-resistant tuberculosis (MDR-TB) who are receiving an optimized background regimen (OBR) of antituberculosis drugs
Objective(s):	The primary objectives of this trial are: • To evaluate the long-term safety and tolerability of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB • To report delamanid and metabolite plasma concentrations at each visit day by age groups and to conduct a population pharmacokinetics (POPPK) analysis of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB The secondary objectives are: • To conduct the pharmacokinetic (PK)/pharmacodynamic (PD) relationship analysis of delamanid and its metabolite DM-6705 plasma concentrations and change in corrected QT interval (QTc) when delamanid is administered in combination with OBR during a 6-month treatment period in pediatric patients with MDR-TB • To evaluate the efficacy of delamanid when administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB • To determine the palatability of the delamanid pediatric formulation

Trial Design:	This is a phase 2, open-label, multiple-dose, multicenter trial to assess the safety, tolerability, PK, and efficacy of delamanid in pediatric patients with MDR-TB over a 6-month treatment period. This long-term trial, an extension of Trial 242-12-232 (Trial 232), will be conducted in patients who have completed Trial 232. The current Trial 242-12-233 (Trial 233) will be conducted sequentially in 4 groups of pediatric patients with MDR-TB.
	
	• Group 1 (ages 12 - 17 years, inclusive) will receive adult formulation delamanid 100 mg BID + OBR (n = 6)
	• Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)
	• Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)
	• Group 4 (ages birth - 2 years, inclusive) will receive the following delamanid pediatric formulation (DPF) dose based on patient's body weight during baseline visit (n = 12):
	  • Patients > 10 kg will receive DPF 10 mg BID + OBR
	  • Patients > 8 and ≤ 10 kg will receive DPF 5 mg BID + OBR
	  • Patients ≤ 8 kg will receive DPF 5 mg QD + OBR
	  • Delamanid dose will be adjusted as needed for Group 4 patients based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).
	
	All groups will have assessments at screening and during the treatment period, the post-treatment period, and the follow-up period, as indicated in the schedule of assessments. All patients must have completed the pediatric PK Trial 232 prior to enrollment into Trial 233. Those patients who have completed Trial 232 and choose to enter Trial 233 must roll over from within 30 days of completing Trial 232. If any patients terminate Trial 232 early or choose not to enter Trial 233, patients will be recruited to first enter and complete Trial 232, and then roll over into Trial 233. Patients who terminate Trial 233 early will not be replaced.

Trial Design (continued):	The trial will comprise the following periods: **Screening Period (Day −30 to −2):** Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the 30-day period immediately after completion of Trial 232 as described in the Schedule of Assessments. **Baseline (Day −1):** Inclusion/exclusion criteria, physical examination, and safety assessments, including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, head circumference (Group 4 only), percentiles for age, body mass index (BMI), and electrocardiogram (ECG) as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications. **Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination, and other safety assessments, including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Vital signs, head circumference (Group 4 only), height, weight, and BMI beginning at Week 2, and collection of adverse events (AEs) and immediately reportable events (IREs), and concomitant medications. **Post-treatment Period (Days 183 to 238):** Physical examination, vital signs, ECGs, safety labs, and sparse blood draws for PK at visits and times described in the Schedule of Assessments. Head circumference (Group 4 only), height, weight, signs and symptoms of TB, audiometry and visual assessments, thyroid function tests (for patients taking ethionamide or para-aminosalicylic acid), OBR administration, and collection of AEs/IREs and concomitant medications. **Follow-up Period (Days 239 to 365) Six Month Post Last Delamanid Dose:** Physical examination, height and weight, BMI, percentiles for age, vital signs, head circumference (Group 4 only), height, weight, signs and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or para-aminosalicylic acid), OBR administration, and collection of AEs/IREs and concomitant medications.

	Treatment Outcome Follow-up (Day 730 [Month 24] + 2 months): All patients will either visit the clinic or be contacted by telephone for clinical assessment. Collection of treatment outcome information as routinely documented in the patient medical records or in national TB program.
Subject Population:	At least 36 male and female MDR-TB patients ages birth to 17 years, inclusive, who successfully completed Trial 232, and meet all of the inclusion criteria and none of the exclusion criteria, and are receiving OBR will be assigned to one of 4 treatment groups based on age. For Groups 1 and 2, a minimum of 6 patients will be included in each age group, and Group 1 (12 to 17 years, inclusive) must include at least 2 but no more than 5 females. For Groups 3 and 4, a minimum of 12 patients will be included in each age group.
Inclusion/Exclusion Criteria:	Key Inclusion Criteria: • Successfully completed Trial 232 • Male or female • Age birth to 17 years, inclusive • Confirmed diagnosis of MDR-TB, ie, culture positive for *Mycobacterium tuberculosis* (MTB) with isoniazid and rifampicin resistance on drug-susceptibility testing, or a positive rapid test demonstrating resistance to rifampicin alone or to rifampicin and isoniazid OR Presumptive diagnosis of pulmonary or extrapulmonary MDR-TB such that the treating physician has decided to treat for MDR-TB the patient who has one of the following: • Clinical specimen (eg, cerebral spinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue specimen) suggestive of tuberculosis (TB) disease • Persistent cough lasting > 2 weeks • Fever, weight loss, and failure to thrive • Findings on recent chest radiograph or other imaging studies (prior to Visit 1) consistent with TB AND • Household contact of a person with known MDR-TB or a person who died while appropriately taking drugs for drug-sensitive TB OR

- On first-line TB treatment but with no clinical improvement
- Negative urine pregnancy test for female patients who have reached menarche
- Study-specific written informed consent/assent obtained from a parent(s) or guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol-required procedures. In addition, for patients in Groups 1 and 2 and as required by local laws, the patient must provide informed assent at screening and must be able to fully understand that he or she can withdraw from the study at any time.

Key Exclusion Criteria:

- Patients who have not completed Trial 232
- Children with laboratory evidence of active hepatitis B or C
- Children with body weight < 5.5 kg
- For patients with HIV co-infection, CD4 cell count ≤ 1000/mm^3 for children 1-5 years old, and ≤ 1500/mm^3 for children less than 1 year old
- History of allergy to metronidazole and any disease or condition in which metronidazole is required
- Use of amiodarone within 12 months prior to the first dose of investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within 30 days prior to the first dose of IMP
- Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment)
- Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds
- Abnormalities in screening electrocardiogram (ECG) (including atrioventricular block, bundle branch block or hemi-block, QRS prolongation > 120 msec, or QT interval corrected using Fridericia's method (QTcF) > 450 msec in both males and females)
- A concomitant condition such as renal impairment

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

Investigational Medicinal Product, Dose, Formulation, Mode of Administration:	Delamanid 50-mg adult formulation tablets administered orally for 6 months to Groups 1 and 2:
	• Group 1 (ages 12 to 17 years, inclusive) - 100 mg (2 x 50-mg tablet) BID
	• Group 2 (ages 6 to 11 years, inclusive) - 50 mg (1 x 50-mg tablet) BID
	
	Delamanid pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension to Groups 3 and 4 for 6 months:
	• Group 3 (ages 3 to 5 years, inclusive) - 25 mg (1 x 25-mg tablet) BID
	• Group 4 (ages birth to 2 years, inclusive) - will receive the following dose depending on patient's weight:
	  • Patient > 10 kg will receive pediatric formulation delamanid 10 mg BID + OBR
	  • Patient > 8 and ≤ 10 kg will receive pediatric formulation delamanid 5 mg BID + OBR
	  • Patient ≤ 8 kg will receive pediatric formulation delamanid 5 mg QD + OBR

	OBR will be provided for all patients in the trial by the investigation site as per the World Health Organization Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis, relevant national guidelines for treating MDR-TB, and the investigator's best clinical judgment. OBR generally comprises 4 or more classes of first-line (other than isoniazid and rifampicin) and second-line anti-TB medications to which the patient's strain of MTB has suspected or documented susceptibility based on previous treatment history and epidemiologic and clinical factors. Whenever possible, 5 or more classes of drugs are preferred for use in treatment, particularly in the initial stage of treatment. The components of OBR include: 1) Any remaining first-line anti-TB medications to which the patient's isolates are likely susceptible such as pyrazinamide 2) An anti-TB medication given by injection; preferred order of selection: amikacin > kanamycin > capreomycin 3) Fluoroquinolone class; preferred order of selection: moxifloxacin, levofloxacin, gatifloxacin > ofloxacin (gatifloxacin to be used with caution secondary to rare but severe side effect of dysglycemia; ciprofloxacin not recommended for use). Moxifloxacin causes QT interval prolongation and should not be used in this trial Other medications include (but are not limited to): 4) Ethionamide or prothionamide 5) Cycloserine 6) Para-aminosalicyclic acid

Criteria for Evaluation (Variables):	The primary criteria for evaluation in this trial are: • Safety and Tolerability: assessed by physical examination, vital signs, treatment-emergent adverse events (TEAEs), ECGs, Holter monitoring (if applicable), and clinical laboratory tests • Pharmacokinetics: Delamanid and metabolite plasma concentrations at each visit day per age and dose group The secondary criteria for evaluation in this trial are: • Pharmacokinetics/Pharmacodynamics: ECG and blood samples for PK/PD analysis for changes in QTc as a function of delamanid and DM-6705 plasma concentrations • Efficacy: evaluated on the basis of results of chest radiography (for patients with pulmonary disease); change in body weight and height measurements; and evaluation of TB symptoms. In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (or provide other biological specimens) for microbiological evaluation according to the requirements of the National TB program • Palatability: The palatability of the delamanid pediatric formulation (Groups 3 and 4 only) will be assessed using an age-appropriate visual hedonic scale and clinical assessment.
Endpoints:	The primary endpoints in this trial are: • Safety and tolerability: Changes in physical examination including visual testing and audiometry during screening, TEAEs, vital signs, ECGs, holter monitoring (if applicable), and clinical laboratory tests • Pharmacokinetics: Descriptive statistics of delamanid and metabolite plasma concentrations at each visit day per age and dose group. In addition, POPPK analysis for delamanid plasma concentrations The secondary endpoints in this trial are: • Pharmacokinetics/Pharmacodynamics: PK/PD analysis for changes in QTc as a function of delamanid and DM-6705 plasma concentrations • Efficacy: Culture conversion, normal chest radiography results, resolution of TB symptoms

Statistical Methods:	No power calculation was performed for this trial because of the limited number of patients expected to be enrolled in the population of interest (ie, pediatrics). No formal statistical analysis is planned due to the small sample sizes; all statistical presentations will be descriptive. An interim analysis review of safety, tolerability, PK, and efficacy of delamanid will be conducted with complete follow-up data in children 6 to 17 years of age.
Trial Duration:	The trial duration per patient will be up to 760 days including the following: 30-day screening period, 182-day treatment period, 56-day post-treatment period, additional follow-up period through Day 365 (ie, 6 months after the last delamanid dose), and treatment outcome follow-up at Day 730 (Month 24) + 2 months (ie, 1 year after the Day-365 follow-up visit).

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List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve from time zero to 24 hours
BID	Twice daily
BMI	Body mass index
CA	Competent authority
CD4 cell	Cluster of differentiation 4 (helper/inducer T-lymphocyte)
CI	Confidence interval
CFU	Colony-forming unit
C_{max}	Peak (maximal) concentration of drug in plasma
CRO	Contract research organization
CSF	Cerebral spinal fluid
CYP	Cytochrome P450
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
DS-TB	Drug-sensitive tuberculosis
EBA	Early bactericidal activity
ECG	Electrocardiogram
eCRF	Electronic case report form
ET	Early termination
FDA	Food and Drug Administration
F/U	Follow up
GCP	Good Clinical Practices
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IDM	Interval duration measurement
IEC	Independent ethics committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional review board

Abbreviation	Definition
IRE	Immediately reportable event
ISR	Immediate safety report
LMP	Last menstrual period
MDR	Multidrug resistant
MDR-TB	Multidrug-resistant tuberculosis
MedDRA	Medical Dictionary for Regulatory Activities
MTB	*Mycobacterium tuberculosis*
n/a	Not applicable
OBR	Optimized background regimen
OEDC	Otsuka Europe Development and Commercialisation, Ltd
OPDC	Otsuka Pharmaceutical Development & Commercialization, Inc.
PD	Pharmacodynamic
P-gp	P-glycoprotein
PIP	Pediatric investigational plan
PK	Pharmacokinetics
POPPK	Population pharmacokinetics
PVRE	Pharmacovigilance Region Europe
QD	Once daily
QTc	Corrected QT interval
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RIF	Rifampicin
SAE	Serious adverse event
SCC	Sputum culture conversion
SD	Standard deviation
SMC	Safety monitoring committee
$t_{1/2}$	Elimination half-life
TB	Tuberculosis
TSH	Thyroid stimulating hormone
TEAE	Treatment-emergent adverse event
ULN	Upper limit of the normal range
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

1 Introduction

The investigational compound delamanid (OPC 67683) is a novel nitro-dihydroimidazo-oxazole derivative being developed by Otsuka Pharmaceutical Co. Ltd., Japan (hereafter referred to as Otsuka) for the treatment of tuberculosis (TB).[1]

Tuberculosis, caused by infection with *Mycobacterium tuberculosis* (MTB), is one of the leading causes of death from infectious disease among adults worldwide.[2] In 1993, the World Health Organization (WHO) declared TB a global emergency. The WHO and partners developed and launched the directly observed therapy short-course strategy as the global framework for the diagnosis, treatment, management, and control of the disease. Despite these efforts, the global burden of TB remains high.[3]

Currently, the global TB epidemic and efforts to control it are complicated by lethal synergy with the global epidemic of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), which has exploded over the past 2 decades, as well as the evolving crisis of drug-resistant TB.[3,4]

As part of a coordinated global response to the HIV-associated TB and the multidrug-resistant tuberculosis (MDR-TB) epidemics, as well as the emergence of extensively drug-resistant tuberculosis (XDR-TB), the WHO and the international community have called for the accelerated development of new anti-TB medications.[5] As a result, Otsuka has undertaken the search for anti-TB medications with new structures and mechanisms of action, with activity against intracellular MTB, and with the ability to target latent TB infection with MDR-TB.[6]

Delamanid is being developed in conjunction with an optimized background regimen (OBR), in agreement with the WHO-recommended MDR-TB treatment paradigm. The intended dosage in adult patients is delamanid 100 mg twice daily (BID; two 50-mg delamanid tablets) given under fed conditions (with a standard meal) for 6 months. It is anticipated that delamanid, used in combination with other registered therapies, will result in higher cure rates, a shorter treatment duration for MDR-TB patients, and fewer side-effects.

Delamanid has shown early bactericidal activity (EBA) in drug-sensitive tuberculosis (DS-TB) patients after 2 weeks of treatment with 100 to 400 mg once daily (QD) dosing. This bactericidal activity measured as a decrease in log colony-forming units (log CFU) reached significance after 3 days of dosing and thereafter at a magnitude similar to the currently recommended 4-drug combination Rifater®. The EBA effect was similar to that

reported for rifamycin, rifabutin, and the aminoglycosides streptomycin and amikacin. However, it was higher than that for pyrazinamide but lower than the highest effect reported for quinolones, isoniazid, ethambutol, linezolid, rifampicin, and rifapentine.[7,8]

A pediatric investigational plan (PIP) for the treatment of children with MDR-TB received a positive opinion from the Pediatric Committee in November 2011. The PIP for delamanid in pediatric MDR-TB patients aims to determine whether delamanid plasma exposure in children of all ages with MDR-TB is similar to the efficacious plasma exposure in adults, and thereby determine the appropriate pediatric dose (using both the adult and pediatric formulations) and to document safety and tolerability. The PIP essentially consists of 3 clinical trials in addition to the pediatric formulation development and juvenile toxicity assessment (EMEA-001113-PIP01-10-M02): a pharmacokinetic (PK) trial (Trial 242-12-232) in children of all ages with MDR-TB on therapy with OBR, followed by a 6-month safety and tolerability extension trial (Trial 242-12-233) in the same patient population, and a bioavailability/bioequivalence trial (Trial 242-12-245) in adults to investigate the comparative bioavailability of the pediatric formulation (5- and 25-mg immediate-dissolving tablets) with the delamanid 50-mg tablet adult formulation.

Tuberculosis Incidence

In 2012, the estimated global incidence of TB was 8.6 million cases. Deaths among HIV-negative persons were 1.0 million and among HIV-infected persons were 0.32 million. The majority of cases in 2012 were in Southeast Asia (29%), Africa (27%) and the Western Pacific Region (12%). India (26%) and China (12%) were the individual countries with the highest proportion of cases.[3]

Although the overall global incidence of TB is decreasing, the number of incident cases in the last few years has remained relatively stable due to population increases. Further, the overall annual incidence of TB in high-income countries remains relatively low.

Multidrug-resistant and Extensively Drug-resistant Tuberculosis

In addition to the effects of the global HIV epidemic, the emergence of MDR-TB or TB caused by strains of MTB resistant to at least isoniazid and rifampicin has further complicated global efforts to control the TB epidemic. Approximately 450,000 people developed MDR-TB globally in 2012 and there were an estimated 170,000 deaths from MDR-TB. There were 94,000 MDR-TB patients detected in 2012; 84,000 of those were confirmed to have resistance to rifampicin and isoniazid and a further 10,000 were found to have rifampicin (RIF) resistance by GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA).[3]

The highest concentrations of MDR-TB are found in Eastern Europe and Central Asia where the percentage of new TB cases that are multidrug resistant (MDR) may reach 20% and the percentage of those previously treated for TB may reach 50%.[3]

Patients with MDR-TB require longer treatment, usually 18 to 24 months, compared with 6 to 8 months for patients with DS-TB. Moreover, the so-called "second-line" drugs used to treat MDR-TB are less potent and more toxic than those used for DS-TB.[9] At least 4 medications from the various classes of second-line anti-TB drugs to which a given MDR-TB patient's disease is susceptible or likely to be susceptible should be used in combination for MDR-TB treatment.[9] Some data suggest that at least 5 different medications should be used to optimize the chance for a successful treatment outcome.[10,11,12] Medications from the fluoroquinolone class of drugs and from the injectable classes — either an aminoglycoside or a cyclic peptide — as well as any remaining first-line medications to which a given patient's disease is susceptible, are integral to an optimized treatment regimen for MDR-TB.[9,10,11,13] Under the best of programmatic conditions, the cure rates achievable for MDR-TB, as demonstrated by studies of treatment outcomes for patient cohorts, are in the range of only 60% to 70%.[14,15] In contrast, cure rates for DS-TB in well-performing programs often exceed 90%.[16]

TB and MDR-TB in Children

It is estimated that 3.6% of the TB cases worldwide are MDR (ie, resistant to isoniazid and rifampicin).[17] Childhood TB comprises approximately 10% to 15% of the global TB disease burden, with higher rates in developing countries.[18] Based on estimates of total MDR-TB cases,[17,18] this translates to a minimum global estimate of approximately 40,000 pediatric cases of MDR-TB per year.[19] If a child presenting with TB is a known contact of an adult with MDR pulmonary TB, the child is a probable MDR-TB case and should be managed accordingly.[20]

Childhood TB disease is very different from adult TB disease. These differences include time from exposure to disease onset, epidemiologic differences in contagiousness, pathophysiology, bacillary load, and clinical and radiographic manifestations. Most cases of childhood TB have a short period between exposure to a contagious individual and manifestation of symptoms.[21] Differences in the pathophysiology and clinical presentation of TB in children make diagnosis more challenging in children than in

adults,[21] and definitions of latent infection and active disease are not as clear.[21] Children are also at a much higher risk of progression to active disease than adults.[22] This risk is greatest for infants and children under 2 years of age.[22,23,24] Overall, the risk of disease is highest in infants and individuals in their late teens; the lowest risk in children is between ages 5 and 10 years, the so-called "safe" school years.[23,25]

Infants have a particularly high rate of morbidity and mortality from TB.[24] Children under the age of 5 years are frequently affected by peripheral lymphadenopathy and 65% to 75% of these children have a thoracic and mediastinal location.[26,27] In a setting with a high incidence of TB and ongoing transmission, the most common clinical presentation of TB in young children, ie, age ≤ 5 years, is likely to be pulmonary TB.[27,28,29,30,31,32] Young children with severe and complicated disease have a much higher mortality rate than older children and adults; some studies report a mortality rate exceeding 50% in children younger than 1 year who have not received anti-TB medication.[33,34]

Older children and adolescents (> 10 years) often present with adult- type cavitary disease with a high bacillary load.[35] Pleural TB typically has been considered a disease of adulthood and is estimated to comprise approximately 4% of disease cases.[36] However, TB pleural effusions can complicate 12% to 38% of cases in children with untreated pulmonary TB.[37,38,39,40,41] Pleural involvement is more common among adolescents, and the mean age at diagnosis is 13 years.[39,40] Adult-type disease is a phenomenon that suddenly appears around puberty and is distinguished by cavitation that occurs predominantly in the lung apices.[41]

Overall, the lifetime risk of progression from infection to active disease is 5% to 20% for immunocompetent older children and 40% to 50% for children in the first 2 years of life.[23] Adolescents have a slightly higher risk of disease progression than adults.[33,34] The age-specific risk of developing TB following MTB infection is shown in Table 1.1-1.

Table 1.1-1	**Age-specific Risks for Developing Tuberculosis after Primary Infection**	
Age at Primary Infection	Disease Status	Risk (%) in Immunocompetent Children[23]
< 2 years	No Disease	50 - 70
	Pulmonary Disease	10 - 30
	Tuberculosis Meningitis or Miliary Disease	2 - 10
2 to 10 years	No Disease	95 - 98
	Pulmonary Disease	2 - 5
	Tuberculosis Meningitis or Miliary Disease	<0.5
> 10 years	No Disease	80 - 90
	Pulmonary Disease	10 - 20
	Tuberculosis Meningitis or Miliary Disease	< 0.5

The diagnosis of childhood TB is challenging.[30,42] Microbiological confirmation is often not available due to the paucibacillary nature of disease and the difficulty of specimen collection (especially sputum) in younger children. The diagnosis usually relies on nonspecific clinical and radiologic signs, as well as a history of exposure (ie, close contact with a TB case).[43] Fever (possibly intermittent or low grade), weight loss or failure to thrive, and persistent cough for > 2 weeks are the most important clinical signs for pulmonary TB.[26]

Children are diagnosed with either confirmed or presumed MDR-TB. Confirmed disease occurs when an organism is isolated from the child and is shown either genotypically or phenotypically to be resistant to isoniazid and rifampicin. Presumed disease occurs when TB is diagnosed in combination with either known contact with an MDR-TB case or after failure of appropriate first-line therapy when adherence has been verified.[19] Incident cases of childhood TB reflect recent transmission, which implies that drug resistance patterns observed among pediatric TB cases reflect primary (transmitted) drug resistance within the community.[44]

Monitoring and describing adverse effects of multidrug anti-TB therapy in children is challenging; young children often cannot articulate pain, nausea, vertigo, peripheral neuropathy, anxiety, or confusion. Rashes are common — frequently resulting from various etiologies — and testing hearing and vision is more difficult than in adults. In addition to life-threatening and unpleasant effects, TB may cause alterations in growth and neurocognitive development. Children treated for MDR-TB are usually on multiple medications, and determining the drug responsible for an adverse effect can be difficult.[19]

1.1 Nonclinical Trials

Efficacy pharmacology studies have shown that delamanid is active against MTB. The minimum inhibitory concentration of delamanid required to inhibit the growth of 90% of organisms is 0.024 µg/mL; this is lower than in existing anti-TB drugs, such as rifampicin and isoniazid, indicating that delamanid is a highly potent drug. Results of microbiology and efficacy pharmacology studies have also demonstrated that delamanid has potent in vitro activity against drug-resistant MTB, including XDR-TB.[6,45,46,47] Delamanid shows no cross-resistance with any of the currently used anti-TB drugs.[46] At inoculum sizes in the range of 10^5-10^7 CFU/mL, delamanid was highly active against MTB and *Mycobacterium bovis*, and was more potent than drugs currently in clinical use. The activity of delamanid was decreased at large inoculum sizes such as 10^8 CFU/mL, which is similar to the activity of isoniazid.[48] Delamanid demonstrated bactericidal activities against both growing bacteria in aerobic conditions and nongrowing bacteria in hypoxic conditions.[49,50]

The metabolites of delamanid have poor activity against MTB, suggesting that delamanid is responsible for the anti-TB activity of the compound.[45,51] The mechanism of action of delamanid is thought to be due to an inhibitory activity against the synthesis of mycolic acid, a key component of the cell wall of MTB.[52] The presumed mechanism of action explains why the compound possesses MTB-specific activity yet no activity against other gram-positive or gram-negative bacteria when tested in vitro.[48] Delamanid also has potent activity against intracellular mycobacteria with a concentration of 0.199 to 0.215 µg/mL needed to inhibit 90% of bacterial growth.[49,50,51]

Delamanid showed greater activity in an animal model of TB than the first-line anti-TB drugs rifampicin and isoniazid. Delamanid demonstrated therapeutic efficacy at a dose of 0.625 mg/kg in an experimental mouse TB model, an efficacy considered to be equivalent to that of rifampicin.[53] The effective plasma and lung concentrations of delamanid at a dose of 0.625 mg/kg were 0.100 µg/mL and 0.273 µg/g, respectively.[54] Delamanid showed no antagonistic activity in vitro or in vivo when used in combination with drugs currently used to treat TB.[55,56,57,58,59] Delamanid showed EBA comparable to the activity of isoniazid in the mouse EBA model, in which the EBA values of the reference drugs correlated well with those seen in clinical studies.[60]

The general safety of delamanid has been evaluated in the following nonclinical safety studies. Single oral dose toxicity studies in rats and dogs, repeated oral dose toxicity studies in rats and dogs, effects on blood coagulation in rabbits, in vitro and in vivo genotoxicity studies, and reproductive and developmental toxicity studies in rats and rabbits. The nontoxic dose of the compound was estimated to be 300 mg/kg in female rats and 30 mg/kg in male rats in a 26-week repeated oral dose toxicity study.[61] The nontoxic dose of delamanid was estimated to be 1 mg/kg for males and 3 mg/kg for females in a 39-week repeated oral dose toxicity study in dogs.[62] In 2-week oral dose toxicity studies in dogs at doses of 25 mg/kg and higher, QT/corrected QT interval (QTc) prolongation was seen.[63] In 13- and 39-week oral dose toxicity studies in dogs, QT/QTc prolongation was seen at doses ≥ 10 mg/kg and ≥ 3 mg/kg, respectively.[62,64] In 2-week repeated oral dose toxicity studies in male or female rabbits, decreases in body weight and food consumption, prolongation of prothrombin time and activated partial thromboplastin time, anemia, and hemorrhage were observed at both 30 mg/kg and 100 mg/kg.[65,66,67]

An embryo-fetal development study in rats showed no maternal general and reproductive toxicity at the maximal feasible dose of 300 mg/kg; there was fetal development toxicity at 300 mg/kg.[68] A 13-day repeated oral dose toxicity study in rabbits showed toxic changes at ≥ 10 mg/kg with decreased food consumption at the 10 mg/kg dose.[69] Additional evaluations of maternal, reproductive, and developmental toxicity in rabbits showed dams had nontoxic doses of 5 mg/kg for maternal general toxicity and 10 mg/kg for reproductive toxicity. The nontoxic dose for embryo-fetal development was 5 mg/kg.[70] A rat fertility/embryonic-development study showed no toxic effect on parent animals, fertility, or early embryonic development at the maximum feasible dose of 300 mg/kg. No genotoxicity of delamanid or its metabolites was observed.[71,72,73,74,75,76,77,78,79,80,81,82,83,85,86,87,88]

The absolute bioavailability of delamanid administered orally at 3 mg/kg in mice, rats, and dogs was 42.2%, 34.9%, and 61.3%, respectively, and a less than dose-dependent increase in area under the plasma time-concentration curve (AUC) was observed in all species.[89,90,91,92,93] Delamanid distributed extensively in tissues with a lung/plasma ratio of ~2,[94,95] and was primarily metabolized by albumin in plasma and to a lesser extent by cytochrome P450 (CYP) enzymes.[96,97,98,99] Delamanid was not transported by P-glycoprotein (P-gp), did not affect P-gp transport, and showed neither inductory nor

inhibitory effects on human CYP activities.[100,101] In rats and dogs, delamanid and its metabolites were essentially excreted in feces and poorly excreted in urine.[94,102] In rats, approximately 35% of the administered dose was excreted in bile and partly underwent enterohepatic recycling.[103]

Additional information on delamanid nonclinical trials can be found in the Investigator's Brochure (IB).[1]

1.2 Clinical Trials

Phase 1 clinical development in healthy subjects included 7 trials with delamanid 50-mg tablets and one mass-balance trial using ^{14}C-delamanid 100-mg capsules. These trials were conducted in the United Kingdom, United States, China, and Japan. In addition to the usual single and repeated dose-ranging trials (including food effect), drug-drug interaction trials were conducted with the anti-TB drug combination Rifater + ethambutol and with the antiretroviral (ARV) drugs tenofovir, lopinavir/ritonavir as Kaletra®, and efavirenz.[1]

Two proof-of-concept trials were conducted with delamanid: Trial 242-03-101[104], a 1-week EBA trial (delamanid jet-milled tablet), followed by 2-week EBA Trial 242-04-101 (delamanid 50-mg tablet).[105] The decrease in log CFU was compared with that observed for the positive controls isoniazid and Rifater, respectively.

Clinical efficacy trials in MDR-TB patients included the 2-month randomized pivotal Trial 242-07-204 (Trial 204) and the 6-month extension Trial 242-07-208 (Trial 208) of delamanid 100 mg BID or delamanid 200 mg BID plus OBR therapy in the same patient population. In addition, a 6-month dose escalation Trial 242-08-210 (Trial 210) was conducted in XDR-TB patients with MDR-TB at delamanid doses of 250 mg BID and 300 mg BID.

Safety/tolerability, PK and PK/pharmacodynamic (PD) for efficacy (ie, EBA) and safety (ie, QTc prolongation), and efficacy of delamanid were investigated throughout this development program. Refer to the IB for details of these findings in healthy subjects and in TB patients.[1]

1.3 Pharmacokinetics

1.3.1 Healthy Subjects

In healthy subjects, the time of peak plasma concentration (t_{max}) of delamanid is 4 hours post dose, the apparent terminal elimination half-life ($t_{1/2z}$) is approximately 30 hours, and steady-state is achieved within 7 to 10 days following dosing. Delamanid has a 2- to 4-fold higher bioavailability when taken with a standard or high-fat meal, respectively, compared with fasting conditions. Systemic exposure to delamanid increased less than proportionally with increasing dose, suggesting dose-limited dissolution and/or absorption.[106] The plasma concentrations for the metabolites were considerably lower (3% to 10% of delamanid concentrations) after 7 days of administration but showed a long (150 to 600 hours) plasma elimination half-life ($t_{1/2}$), suggesting further accumulation upon repeated dosing. Delamanid is not excreted in urine, and delamanid metabolites are poorly excreted in urine.

When coadministered with other drugs, delamanid did not affect the plasma exposure of anti-TB agents such as Rifater (isoniazid, rifampicin, and pyrazinamide) and ethambutol, or ARV drugs such as tenofovir, Kaletra (lopinavir/ritonavir), or efavirenz. Delamanid concentrations were decreased by 45% with Rifater and ethambutol. Delamanid exposure was not markedly affected (< 25% change) by ARV drugs; a ~22% increase in delamanid exposure was noted with Kaletra.[1]

Additional information on delamanid in healthy subjects is provided in the IB.[1]

1.3.2 Patients with Tuberculosis

Available results indicate that the PK profile of delamanid in patients with TB is similar to the PK profile in healthy subjects. In the 14-day EBA trial (Trial 242-06-101) in TB patients receiving delamanid 100, 200, 300, and 400 mg QD with food, delamanid concentrations increased less than dose-proportionately from 100 to 300 mg, were similar for the 300 and 400 mg doses, and accumulated 2-fold over time. On Day 14 after the doses of delamanid 200 mg QD, delamanid mean maximal concentration of drug in plasma (C_{max}) was 228 ng/mL and the area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24h}) was 3351 ng•h/mL.[8]

In MDR-TB patients in Trial 204 receiving delamanid 100 mg and 200 mg BID for 2 months, delamanid exposure reached steady state after 2 weeks (38 hour $t_{1/2}$), and metabolite exposure continued to increase. On Day 56, after the 100-mg BID and

200-mg BID doses, mean delamanid C_{max} was 414 (ng/mL and 611 ng/mL, respectively, and the AUC_{0-24h} was 7925 ng•h/mL and 11,837 ng•h/mL, respectively.

Trial 208 demonstrated that, in general, steady-state exposure was reached by 8 weeks of dosing for DM-6705 and by 8 to 14 weeks of dosing for the other metabolites.

PK/PD analysis of delamanid and DM-6705 plasma concentrations as a function of QTc changes were performed. The results indicated that the predicted changes were similar to the observed increases in QTc.

Additional information may be found in the IB.[1]

1.4 Known and Potential Risks and Benefits

1.4.1 Delamanid

As of 31 Jan 2016, a total of 949 adult subjects (484 healthy adult subjects, 60 adult patients with uncomplicated DS-TB, 395 adult patients with MDR-TB, 10 adult patients with MDR-TB refractory to treatment) have been exposed to oral doses of delamanid in 19 completed trials.

In addition, a total of 22 healthy adult subjects and 511 adult subjects with MDR-TB have been exposed to either delamanid or placebo (trial is still blinded) in ongoing trials (Trials 242-201-00001 and 242-09-213, respectively).

Fourteen children (ages 3 - 17 years) with MDR-TB have also been exposed to oral doses of delamanid in 2 ongoing, open-label, pediatric trials (Trials 242-12-232 and 242-12-233).

Delamanid is well tolerated by healthy adult subjects and adult patients with TB.[1] One observational study (Trial 242-10-116) also was conducted that follows long-term outcome patients who were enrolled in Trial 204, Trial 208, or Trial 210. No safety data was collected and no delamanid was administered in Trial 242-10-116.

In Trial 242-05-101, single oral doses of delamanid up to a maximum of 400 mg administered after a high-fat meal were well tolerated in healthy subjects; delamanid was also well tolerated with 10 days of repeated dosing after a standard meal in healthy subjects.[106] There were no serious adverse events (SAEs) and no severe adverse events (AEs), and no subjects were withdrawn as a result of AEs.

In the 14-day EBA trial in patients with DS-TB (Trial 242-06-101), 5 treatment-emergent adverse events (TEAEs) considered serious were reported: 3 patients with

electrocardiogram (ECG) QT interval prolongation corrected by Bazett's formula (QTcB) in the delamanid 100 mg, 200 mg, and 300 mg groups, respectively; and 2 patients with increased hepatic transaminases in the delamanid 300 mg and 400 mg groups, respectively. All 5 events were mild in severity.[7] In this trial, QTc interval prolongation was defined as QTc > 450 msec for males or > 470 msec for females. One [redacted] patient had a QTcB of [redacted] msec prior to receiving delamanid. One [redacted] patient had a QTcB > 470 msec at the follow-up visit after discontinuation of delamanid. Another [redacted] patient had a QTcB > 450 msec during the treatment period. No patients experienced QTcB or QT interval corrected by Fridericia's formula (QTcF) > 480 msec at any of the time points assessed. It is important to note that in patients with increased heart rate, QTcB may not be a reliable measure of QTc interval prolongation, as TB patients often have fever or respiratory compromise. Among the 3 reports of ECG QTc interval prolongation, only one episode ([redacted], 200 mg group) that occurred during active treatment was considered by the investigator to be probably treatment related; the other 2 events were judged unlikely to be related to treatment. All patients recovered fully. The mild and moderate AEs were evenly distributed between the treatment and placebo groups and revealed no trends. No patients discontinued delamanid due to AEs, and there were no deaths.

The safety of delamanid and its effects on QT interval duration were evaluated in Trial 204, a randomized, double-blind trial evaluating delamanid 100 mg or 200 mg BID orally in combination with OBR versus placebo with OBR for 56 days. TEAEs were reported for > 90% of patients in all treatment groups (including the placebo + OBR group). Most TEAEs were mild or moderate in intensity. In this trial, the incidences of most TEAEs were similar (difference < 5 percentage points) between the delamanid 100 mg BID + OBR group and the placebo + OBR group. Chest pain (9.9% vs 4.4%) and prolonged QT interval (9.9% vs 3.8%) were the only TEAEs reported at an incidence of ≥ 5 percentage points more in the delamanid 100 mg BID + OBR group than the placebo + OBR group. QT prolongation (13.1% vs 3.8%) was the only TEAE reported at an incidence of ≥ 5 percentage points more in the delamanid 200 mg BID + OBR group than in the placebo + OBR group; the incidence of chest pain was similar between groups (8.8% vs 4.4%). In Trial 204, there appeared to be a dose response for the following TEAEs (> 5 percentage points lower in the delamanid 100 mg BID + OBR group compared with the delamanid 200 mg BID + OBR group): vomiting (29.8% vs 36.3%), dyspepsia (3.7% vs 8.8%), pyrexia (5.6% vs 11.3%), decreased appetite (14.9% vs

23.1%), hypokalemia (12.4% vs 19.4%), arthralgia (19.9% vs 26.9%), neck pain (0.6% vs 6.9%), insomnia (26.1% vs 32.5%), and depression (2.5% vs 8.1%).

Trial 208[107] served as a treatment extension trial to provide safety and tolerability data for longer-term exposure to delamanid for up to 6 additional months beyond the exposure in Trial 204. Although delamanid was administered for 6 months in this open-label trial (at least 4 months longer than in previous delamanid trials), no new safety concerns were identified when the data were compared with previous trials. Additionally, QTcF data were not calculated from time-matched samples as in Trial 204 and, therefore, may have shown more variability because of normal expected diurnal variations during a given day. Overall, the mean QTcF interval stabilized after Week 6; differences from time point to time point were minor and not clinically relevant. Only 6 (2.8%) patients had reported TEAEs related to prolonged QT. A low percentage of patients (3.8%, 8/213) had a change in QTcF of > 60 msec. These data do not suggest that further increases in QTcF duration occur with longer-term (6 months, 26 weeks) dosing of delamanid beyond the 2-month (56 days) period of dosing in Trial 204, using the same dose levels.

In Trial 208, no new clinically important TEAEs were reported relative to those in Trial 204. The incidence of the following TEAEs were increased in Trial 208 relative to Trial 204 (> 5 percentage points higher in Trial 208 than in Trial 204 for the delamanid 100 mg + OBR group): hyperbilirubinemia (6.6% vs 0.6%), nasopharyngitis (8.8% vs 2.5%), upper respiratory infection (8.0% vs 1.2%), increased blood cortisol (8.8% vs 2.5%), and headache (30.7% vs 23.6%).

In Trial 242-07-209[108] (14 days) evaluating coadministration of delamanid 100 mg BID with ARV treatment medications in healthy non-HIV infected adults, 2 SAEs were reported: one subject who received delamanid with efavirenz discontinued due to anxiety and the following day reported an SAE of acute delirium; another subject who was taking delamanid and the ARV medication Kaletra experienced an SAE of ischemic colitis. In addition to the discontinuation mentioned above, one subject who received delamanid with the ARV medication tenofovir discontinued due to vomiting. Additionally, one subject in the delamanid plus efavirenz group had a severe TEAE (hepatic enzyme elevation). Multiple oral doses of delamanid 200 mg were generally well tolerated alone and in combination with tenofovir and Kaletra. Overall, the most common side effects observed in the trial included nervous system (28/89 subjects, 31.5%), gastrointestinal (21/89 subjects, 23.6%), and psychiatric (14/89 subjects, 15.7%) side effects. Nervous system and psychiatric side effects occurred in 3 of 4 (75%) subjects who received delamanid with efavirenz; these effects occurred less frequently in subjects who received

delamanid alone (4/15 subjects [26.7%] had nervous system side effects and 1/15 subjects [6.7%] had psychiatric side effects) or efavirenz alone (1/5 subjects [20.0%] had nervous system side effects and psychiatric side effects). The efavirenz and efavirenz plus delamanid groups were placed on hold pending evaluation of the observed events, and then discontinued prior to Day 14; therefore, PK profiles were not obtained.

The primary objectives of Trial 210[109] were to evaluate the safety, tolerability, and PK of orally administered delamanid BID given in sequentially escalated doses for up to 196 days (28 weeks) at each dose to individual cohorts of MDR-TB patients refractory to treatment with OBR and to determine the potential dose-limiting factors and, potentially, the maximum tolerated dose in patients treated with delamanid. Drug exposure did not increase with these higher doses, apparently due to lack of further absorption and limited increases in concentration.

In Trial 210, all patients reported at least one TEAE. Most TEAEs were mild to moderate in severity. The most frequently reported TEAEs (> 2 patients) were hyperglycemia (6/10 patients; 60%), tuberculosis (ie, progressive tuberculosis, 5/10 patients; 50%), viral upper respiratory tract infection (4/10 patients; 40%), nausea (4/10 patients; 40%), vomiting (3/10 patients; 30%), hepatomegaly (3/10 patients; 30%), decreased appetite (3/10 patients; 30%), and cough (3/10 patients; 30%).

A total of 10 patients received at least one dose of the investigational medicinal product (IMP) in this trial and delamanid was analyzed for safety and efficacy. Due to the resistance patterns in this heavily treated patient population, most patients were treated with an OBR composed of less potent anti-TB medications from categories 4 and 5. Seven of the 10 patients enrolled in the trial who had a ≥ 9-month history of previous treatment with second-line drugs for MDR-TB had XDR-TB at baseline, greatly limiting options for anti-TB drugs to use in combination with delamanid. Five patients each were administered delamanid 250 mg or 300 mg BID (500 or 600 mg/day, respectively) plus OBR. Overall, 7/10 (70.0%) patients completed the trial. Please see the IB for more details.

In Trial 242-08-211[110], which evaluated 10 days of delamanid comparing the PK of 300 mg QD vs 150 mg BID versus 100 mg 3 times daily among 36 healthy subjects, no SAEs occurred. Eight subjects discontinued the trial prematurely due to AEs, including 3 events of hematochezia, 3 events of headache, 1 event of diarrhea, and 1 event of hematemesis. All of these AEs were mild or moderate in severity and all were considered causally related to the IMP except for an event of hematochezia.

Trial 242-08-212[111] was a randomized, multiple-dose trial conducted in healthy subjects to investigate the PK and safety of delamanid when administered in combination with efavirenz. No SAEs, including neuropsychiatric SAEs, were observed in subjects receiving the combination of delamanid and efavirenz. Coadministration of efavirenz did not appear to affect (< 25% change) delamanid exposure. There were no serious neuropsychiatric TEAEs and no discontinuations due to neuropsychiatric TEAEs.

As of 31 Jan 2016 in Trial 242-09-213, the ongoing phase 3, randomized, double-blind, and placebo-controlled trial conducted in MDR-TB patients to determine the safety, PK, and efficacy of delamanid plus OBR versus placebo plus OBR, enrollment was complete and 511 patients had begun blinded treatment. A total of 238 serious TEAEs occurred. The most frequently reported serious TEAEs were hypokalaemia (12 [2.3%]), tuberculosis (14 [2.7%]), deafness bilateral (8 [1.6%]), acute kidney injury (8 [1.6%]), electrocardiogram QT prolonged (7 [1.4%]), haemoptysis (5 [1.0%]), and hepatotoxicity (5 [1.0%]). Nineteen deaths (19/511; [3.7%]) were reported for patients with MDR TB. Two patients died due to acute respiratory failure (one of these patients also had worsening of MDR-TB), 2 patients died due to haemoptysis, 2 patients died due to disseminated tuberculosis and sepsis, one due to cardiac arrest and pneumonia, and one patient each died of cardiopulmonary failure, myocardial ischemia, pulmonary edema, pulmonary embolism, respiratory failure, acute myocardial infarction, hypothermia, metastatic neoplasm of unknown primary site, squamous cell carcinoma of lung, renal impairment, lung adenocarcinoma metastatic, and completed suicide. All of these events were considered by the investigator as unrelated or unlikely related to IMP.[1]

In the ongoing trials in pediatric patients with MDR TB (Trials 242-12-232 and 242-12-233), there was 1 serious TEAE of non-Hodgkin's lymphoma reported as of the cutoff date of 31 Jan 2016. [1]

Refer to the IB for additional information on the delamanid safety profile.[1]

1.4.2 Antituberculosis Medications for Treating MDR-TB

The design of treatment regimens for MDR-TB is highly complex. Often it is empiric in the initial stages of treatment until full information on drug susceptibility testing of the clinical isolate is available to tailor a patient's regimen. Up until that point, the patient's previous treatment history for TB, information on drug resistance patterns of known MDR-TB patients with whom a given patient has been in close contact, and the patient's HIV status are used to guide the choice of anti-TB drugs. Treatment is generally divided into an initial intensive phase, which is focused on achieving sputum culture conversion

(SCC) from positive growth of MTB to a negative culture as soon as possible. Thereafter, a much longer continuation phase of treatment ensues, focused on ensuring sterilization. For the intensive phase, at least 4 drugs that are known or suspected to have efficacy for a given patient's MTB isolate are used; however, whenever possible, 5 drugs should be used to ensure a higher likelihood of a response to treatment. The drugs comprising a patient's treatment regimen are selected in a stepwise manner, as recommended by the WHO Programmatic Guidelines for the Management of Drug-resistant Tuberculosis for 2011[112] and outlined in Table 1.4.2-1. Whenever possible, the regimen includes one injectable agent (amikacin, kanamycin, or capreomycin), as these agents are among the most potent of the second-line drugs available for treating MDR-TB. The injectable agent is usually continued for 8 months, however, at least 4 months beyond achieving sustained SCC defining the end of the intensive phase of treatment. Thereafter, the continuation phase of treatment — the part more readily delivered in an ambulatory setting — ensues, and a full treatment course can last for 24 months.

Table 1.4.2-1 Step-wise Approach in the Treatment of Multidrug-resistant Tuberculosis (Resistance to at Least Rifampicin and Isoniazid)

Step 1	**Group 1:** Available first-line oral agents as well as pyrazinamide	Group 1 drugs, the most potent and best tolerated, should be used if there is good laboratory evidence and clinical history to suggest that a drug from this group is effective. The WHO (2011) no longer recommends ethambutol as part of a routine standard treatment, although continues to recommend pyrazinamide use for all patients.
Step 2	**Group 2:** At least one injectable agent: kanamycin (or amikacin); capreomycin; streptomycin	All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. Kanamycin or amikacin is generally the first choice, given the high rates of streptomycin resistance in this population.
Step 3	**Group 3:** At least one fluoroquinolone: moxifloxacin; levofloxacin; gatifloxacin; ofloxacin	A fluoroquinolone should be added based on DST and treatment history. In cases when resistance to ofloxacin is suspected, a higher-generation fluoroquinolone should be used. (Gatifloxacin should be used with caution and close monitoring, secondary to previous reports of a rare but severe side effect of dysglycemia.)
Step 4	**Group 4:** One or more second-line oral bacteriostatic agents: p-amino-salicylic acid; cycloserine (or terizadone), ethionamide (or protionamide)	Group 4 drugs are added until the patient is receiving at least four drugs likely to be effective. The best choice is based on treatment history, adverse effect profile, and cost. DST is not standardized for the drugs in this group.

Table 1.4.2-1	Step-wise Approach in the Treatment of Multidrug-resistant Tuberculosis (Resistance to at Least Rifampicin and Isoniazid)	
Step 5	**Group 5:** Drugs of unclear role in DR-TB: clofazimine; linezolid; amoxicillin/clavulanate; thioacetazone imipenem/ cilastatin; high-dose H; clarithromycin	The efficacy of Group 5 drugs in multidrug regimens is unclear and should only be considered if there are not four drugs likely to be effective from Groups 1- 4. Consultation with an MDR-TB expert should be considered. If drugs are needed from this group, it is recommended to add at least two. DST is not standardized for the drugs in this group.

DR: drug resistant; DST: drug susceptibility testing; WHO: World Health Organization.
Derived from WHO source.

Although long-term treatment with multiple anti-TB drugs based on drug susceptibility testing (DST) is likely to be effective for a given patient, the failure rate for MDR-TB remains high. In a meta-analysis of cohort and case-control studies performed over a 3-decade period that included data on nearly 5000 MDR-TB patients treated in 21 countries, successful outcome was reported for only 62% (range: 39% to 77%) of patients; unsuccessful outcome was reported for 38% (range: 23% to 61%) of patients, including death that specifically occurred among 11% of patients (range: 0% to 32%).[15,113]

Given the high proportion of patients with MDR-TB whose disease does not resolve with available treatment, and that many of them die, it is clear that new medications that have potent activity against MDR-TB are urgently needed to improve the outcome of this patient group and to reduce the risk of further global spread of MDR-TB. With the advent of new medications for MDR-TB, new cotoxicities may be encountered. For example, delamanid, as well as bedaquiline, moxifloxacin, and clofazimine, have been associated with QT prolongation and, in most instances, the combined QTcF prolongation of 2 or more of these drugs has not yet been characterized.[114,115]

Treatment of MDR-TB in Pediatric Patients

The principles for treating adults with drug-resistant TB have demonstrated over time that they generally apply to infants, children, and adolescents, and the regimens recommended by the WHO for childhood-type TB continue to be essentially the same as for adult-type TB.[116] WHO guidelines for the treatment of drug-resistant TB in adults are based on evidence from meta-analyses of individual patient data.[112] However, recommendations for children are based on expert opinion, drawing on data from case series and cohort

studies, often with small sample sizes. Consequently, variation exists in programmatic choices of treatment regimens, with the choice of drugs informed by previous drug exposure and DST results, if available. Recent interest in pediatric TB resulted in a critical review of existing treatment recommendations and a number of new recommendations have been made regarding the appropriate dosing of first-line TB drugs in children.[117]

Children with MDR-TB are managed in much the same way as adults, although there are some differences. Confirmation of MDR-TB may not be possible in children and child TB cases in recent close contact with an adult MDR-TB case or failing to respond to adherent first-line treatment should be empirically treated as MDR-TB cases. Because of the paucibacillary nature of early primary disease (contained primary lung lesion or uncomplicated hilar/mediastinal lymph node enlargement), these children may need fewer drugs and shorter durations of treatment, although there are no randomized studies to confirm this.[118,119] Children are best managed with empirical or individualized treatment regimens that utilize the same rationale. Empirical treatment is designed on the basis of the previous treatment history and DST of the child (or likely source case); individualized treatment is based on the patient's own current DST result and previous treatment history.[120]

Traditionally in TB therapy, pediatric dosing has been extrapolated from adult PK studies; however, children generally metabolize more rapidly than adults, which leads to lower drug concentrations by weight.[121,122] Alternatively, neonates and very young infants who have immature liver and enzyme development seem to metabolize drugs less rapidly than older children. Care must be taken when prescribing for this subpopulation.[122] Most second-line drugs have been minimally studied in children with TB. Additionally, few drugs are available in pediatric formulations and adult-sized preparations are frequently inappropriate for small children. Tablets, for example, must frequently be broken and segments crushed before delivery. However, this approach is associated with dosing errors that could lead to lowered effectiveness or toxic effects.[19]

Regular weight-based dose adjustment is also important, particularly in young and/or malnourished children during the intensive phase of treatment when weight gain may be pronounced and rapid.[123]

2 Trial Rationale and Objectives

2.1 Trial Rationale

Delamanid has been extensively studied in healthy adults and in patients with both uncomplicated TB and with MDR-TB. Delamanid has shown low toxicity and good tolerability in all populations studied. For adults, marketing authorization has been obtained in the European Union, Japan, and Korea for the use of delamanid with OBR during the 6-month intensive phase of OBR treatment. However, until Trial 232, delamanid had not been studied in the pediatric population.

Trial 232 was designed to define the pediatric dose in patients between 0-17 years of age that will result in a delamanid systemic exposure (AUC) equivalent to that observed in the pivotal adult trials where efficacy against MDR-TB has been demonstrated. Trial 233 will investigate the safety, tolerability, PK, and efficacy of delamanid administered in a pediatric population also on concomitant OBR. The goals of this extension trial are to evaluate the long-term safety and tolerability of the age-specific delamanid doses used in Trial 232 and to determine, in pediatric MDR-TB patients, the dose that will result in delamanid plasma exposure similar to effective plasma exposure in adult MDR-TB patients. The study will also assess the palatability of the pediatric formulation using an age-appropriate visual hedonic scale and clinical assessment.

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

Delamanid plasma concentrations in the pediatric population will be analyzed using a population pharmacokinetics (POPPK) approach of the data collected in Trials 232 and 233.

In addition, a PK/PD analysis will be performed for changes in QTc as a function of delamanid and DM-6705 plasma concentrations of the data collected in Trials 232 and 233.

Patients in each age group will be sequentially enrolled into this 6-month treatment extension trial (Trial 233) to evaluate the safety, tolerability, PK, efficacy, and palatability of delamanid during the extended time period planned in this trial for treatment of MDR-TB. To be eligible for Trial 233, all patients must rollover within 30 days of completing Trial 232.

This trial will be conducted in accordance with the 2010 "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations" of the American Academy of Pediatrics[124] and the 2001 "Ethical Considerations for Clinical Trials performed in Children" from the European Union Directive.[125]

2.2 Dosing Rationale

Delamanid will be administered to pediatric MDR-TB patients on OBR therapy. Children will be given delamanid BID (except for the 5.5-8 kg group who will receive a QD dose) in agreement with the delamanid dosing regimen for adult MDR-TB patients, which is BID treatment for 6 months. Delamanid will be administered with water and food as a morning and evening dose, approximately 10 hours apart. Food composition will be equivalent to a standard meal and typical for the childrens' ages and needs.

Children 6 to 17 years, inclusive, will receive the delamanid 50-mg tablet adult formulation. Adolescents (12 to 17 years) will be given delamanid at the adult dose, 100 mg BID, while children 6 to 11 years will be given one half of the adult dose, 50 mg BID.

Younger children (ages birth to 5 years, inclusive) will be given pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension. Children ages 3 to 5 years, inclusive (Group 3) will be given pediatric delamanid formulation 25 mg BID.

The delamanid dose for children ages birth to 2 years, inclusive (Group 4), will be determined based on body weight during baseline visit. Children with weight > 10 kg will be given delamanid pediatric formulation (DPF) , 10 mg BID, those with weight > 8 and ≤ 10 kg will be given DPF 5 mg BID, while children with weight ≤ 8 kg will receive DPF 5 mg QD. Delamanid dose will be adjusted as needed for Group 4 patients based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).

Delamanid doses in younger children were confirmed using the PK, safety, and tolerability findings in the older age groups and based on the bioavailability of the pediatric formulation.

2.3 Trial Objectives

The primary objectives of this trial are:

- To evaluate the long-term safety and tolerability of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in pediatric

patients with MDR-TB for the age-specific delamanid doses determined in Trial 232

- To report delamanid and metabolite plasma concentrations at each visit day by age groups and to conduct a population pharmacokinetics (POPPK) analysis of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB

The secondary objectives are:

- To evaluate the PK/PD relationship of delamanid and its metabolite DM-6705 plasma concentrations and change in QTc when delamanid is administered in combination with OBR during a 6-month treatment period in pediatric patients with MDR-TB
- To evaluate the efficacy of delamanid when administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB
- To determine the palatability of the delamanid pediatric formulation

3 Trial Design

3.1 Type/Design of Trial

This is a phase 2, open-label, multiple-dose, age de-escalation trial to assess the long-term safety, tolerability, PK, and efficacy of delamanid plus OBR over a 6-month period in pediatric patients with MDR-TB who have successfully completed Trial 232.

This trial will be conducted at multiple phase 2 sites qualified to treat pediatric patients with MDR-TB. The protocol will be approved by the appropriate national competent authorities (CAs) and the respective independent ethics committees (IECs) or institutional review boards (IRBs). Compliance with any other regional or local notification or approval requirements will be met and maintained.

All patients must have completed the pediatric PK Trial 232 prior to enrollment into Trial 233. Those patients who have completed Trial 232 and choose to enter Trial 233 must rollover from Trial 232 within 30 days of completing that Trial. If any patients terminate Trial 232 early or choose not to enter Trial 233, patients will be recruited to first enter and complete Trial 232, and then to rollover into Trial 233. Patients who terminate Trial 233 early will not be replaced.

Delamanid will be administered for 182 days. The trial will be conducted sequentially in 4 groups of pediatric patients:

- Group 1 (ages 12 - 17 years, inclusive) will receive adult formulation delamanid 100 mg BID + OBR (n = 6)
- Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)
- Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)
- Group 4 (ages birth - 2 years, inclusive) will receive the following delamanid pediatric formulation (DPF) dose based on body weight during baseline visit (n = 12):
  - Patient > 10 kg will receive DPF 10 mg BID + OBR
  - Patient > 8 and ≤ 10 kg will receive DPF 5 mg BID + OBR
  - Patient ≤ 8 kg will receive DPF 5 mg QD + OBR
  - Delamanid dose will be adjusted as needed for Group 4 patients based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).

The trial will comprise the following periods:

- **Screening Period (Day −30 to −2):** Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the post-Trial 232 thirty (30)- day screening period for Trial 233, as described in the Schedule of Assessments
- **Baseline (Day −1):** Inclusion/exclusion criteria, physical examination, and safety assessments including laboratory tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, head circumference (Group 4 only), percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications
- **Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid. PK sampling every 2 weeks through Week 14 at 0 hours predose, then as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination, and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Vital signs, head circumference (Group 4 only), height, weight, and BMI beginning at Week 2. OBR administration as prescribed by the investigator and collection of AEs, immediately reportable events (IREs), and concomitant medications
- **Post-treatment Period (Days 183 to 238):** Physical examination, vital signs, ECGs, safety labs, blood draws for PK at visits and times described in the Schedule of Assessments. Head circumference (Group 4 only), height, weight, signs and symptoms of TB, audiometry and visual assessments, thyroid function tests (for patients taking ethionamide or para-aminosalicylic acid), OBR

administration as prescribed by the investigator and collection of AEs/IREs, and concomitant medications

- **Follow-up Period (Days 239 to 365, 6 month Post Last Delamanid Dose Visit):** Physical examination, height and weight, BMI, percentiles for age, vital signs, head circumference (Group 4 only), height, weight, signs and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or para aminosalicylic acid), OBR administration as prescribed by the investigator and collection of AEs/IREs and concomitant medications
- **Treatment Outcome Follow-up (Day 730 [Month 24] + 2 months:** All patients will either visit the clinic or be contacted by telephone for clinical assessment. Collection of treatment outcome information as routinely documented in the patient medical records or in a national TB program

See **Figure 3.1-1** for a schematic of the overall trial design.

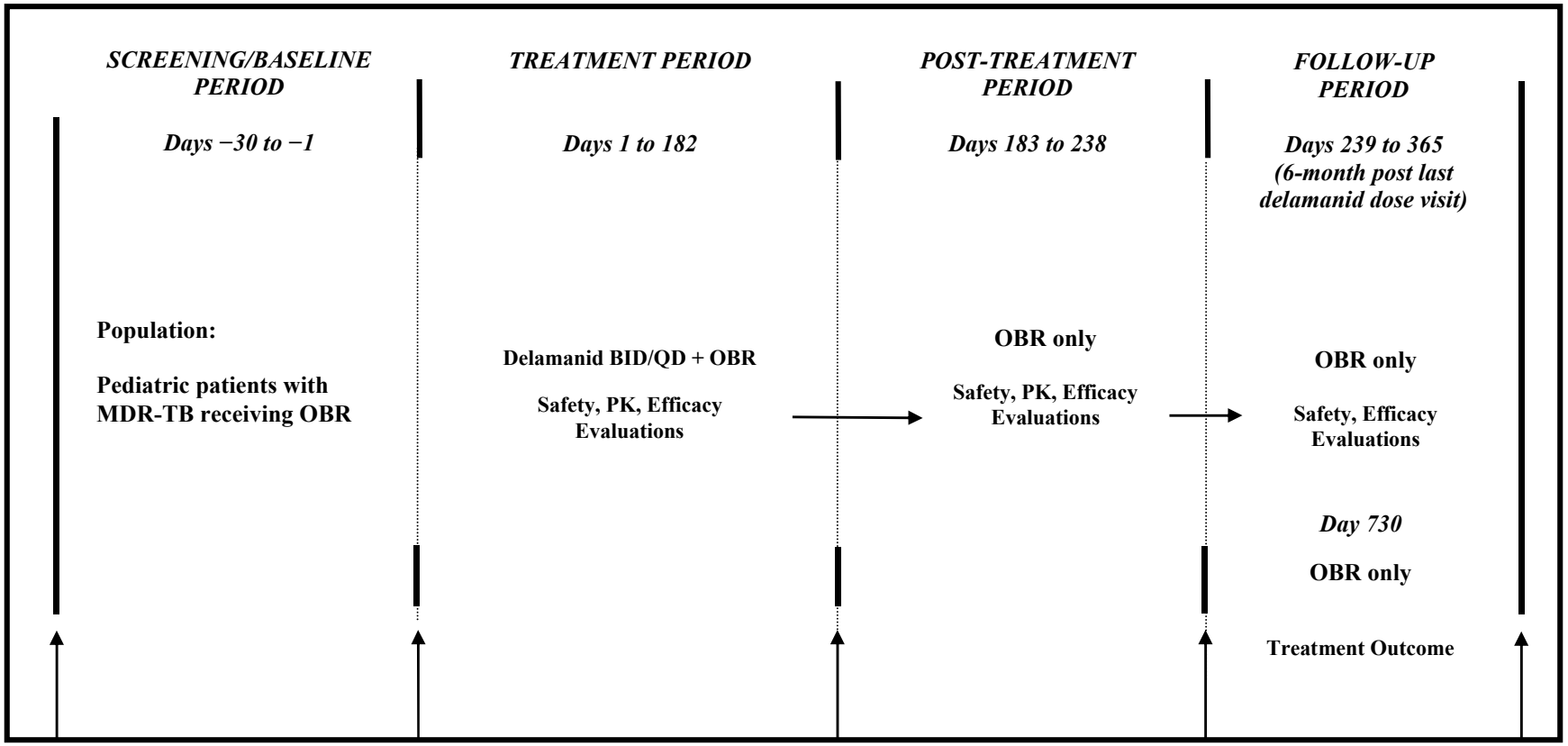

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

Patients will be assigned by age group to receive one of the following treatments for 182 days:

1) Group 1 (12 to 17 years, inclusive): adult formulation delamanid 100 mg BID (administered as 2 x 50-mg tablets BID) + OBR

2) Group 2 (6 to 11 years, inclusive): adult formulation delamanid 50 mg BID (administered as 1 x 50-mg tablet BID) + OBR

3) Group 3 (3 to 5 years, inclusive): pediatric formulation delamanid 25 mg BID (administered as 1 x 25-mg tablet BID) + OBR

4) Group 4 (birth to 2 years, inclusive): pediatric formulation delamanid based on body weight + OBR. Children with weight > 10 kg will be given delamanid pediatric formulation (DPF) 10 mg BID (administered as 2 x 5-mg dispersible tablet) + OBR; Children with weight > 8 and ≤ 10 kg will be given DPF 5 mg BID (administered as 1 x 5-mg dispersible tablet) + OBR, and children with weight ≤ 8 kg will be given DPF delamanid 5 mg QD (administered as 1 x 5-mg dispersible tablet) + OBR.

Patient age group and dosing (Groups 1, 2 and 3) will be determined at the time of enrollment into Trial 232 and will not change during rollover into Trial 233. Dosing for Group 4 will be determined during baseline visit and will be adjusted based on weight measurement during specific study visits (Visits 5, 7, 9, 11 and 12).

3.2.1 Administration of Delamanid

All doses for Groups 1 and 2 will be given orally as the appropriate number of 50-mg adult formulation delamanid tablets (Section 3.2). Adult formulation delamanid tablets should be taken with water. Children in Groups 3 and 4 will be given delamanid as an extemporaneous suspension using the delamanid pediatric dispersible tablet formulation.

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

documented when patients are in the hospital or clinic or for regularly scheduled assessments or for observation.

3.2.2 Administration of OBR

The specific medications comprising OBR for each patient will be selected by the lead investigator, who is a clinical expert on pediatric MDR-TB treatment and management. Selection and administration of the treatment medications will generally be based on WHO guidelines[126] in conjunction with national TB program guidelines. Moxifloxacin, a fluoroquinolone commonly used to treat MDR-TB, will not be used because of its known effect on QT prolongation. Gatifloxacin, although not disallowed, will only be used with caution, secondary to the rare but serious side effect dysglycemia; close monitoring of blood glucose levels is recommended for those patients investigators choose to treat with gatifloxacin as per the WHO guidelines. At any time during the trial, the lead investigator for a given site may change OBR for a given patient based on patient tolerability and subsequent DST results.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

At least 36 males and females ages birth to 17 years, inclusive, who have successfully completed Trial 232 and who are receiving OBR for confirmed or presumptive MDR-TB will be enrolled in 4 sequential age groups. These patients (and age groups) will be the same groups who successfully completed Trial 232: Group 1 (ages 12 to 17 years) will contain a minimum of 6 patients and must include at least 2 but no more than 5 females. Group 2 (ages 6 to 11 years, inclusive) will contain a minimum of 6 patients. Group 3 (ages 3 to 5 years, inclusive) and Group 4 (ages birth to 2 years, inclusive) each will contain a minimum of 12 patients. Groups 2, 3, and 4 will include both genders.

3.3.2 Subject Selection and Numbering

All patients must have completed Trial 232 prior to enrollment in Trial 233. Subjects who enter Trial 233 will retain the same unique identification number assigned to them in Trial 232. Patients who terminate Trial 233 early will not be replaced.

3.4 Eligibility Criteria

3.4.1 Informed Consent

Written informed consent and/or assent will be obtained from all patients (or their parents, guardian, or legal representative), as applicable for local laws, before any

trial-related procedures (including any pretreatment procedures) are performed. Investigators may discuss the availability of the trial and the possibility for entry with a potential patient and his/her parent, guardian, or legal representative without first obtaining consent/assent. However, assent of the adolescent and informed consent of the parent, guardian, or legal representative, as applicable for local laws, must be obtained and documented prior to the initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of or in preparation for the research, it is considered to be part of the research. When a screening informed consent form (ICF)/assent form is used for general health assessment prior to identifying or consenting candidates for this specific trial, the screening ICF/assent form will also become part of this study's file and the patient's chart. Parent/guardian/legal representative informed consent and patient assent will be obtained in conformance with "Ethical Considerations for Clinical Trials Performed in Children," Guidelines for Implementing Directive 2001/20 /EC, 6 October 2006.[124]

The investigator(s) have both ethical and legal responsibility to ensure that each patient being considered for inclusion in the trial and his/her parent(s), guardian(s), or legal representative(s) are given a full explanation of the protocol. This shall be documented on a written ICF, which shall be approved by the same IRB/IEC responsible for approval of this protocol. Each ICF shall include the elements required by the United States Food and Drug Administration (FDA) regulations in 21 Code of Federal Regulations Part 50 and International Conference on Harmonisation (ICH) Good Clinical Practices (GCP), and must adhere to the ethical principles that have their origin in the Declaration of Helsinki, as well as local regulatory requirements. The investigator agrees to obtain approval from the sponsor of any written ICF used in the trial, preferably prior to submission to the IRB/IEC with the exception of a screening ICF. However, the screening ICF must have been approved by the IRB/IEC.

Once appropriate essential information has been provided to the parent, guardian, or legal representative and/or the patient and fully explained in layman's language by the investigator (or a qualified designee) and it is felt the parent/guardian/legal representative understands the implications of participating in the trial, the IRB/IEC-approved written assent and ICF shall be signed and dated by the patient and his/her parent/guardian/legal representative and the person obtaining consent (investigator or designee), and by any other parties required by the IRB/IEC. The parent/guardian/legal representative and/or patient shall be given a copy of the signed ICF/assent form; the original shall be kept on

file by the investigator. All of the above-mentioned activities must be completed prior to the patient participating in the trial.

Patients for whom an ICF/assent form is signed but who are not started on treatment are permitted to be rescreened under the conditions specified in Section 3.9. In the event the patient is rescreened for trial participation, a new ICF/assent form must be signed.

If any patient should turn 18 years of age (or the age of adulthood as specified by local laws or regulations) within 4 weeks prior to entry into Trial 233 or during Trial 233 participation, an ICF must be signed by the patient. The patient shall be given a copy of the signed ICF/assent, and the original shall be kept on file by the investigator. A patient who turns age 18 (or the age of adulthood as specified by local laws or regulations) during the study must sign an appropriate ICF/assent form for himself/herself at that time. In addition to the English version of the ICF/assent form, the document may also be translated into local languages for use in this study. Translation with back-translation for confirmation will be used to ensure accuracy.

In accordance with applicable regulations and guidance for subject data protection, patients who have completed the Post-treatment Follow-up Period (Visit 19) prior to regulatory authority and EC approval of this protocol will be asked to sign an ICF/assent form authorizing the release of TB-related clinical information from the treatment centers. The parent/guardian/legal representative and/or patient shall be given a copy of the signed ICF/assent form; the original shall be kept on file by the investigator.

3.4.2 Inclusion Criteria

Subjects are required to meet the inclusion criteria listed in Table 3.4.2-1 prior to enrollment:

Table 3.4.2-1 Inclusion Criteria

1.	Patient must have successfully completed Trial 232 and have and met all inclusion criteria for that trial
2.	Male or female
3.	Age birth to 17 years, inclusive
4.	Confirmed diagnosis of MDR-TB,[a,b] ie, culture positive for MTB with isoniazid and rifampicin resistance on DST, or a positive rapid test demonstrating resistance to rifampicin alone or to rifampicin and isoniazid OR Presumptive diagnosis of pulmonary or extrapulmonary MDR-TB[b] such that the treating physician has decided to treat the patient for MDR-TB[a] who has one of the following: -Clinical specimen (eg, cerebrospinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of tuberculosis disease

Table 3.4.2-1 Inclusion Criteria	
	-Persistent cough lasting > 2 weeks -Fever, weight loss, and failure to thrive -Findings on recent chest radiograph (prior to Visit 1) consistent with TB AND -Household contact with a person with known MDR-TB or with a person who died while appropriately taking drugs for sensitive TB OR -On first-line TB treatment but with no clinical improvement
5.	Negative urine pregnancy test for female patients who have reached menarche
6.	Study-specific written informed consent/assent obtained from a parent/guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol-required procedures. In addition, for patients in Groups 1 and 2 or as required by local law, the patient must provide informed assent at screening and must be able to fully understand that he or she can withdraw from the study at any time.

[a] Patients should be on OBR for at least 2 weeks prior to baseline assessments.

[b] Includes pre−XDR TB.

3.4.3 Exclusion Criteria

Subjects will be excluded from the trial if they meet any of the exclusion criteria listed in Table 3.4.3-1 prior to enrollment in Trial 233.

Table 3.4.3-1 Exclusion Criteria	
1.	Patients who have not completed Trial 232
2.	Children with laboratory evidence of hepatitis B or C
3.	Children with body weight < 5.5 kg.
4.	For patients with HIV co-infection, CD4 cell count ≤ 1000/mm3 for children 1-5 years old, and ≤ 1500/mm3 for children less than 1 year old
5.	History of allergy to metronidazole and any disease or condition in which the use of metronidazole is required
6.	Use of amiodarone within 12 months prior to the first dose of IMP or use of other predefined antiarrhythmic medications within 30 days prior to the first dose of IMP
7.	Serious concomitant conditions (cardiovascular disorders; severe respiratory disease; severe diarrheal disease; or renal, hepatic, or neurological impairment)
8.	Abnormalities in screening ECG (including atrioventricular block, bundle branch block or hemi-block. QRS prolongation > 120 msec or QTcF interval > 450 msec in both males and females)
9.	Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds
10.	A concomitant condition such as renal impairment characterized by serum creatinine levels >1.5 mg/dL, hepatic impairment (ALT or AST > 3 x ULN), or hyperbilirubinemia characterized by total bilirubin > 2 x ULN
11.	Concurrent diagnosis of severe malnutrition or kwashiorkor
12.	Positive urine drug screen (Groups 1 and 2 only)
13.	Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP and/or any prior concurrent use of bedaquiline
14.	Lansky Play Performance Score < 50 (not applicable for children < 1 year old) or Karnofsky Score < 50

Table 3.4.3-1	Exclusion Criteria
15.	Administered an IMP within 1 month prior to Visit 1 other than delamanid given as IMP in Trial 232
16.	Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form (Groups 1 and 2 only)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; QTcF = QT interval corrected using Fridericia's method; ULN = upper limit of normal.

Patients ages 6 to 17 years excluded for a positive drug/alcohol screen are not eligible to be rescreened for participation in the trial. However, a positive urine drug screen could be the result of authorized medications prescribed by a physician for a nonabuse-related indication and the investigator will need to ascertain relevant information to make this distinction before proceeding further with screening and enrollment. Patients excluded for any other reason may be rescreened at any time if the exclusion characteristic has changed. In the event that the subject is rescreened, a new ICF/assent form must be signed and a new screening number assigned.

3.5 Outcome Variables

3.5.1 Primary Outcome Variables

3.5.1.1 Safety Outcome Variables

Safety and tolerability of delamanid will be assessed by the following variables:

- Reported TEAEs
- Physical examination including visual testing and audiometry
- Vital signs
- ECGs
- Holter monitoring (if applicable)
- Clinical laboratory assessments (hematology, serum chemistry, urinalysis, and other laboratory tests [see Table 3.7.3.1-1])

3.5.1.2 Pharmacokinetic Variables

PK parameters from the population pharmacokinetic analysis, using data from this trial and from the -232 trial, will be reported.

3.5.2 Secondary Variables

3.5.2.1 Pharmacokinetic/Pharmacodynamic Variables

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

3.5.2.2 Efficacy Outcome Variables

The efficacy of delamanid in treating pediatric MDR-TB patients will be assessed by chest radiography (patients with pulmonary disease), body weight/height, and resolution of TB symptoms (based on investigator evaluation).

In addition, SCC (for culture-positive patients) will be assessed in patients who are able to produce sputum (or provide other biological specimens) for microbiological evaluation according to the requirements of the National TB Program. Microbiological assessment of sputum or other biological specimens (eg, cerebrospinal fluid, pleural fluid, ascitic fluid, joint fluid, lymph node aspirates) are not required as part of this protocol; however, they may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (or provide other specimens) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.

3.5.2.3 Palatability

The palatability of the pediatric formulation will be assessed using an-age appropriate visual hedonic scale and clinical assessment (Groups 3 and 4 only).

3.6 Measures to Minimize/Avoid Bias

This is an open-label, noncontrolled PK and safety trial of delamanid in pediatric patients with MDR-TB and who are also receiving OBR.

3.6.1 Randomization

Randomization of patients is not planned.

3.7 Trial Procedures

Delamanid will be administered with a standard meal for the duration of the trial. OBR will be administered as prescribed, under the DOTS guidelines of the WHO.

Each patient will participate in the trial for up to 760 days. The trial will comprise the screening period (29 days); baseline (Day −1); treatment period (182 days of delamanid

plus OBR administration); post-treatment period (56 days with visits at Days 189, 196, 203, 210, and 238 [Day 238 corresponds to 2 months post last delamanid dose]); and a follow-up period with a visit at 6 months after the last delamanid dose (Day 365) and an additional 365-day treatment outcome follow-up period from the last follow-up visit. Trial assessment time points are summarized in Table 3.7-1.

Table 3.7-1 Schedule of Assessments

Trial Period	SCR	BSL		Treatment Period											Post-treatment Period					F/U	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ET**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Day	**−30 to −2**	**−1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**126**	**154**	**182**	**n/a**	**189**	**196**	**203**	**210**	**238**	**365**	**730**
and	**n/a**			**± 2 days**																**± 5 days**	**+ 2M[s]**
Visit Window																					
Week				**2**	**4**	**6**	**8**	**10**	**12**	**14**	**18**	**22**	**26**	**n/a**	**27**	**28**	**29**	**30**	**34**	**52**	
Informed consent/assent[a]	X[a]																				
Inclusion/ exclusion criteria	X[b]	X																			
Diagnosis of MDR-TB	X [b,f]																				
Demographic data	X[b]																				
Medical history	X																				
Complete PE	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body mass index and percentiles for age	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Date of birth and gender	X																				
Vital signs[g]	X[g,h]	X[g,h]	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	X[g,h]	X[g]	X[g,h]	X[g,h]	X[g,h]	X[g,h]	X[g, h]	X[g]	X[g]	X[g]	X[g,h]	X[g,h]	X[g,h]	
12-Lead ECG	X[c]	X	X[j]		X[i]		X[j]		X[i]		X[i]	X[j]	X[j]	X[i]				X			
Signs and symptoms of TB	X[b]	X			X		X		X		X	X	X					X	X	X	
Chest radiograph (only for patients with pulmonary TB)	X[b]												X							X	
Audiometry assessment	X[b]	X			X		X		X		X	X	X					X	X	X	
Visual assessment	X[b]	X			X		X		X		X	X	X					X	X	X	
Urinalysis	X[b]	X			X		X		X		X	X	X	X				X		X	

Table 3.7-1 Schedule of Assessments

Trial Period	**SCR**	**BSL**		**Treatment Period**											**Post-treatment Period**					**F/U**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ET**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Day	**−30 to −2**	**−1**	**1**	**14**	**28**	**42**	**56**	**70**	**84**	**98**	**126**	**154**	**182**	**n/a**	**189**	**196**	**203**	**210**	**238**	**365**	**730**
and	**n/a**			**± 2 days**																**± 5 days**	**+ 2M[s]**
Visit Window																					
Week				**2**	**4**	**6**	**8**	**10**	**12**	**14**	**18**	**22**	**26**	**n/a**	**27**	**28**	**29**	**30**	**34**	**52**	
Urine pregnancy test (only female patients who have reached menarche)	X[d,k]												X[k]	X[k]							
Urine drug screen (Groups 1 and 2 only)	X[d]																				
Hematology[l]	X[b]	X			X		X		X		X	X	X	X				X		X	
Serum chemistry	X[b]	X			X		X		X		X	X	X	X				X		X	
HIV test	X[b,v]																				
CD4 cell count	X[b,w]																				
HBsAg test	X[b]																				
Anti-HCV test	X[b]																				
ACTH test	X[b]														X						
Adrenal function (cortisol)	X[b]														X						
Thyroid function[m]	X[b,m]								X[m]						X[m]				X[m]	X[m]	
C-reactive protein (Groups 1 and 2 only)	X[b]												X								
PK blood draw			X[n]	X[p]			X[n]			X[p]		X[n]	X[n]	X[e]	X[p]	X[p]	X[p]	X[o]	X[p]		
Delamanid dosing			X	X	X[t]	X	X[t]	X	X[t]	X	X[t]	X[t]	X									
Palatability assessment (Groups 3 and 4 only)			X		X		X						X	X[q]							
OBR administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 3.7-1 Schedule of Assessments

Trial Period	SCR	BSL		Treatment Period											Post-treatment Period					F/U	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	ET	14	15	16	17	18	19	20
Day and Visit Window	−30 to −2	−1	1	14	28	42	56	70	84	98	126	154	182	n/a	189	196	203	210	238	365	730
	n/a			± 2 days																± 5 days	+ 2M[s]
Week				2	4	6	8	10	12	14	18	22	26	n/a	27	28	29	30	34	52	
Record AEs and IREs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Record prior anti-TB medications	X																				
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Menarche/LMP assessment (Groups 1 and 2 only)	X[d]			X		X		X		X	X	X	X	X				X	X		
Follow-up contact for ET														X[r]							
Collection of treatment outcome data																					X
Holter Monitoring[u]			X		X		X		X		X	X	X	X				X		X	

ACTH = adenocorticotropic hormone; aPTT = activated partial thromboplastin time; BP = blood pressure; bpm = beats per minute; BSL = baseline; d = days; CD4 = cluster of differentiation 4; ET = early termination; F/U = follow up; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HR = heart rate; IRE = immediately reportable event; LMP = last menstrual period; n/a = not applicable; OBR = optimized background regimen; PE = physical examination; PT = prothrombin time; RR = respiratory rate; SCR = screening; TB = tuberculosis.

[a]Consenting/Assenting for Trial 233 can occur prior to Day −30.

[b]Information to be obtained from screening visit of Trial 232.

[c]Information to be obtained from Day 10 of Trial 232.

[d]For Groups 1 and 2 only, information to be obtained during Screening for this Trial 233, between Days −30 to −1.

[e]For the early termination visit, the PK blood sample will be labeled with the study day, date, and time of the PK blood draw.

[f]Confirmed or presumptive diagnosis of MDR-TB (based on inclusion criteria no. 4, Table 3.4.2-1).

[g]Vital signs include systolic and diastolic BP (mm Hg), HR (bpm), RR (bpm), and body temperature (C) after the patient has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4), height (cm), and weight (kg). Note: height and weight do not need to be measured on Day 1.

[h]Head circumference should also be measured for children in Group 4 (ages birth - 2 years, inclusive).

[i]Three consecutive 12-lead ECGs must be performed predose after the subject has been in a supine or semi-recumbent position and at rest for ≥ 10 minutes (as possible for Groups 3 and 4).

[j]ECG paired with PK blood sampling: Three consecutive 12-lead ECGs must be performed predose after the subject has been in a supine or semi-recumbent position and at rest for ≥ 10 minutes (as possible for Groups 3 and 4), followed by PK blood draw, and then patients will receive their dose of delamanid.
[k]Urine pregnancy test will be performed for all females who have reached menarche .
[l]Coagulation tests (activated partial thromboplastin time and prothrombin time) performed with safety laboratory assessments.
[m]Thyroid tests (T4 and thyroid stimulating hormone) performed for patients taking ethionamide or p-aminosalicylic acid.
[n]PK blood draw paired with 12-lead ECG at predose (0 hours during treatment).
[o]PK blood draw paired with 12-lead ECG at theoretical predose.
[p]PK blood draw to be obtained at any time point.
[q]Only in Groups 3 and 4 and only if within 25 - 30 minutes postdose and prior to Day 182.
[r]Follow-up contact for patients who terminate early from Trial 233 should occur 28 to 32 days after the early termination visit to assess for AEs and IREs. All patients will continue treatment with OBR as prescribed by the investigator according to WHO guidelines.
[s]Day 730 (Month 24) + 2 months.
[t] For Group 4 only, delamanid dose will be adjusted based on the subject's weight measurement during study visit
[u]Twenty-four-hour Holter monitor tracing if QTcF>490 msec.
[v] Not required if patientt had a documented HIV test and result within 1 year prior to the screening visit AND there is no known exposure to HIV.
w Screening CD4 cell count test will only be performed for patients with positive HIV test results unless the patient has documented CD4 cell count test and results within 3 months prior to screening visit.

3.7.1 Schedule of Assessments

All patients participating in the trial must be evaluated according to the assessment schedule of the trial outlined in Table 3.7-1.

3.7.1.1 Visit 1, Screening/Enrollment (Days −30 to −2)

For patients who elect to be rolled over from Trial 232 into Trial 233, the following procedures will either be collected from screening data for Trial 232 or from Day 10 data of Trial 232, or will be assessed/performed within 30 days prior to Trial 233.

The following information will be taken from the screening data of Trial 232 and used as screening data for this Trial 233:

- Inclusion/exclusion criteria
- Diagnosis of MDR-TB, confirmed or suspected
- Demographic data
- Complete physical examination
- Signs and symptoms of TB
- Audiometry and visual assessments
- Chest radiograph for confirmation of radiological picture compatible with TB
- Laboratory assessments including serum chemistry, hematology and coagulation, urinalysis, HIV, CD4 cell count (if HIV test is positive), hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), adrenocorticotropic hormone (ACTH), adrenal function (cortisol), C-reactive protein (Groups 1 and 2 only), and thyroid function tests (T4 and thyroid stimulating hormone [TSH])

The following information will be taken from Day 10 data of Trial 232 and used as screening data for this Trial 233:

- 12-lead ECG

The following information will be obtained during the screening period of this Trial 233 between Days −30 and −2:

- Informed consent/assent (may be completed prior to Day −30)
- Medical history
- Vital signs assessments (blood pressure, heart rate, respiratory rate, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Date of birth and gender
- Urine pregnancy test for all female subjects who have reached menarche

- For Groups 1 and 2 only, urine drug screen (as per Table 3.7-1)
- Record prior concomitant medications including prior concomitant anti-TB medications. (Note: Patients will have been on OBR in Trial 232 for at least 2 weeks prior to baseline assessments)
- Groups 1 and 2 only, record date of menarche and/or date of last menstrual period (LMP)

3.7.1.2 Visit 2, Baseline (Day −1)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's electronic case report form (eCRF) for Baseline (Day −1):

- Review of inclusion/exclusion criteria
- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (blood pressure, heart rate, respiratory rate, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Three consecutive 12-lead ECGs after the patient has been in a supine or semi-recumbent position and at rest for ≥ 10 minutes (as possible for Groups 3 and 4)
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- OBR administration, as prescribed by investigator
- Record concomitant medications including concomitant anti-TB medications

3.7.1.3 Visit 3 (Day 1)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 1:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4). Note: height and weight do not need to be measured at this visit

- Three consecutive 12-lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4) prior to blood draw for PK. Sequence should be ECG assessment, then blood draw for PK, then administration of delamanid
- Blood draw for PK at predose (0 hours) (see Section 3.7.4)
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). For Group 4, delamanid dosing will be determined based on weight measurement during baseline visit.
- Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec following the first dosing of delamanid pediatric formulation.

3.7.1.4 Visit 4, Day 14 ± 2 Days (Week 2)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 14:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Blood draw for PK at any time point (see Section 3.7.4)
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator).
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications.
- Groups 1 and 2 only, record date of menarche and/or date of LMP

3.7.1.5 Visit 5, Day 28 ± 2 Days (Week 4)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 28:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed.
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- Three consecutive 12-lead ECGs Three consecutive 12-lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4). Sequence should be ECG assessment then administration of delamanid
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.
- Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.6 Visit 6, Day 42± 2 Days (Week 6)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 42:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator).
- Record AEs and IREs

- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP

3.7.1.7 Visit 7, Day 56± 2 Days (Week 8)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 56:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- Three consecutive 12-lead ECGs. Sequence should be ECG assessment then PK blood draw followed by administration of delamanid
- Blood draw for PK at predose (0 hours) (see Section 3.7.4)
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.
- Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.8 Visit 8, Day 70 ± 2 Days (Week 10)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 70:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed

- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator).
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP

3.7.1.9 Visit 9, Day 84 ± 2 Days (Week 12)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 84:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- Blood draw for thyroid function tests (T4 and TSH) for patients taking ethionamide or PAS
- Three consecutive 12-lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4). Sequence should be ECG assessment then administration of delamanid
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). For Group 4 delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.10 Visit 10, Day 98 ± 2 Days (Week 14)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 98:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Blood draw for PK at any time point (see Section 3.7.4)
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator).
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP

3.7.1.11 Visit 11, Day 126 ± 2 Days (Week 18)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 126:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- Three consecutive 12-lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4). Sequence should be ECG assessment then administration of delamanid
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement

during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.

- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.12 Visit 12, Day 154 ± 2 Days (Week 22)

The following procedures will be conducted and/or recorded in the patient's eCRF for Day 154:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- Three consecutive 12-Lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4) and prior to blood draw for PK. Sequence should be ECG assessment, then blood draw for PK, then administration of delamanid.
- Blood draw for PK at predose (0 hours) (see Section 3.7.4)
- Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.13 Visit 13, Day 182 ± 2 Days (Week 26)

Note: Day 182 is the last day of delamanid dosing. For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 182:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Signs and symptoms of TB
- Chest radiograph
- Audiometry and visual assessments
- Urine pregnancy test for all female subjects who have reached menarche
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, C-reactive protein (Groups 1 and 2 only) testing and urinalysis
- Three consecutive 12-lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4). Sequence should be ECG assessment then PK blood draw followed by administration of delamanid
- Blood draw for PK at predose (0 hours) (see Section 3.7.4)
- Delamanid dosing (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). NOTE: This is the last day of delamanid dosing
- Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.14 Visit 14, Day 189 ± 2 Days (Week 27)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 189:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight
- BMI and percentiles for age
- Blood draw for ACTH and adrenal function (cortisol)
- Blood draw for thyroid function tests (T4 and TSH) for patients taking ethionamide or PAS
- Blood draw for PK at any time point (see Section 3.7.4)
- OBR administration, as prescribed by investigator
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications

3.7.1.15 Visit 15, Day 196 ± 2 Days (Week 28)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 196:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight
- BMI and percentiles for age
- Blood draw for PK at any time point (see Section 3.7.4)
- OBR administration, as prescribed by investigator
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications

3.7.1.16 Visit 16, Day 203 ± 2 Days (Week 29)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 203:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight
- BMI and percentiles for age

- Blood draw for PK at any time point (see Section 3.7.4)
- OBR administration, as prescribed by investigator
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications

3.7.1.17 Visit 17, Day 210 ± 2 Days (Week 30)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 210:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- Three consecutive 12-lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4). Sequence should be ECG assessment then PK blood draw at the theoretical predose
- Blood draw for PK at theoretical predose (0 hours) (see Section 3.7.4)
- OBR administration, as prescribed by investigator
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.18 Visit 18, Day 238 ± 2 Days (Week 34)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 238:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for

Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)

- Blood draw for PK at any time point (see Section 3.7.4)
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Thyroid function tests for those patients taking ethionamide or PAS
- OBR administration, as prescribed by investigator
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP

3.7.1.19 Visit 19, Day 365 ± 5 Days (Week 52, 6 months post last delamanid dose)

For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 365:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Signs and symptoms of TB
- Audiometry and visual assessments
- Thyroid function tests for those patients taking ethionamide or PAS
- Chest radiograph
- Clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- OBR administration, as prescribed by investigator
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.20 Treatment Outcome Follow-up (Day 730 [Month 24] + 2 Months)

All patients who complete the study will come into the clinic or be contacted by telephone on Day 730 (Month 24) + 2 months for clinical assessment. Treatment

outcome and microbiology information will be collected as routinely documented in the patient medical records or in a National TB Program.

3.7.1.21 Early Termination Visit

For all patients who terminate early from the trial, the following procedures will be conducted and/or recorded in the eCRF:

- Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed
- Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)
- BMI and percentiles for age
- Blood draw for PK (see Section 3.7.4)
- Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis
- Three consecutive 12-Lead ECGs after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4)
- Urine pregnancy test for all female subjects who have reached menarche
- Groups 3 and 4 only and only if prior to Day 182 and within 25 - 30 minutes postdose, palatability assessment of the delamanid pediatric formulation (see trial operations manual for details)
- OBR administration, as prescribed by investigator
- Record AEs and IREs
- Record concomitant medications including concomitant anti-TB medications
- Groups 1 and 2 only, record date of menarche and/or date of LMP
- Patients who terminate early from Trial 233 prior to their last scheduled visit will have a follow-up contact (phone call or visit) 28 to 32 days after the Early Termination Visit to assess for AEs and IREs. All patients will continue treatment with OBR as prescribed by the investigator according to WHO guidelines
- Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec

3.7.1.22 Post Treatment and Follow-up

The last dose of delamanid will be given on Day 182. Patients will continue on OBR, as prescribed by the investigator, and have post-delamanid treatment visits on Days 189, 196, 203, 210, 238 (2-month post last dose), and 365 (6-month post last dose), and a treatment outcome follow-up on Day 730 (Month 24) + 2 months.

3.7.2 Efficacy Assessments

This is a safety, tolerability, PK, and efficacy trial of delamanid administered for 6 months to patients with MDR-TB who are also receiving OBR for their disease. There is no placebo or control group, and the sample size is small, comprising only patients who have completed Trial 232. All efficacy evaluations will be performed by the investigator at his/her discretion and will be analyzed and presented in a descriptive manner.

Efficacy assessments will include:

- assessment of clinical signs and symptoms of TB
- chest radiograph
- abnormality/extent of abnormality

In addition, although microbiological assessment of sputum or other biological specimens (eg, cerebral spinal fluid [CSF], pleural fluid, ascitic fluid, joint fluid, lymph node aspirates, etc.) are not required as part of this protocol, they may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (or provide other specimens) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.

3.7.3 Safety Assessments

3.7.3.1 Clinical Laboratory Tests

The tests listed in Table 3.7.3.1-1 will be performed at the times listed in Table 3.7-1 and will be processed in accordance with directions from the analytical laboratory.

Table 3.7.3.1-1 Clinical Laboratory Tests

Hematology:	Serum Chemistry:
White blood cell count with differential	Blood urea nitrogen
Red blood cell count	Creatinine
Hematocrit	Aspartate transaminase
Hemoglobin	Alanine transaminase
Mean corpuscular volume	Gamma glutamyl transferase
Mean corpuscular hemoglobin concentration	Lactic dehydrogenase
Prothrombin time	Alkaline phosphatase
Activated partial thromboplastin time	Total bilirubin
Platelets	Triglycerides (Groups 1 and 2 only)
International normalized ratio	Cholesterol (Groups 1 and 2 only)
	Calcium
Urinalysis	Glucose
Color	Magnesium
pH	Sodium
Specific gravity	Potassium
Protein	Chloride
Bilirubin	Total protein
Urobilinogen	Uric acid
Blood	Inorganic phosphorous
Glucose	Albumin
Ketones	Globulin
Leukocytes	Albumin/globulin ratio
Nitrites	
Microscopic examination when urinalysis is abnormal: casts, crystals, red blood cells, white blood cells, bacteria	Other Laboratory Tests
	Morning cortisol
	Thyroid function tests (serum thyroid stimulating hormone and free T4)
Drug Screen (Groups 1 and 2 only)	Urine pregnancy test (for female patients who have reached menarche)
Alcohol	Adrenocorticotrophic hormone
Amphetamine/methamphetamine	HIV (screening only[a])
Barbiturates	CD4 cell count (screening only[b])
Benzodiazepines	Hepatitis B surface antigen (screening HBsAg only)
Cannabinoids	Antibody to hepatitis C virus (screening only)
Cocaine	C-reactive protein (Groups 1 and 2 only)
Cotinine	
Methadone	
Opiates	
Tetrahydrocannabinol	

[a] Not required if patient had a documented HIV test and result within 1 year prior to the screening visit AND there is no known exposure to HIV.

[b] Screening CD4 cell count test will only be performed for patients with positive HIV test results unless the patient has documented CD4 cell count test and results within 3 months prior to screening visit.

3.7.3.2 Physical Examination and Vital Signs Assessments

A complete medical history will be taken at the screening visit, and physical examinations and vital signs measurements will be performed according to the schedule provided in Table 3.7-1.

A complete physical examination will include examination of the head, eyes, ears, nose, throat, thorax, abdomen, skin and mucosae, lymph nodes, extremities, and urogenital (for Groups 3 and 4, required only at screening and subsequently at the discretion of the investigator) systems. The physical examination will also include a neurological examination and a psychiatric assessment (Groups 1 and 2 only) as described in the trial operations manual. The principal investigator or appointed medical doctor designee is primarily responsible for performing the physical examination. Whenever possible, the same individual should perform all physical examinations for each patient. If the appointed medical doctor designee is to perform the physical examination, he or she must be permitted by local regulations and his or her name must be included on FDA Form 1572. Any clinically significant condition present at the post-treatment examination that was not present at the baseline examination should be documented as an AE and followed to satisfactory conclusion.

Vital signs assessments include head circumference for patients in Group 4 (ages birth - 2 years, inclusive), blood pressure, heart rate, respiration rate, and body temperature. Vital signs are to be recorded after the patient has remained in a supine or semi-recumbent position and at rest for ≥ 3 minutes (as possible for Groups 3 and 4). When vital signs and safety ECGs are scheduled for the same nominal time, vital signs assessments should be obtained prior to the ECG.

Body weight and height, BMI, and age percentiles will also be recorded.

3.7.3.3 Electrocardiogram Assessments

Electrocardiograms for on-site evaluation of safety will be recorded at the nominal times according to the schedule outlined in Table 3.7-1. Twelve-lead ECGs will be recorded with the subject in a supine or semi-recumbent position and at rest for ≥ 10 minutes (as possible for Groups 3 and 4). ECGs should be taken before PK blood draws when assessments are scheduled on the same day (Visit). Three tracings will be obtained at each time point (approximately 3 to 5 minutes between each tracing) with the ECG leads left in place. Heart rate, PR interval, QRS interval, QT interval, QTcF, and QTcB will be recorded. The principal investigator or designated medical doctor will review, sign, and date each ECG reading. Whenever possible, the same reviewer should evaluate, sign, and date the ECGs. The reviewer must be listed on FDA Form 1572. Original ECG tracings will be added to the patient's medical record with the reviewer's interpretation recorded. In addition to the initial clinical interpretation for ongoing safety evaluation by the investigator, all ECGs will be analyzed by a specialized central laboratory. Specific guidance for investigators for determining AEs related to ECG results is available in the trial operations manual.

Digitally acquired ECGs will be received by the central laboratory for processing. Graphic tools will be used to perform manual measurements, including the RR, PR, QRS, and QT interval durations. Parameters will also be measured electronically.

The onset of the QRS complex and the end of the T wave will be identified to define the QT interval. The RR duration will similarly be determined by selecting the peak of 2 consecutive R waves (starting with the previous R from the first PQRST complex). In addition to the parameters directly drawn on the ECG image, a number of independent parameters will automatically be derived and stored in memory (eg, QTcB, QTcF).

Technicians will be responsible for performing the interval duration measurements (IDMs) using specialized technology linked into the central laboratory's data management system. The IDMs will be transferred to the data management system following a quality control process and will automatically be populated in a worksheet for a cardiologist to review in conjunction with the ECG.

ECG analyses will be provided by the central laboratory according to the specific requirements of Otsuka. Measurements of the following intervals will be made for each ECG tracing:

- 3 RR mean RR will be reported
- 3 PR mean PR interval will be reported
- 3 QRS mean QRS width will be reported
- 3 QT mean QT interval will be reported

Highly trained physician electrocardiographers will be available to interpret all standard 12-lead ECGs generated from this trial. Cardiologist ECG assessments will include standard comments on normal/abnormal, rhythm, arrhythmia, conduction, morphology, myocardial infarction, ST segment, T wave, and U wave observations. Each ECG report will include the following:

- Patient information
  - Select Summary Information
- Interpretation
  - Normal
  - Abnormal
  - Unable to evaluate
- Interval duration measurements
  - Rhythm

  - Arrhythmia
  - Conduction
  - Morphology
  - Myocardial infarction
  - ST segment
- T wave observations
- U wave observations
- Physician's comments

Following completion of all internal quality procedures, the dataset will be transferred in electronic format to Otsuka or Otsuka's designee for the generation of tables and listings for inclusion in the trial report.

3.7.4 Pharmacokinetic Assessments

Approximately 3 mL of blood will be collected per PK sample in the 12- to 17-year-old children (Group 1); 2 mL per PK sample in the 3- to 11-year-old children (Groups 2 and 3) and 0.6 mL per PK sample for children ages 2 years and younger (Group 4). Delamanid data from this trial are to be combined with PK data from Trial 232 for the POPPK analysis.

3.7.4.1 Blood Collection Times

Blood collection for PK will occur on Days 1 to 2 and 10 to 11. Blood draws will occur at predose (0 hours during treatment) paired with the 12-lead ECGs on Days 1, 56, 154, and 182. A PK blood sample will be obtained on Day 210 paired with the 12-lead ECG at the theoretical predose. Additional PK blood samples will be drawn on Days 14, 98, 189, 196, 203, and 238. A PK blood draw will be collected at ET. When blood collection for PK is paired with ECGs, the ECG will be performed first, followed by the PK blood draw, and then dosing with delamanid.

3.7.4.2 Pharmacokinetic Assessment of Cerebral Spinal Fluid

In patients in whom a lumbar puncture is clinically indicated during the routine management of a child enrolled in the trial, CSF concentrations of delamanid will be measured. The timing of the lumbar puncture will be recorded in relation to the timing of the dose of delamanid and any proximate blood collections. See the trial manual of operations for specific information about handling, processing, and storage of CSF samples.

3.7.4.3 Sample Handling and Processing

Specific information about blood sample collection processing, storage, and shipping is provided in Appendix 3.

3.7.5 Pharmacodynamic Assessments

ECGs and PK measurements for determination of delamanid and DM-6705 plasma concentrations will be collected (see Section 3.7). These assessments should be time-matched if possible.

3.7.6 Other Assessments

The palatability of the delamanid pediatric formulation will be assessed (Groups 3 and 4 only) within 25 - 30 minutes after the morning dose on Days 1, 28, 56, 182, and ET if prior to Day 182 using an age-appropriate visual hedonic scale and clinical assessment. See the trial operations manual for details.

3.7.7 End of Trial

The end-of-trial date is defined as the last date of contact or the date of the final contact attempt from the post-treatment follow-up eCRF for the last subject completing or withdrawing from the trial.

3.7.8 Safety Monitoring Committee

A safety monitoring committee (SMC) composed of external consultants with expertise in pediatric TB and pediatric cardiology will review safety and laboratory test results during the conduct of the trial. The SMC will comprise not less than 2 members who are not involved with enrolling patients into the trial. The SMC will convene and operate based on the availability of patient safety information. The SMC will seek additional independent expertise, if needed.

The primary responsibility of the SMC will be to monitor safety and to determine whether or not the safety concerns merit stopping the trial.

3.8 Stopping Rules, Withdrawal Criteria, and Procedures

3.8.1 Entire Trial or Treatment Arm(s)

If a subject discontinues from the trial, the reason given must be fully evaluated and recorded appropriately in source documentation and in the eCRF. If the subject is being withdrawn because of an AE, that AE must be indicated as the reason for withdrawal. All assessments scheduled to be completed at the final trial visit will be performed at early termination. If delamanid is stopped due to an AE and/or investigator

decision, subjects should continue with visits/assessments for the rest of the trial with the exception of taking delamanid. This will allow analysis of comparable assessments between those who stopped and those who completed delamanid dosing.

All subjects have the right to withdraw from the trial at any point during treatment without prejudice. The investigator can discontinue a subject at any time, if medically necessary. In addition, subjects who meet any of the following criteria must be withdrawn from the trial:

1) Occurrence of any AE, intercurrent illness, or laboratory abnormality that, in the opinion of the investigator, warrants the subject's permanent withdrawal from the trial
2) Occurrence of QTcF > 500 msec or occurrence of proarrhythmic events
3) Treatment with a prohibited concomitant medication other than the use of appropriate medications for the treatment of AEs under direction of the investigator
4) Patient noncompliance, defined as refusal or inability to adhere to the trial schedule. Please refer to the trial Operations Manual for further information on the definition of noncompliance
5) At the request of the patient or patient's parent/guardian, investigator, Otsuka Pharmaceutical Development & Commercialization, Inc., or regulatory authority
6) Subject is lost to follow-up

The sponsor should be notified promptly when a patient is withdrawn or if the trial is stopped. Patients in this trial who terminate early will not be replaced.

If the sponsor terminates or suspends the trial for safety or unanticipated other reasons, prompt notification will be given to investigators, IRBs/IECs, and regulatory authorities in accordance with regulatory requirements.

3.8.2 Individual Site

The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site. A particular site may be terminated from the trial at the discretion of the investigator, sponsor, or IRB/IEC, eg, for nonenrollment of subjects or noncompliance with the protocol.

3.9 Screen Failures

A screen failure patient is one from whom informed consent is obtained and is documented in writing (ie, patient and parent/designee sign an ICF/assent) but who is not started on treatment, whether through randomization or open assignment. Patients excluded from the trial because of a positive drug or alcohol screen are not eligible to be

rescreened; however, patients excluded for any other reasons may be rescreened at any time, if the exclusion characteristic has changed. In the event a patient is rescreened, a new ICF/assent must be signed and a new screening number assigned.

3.10 Definition of Completed Patients

The treatment period is defined as the time period during which patients are evaluated for primary and/or secondary objectives of the trial regardless of whether or not the patients actually consumed all doses of trial medication. Patients who are evaluated at the last scheduled visit of the trial, the follow-up visit (Visit 19, Day 365), will be defined as trial completers.

3.11 Definition of Lost to Follow-up

Patients who cannot be contacted on or before the scheduled M24 follow-up visit and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as "lost to follow-up" as the reason for discontinuation. The site will make 3 attempts to contact the patient or parent/guardian/legal representative by telephone and in the event the site is unable to reach the patient or parent/guardian/legal representative by telephone, the site will attempt to contact the patient or parent/guardian/legal representative via certified mail or an alternative similar method, as appropriate.

3.12 Patient Compliance

The time and dose of each IMP administered will be recorded on the source documents and on the eCRF. Information regarding any missed or inappropriately administered doses will also be documented on the source document and on the eCRF. Compliance will be ensured by a hand and mouth check during the oral dosing administration.

3.13 Protocol Deviations

This trial is intended to be conducted as described in this protocol. In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the sponsor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator and the sponsor and reviewed by the monitor.

4 Restrictions

4.1 Prohibited Medications

Table 4.1-1 List of Medications Prohibited During the Trial	
Antiarrhythmic Medications with Potential for QT Interval Prolongation	
1.	Quinidine
2.	Procainamide
3.	Disopyramide
4.	Encainide
5.	Flecainide
6.	Sotalol
7.	Amiodarone
8.	Digitalis
Other Medications With Potential For QT Interval Prolongation	
1.	Moxifloxacin
Other Medications	
1.	Rifampicin
2.	Bedaquiline

5 Reporting of Adverse Events

The investigator is to use the following definitions when entering details on AEs or immediately reportable events (IREs) in the CRF or on the immediate safety report (ISR) Form.

5.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial patient and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including eg, an abnormal laboratory assessment result), symptom or disease temporally associated with participation in the clinical trial, whether or not it is considered causally related to the medicinal product or procedures of the clinical trial. An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening, ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Requires in-patient hospitalization or prolongs hospitalization. The following hospitalizations, including hospitalizations for social purposes, are not considered SAEs for the clinical trial:

  - A visit to the emergency room or other hospital department < 24 hours that does not result in admission (unless considered "important medical event" or life-threatening event)
  - Hospitalizations as outlined in the protocol that are part of the clinical trial conduct
  - Routine health assessment requiring admission for baseline/trending of health status
  - Medical/surgical admission (hospitalization) for a purpose other than remedying ill health state and such hospitalizations that were planned prior to entry into the trial, ie, prior to signing the ICF/assent. Appropriate documentation is required in these cases
  - Hospital admission(s) encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative reasons), ie, for social reasons
  - A hospitalization due to an unmanageable distance between the patient's domicile and the investigational site
- Congenital anomaly/birth defect
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse

Nonserious adverse events are all AEs that do not meet the criteria of a "serious" AE.

Immediately Reportable Event:

- Any SAE
- Any AE that necessitates discontinuation of delamanid
- Any increase of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal (ULN), with an increase in total bilirubin ≥ 2 times the ULN
- QTcF interval prolongation > 500 msec or occurrence of proarrhythmic events
- Pregnancies are also defined as IREs; although a normal pregnancy is not an adverse event, it will mandate delamanid discontinuation and must be reported on an IRE form to Otsuka Europe Development and Commercialisation Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) (See also Section 5.4). This includes pregnancies occurring in the female partner of a male patient. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication
- All events involving overdose, misuse, and abuse. This includes accidental overdose by investigator or patient. It also includes all such events, whether the course is symptomless, or whether an AE or SAE results. These events may

involve delamanid or any other medicinal products or illicit drugs (see also Section 5.5)

Clinical Laboratory Changes: It is the investigator's responsibility to review the results of all laboratory tests as they become available. This review will be documented by the investigator's dated signature on the laboratory report. For each abnormal laboratory test result, the investigator needs to ascertain if this is a clinically significant abnormal change from baseline for that individual patient. (This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests). If this laboratory value is determined by the investigator to be a clinically significant abnormal change from baseline for that patient, it is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated on the eCRF. The intensity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity
3 = Severe:	Inability to work or perform normal daily activity

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP (delamanid) or conduct of trial procedure:

Related:	The AE and the administration of delamanid are related in time and a direct association can be demonstrated
Possibly related:	The AE and the administration of delamanid are reasonably related in time and the AE can be equally well explained by causes other than delamanid administration. The result of dechallenge is lacking or unclear
Unlikely related:	A temporal relationship to the administration of delamanid cannot be ruled out, but the AE can be more likely explained by reasons other than the delamanid administration
Not related:	The AE is clearly explained by another cause not related to the delamanid administration.

5.2 Collecting and Reporting Safety Information to the Sponsor

5.2.1 Period of Observation for Adverse Events and Immediately Reportable Events

All AEs and IREs will be collected and documented from the time of first dosing in Trial 233 until the end of the Post-treatment Follow-up Period for the individual patient. (Exceptions are pregnancy and SAEs considered possibly causally related to delamanid or trial procedures; see Section 5.4 and Section 5.3, respectively). If there are any ongoing AEs at the end of the post-treatment follow-up period, a 1-month follow-up visit should be scheduled.

A clinically significant worsening in the health of the patient compared with the patient's health status documented at baseline constitutes an AE. Abnormal assessment results from screening or baseline examinations are not AEs.

5.2.2 Adverse Events

The investigator must assess patients for the occurrence of AEs at each trial visit, whether scheduled or unscheduled, during the period of observation for safety. In order to avoid bias in inquiring about AEs, patients should be asked the following nonleading question: "How have you been feeling since the last visit?"

The investigator must also promptly review all results of assessments performed as part of the clinical trial (eg, laboratory assessment results, ECGs, vital signs monitoring, physical examinations, and urinalysis) and assess them for clinically relevant changes (worsenings) compared with baseline, which constitute AEs.

All AEs occurring during the period of observation must be entered into the source documents and also on the AE page of the patient's eCRF. The investigator is also responsible for providing or arranging appropriate supportive care for the patient.

An AE that has been entered into the eCRF and undergoes a clinically significant worsening in severity, or that changes and fulfills a criterion of seriousness, must be entered as a new AE. See instructions for completing AE pages in the eCRF Completion Guidelines.

5.2.3 Immediately Reportable Events

In addition to the documentation of all SAEs as defined in Section 5.1, some events must be reported to the sponsor immediately, according to the procedures outlined below.

IREs for this clinical trial are:

- SAEs, as defined above

  - Note: Hospitalization in order to conduct this clinical trial does not constitute an SAE and should not be reported as an IRE, nor entered in the eCRF as an SAE. Section 5.1 provides additional information about which hospitalizations are not considered SAEs
- AEs (serious or nonserious) that result in premature discontinuation of IMP
- Any increase of AST or ALT ≥ 3 times ULN with an increase in total bilirubin ≥ 2 times ULN
- QTcF interval prolongation > 500 msec or occurrence of proarrhythmic events
- Pregnancies in trial patients or their partners (see also Section 5.4)
- All events involving overdose, misuse, and abuse. This includes accidental overdose by investigator or patient. It also includes all such events, whether the course is symptomless or whether an AE or SAE results. These events may involve delamanid or any other medicinal product or illicit drugs (see also Section 5.5)

All SAEs must be reported to the medical monitor via telephone when they occur (see Appendix 1).

As soon as the investigator becomes aware of an IRE in a patient (this includes SAEs and is in addition to reporting the SAE to the medical monitor by telephone), he/she must fill out the ISR form as completely as possible and send it, within 24 hours, as a password-protected attachment to an e-mail, or as a fax to:

E-mail: [redacted]
Fax: [redacted]

The investigator should sign the ISR form personally.

If the ISR cannot be sent successfully electronically or on time (eg, due to technical difficulties) using the contact information above, the report should be made by fax or, if not possible, via phone to the contact person above.

Receipt of the ISR by the sponsor will be confirmed as soon as possible, usually within 24 hours. If further information is required, the sponsor will contact the investigator (usually via the clinical research associate responsible for the site). The investigator is responsible for promptly providing any additional information that is requested.

It can be arranged for the ISRs to be sent to the sponsor via the local contract research organization (CRO) or Otsuka affiliate, but the timelines described above must still be fulfilled.

5.3 Follow-up of Adverse Events and Immediately Reportable Events

All AEs must be followed up until they have resolved (returned to normal or baseline status), stabilized, or been explained.

Adverse events that have not resolved at the end of the period of observation, or that become known at the last visit of the period of observation, must be followed up beyond this visit until satisfactorily resolved, as described above. These AEs must be treated, reported, and documented as described in Section 5.2. Any exceptions must be agreed upon with the safety contact of the sponsor.

In general, events with onset after the period of observation is over are not AEs and do not need to be collected, reported, and documented. (Exceptions: see below.)

Follow-up information on IREs should be reported to the safety contact of the sponsor as soon as possible.

Note: SAEs that are possibly causally related to delamanid or the trial procedures remain reportable after the period of observation is over. There is no time limit for this reportability.

Note: The period of observation and the follow-up for pregnancy are different. See Section 5.4.

5.3.1 Safety Monitoring Committee

The SMC will actively review AEs throughout the trial. See Section 3.7.8 for full details on the constituents, operational processes, and responsibilities of the SMC for this trial.

5.4 Pregnancy

Females of childbearing potential and males who are sexually active must avoid pregnancy or fathering a child for 8 weeks after the last dose of delamanid and abstain from sex during the clinical trial. Pregnancy testing will be performed during the screening period prior to study enrollment and at the end of the trial according to the schedule of assessments for all female patients who have reached menarche.

If the patient or investigator suspects the patient may be pregnant prior to delamanid administration, delamanid must be withheld until the results of urine pregnancy tests are available. A confirmed pregnancy before first administration of delamanid must result in immediate exclusion or withdrawal from the trial. If pregnancy is suspected while the patient is taking delamanid during the trial, delamanid must be withheld immediately. If pregnancy is confirmed, the delamanid will be permanently discontinued but the patient will not be automatically withdrawn from the trial.

The investigator must immediately notify the sponsor of any pregnancy during delamanid exposure, including and for 8 weeks after the last dose of delamanid, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the pregnancy surveillance form(s) for monitoring the outcome of the pregnancy.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy (eg, radiograph studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

Pregnancy in a female patient or in the female partner of a male patient is an IRE and must be reported immediately as such using the ISR form. It is not an AE, and should not be entered as such in the eCRF.

Upon receipt of an ISR concerning pregnancy, the safety contact of the sponsor will inform the investigator of the further information required. The investigator must report to the sponsor, on appropriate pregnancy surveillance form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months. Any congenital anomaly or birth defect constitutes an SAE and must be entered as follow-up information on the ISR form and on the AE eCRF.

5.5 Overdose, Misuse, Abuse

Overdose, misuse, or abuse of delamanid or any other medication or illicit drug constitute IREs, and must be reported and recorded as such.

If such an event fulfills the definition of an AE or an SAE, it must be documented as such on the AE eCRF as well.

5.6 Safety Submissions to Regional and National Competent Authorities, IECs/IRBs, and Notifications to Investigators

The safety contact of the sponsor is responsible for conducting or organizing the submission of safety reports according to international guidelines (eg, ICH), regional and national regulatory requirements, and the applicable standard operating procedures. This includes expedited submissions of individual case safety reports and aggregate periodic safety reports, as required for the European Medicines Agency, FDA, other CAs, national and local IECs/IRBs, and investigators.

The investigator is responsible for any direct submissions from the investigator to the CA or IEC/IRB, as locally required.

Further details are provided in the safety reporting plan for this trial.

6 Pharmacokinetic Analysis

6.1 Pharmacokinetic Methods

Delamanid and metabolite plasma concentrations will be reported with descriptive statistics at each visit day per age group. In addition, delamanid plasma concentrations will be analyzed using a POPPK approach.

6.2 Pharmacokinetic/Pharmacodynamic Methods

Delamanid and DM-6705 plasma concentrations will be examined in conjunction with QTcF data to explore if there is a PK/PD correlation.

7 Statistical Analysis

7.1 Sample Size

No formal sample size calculation was performed because this is a trial in a pediatric population. The primary objectives of this trial are to construct long-term profiles of safety and tolerability, PK, and efficacy of the 6-month use of delamanid for the treatment of pediatric patients with MDR-TB.

7.2 Analysis of Demographic and Baseline Characteristics

Demographic and baseline characteristics of the trial population will be summarized for each age group using descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum for continuous variables [eg, age], and the number and percentage of patients for discrete variables [eg, race and gender]). Individual demographic data will be presented in the data listings.

7.3 Safety Analyses

Safety analysis will be conducted based on the safety population, which is defined as all patients who take at least 1 dose of IMP. Safety variables to be analyzed include clinical laboratory tests, vital signs, ECGs, and TEAEs.

7.3.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent AEs, defined as all AEs that occur after the administration of IMP, will be summarized for each age group by system organ class and preferred term, maximum severity, and potential relationship to IMP, as well as TEAEs with an outcome of death, serious TEAEs, and discontinuations due to TEAEs. A

complete listing of TEAEs for each patient will be provided, including severity, relationship to trial drug, onset, duration, and outcome.

7.3.2 Clinical Laboratory Data

The quantitative change in clinical chemistry, hematology, coagulation, and urinalysis assessment results will be calculated relative to baseline. Baseline is defined as the last measurement before the first administration of delamanid. Summary statistics for quantitative laboratory assessment results will be presented by treatment (age) group and visit for the change from baseline (Day −1) will be provided. Shift tables will be produced for assessing changes from baseline in clinical laboratory measurements.

All laboratory data, including unscheduled assessments, will be presented in data listings. The incidence rate of abnormal laboratory assessment results and clinically significant laboratory abnormalities will be summarized as appropriate.

7.3.3 Physical Examination and Vital Signs Data

By-subject listings will be provided for physical examinations. Summary statistics for changes from baseline (predose Day 1) in vital signs will be provided for each treatment (age) group. All vital signs data will be presented in a data listing by patient.

7.3.4 ECG Data

Summary statistics for changes from baseline (average of screening and baseline predose ECGs) in ECG intervals (PR, QRS, QT, QTcF, and QTcB) will be provided for each treatment (age) group. Categorical changes in ECG results will also be summarized. Electrocardiogram data from all subjects will be presented in data listings.

7.4 Efficacy Analyses

Because of the small sample sizes per group, large-sample-based statistical methods cannot be used. Exact methods, if available, will be pursued. All statistical presentations will be descriptive.

7.5 Palatability Analysis

The palatability of the delamanid pediatric formulation will be assessed (Groups 3 and 4 only) using an age-appropriate visual hedonic scale and clinical assessment. The data will be summarized by descriptive statistics (mean, SD, min, max).

7.6 Interim Analysis

An interim analysis of safety, tolerability, PK, and efficacy of delamanid in children 6 to 17 years of age is planned in the 1st quarter of 2019.

8 Trial Drug Management

8.1 Packaging and Labeling

Investigational medicinal product will be provided to the investigator(s) by the sponsor (or designated agent). The IMP will be packaged in blister cards. Each blister card used in the dosing period will be labeled to clearly disclose the compound ID, protocol number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements (see Section 8.1.1).

8.1.1 Delamanid

Each blister card of delamanid used during the 182-day dosing period will be labeled to clearly disclose the following information:

- Trial/protocol number
- Compound ID
- Patient ID number and/or initials (to be filled in by the investigator/designee when delamanid is assigned and/or dispensed to the patient)
    - Name/number of the trial site and the name of the principal investigator of the trial site (to be filled in by the investigator/designee when delamanid is assigned and/or dispensed to the patient)
    - Name and address of the sponsor of the trial
    - Storage instructions
    - Expiration/retest date
    - Batch number
    - The statement “Clinical Trial Material - for investigational use only,” or similar statement
    - Instructions on how to use the IMP

8.1.2 Optimized Background Treatment Regimen

Medications for the OBR for MDR-TB treatment for each trial patient will be procured through the standard mechanisms available for a given site ordinarily used for procurement of OBR medications for treating MDR-TB patients. The second-line

medications generally used in developing OBR for MDR-TB patient treatment are as follows:

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

Medications with an unclear role in the treatment of MDR-TB and not recommended for routine use for MDR-TB treatment, though sometimes used for highly drug-resistant MDR-TB patients, are described in the WHO treatment guidelines for MDR-TB.[2]

8.2 Storage

Trial drugs will be stored in a securely locked cabinet or enclosure. Access should be strictly limited to the investigators and their designees. Neither the investigators nor any designees may provide IMP to any subject not participating in this protocol.

The IMP will be stored according to the conditions specified in the IMP blister card label. The clinical site staff will maintain a temperature log in the drug storage area, recording the temperature at least once each working day.

The OBR medications should be stored, dispensed, and administered per the package inserts and the trial site standard operating procedures.

8.3 Accountability

The investigator or designee must maintain an inventory record of IMP received, dispensed, administered, and returned. The IMP sent to the trial centers will be verified by the investigators or designees regarding the amount sent, date received, and that supplies were undamaged and not adulterated on arrival. This will be documented by

signing and dating the appropriate accountability documents. The investigator or designee will record the subject's number and initials and the date dispensed on the drug accountability form.

The investigators must keep an accurate running accountability of IMP that will include the batch number and shipment tracking number, as well as the date and patient number of the container dispensed to each patient. All used and unused/unopened IMP containers must be inventoried and accounted for and kept at the site until return of the containers and any unused IMP is authorized by Otsuka. An overall accountability of IMP will be performed and verified throughout the trial and at the site closeout by Otsuka or the designated CRO monitor.

Accountability of OBR medications will be performed per the trial site's standard operating procedures.

8.4 Returns and Destruction

Upon completion or termination of the trial, all unused and/or partially used IMP must be returned to Otsuka (or a designated contractor) unless authorized by Otsuka (in writing).

All IMP returned to Otsuka must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers. The assigned trial monitor will facilitate the return of unused and/or partially used IMP.

If IMP is authorized to be destroyed at the trial site by Otsuka (in writing), it is the investigator's responsibility to ensure that arrangements have been made for the disposal. Written authorization should be issued by Otsuka, procedures for proper disposal should be established according to applicable regulations, guidelines, and procedures, and appropriate records of the disposal should be documented and forwarded to Otsuka.

9 Records Management

9.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons. Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons, as defined in the ICF.

9.2 Data Collection

For each day of the trial during the subject's hospitalization, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent/assent process, including any revised consents/assents
- The date of the visit and the corresponding visit or day in the trial schedule
- General subject status remarks including any *significant* medical findings. The severity, frequency, and duration of any AEs and the investigator's assessment of relationship to IMP must also be recorded
- Any changes in concomitant medications or dosages
- A general reference to the procedures completed
- The signature (or initials) and date of all clinicians who made an entry in the progress notes

In addition, any contact with the patient via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above. Any changes to information in the trial progress notes, other source documents, and eCRFs will be initialed and dated on the day the change is made by a site trial staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source document adjacent to the change by the clinician.

Information from the trial progress notes and other source documents will be promptly and LEGIBLY transcribed to eCRFs for transmission to the sponsor. Changes will be made using the same process described above.

9.3 File Management at the Trial Site

The investigator will ensure that the trial center file is maintained in accordance with Section 8 of the ICH GCP guideline and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

9.4 Records Retention at the Trial Site

FDA regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of ≥ 3 years following the date on which a new drug application is approved by the FDA.
- A period of 3 years after the sponsor notifies the investigator that no further application is to be filed with the FDA
- Longer, region-specific storage requirements, if applicable

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) providing an opportunity for the sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard-copy source documents of all observations and data generated during this trial, including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory agencies. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10 Quality Control and Quality Assurance

10.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in a detailed and orderly manner in accordance with established research principles, the ICH GCP guidelines, FDA regulations, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone and written communication(s).

10.2 Auditing

The sponsor's quality management unit (or representative) may conduct trial site audits. Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits.

Regulatory authorities worldwide may inspect the investigative site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

11 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, the ICH GCP guidelines, and all other applicable local laws and regulatory requirements. The patient's informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (Tokyo 2004), the applicable guidelines for GCP, and any local regulations.

Details of the trial and regular progress reports will be submitted to the appropriate IRB/IEC and CAs as required.

An IRB/IEC should safeguard the dignity, rights, safety, and well-being of all trial participants. Special attention should be given to trials that may include vulnerable participants, such as children.

At a minimum, the IRB/IEC should be supplied with the following documents: trial protocol(s)/amendment(s), written ICFs and ICF/assent form updates that the investigators propose for use in the trial, patient recruitment procedures (for example, advertisements), written information to be provided to participants, IB, additional available safety information, information about payments and compensation available to participants, the investigator's current *curriculum vitae* and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfill its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

- Approval
- Modifications required prior to its approval
- Disapproval
- Termination/suspension of any prior approval

The IRB/IEC should consider the qualifications of the investigators for the proposed trial as documented in their *curricula vitae* and/or by any other relevant documentation the IEC requests.

The IRB/IEC should conduct a continuing review of each ongoing trial at intervals appropriate to the degree of risk to human participants, but at least once per year.

Where the protocol indicates that prior consent of the trial patient or the patient's legally acceptable representative is not possible, the IRB/IEC should determine the appropriate means of meeting ethical requirements.

Financial aspects, patient insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

Otsuka will also obtain CA approval, as applicable, in accordance with applicable regulations and laws.

12 Confidentiality

All information generated in this trial will be considered highly confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. However, authorized regulatory officials and sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Patients will be identified only by initials and unique subject numbers in eCRFs. Their full names may, however, be made known to a regulatory agency or other authorized officials, if necessary. The investigators will maintain a current confidential patient identification code list of names of all patients allocated to patient ID numbers in this trial. This information will be held in the strictest confidence and will only be used for emergency purposes, if needed.

The eCRFs will be designed by Otsuka. eCRFs are used to transmit the information collected in the conduct of this trial to Otsuka and CAs, as appropriate.

13 Amendment Policy

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval by the IRB/IEC. Any permanent change to the protocol, whether it be an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC. Except for nonsubstantial (ie, administrative) amendments, investigators will wait for IRB/IEC approval of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety or physical or mental integrity of the research patients, the conduct or management of the trial, the scientific value of the trial, or the quality or safety of IMP(s) used in the trial. However, a protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, followed by IRB/IEC notification within 5 working days. The sponsor will submit protocol amendments to the FDA or other regulatory agencies.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval of the new ICF by the IRB/IEC, repeat informed consent will be obtained from patients in a timely manner before expecting continued participation in the trial.

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Appendix 1 Important Sponsor Contacts

Report Immediately Reportable Events to:

Otsuka Europe Development and Commercialisation, Ltd (OEDC)
Pharmacovigilance Region Europe (PVRE)
Fax: [redacted]
E-mail: [redacted]

For Medical Emergencies in the Philippines or South Africa:

[redacted], [redacted]
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E-mail: [redacted]

Additional Personnel:

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Rockville, MD 20850
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Appendix 2 Institutions Concerned With the Trial

Otsuka (Philippines) Pharmaceutical Inc. (OPPI)

3F King's Court II Building

2126 Chino Roces Avenue

Makati City, Philippines

Covance Central Lab Services

8211 SciCor Drive

Indianapolis, IN 46214

eResearch Technology

1818 Market Street, Suite 1000

Philadelphia, PA 19103-3638

IVRS/IWRS

S-Clinica

6, chaussée de Boondael

B-1050 Brussels

Belgium

Quintiles East Asia Pte Ltd

79 Science Park Drive #06-08

CINTECH IV, Science Park One

Singapore 118264

Appendix 3 Handling and Shipment of Bioanalytical Samples

All tubes must be labeled using the central lab's bar code labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regard to the PK sample information. On the sample tube, the subject ID/screening number and subject initials must be handwritten on the label. On the requisition form, it is important to note the date and exact time of the blood collection.

Plasma Samples for Delamanid

Blood (0.6 - 3 mL) will be collected into green-top Vacutainer® tubes containing sodium heparin/lithium heparin anticoagulant. The tubes must be gently inverted 3 to 4 times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from each tube should then be divided equally between the 2 barcode-labeled polypropylene tubes (Groups 1-3). For Group 4, the separated plasma should be transferred to a single barcode-labeled polypropylene tube. The PK sample must be stored at −65°C or below.

One PK tube (primary sample) will be shipped on dry ice to the central lab (Groups 1-4). Following confirmation that the first tube arrived safely, the second tubes (backup samples) can also be shipped to the central lab (Groups 1-3). There will be no backup samples for Group 4.

Shipment of Plasma

Each frozen specimen must be sealed in a vial and labeled with a waterproof pen. The label containing the subject ID number and date of collection must correspond to the requisition form, and must be firmly attached to the tube. The requisition form must contain the name, address, and telephone number of the contact person from the trial site. Samples must be neatly packed in the specimen collection bag and restrained in a Styrofoam® container (place the Styrofoam container within the shipping box). Boxes should be completely filled with dry ice to avoid air spaces that allow more rapid evaporation of the dry ice. Follow all instructions included in the sample collection kit provided by the central lab.

Appendix 4 Protocol Amendments

Amendment Number: 1

Issue Date: 11 Mar 2013

PURPOSE: The purpose of this amendment is to delete information in the introduction that is specific to childhood tuberculosis in the Philippines, to modify the exclusion criteria, to change the start of the AE observation period, to make modifications and additions/deletions to the schedule of assessments and the associated text, to change the number of doses to be given under direct observation, to add INR to the list of coagulation tests, and to modify the definition of IRE.

BACKGROUND: In the previous protocol, it was anticipated that this trial would be conducted at a single center in the Philippines; however, since the protocol for Trial 232 (parent trial to Trial 233) has been amended to include multiple phase 1 sites not specifically in the Philippines, it is necessary to amend this protocol accordingly. Additional changes are to add or delete assessments, modify eligibility criteria, and to provide more detail or clarifications on how and when to perform certain procedures.

MODIFICATIONS TO PROTOCOL:

Bold and underlined text: Changed Text

~~**Bold and strike through text**~~: Deleted Text

Bold and italicized text: Added Text

Global Changes:

- Corrected minor typographical, grammatical, and formatting errors.
- Removed the subsection in the Introduction (Section 1) specific to childhood tuberculosis in the Philippines.
- Modified the exclusion criteria.
- Change the start of the AE observation period from informed consent/assent to the time of first dose in Trial 233.

- Added medical history to the assessment schedule and the related text and delete it as being obtained from Trial 232.
- Added collection of date of birth and gender to the assessment schedule and the related text for screening.
- Added BMI to the assessment schedule and the related text at all visits at which height and weight are collected.
- Added Menarche/LMP Assessment to the assessment schedule and the related text for Visits 1 (screening), 4, 6, 8, 10, 11, 12, 13, 17, 18, and Early Termination.
- Added assessment of C-reactive protein at Visit 13
- Changed the number of doses to be given under direct observation.
- Clarified that sputum culture conversion is a secondary efficacy outcome variable in Section 3.5 and renumbered the subsections under Sections 3.5.1 and 3.5.2 accordingly.
- Added INR as a coagulation test.
- Updated the criterion related to hepatic enzymes in the definition of IRE.

Sectional Revisions:

Location	Old Text	Updated Text
Title Page	Added text.	Amendment 1 Issue Date 11 March 2013
Synopsis (Trial Design)	**Baseline (Day 0): Inclusion/exclusion criteria**, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), sputum culture (results will be obtained from the National TB Program or the patient's care provider), audiometry and visual assessments, vital signs, and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of adverse events (AEs)/immediately reportable events (IREs), and concomitant medications.	**Baseline (Day 0): Inclusion/exclusion criteria**, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of adverse events (AEs)/immediately reportable events (IREs), and concomitant medications.
Synopsis (Trial Design)	**Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, sputum culture (results will be obtained from the National TB Program or the patient's care provider), and ECG at weeks and times shown in the Schedule of Assessments. Height and weight beginning Week 2 and assessed monthly, and collection of AEs/IREs, and concomitant medications.	**Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly, and collection of AEs/IREs, and concomitant medications.
Synopsis (Trial Design)	**Follow-up Period (Days 239 to 365, 6 month Post Last Delamaid Dose Visit):** Physical examination, height and weight, percentiles for age, vital signs, and symptoms of TB, sputum culture (results will be obtained from the National TB program or the patient's care provider), chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications.	**Follow-up Period (Days 239 to 365, 6 month Post Last Delamaid Dose Visit):** Physical examination, height and weight, BMI, percentiles for age, vital signs, and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications.
Synopsis (Inclusion/ Exclusion Criteria)	Key Exclusion Criteria: •Patients who have not completed Trial 232 •Children with a positive test for human immunodeficiency virus (HIV) or who have been previously identified as having HIV or with laboratory evidence of hepatitis B or C •History of allergy to metronidazole and any disease or condition in which metronidazole is required •Prior use of predefined medications: amiodarone at any time over	Key Exclusion Criteria: •Patients who have not completed Trial 232 •Children with a positive test for human immunodeficiency virus (HIV) or who have been previously identified as having HIV or with laboratory evidence of hepatitis B or C •History of allergy to metronidazole and any disease or condition in which metronidazole is required •Use of amiodarone within 12 months prior to the first dose of

Location	Old Text	Updated Text
	the past 12 months or use of other predefined antiarrhythmic medications over the last 30 days •Current use of rifampicin and/or moxifloxacin •Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment) •Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds •A concomitant condition such as renal impairment characterized by serum creatinine levels >1.5 mg/dL or hepatic impairment (ALT or AST >3 x ULN) •Abnormalities in screening ECG (including atrioventricular [AV] block, bundle branch block [BBB] or hemi-block, QRS prolongation >120 msec, or QTcF >420 msec in both males and females) •Positive urine drug screen •Concurrent diagnosis of severe malnutrition or kwashiorkor •Lansky Play Performance Score < 50 or Karnofsky Score < 50	investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within the 30 days prior to the first dose of IMP •Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP •Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment) •Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds •A concomitant condition such as renal impairment characterized by serum creatinine levels >1.5 mg/dL, hepatic impairment (ALT or AST >3 x ULN), or hyperbilirubinemia characterized by total bilirubin > 2x ULN •Abnormalities in screening ECG (including atrioventricular [AV] block, bundle branch block [BBB] or hemi-block, QRS prolongation >120 msec, or QTcF >450 msec in both males and females) •Positive urine drug screen •Concurrent diagnosis of severe malnutrition or kwashiorkor •Lansky Play Performance Score < 50 or Karnofsky Score < 50
Synopsis (Outcome Variables)	Efficacy: assessed by determining the percentage of culture positive patients achieving sputum culture conversion (SCC); results of chest radiography (for patients with pulmonary disease); change in body weight and height measurements; and evaluation of TB symptoms.	Efficacy: assessed by results of chest radiography (for patients with pulmonary disease); change in body weight and height measurements; and evaluation of TB symptoms. In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program.
List of Abbrev-iations	Added text.	INR International normalized ratio LMP Last menstrual period
Section 1	Deleted Text	~~Childhood tuberculosis in the Philippines~~ ~~Among the 22 countries with the highest TB burden, the Philippines ranks fifth in prevalence (502 cases/100,000 population), eighth in incidence (275/100,000) and tenth in mortality (33/100,000).~~[129] ~~Children with TB are usually infected by adults or adolescents in the immediate household with positive sputum acid-fast bacilli (AFB)~~

Location	Old Text	Updated Text
		~~smear and/or culture for MTB.~~ ~~There were over 163,000 new cases of TB reported in 2010 in the Philippines; of these, 965 occurred in patients <15 years of age.~~[129] ~~Of the total new TB cases, 4% (95% CI, 2.9 – 5.5%) were MDR-TB for a total of 6500 cases (95% CI, 4700-8900).~~[129] ~~In a study of the contacts of 62 reference TB patients in a Philippine clinic (44 patients or 71%, with MDR-TB), there were 166 child contacts.~~[114] ~~Of these, 153 completed the screening procedures. In 68 (52%) of 130 child contacts interviewed, the reference case was a parent, in 12 (9%) it was a sibling, in 11 (9%) it was a grandparent, and in 36 (28%) it was another family member. A live-in household helper or a baby sitter was the reference case for the remaining three (2%) children. Fifty-eight (38%) contacts had symptoms attributable to TB at the time of the study. Lymphadenopathy was noted in 44 (30%) of 148 children examined. Cough of more than 2 weeks duration was experienced by 15 (10%) and weight loss by 26 (17%) of 153 contacts. Of the 153 contacts, five (3.3%) individuals had TB disease, and one (0.65%) had bacillary TB. Excluding 23 who had no tuberculin skin test (TST), 90 (69.2%) of 130 examined had LTBI, and 40 (30.8%) were exposed but not infected. The majority of the reference cases included in the study had MDR-TB. No difference was found in the transmission of MDR-TB compared with non-MDR-TB,~~[6] ~~as has previously been reported.~~[130,131]
Section 3.1	**Baseline (Day 0): Inclusion/exclusion criteria**, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), sputum culture (results will be obtained from the National TB Program or the patient's care provider), audiometry and visual assessments, vital signs, and ECG as described in the Schedule of Assessments. OBR administration as	**Baseline (Day 0): Inclusion/exclusion criteria**, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of adverse events

Location	Old Text	Updated Text
	prescribed by investigator, and recording of adverse events (AEs)/immediately reportable events (IREs), and concomitant medications.	(AEs)/immediately reportable events (IREs), and concomitant medications.
Section 3.1	**Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, sputum culture (results will be obtained from the National TB Program or the patient's care provider), and ECG at weeks and times shown in the Schedule of Assessments. Height and weight beginning Week 2 and assessed monthly, and collection of AEs/IREs, and concomitant medications.	**Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly, and collection of AEs/IREs, and concomitant medications.
Section 3.1	**Follow-up Period (Days 239 to 365, 6 month Post Last Delamaid Dose Visit):** Physical examination, height and weight, percentiles for age, vital signs, and symptoms of TB, sputum culture (results will be obtained from the National TB program or the patient's care provider), chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications.	**Follow-up Period (Days 239 to 365, 6 month Post Last Delamaid Dose Visit):** Physical examination, height and weight, BMI, percentiles for age, vital signs, and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications.
Section 3.2.1	All doses will be given under direction observation per standard practice for the investigational site.	According to the country-specific DOT plan, one dose per day for a minimum of 5 days per week will be given under direct observation.
Table 3.4.3-1	Key Exclusion Criteria: 1. Patients who have not completed Trial 232 2. Children with a positive test for human immunodeficiency virus (HIV) or who have been previously identified as having HIV or with laboratory evidence of hepatitis B or C 3. History of allergy to metronidazole and any disease or condition in which metronidazole is required 4. Prior use of predefined medications: amiodarone at any time over the past 12 months or use of other predefined antiarrhythmic medications over the last 30 days 5. Current use of rifampicin and/or moxifloxacin 6. Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment) 7. Preexisting cardiac conditions including but not limited to	Key Exclusion Criteria: 1. Patients who have not completed Trial 232 2. Children with a positive test for human immunodeficiency virus (HIV) or who have been previously identified as having HIV or with laboratory evidence of hepatitis B or C 3. History of allergy to metronidazole and any disease or condition in which metronidazole is required 4. Use of amiodarone within 12 months prior to the first dose of investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within the 30 days prior to the first dose of investigational medicinal product 5. Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP 6. Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or

Location	Old Text	Updated Text
	structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds 8. A concomitant condition such as renal impairment characterized by serum creatinine levels >1.5 mg/dL or hepatic impairment (ALT or AST >3 x ULN) 9. Abnormalities in screening ECG (including atrioventricular [AV] block, bundle branch block [BBB] or hemi-block, QRS prolongation >120 msec, or QTcF >420 msec in both males and females) 10. Positive urine drug screen 11. Concurrent diagnosis of severe malnutrition or kwashiorkor 12. Lansky Play Performance Score < 50 or Karnofsky Score < 50	neurological impairment) 7. Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds 8. A concomitant condition such as renal impairment characterized by serum creatinine levels >1.5 mg/dL, hepatic impairment (ALT or AST >3 x ULN), or hyperbilirubinemia characterized by total bilirubin > 2x ULN 9. Abnormalities in screening ECG (including atrioventricular [AV] block, bundle branch block [BBB] or hemi-block, QRS prolongation >120 msec, or QTcF >450 msec in both males and females) 10. Positive urine drug screen 11. Concurrent diagnosis of severe malnutrition or kwashiorkor 12. Lansky Play Performance Score < 50 or Karnofsky Score < 50
Table 3.4.3-1	ALT = alanine aminotransferase; AST = aspartate aminotransferase; AV = atrioverntricular; BBB = bundle branch block; ECG = electrocardiogram; HIV = human immunodeficiency virus; ULN = upper limit of normal.	ALT = alanine aminotransferase; AST = aspartate aminotransferase; AV = atrioverntricular; BBB = bundle branch block; ECG = electrocardiogram; HIV = human immunodeficiency virus; IMP = investigational medicinal product; ULN = upper limit of normal.
Section 3.5.1.2	3.5.1.2 Efficacy Outcome Variables The efficacy of delamanid in treating pediatric MDR-TB patients will be assessed by culture conversion (for culture-positive patients), chest radiography (patients with pulmonary disease), body weight/height, and resolution of TB symptoms (based on investigator evaluation).	3.5.2.2 Efficacy Outcome Variables The efficacy of delamanid in treating pediatric MDR-TB patients will be assessed by chest radiography (patients with pulmonary disease), body weight/height, and resolution of TB symptoms (based on investigator evaluation). In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program. Sputum collection is not required as part of this protocol; however, it may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.
Table 3.7-1	Added row	Visit window for visits during Days 2 - 238 is ± 2 days. Visit window for visit on Day 356 is ± 5 days.
Table 3.7-1	For Medical History at Visit 1: X[a]	For Medical History at Visit 1: X[c]

Location	Old Text	Updated Text
Table 3.7-1	Height (cm) Weight (kg)	Height (cm) Weight (kg) Body mass index
Table 3.7-1	Added row.	Date of birth and Gender collected at Visit 1 X[c]
Table 3.7-1	Added row.	Menarche/LMP Assessment (Visits 1 [X[c]], 4, 6, 8, 10, 11, 12, 13, ET, 17, 18)
Table 3.7-1	Chest radiograph Serum chemistry Hematology Urinalysis Thyroid function C-reactive protein	added assessment at Visit 13 deleted assessments at Visits 4, 6, 8, 10 deleted assessments at Visits 4, 6, 8 10 deleted assessments at Visits 4, 6, 8, 10 added assessment at Visit 9 added assessment at Visit 13
Table 3.7-1	Added text to list of abbreviations.	LMP = last menstrual period
Section 3.7.1.1	The following information will be taken from screening data of Trial 232 and used as screening data for this Trial 233: • Inclusion/exclusion criteria • Diagnosis of MDR-TB, confirmed or suspected • Demographic data • Medical history and signs and symptoms of TB • Signs and symptoms of TB • Audiometry and visual assessments • Chest radiograph for confirmation of radiological picture compatible with TB. Final official interpretation must be available prior to enrollment • Laboratory assessments including HIV, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibody, adrenocorticotropic hormone (ACTH), adrenal function (cortisol), thyroid function tests (T4 and thyroid stimulating hormone [TSH]), and C reactive protein testing	The following information will be taken from screening data of Trial 232 and used as screening data for this Trial 233: • Inclusion/exclusion criteria • Diagnosis of MDR-TB, confirmed or suspected • Demographic data • Medical history and signs and symptoms of TB • Signs and symptoms of TB • Audiometry and visual assessments • Chest radiograph for confirmation of radiological picture compatible with TB. Final official interpretation must be available prior to enrollment • Laboratory assessments including HIV, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibody, adrenocorticotropic hormone (ACTH), adrenal function (cortisol), thyroid function tests (T4 and thyroid stimulating hormone [TSH]), and C reactive protein testing
Section 3.7.1.1	The following information will be obtained during the screening period of this Trial 233 between Days −30 and −1: • Informed consent/assent (may be completed prior to Day −30) • Sputum culture results will be obtained from patient records and documentation used from the National TB program or the patient's care provider • Vital signs assessments (blood pressure [BP], HR,	The following information will be obtained during the screening period of this Trial 233 between Days −30 and −1: • Informed consent/assent (may be completed prior to Day −30) • Medical history • Vital signs assessments (blood pressure [BP], HR, respiratory rate [RR], and body temperature) after the subject has been supine for ≥ 3 minutes • Height, weight, and BMI

Location	Old Text	Updated Text
	respiratory rate [RR], and body temperature) after the subject has been supine for ≥ 3 minutes • Height and weight • Percentiles for age • Urine pregnancy test for all female subjects who have reached menarche • Urine drug screen (as per Table 3.7-1) • Record AEs and immediately reportable events (IREs) • Record prior concomitant medications including prior concomitant anti-TB medications. (Note: Patients will have been on OBR in Trial 232 for at least two weeks prior to baseline assessments)	• Date of birth and gender • Percentiles for age • Urine pregnancy test for all female subjects who have reached menarche • Urine drug screen (as per Table 3.7-1) • Record AEs and immediately reportable events (IREs) • Record prior concomitant medications including prior concomitant anti-TB medications. (Note: Patients will have been on OBR in Trial 232 for at least two weeks prior to baseline assessments) • Record start date of menstrual period and/or date of last menstrual period (LMP)
Section 3.7.1.2	• Height and weight	• Height, weight, and BMI
Section 3.7.1.4	• Height and weight	• Height, weight, and BMI
Section 3.7.1.4	Added bullet. Deleted bullet.	• Record start date of menstrual period and/or date of LMP • ~~Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis~~
Section 3.7.1.6	• Height and weight	• Height, weight, and BMI
Section 3.7.1.6	Added bullet. Deleted bullet.	• Record start date of menstrual period and/or date of LMP • ~~Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis~~
Section 3.7.1.8	• Height and weight	• Height, weight, and BMI
Section 3.7.1.8	Added bullet. Deleted bullet.	• Record start date of menstrual period and/or date of LMP • ~~Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis~~
Section 3.7.1.9	• Added bullet.	• Blood draw for thyroid function tests (T4 and thyroid stimulating hormone [TSH]) for patients taking ethionamide or PAS.
Section	• Height and weight	• Height, weight, and BMI

Location	Old Text	Updated Text
3.7.1.10		
Section 3.7.1.10	Added bullet. Deleted bullet.	• Record start date of menstrual period and/or date of LMP • ~~Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis~~
Section 3.7.1.11	• Height and weight	• Height, weight, and BMI
Section 3.7.1.11	Added bullet.	• Record start date of menstrual period and/or date of LMP
Section 3.7.1.12	• Height and weight	• Height, weight, and BMI
Section 3.7.1.12	Added bullet.	• Record start date of menstrual period and/or date of LMP
Section 3.7.1.13	• Height and weight	• Height, weight, and BMI
Section 3.7.1.13	Added bullet. Added bullet	• Record start date of menstrual period and/or date of LMP • Chest radiograph
Section 3.7.1.13	•Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis	• Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, C reactive protein testing and full urinalysis
Section 3.7.1.17	• Height and weight	• Height, weight, and BMI
Section 3.7.1.17	Added bullet.	• Record start date of menstrual period and/or date of LMP
Section 3.7.1.18	• Height and weight	• Height, weight, and BMI
Section 3.7.1.18	Added bullet.	• Record start date of menstrual period and/or date of LMP
Section 3.7.1.19	• Height and weight	• Height, weight, and BMI
Section 3.7.1.20	• Height and weight	• Height, weight, and BMI
Section 3.7.1.20	Added bullet.	• Record start date of menstrual period and/or date of LMP
Sections 3.7.1.4 -	Added visit window	± 2 days

Location	Old Text	Updated Text
3.7.1.18, 3.7.1.20		
Sections 3.7.1.1, 3.7.1.2, 3.7.1.5, 3.7.1.7, 3.7.1.9, 3.7.1.11-3.7.1.13, 3.7.1.17-3.7.1.19	Deleted bullet	• ~~Sputum culture results from NTBP~~
Section 3.7.1.20	Added visit window	± 5 days
Section 3.7.2	Efficacy assessments will include: sputum cultures • Patients will be assessed as having achieving SCC from positive growth of MTB to negative growth. SCC is defined as a sputum specimen from a patient negative for growth of MTB, followed by at least one confirmatory negative sputum culture at least 27 days after the first negative sputum test and not followed by any sputum cultures positive for growth. • assessment of clinical signs and symptoms of TB • list provided in eCRF • chest radiograph • abnormality/extent of abnormality	Efficacy assessments will include: • assessment of clinical signs and symptoms of TB • chest radiograph • abnormality/extent of abnormality In addition, although sputum collection is not required as part of this protocol, sputum may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.
Table 3.7.3.1-1	Renumbered table. Added test under Coagulation Tests	International normalized ratio (INR)
Section 3.8.1	4) Patient noncompliance, defined as refusal or inability to adhere to the trial schedule.	4) Patient noncompliance, defined as refusal or inability to adhere to the trial schedule. Please refer to the trial Operations Manual for further information on the definition of non-compliance.
Section 5.1	• Any increase of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal (ULN), an increase in total bilirubin ≥ 2 times the ULN	• Any increase of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal (ULN) with an increase in total bilirubin ≥ 2 times the ULN

Location	Old Text	Updated Text
Section 5.2.1	All AEs and IREs will be collected and documented from the time the ICF/assent is signed in Trial 233 until the end of the Post-treatment Follow-up Period for the individual patient.	All AEs and IREs will be collected and documented from the time of first dosing in Trial 233 until the end of the Post-treatment Follow-up Period for the individual patient.
Appendix 1	For Medical Emergencies: [redacted] 2440 Research Blvd Rockville, MD 20850 Phone: [redacted] Global phone: [redacted] Fax: [redacted] E-mail: [redacted] [redacted] Otsuka (Philippines) Pharmaceutical Inc. 3F King's Court II Building 2126 Chino Roces Avenue Makati City, Philippines Phone: [redacted] Fax: [redacted] E-mail: [redacted]	**For Medical Emergencies in the Philippines or South Africa:** [redacted] 2440 Research Blvd Rockville, MD 20850 Phone: [redacted] Fax: [redacted] E-mail: [redacted] **For Medical Emergencies in the Philippines:** [redacted] Otsuka (Philippines) Pharmaceutical Inc. 3F King's Court II Building 2126 Chino Roces Avenue Makati City, Philippines Phone: [redacted] Fax: [redacted] E-mail: [redacted]
Appendix 2	Added text.	**IVRS/IWRS** S-Clinica 6, chaussée de Boondael B-1050 Brussels Belgium Quintiles East Asia Ptd Ltd 79 Science Park Drive #06-08 CINTECH IV, Science Park One Singapore 118264

ADDITIONAL RISK TO THE SUBJECT:
This amendment will not affect the safety of patients, the scope of the investigation, or the scientific quality of the trial.

Amendment Number: 2

Issue Date: 14 October 2014

PURPOSE: The purpose of this amendment is to add to and slightly modify the inclusion/exclusion criteria, to update the list of prohibited medications, to add a PK blood draw at the early termination visit on the table of assessments and in the corresponding text, to add collection of treatment outcome information, to update the footnotes to the table of assessments, to make minor corrections and editorial changes to the text and references, and to update sponsor representative information. It also updates the contraceptive language which reflects the stage of clinical development and available animal safety data.

BACKGROUND: In the previous protocol, eligibility criteria related to prior exposure to an investigational medicinal product and pregnancy were not included, and the presumptive diagnosis of MDR-TB was incomplete.

MODIFICATIONS TO PROTOCOL:

Bold and underlined text:	Changed Text
~~**Bold and strike through text**~~:	Deleted Text
Bold and italicized text:	Added Text

Global Changes:

- Corrected minor typographical, grammatical, and formatting errors.
- Made minor corrections to the introduction, including references.
- Updated and corrected table of contents, section numbering, and cross referencing.
- In the inclusion criteria, revised the definition of presumptive diagnosis of MDR-TB.
- Modified the exclusion criteria to exclude children who were administered an investigational medicinal product within 1 month prior to Visit 1 and Patients who are pregnant, breastfeeding, or planning to conceive or father a child within the timeframe described in the informed consent form.

Sectional Revisions:

Location	Old Text	Updated Text
Title Page	[redacted] [redacted] 2440 Research Boulevard Rockville, MD 20850, United States Phone: [redacted] Fax: [redacted] E-mail: [redacted]	[redacted] [redacted] 2440 Research Boulevard Rockville, MD 20850, United States Phone: [redacted] Fax: [redacted] E-mail: [redacted]
Title Page	Immediately Reportable: Events [redacted] PharmacoVigilance Region Europe (PVRE) Otsuka Frankfurt Research Institute GmbH Hochhaus am Park, Grüneburgweg 102 60323 Frankfurt am Main Germany Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry)	Immediately Reportable [redacted] ~~Otsuka Frankfurt Research Institute GmbH~~ ~~Hochhaus am Park~~ ~~Grüneburgweg 102~~ ***Otsuka Europe Development and Commercialisation, Ltd (OEDC)*** Pharmacovigilance Region Europe (PVRE) ***Zweigniederlassung Frankfurt am Main*** ***Europa-Allee 52*** **60327** Frankfurt am Main Germany Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry)
Title Page	Added text.	***Amendment 2 Issue Date 14 October 2014***
Synopsis (Trial Design)	Baseline (Day 0): Inclusion/exclusion criteria, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of adverse events (AEs)/immediately reportable events (IREs), and concomitant medications. Treatment Period (Days 1 to 182): Morning and evening dosing of delamanid with meal. OBR administration as prescribed by	Baseline (Day 0): Inclusion/exclusion criteria, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of~~ adverse events (AEs)/immediately reportable events (IREs), and~~ concomitant medications. Treatment Period (Days 1 to 182): Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator.

Location	Old Text	Updated Text
	investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly, and collection of AEs/IREs, and concomitant medications. Post-Treatment Period (Days 183 to 238): Physical examination, vital signs, ECGs, safety labs, sparse blood draws for PK at visits and times described in the Schedule of Assessments. OBR dosing and collection of AEs/IREs, and concomitant medications. Follow-up Period (Days 239 to 365) Six Month Post Last Delamanid Dose: Physical examination, height and weight, BMI, percentiles for age, vital signs, and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications.	Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly, and collection **of adverse events (AEs) and immediately reportable events (/IREs)**, and concomitant medications. Post-Treatment Period (Days 183 to 238): Physical examination, vital signs, ECGs, safety labs, sparse blood draws for PK at visits and times described in the Schedule of Assessments. OBR dosing and collection of AEs/IREs, and concomitant medications. Follow-up Period (Days 239 to 365) Six Month Post Last Delamanid Dose: Physical examination, height and weight, BMI, percentiles for age, vital signs, ***signs*** and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications. ***Treatment Outcome Follow-up (Day 730 (M24) or until treatment for MDR-TB is completed or discontinued, whichever comes first): Collection of treatment outcome information as routinely documented in the patient medical records or in a National TB Program.***
Synopsis	Twelve to sixteen pediatric patients will be enrolled to obtain a minimum of twelve male and female patients, at least six each in Group 1 (ages 12 to 17 years) and in Group 2 (ages 6 to 11 years) who have MDR-TB and are also receiving an OBR. Group 1 (ages 12 to 17 years) must contain at least two but no more than five females.	**At least twelve male and female pediatric patients who have successfully completed Trial 232 will be enrolled in two sequential age groups**, at least six each in Group 1 (ages 12 to 17 years) and in Group 2 (ages 6 to 11 years) who have confirmed or presumptive MDR-TB and are also receiving an OBR. Group 1 (ages 12 to 17 years) must contain at least two but no more than five females.
Synopsis (Inclusion Criteria)	• Presumptive diagnosis of MDR TB such that the treating physician has decided to treat the patient for MDR-TB who has one of the following: - Persistent cough lasting > 2 weeks - Fever, weight loss, and failure to thrive - Findings on recent chest radiograph (within 4 weeks prior to Visit 1) consistent with TB - Sputum smear positive for acid-fast bacilli (AFB) - AND - Household contact of a person with known MDR TB or a person who died while appropriately taking drugs for sensitive TB/OR	• Presumptive diagnosis of MDR-TB such that the treating physician has decided to treat the patient for MDR-TB who has one of the following: - **Sputum smear positive for acid-fast bacilli (AFB)** - ***Clinical specimen (eg, cerebral spinal fluid [CSF], pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of tuberculosis disease*** - Persistent cough lasting > 2 weeks - Fever, weight loss, and failure to thrive - Findings on recent chest radiograph consistent with TB AND

Location	Old Text	Updated Text
	- On first-line TB treatment but with no clinical improvement - Trial-specific written informed consent/assent obtained from a parent(s) or guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol required procedures. In addition, the subject must provide informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial center's institutional review board/ethics committee (IRB/EC) and local regulatory requirements	- Household contact of a person with known MDR TB or a person who died while appropriately taking drugs for sensitive TB OR - On first-line TB treatment but with no clinical improvement ***- Negative urine pregnancy test for female patients who have reached menarche*** - Trial-specific written informed consent/assent obtained from a parent(s) or guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol required procedures. In addition, the subject must provide informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time. All informed consent/assent procedures must be in accordance with the trial center's institutional review board/ethics committee (IRB/EC) and local regulatory requirements
Synopsis (Exclusion Criteria)	• Added text	• ***Administered an IMP within 1 month prior to Visit 1.*** • ***Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form.***
Synopsis (Criteria for Evaluation)	• Efficacy: assessed by results of chest radiography (for patients with pulmonary disease); change in body weight and height measurements; and evaluation of TB symptoms. In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program.	• Efficacy: assessed by results of chest radiography (for patients with pulmonary disease); change in body weight and height measurements; and evaluation of TB symptoms. In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (**or provide other biological specimens**) for microbiological evaluation according to the requirements of the National TB Program.
Synopsis (Trial Duration)	The trial duration per patient (Screening, Baseline, Treatment, Post Treatment, and Follow-up Periods) will be 395 days including the following: 30-day Screening period, 182-day Treatment period, 56-day Post-treatment period, and a 127-day follow-up period (incorporating a 6 month post last delamanid dose follow-up visit).	The trial duration per patient (Screening, Baseline, Treatment, Post Treatment, and Follow-up Periods) will be **760 days** including the following: 30-day Screening period, 182-day Treatment period, 56-day Post-treatment period, and a ***492-day follow-up period (127-day from the last Post-treatment period, incorporating a 6 month post last delamanid dose follow-up visit and additional 365-day treatment outcome follow up period from the last follow up visit or until treatment for MDR-TB is completed or discontinued, whichever comes first)***.

Location	Old Text	Updated Text
List of Abbrevia-tions	Added text	***OEDC Otsuka Europe Development and Commercialisation, Ltd*** ***PAS p-aminosalicylic acid***
Section 1 - 1.4.2	Made minor corrections to text and references.	
Section 1.4.1	As of 31 January 2012, there had been 887 subjects and patients exposed to delamanid in clinical trials.[3]	**A total of 887 subjects and patients have been exposed to delamanid in 17 completed clinical trials.**[3]
Section 2.2	Adolescents (ages 12 to 17 years) will be given delamanid at the adult dose, which will be delamanid 100 mg BID; children (ages 6 to 11 years) will be given half the adult dose, which will be delamanid 50 mg BID. Delamanid will be given as delamanid 50 mg tablets, not crushed	Adolescents (ages 12 to 17 years) will be given delamanid at the adult dose, which will be delamanid 100 mg BID; children (ages 6 to 11 years) will be given half the adult dose, which will be delamanid 50 mg BID. Delamanid will be given as delamanid 50 mg tablets~~, not crushed~~.
Section 3.1	A total of twelve male and female patients will be enrolled to obtain a minimum of 12 completed patients, at least 6 in each age group. Patients will be assigned to one of two treatment groups based on age:	**At least 12** male and female patients will be enrolled to obtain a minimum of 12 completed patients, at least 6 in each age group. Patients will be assigned to one of two treatment groups based on age:
Section 3.1	Baseline (Day 0): Inclusion/exclusion criteria, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of adverse events (AEs)/immediately reportable events (IREs), and concomitant medications. Treatment Period (Days 1 to 182): Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly, and collection of AEs/IREs, and concomitant medications. Post-Treatment Period (Days 183 to 238): Physical examination, vital signs, ECGs, safety labs, sparse blood draws for PK at visits and times described in the Schedule of Assessments. OBR dosing and collection of AEs/IREs, and concomitant medications. Follow-up Period (Days 239 to 365, 6 month Post Last Delamanid	Baseline (Day 0): Inclusion/exclusion criteria, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and ~~recording of adverse events (AEs)/immediately reportable events (IREs), and~~ concomitant medications. Treatment Period (Days 1 to 182): Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly, and collection **of adverse events (AEs) and immediately reportable events (/IREs)**, and concomitant medications. Post-Treatment Period (Days 183 to 238): Physical examination, vital signs, ECGs, safety labs, sparse blood draws for PK at visits and times described in the Schedule of Assessments. OBR dosing and collection of AEs/IREs, and concomitant medications. Follow-up Period (Days 239 to 365, 6 month Post Last Delamanid

Location	Old Text	Updated Text
	Dose): Physical examination, height and weight, BMI, percentiles for age, vital signs, and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications.	Dose): Physical examination, height and weight, BMI, percentiles for age, vital signs, signs and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or PAS), OBR administration, and collection of AEs/IREs and concomitant medications. ***Treatment Outcome Follow-up (Day 730 (M24) or until treatment for MDR-TB is completed or discontinued, whichever comes first): Collection of treatment outcome information as routinely documented in the patient medical records or in a National TB Program.***
Figure 3.1-1	Added Text	***Day 730*** ***Group 1 and 2 OBR only*** ***Treatment Outcome***
Section 3.3.1	A total of 12 male and female patients from 6 to 17 years of age inclusive, who have successfully completed Trial 232, who are receiving OBR for confirmed or presumptive MDR-TB will be enrolled in two sequential age groups.	**At least 12** male and female patients from 6 to 17 years of age, inclusive, who have successfully completed Trial 232, who are receiving OBR for confirmed or presumptive MDR-TB will be enrolled in two sequential age groups.
Section 3.4.1	Added Text	***In accordance with applicable regulations and guidance for subject data protection, patients who have completed the Post-treatment Follow-up Period (V19) prior to regulatory authority and EC approval of this protocol will be asked to sign a patient informed consent form (ICF) authorizing the release of MDR-TB treatment outcome from the treatment centers. The parent/ guardian/legal representative and/or patient shall be given a copy of the signed ICF/Assent Form; the original shall be kept on file by the investigator.***
Section 3.4.2	Presumptive diagnosis of MDR TB such that the treating physician has decided to treat the patient for MDR-TB who has one of the following: -Sputum smear positive for AFB -Persistent cough lasting > 2 weeks -Fever, weight loss, and failure to thrive -Findings on recent chest radiograph (within 4 weeks prior to Visit 1) consistent with TB AND -Household contact of a person with known MDR-TB or of a person who died while appropriately taking drugs for sensitive TB, OR -On first-line TB treatment but with no clinical improvement	Presumptive diagnosis of MDR-TB such that the treating physician has decided to treat the patient for MDR-TB who has one of the following: -Sputum smear positive for AFB ***-Clinical specimen (eg, CSF, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of tuberculosis disease*** -Persistent cough lasting > 2 weeks -Fever, weight loss, and failure to thrive -Findings on recent chest radiograph (within 4 weeks prior to Visit 1) consistent with TB AND -Household contact **with** a person with known MDR-TB or **with** a person who died while appropriately taking drugs for sensitive TB OR -On first-line TB treatment but with no clinical improvement
Section	Added text	***13. Administered an IMP within 1 month prior to Visit 1***

Location	Old Text	Updated Text
3.4.3		***14. Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form***
Section 3.5.2.2	In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program. Sputum collection is not required as part of this protocol; however, they may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.	In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (**or provide other biological specimens**) for microbiological evaluation according to the requirements of the National TB Program. ***Microbiological assessment of sputum or other biological specimens (e.g. CSF, pleural fluid, ascitic fluid, joint fluid, lymph node aspirates, etc.) are*** not required as part of this protocol; however, ***they*** may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (**or provide other specimens**) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.
Section 3.7	Each patient will participate in the trial for up to 395 days. The trial will be comprised of the Screening Period (30 days); Baseline (Day 0); Treatment Period (182 days of delamanid plus OBR administration); Post-treatment Period (56 days with visits at Days 189, 196, 203, 210, and 238 [Day 238 corresponds to 2-months post last delamanid dose]); and a Follow-up Period with a visit at 6 months post last delamanid dose (Day 365). Trial assessment time points are summarized in Table 3.7-1.	Each patient will participate in the trial for up to **760 days**. The trial will be comprised of the Screening Period (30 days); Baseline (Day 0); Treatment Period (182 days of delamanid plus OBR administration); Post-treatment Period (56 days with visits at Days 189, 196, 203, 210, and 238 [Day 238 corresponds to 2-months post last delamanid dose]); and a Follow-up Period with a visit at 6 months post last delamanid dose (Day 365) ***and additional 365-day treatment outcome follow up period from the last follow up visit or until treatment for MDR-TB is completed or discontinued, whichever comes first).*** Trial assessment time points are summarized in Table 3.7-1.
Table 3.7-1	Added text	Added ***X*** mark for the Early Termination Visit PK blood draws Added column labeled as ***Visit 20***, ***Day 730*** in the Follow up Period Added row ***"Collection of treatment outcome data"*** Added ***X*** mark for the Day 730 Collection of treatment outcome data
Table 3.7-1	Deleted text	Deleted X mark for Record AEs and IEs at Visits 1 and 2.
Table 3.7-1	[a] Information to be obtained from Screening visit of Trial 232. [b] Information to be obtained from Day 10 of Trial 232. [c] Information to be obtained during Screening for this Trial 233, between Days -30 to -1. [d] Follow-up 6 months post last dose of delamanid. [f] Consenting/Assenting for Trial 233 can occur prior to Day -30. [g] Confirmed or presumptive diagnosis of MDR-TB (based on inclusion criteria #3, Table 3.4.2-1) [h] Vital signs include systolic and diastolic BP (mm Hg), HR	[a] Information to be obtained from Screening visit of Trial 232. [b] Information to be obtained from Day 10 of Trial 232. [c] Information to be obtained during Screening for this Trial 233, between Days -30 to -1. [d] ~~Follow-up 6 months post last dose of delamanid.~~ ***[d] For the early termination visit, the PK blood sample will be labeled with the date, study day, and time of the PK blood draw.*** [e] Consenting/Assenting for Trial 233 can occur prior to Day -30.

Location	Old Text	Updated Text
	(bpm), RR (bpm), and body temperature (C) after the patient has been supine for ≥3 minutes. [i] Three consecutive 12-Lead ECGs must be performed predose. [j] ECG paired with PK blood sampling: Three consecutive 12-Lead ECGs must be performed predose, followed by PK blood draw, and then patients will receive their dose of delamanid. [k] Urine pregnancy test will be performed for all females who have reached menarche. Urine pregnancy testing will be performed at screening, and Day 182 or the early termination visit. [l] Coagulation tests (aPTT and PT) performed with safety labs. [m] Thyroid tests performed for patients taking ethionamide or PAS. [n] PK blood draw (3 mL) paired with 12-lead ECG at predose (0 hours during treatment). [o] PK blood draw (3 mL) paired with 12-lead ECG at theoretical predose. [p] PK blood draw (3 mL) to be obtained at any time point. [q]Follow-up contact for patients who early terminate from Trial 233 should occur 28 to 32 days after the early termination visit.	[f] Confirmed or presumptive diagnosis of MDR-TB (based on inclusion criteria #3, Table 3.4.2-1) [g] Vital signs include systolic and diastolic BP (mm Hg), HR (bpm), RR (bpm), and body temperature (C) after the patient has been supine for ≥3 minutes. [h] Three consecutive 12-Lead ECGs must be performed predose. [i] ECG paired with PK blood sampling: Three consecutive 12-Lead ECGs must be performed predose, followed by PK blood draw, and then patients will receive their dose of delamanid. [j] Urine pregnancy test will be performed for all females who have reached menarche. Urine pregnancy testing will be performed at screening, and Day 182 or the early termination visit. [k] Coagulation tests (aPTT and PT) performed with safety labs. [l] Thyroid tests ***(T4 and thyroid stimulating hormone)*** performed for patients taking ethionamide or **p-aminosalicylic acid**. ***[m] PK blood draw (3 mL) paired with 12-lead ECG at predose (0 hours during treatment).*** [n] PK blood draw (3 mL) paired with 12-lead ECG at ***theoretical*** predose. [o] PK blood draw (3 mL) to be obtained at any time point. [p] Follow-up contact for patients who early terminate from Trial 233 should occur 28 to 32 days after the early termination visit to assess for AEs and IREs. ***All patients will continue treatment with OBR as prescribed by the investigator according to WHO guidelines.*** q ***Day 730 (M24) or until treatment for MDR-TB is completed or discontinued, whichever comes first***

Location	Old Text	Updated Text
Section 3.7.1.1	The following information will be obtained during the screening period of this Trial 233 between Days -30 and -1: • Informed consent/assent (may be completed prior to Day -30) • Medical history • Vital signs assessments (blood pressure [BP], HR, respiratory rate [RR], and body temperature) after the subject has been supine for ≥ 3 minutes • Height,weight, and BMI • Date of birth and gender • Percentiles for age • Urine pregnancy test for all female subjects who have reached menarche • Urine drug screen (as per Table 3.7-1) • Record AEs and immediately reportable events (IREs) • Record prior concomitant medications including prior concomitant anti-TB medications. (Note: Patients will have been on OBR in Trial 232 for at least two weeks prior to baseline assessments) • Record start date of menstrual period and/or date of last menstrual period (LMP)	The following information will be obtained during the screening period of this Trial 233 between Days -30 and -1: • Informed consent/assent (may be completed prior to Day -30) • Medical history • Vital signs assessments (blood pressure [BP], HR, respiratory rate [RR], and body temperature) after the subject has been supine for ≥ 3 minutes • Height,weight, and BMI • Date of birth and gender • Percentiles for age • Urine pregnancy test for all female subjects who have reached menarche • Urine drug screen (as per Table 3.7-1) ~~• Record AEs and immediately reportable events (IREs)~~ • Record prior concomitant medications including prior concomitant anti-TB medications. (Note: Patients will have been on OBR in Trial 232 for at least two weeks prior to baseline assessments) • Record start date of menstrual period and/or date of last menstrual period (LMP)
Section 3.7.1.2	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Baseline (Day 0): • Review of inclusion/exclusion criteria • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Height,weight, and BMI • Percentiles for age • Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Signs and symptoms of TB • Audiometry and visual assessments • Three consecutive 12-lead ECGs. • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti TB medications.	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Baseline (Day 0): • Review of inclusion/exclusion criteria • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Height,weight, and BMI • Percentiles for age • Vital signs assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Signs and symptoms of TB • Audiometry and visual assessments • Three consecutive 12-lead ECGs. • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis • OBR administration, as prescribed by investigator ~~• Record AEs and IREs~~ • Record concomitant medications including concomitant anti TB medications.

Location	Old Text	Updated Text
Section 3.7.1.13	• Delamanid dispensed (plusOBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). NOTE: This is the last day of delamanid dosing.	• Delamanid dispensed, ~~if needed~~ (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). NOTE: This is the last day of delamanid dosing.
Section 3.7.1.19	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 546:	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day **365**:
Section 3.7.1.20	Added Text	***Treatment Outcome Follow-up (Day 730 (M24) or until treatment for MDR-TB is completed or discontinued, whichever comes first)*** ***Treatment outcome information will be collected as routinely documented in the patient medical records or in a National TB Program.***
Section 3.7.1.21	Added text	• ***Blood draw (3 mL) for PK***
Section 3.7.1.22	Added text	***The last dose of delamanid will be given on Day 182. Patients will continue on OBR, as prescribed by the investigator, and have post-delamanid treatment visits on Days 189, 196, 203, 210, 238 (2-month post last dose), Day 365 (6-month post last dose), treatment outcome follow-up on (Day 730 (M24) or until treatment for MDR-TB is completed or discontinued, whichever comes first).***
Section 3.7.2	In addition, although sputum collection is not required as part of this protocol, it may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (or other specimen) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.	In addition, ***although microbiologic assessment of sputum or other biologic specimens (e.g. CSF, pleural fluid, ascitic fluid, joint fluid, lymph node aspirates, etc.) are*** not required as part of this protocol, **they** may be collected by the investigator as part of routine management of the subject. In patients who are able to produce sputum (**or *provide* other specimens**) for microbiological evaluation according to the requirements of the National TB Program, all available results for smear microscopy, culture, identification, and drug susceptibility will be collected from the patient chart as an unscheduled visit.
Section 3.7.3.1	Added text	***The tests listed in Table 3.7.3.1-1 will be collected at the times presented in Table 3.7-1, and processed in accordance with directions from the analytical laboratory.***

Location	Old Text	Updated Text
Section 3.7.3.3	Electrocardiograms for on-site evaluation of safety will be recorded at the nominal times according to the schedule outlined in Table 3.7-1. Twelve-lead ECGs will be recorded with the subject supine and at rest for ≥10 minutes. ECGs should be taken before PK blood draws when assessments are scheduled on the same day (Visit). Three tracings will be obtained at each time point (approximately 5 to 10 minutes between each tracing) with the ECG leads left in place. Heart rate, PR interval, QRS interval, QT intervals and QTc (including both QTcB and QTcF), will be recorded. The principal investigator or appointed MD designee will review, sign, and date each ECG reading. Whenever possible, the same reviewer should evaluate, sign, and date the ECGs. The reviewer must be listed on the FDA Form 1572. Original ECG tracings will be added to the patient's medical record with the reviewer's interpretation recorded. In addition to the initial clinical interpretation for ongoing safety evaluation by the investigator, all ECGs will be analyzed by a specialized central laboratory. Specific guidance for investigators for determining AEs related to ECG results is available in the trial operations manual.	Electrocardiograms for on-site evaluation of safety will be recorded at the nominal times according to the schedule outlined in Table 3.7-1. Twelve-lead ECGs will be recorded with the subject supine and at rest for ≥10 minutes. ECGs should be taken before PK blood draws when assessments are scheduled on the same day (Visit). Three tracings will be obtained at each time point (approximately **3 to 5** minutes between each tracing) with the ECG leads left in place. Heart rate, PR interval, QRS interval, QT intervals and QTc (including both QTcB and QTcF), will be recorded. The principal investigator or appointed MD designee will review, sign, and date each ECG reading. Whenever possible, the same reviewer should evaluate, sign, and date the ECGs. The reviewer must be listed on the FDA Form 1572. Original ECG tracings will be added to the patient's medical record with the reviewer's interpretation recorded. In addition to the initial clinical interpretation for ongoing safety evaluation by the investigator, all ECGs will be analyzed by a specialized central laboratory. Specific guidance for investigators for determining AEs related to ECG results is available in the trial operations manual.
Section 3.7.5.1.1	deleted section	~~3.7.5.1.1Laboratory Tests~~ ~~The tests listed in Section 3.7.3.1 will be collected at the times presented in the schedule of assessments, Table 3.7-1, and processed in accordance with directions from the analytical laboratory.~~
Section 3.7.5.1.2	3.7.5.1.2 End of Trial	3.7.**6** End of Trial
Section 3.7.5.2	Section 3.7.5.2 Safety Monitoring Committee	3.7.**7** Safety Monitoring Committee
Section 3.8.1	If a subject discontinues from the trial, the reason given must be fully evaluated and recorded appropriately in source documentation and in the eCRF. If the subject is being withdrawn because of an AE, that AE must be indicated as the reason for withdrawal. All assessments scheduled to be completed at the final trial visit will be performed at early termination.	If a subject discontinues from the trial, the reason given must be fully evaluated and recorded appropriately in source documentation and in the eCRF. If the subject is being withdrawn because of an AE, that AE must be indicated as the reason for withdrawal. All assessments scheduled to be completed at the final trial visit will be performed at early termination. ***If delamanid is stopped due to an AE and/or Investigator decision, subjects should continue with visits/assessments for the rest of the trial with the exception of taking delamanid. This will allow analysis of comparable assessments between those who stopped and those who completed delamanid dosing.***
Section 3.10	Patients who are evaluated at the last scheduled visit during the treatment period (complete Day 182 assessments) will be defined as	Patients who are evaluated at the last scheduled **visit of the trial, the follow-up visit (Visit 19, Day 365),** will be defined as trial completers.

Location	Old Text	Updated Text
	trial completers.	
Table 4.1-1	Table 4.1-1 List of Medications Prohibited During the Trial 1. Quinidine 2. Procainamide 3. Disopyramide 4. Encainide 5. Flecainide 6. Sotalol 7. Amiodarone 8. Rifampicin 9. Moxifloxacin	Table 4.1-1 List of Medications Prohibited During the Trial Anti-Arrhythmic medications with potential for QT interval prolongation 1. Quinidine 2. Procainamide 3. Disopyramide 4. Encainide 5. Flecainide 6. Sotalol 7. Amiodarone 8. Digitalis ***Other Medications With Potential For QT Interval Prolongation*** ***1. Moxifloxacin*** ***Other Medications*** ***1. Antiretroviral Medications*** ***2. Rifampicin***
Section 5.4	Females of childbearing potential (FOCBP) and males who are sexually active must avoid pregnancy or fathering a child for 22 weeks for a female patient and 30 weeks for a male patient after the last dose of delamanid and abstain from sex during the clinical trial. Pregnancy testing will be performed during the screening period prior to trial enrollment and at the end of the trial according to the Schedule of Assessments for FOCBP who have reached menarche. If the patient or investigator suspects the patient may be pregnant prior to delamanid administration, delamanid must be withheld until the results of urine pregnancy tests are available. A confirmed pregnancy before first administration of delamanid must result in immediate exclusion or withdrawal from the trial. If pregnancy is suspected while the patient is taking delamanid during the trial, delamanid must be withheld immediately and if pregnancy is confirmed, the delamanid will be permanently discontinued and the	Females of childbearing potential (FOCBP) and males who are sexually active must avoid pregnancy or fathering a child **for 8 weeks** ~~for a female patient and 30 weeks for a male patient~~ after the last dose of delamanid and abstain from sex during the clinical trial. Pregnancy testing will be performed during the screening period prior to trial enrollment and at the end of the **treatment period** according to the Schedule of Assessments for FOCBP who have reached menarche. If the patient or investigator suspects the patient may be pregnant prior to delamanid administration, delamanid must be withheld until the results of urine pregnancy tests are available. A confirmed pregnancy before first administration of delamanid must result in immediate exclusion or withdrawal from the trial. If pregnancy is suspected while the patient is taking delamanid during the trial, delamanid must be withheld immediately and if pregnancy is confirmed, the delamanid will be permanently discontinued ~~**and the patient must be withdrawn**~~

Location	Old Text	Updated Text
	patient must be withdrawn from the trial. The investigator must immediately notify the sponsor of any pregnancy associated with delamanid exposure, including and for 22 weeks for a female patient and 30 weeks for a male patient after the last dose of delamanid and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.	~~**from the trial.**~~ The investigator must immediately notify the sponsor of any pregnancy associated with delamanid exposure, **during the course of the trial and for 8 weeks** after the last dose of delamanid and record the event on the IRE form and forward it to the sponsor. The sponsor will forward Pregnancy Surveillance Form(s) for monitoring the outcome of the pregnancy.
Appendix 1	[redacted] PharmacoVigilence Region Europe (PVRE) Otsuka Frankfurt Research Institute GMbH Hochhaus am Park, Grüneburgweg 102 60323 Frankfurt am Main Germany Phone: [redacted] (24h/7d PVRE Blackberry) Fax: [redacted]	[redacted] ~~Otsuka Frankfurt Research Institute GMbH~~ ~~Hochhaus am Park, Grüneburgweg 102~~ ***Otsuka Europe Development and Commercialisation, Ltd (OEDC)*** ***Pharmacovigilance Region Europe (PVRE)*** ***Zweigniederlassung Frankfurt am Main*** ***Europa-Allee 52*** **60327** Frankfurt am Main Germany Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry) E-mail: [redacted]
Appendix 1	For Medical Emergencies in the Philippines or South Africa: [redacted] 2440 Research Blvd Rockville, MD 20850 Phone: [redacted] Fax: [redacted] E-mail: [redacted]	For Medical Emergencies in the Philippines or South Africa: [redacted] 2440 Research Blvd Rockville, MD 20850 Phone: [redacted] Fax: [redacted] E-mail: [redacted]
Appendix 3	Appendix 3 Handling and Shipment of Bioanalytical Samples Handling of Specimens All tubes must be labeled using the central lab's bar code labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regards to the PK sample information. On the sample tube, the subject ID/screening number and subject initials must be handwritten on the label. On the	Appendix 3 Handling and Shipment of Bioanalytical Samples ~~Handling of Specimens~~ All tubes must be labeled using the central lab's bar code labels provided with the sample collection kits. The central lab's requisition form must be completely filled out in regards to the PK sample information. On the sample tube, the subject ID/screening number and subject initials must be handwritten on the label. On the requisition

Location	Old Text	Updated Text
	requisition form, it is important to note the date and exact time of the blood collection.	form, it is important to note the date and exact time of the blood collection.
Appendix 3	Appendix 3 Handling and Shipment of Bioanalytical Samples Plasma Samples for Delamanid Blood (1.5-3 mL) will be collected into green-top Vacutainer tubes containing sodium heparin anticoagulant. The tubes must be gently inverted 3 to 4 times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from each tube should then be divided equally between the 2 bar-code labeled polypropylene tubes. The PK sample must be stored at -70°C or below.	Appendix 3 Handling and Shipment of Bioanalytical Samples Plasma Samples for Delamanid Blood (1.5-3 mL) will be collected into green-top Vacutainer tubes containing sodium heparin anticoagulant. The tubes must be gently inverted 3 to 4 times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from each tube should then be divided equally between the 2 bar-code labeled polypropylene tubes. The PK sample must be stored at **-65**°C or below.
Appendix 4	Appendix 3 Protocol Amendment	Appendix **4** Protocol Amendments

ADDITIONAL RISK TO THE SUBJECT:
This amendment will not affect the safety of patients, the scope of the investigation, or the scientific quality of the trial.

Amendment Number: 3

Issue Date: 29 June 2015

PURPOSE: The purpose of this amendment is to add information for Groups 3 and 4 to the protocol including dosage for group 3, to remove certain laboratory assessments to decrease the required blood volume for younger age groups as mandated by the applicable EC in South Africa, to simplify the text associated with the schedule of assessments, to clarify that the safety monitoring committee is composed of only external consultants, to make minor editorial changes to the text, make minor content and editorial changes to the Introduction and references.

BACKGROUND: In the previous protocol, information was only included for Groups 1 and 2 and now information for Groups 3 and 4 has been added. In addition, the text associated with the schedule of assessments was unnecessarily lengthy. Due to the maximum blood volumes allowed to be drawn within a specified time period for pediatric patients of certain weights (as mandated by the University of Stellenbosch Ethics Committee), certain laboratory and PK assessments have been removed from the protocol to comply with these guidelines. Various minor editorial changes to the text have been made to increase clarity and consistency with the 242-12-232 protocol.

MODIFICATIONS TO PROTOCOL:

Bold and underlined text: Changed Text

~~**Bold and strike through text**~~: Deleted Text

Bold and italicized text: Added Text

Global Changes:

- Corrected minor typographical, grammatical, and formatting errors.
- Made minor content and editorial changes, including references, to the Introduction.
- Added an objective to assess the palatability of the delamanid pediatric formulation.
- Updated and corrected table of contents, section numbering, and cross references.
- Added an objective to assess the palatability of the delamanid pediatric formulation.
- Clarified that the minimum number of patients to be enrolled is 36.

- Clarified that patients should be in a supine or semi-recumbent position prior to vital signs and ECGs.
- Updated the schedule of assessments.
- Added dosing and assessment information for Groups 3 and 4.

Sectional Revisions:

Location	Old Text	Updated Text
Title Page	Immediately Reportable: [redacted] Events PharmacoVigilance Region Europe (PVRE) Otsuka Frankfurt Research Institute GmbH Hochhaus am Park, Grüneburgweg 102 60323 Frankfurt am Main Germany Fax: [redacted] Phone: [redacted] (24h/7d Blackberry) PVRE	Immediately Reportable Events Otsuka Europe Development and Commercialisation, Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) Grüneburgweg 102 60323 Frankfurt am Main Germany Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry)
Title Page	Added text.	Amendment 3 Issue Date 29 June 2015
	• Pharmacokinetics: To report delamanid and metabolite plasma concentrations at each visit by age groups and to conduct population pharmacokinetics (POPPK) of delamanid when delamanid is administered in combination with an OBR during a 6 month treatment period in pediatric patients with MDR TB.	• To report delamanid and metabolite plasma concentrations at each visit day by age groups and to conduct a population pharmacokinetics (POPPK) analysis of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR TB
Synopsis (Objectives)	• To conduct the pharmacokinetic (PK)/ pharmacodynamics (PD) relationship analysis of the metabolite DM-6705 plasma concentrations and QTc prolongation when delamanid is administered in combination with OBR during a 6 month treatment period in pediatric patients with MDR-TB	• To conduct the pharmacokinetic (PK)/pharmacodynamic (PD) relationship analysis **of delamanid and its metabolite DM-6705 plasma concentrations and change in corrected QT interval (QTc) when delamanid is administered in combination with OBR during a 6 month treatment period in pediatric patients with MDR-TB** • ***To determine the palatability of the delamanid pediatric formulation***
Synopsis (Trial Design)	The current Trial 242-12-233 (Trial 233) will initially be conducted sequentially in two groups of pediatric patients ~~by age group: Group 1 (ages 12 to 17 years) and Group 2 (ages 6 to 11 years).~~ ~~Younger age groups (Group 3, [3 to 5 years] and Group 4, [0 to 2 years]) will be enrolled when the pediatric formulation becomes available. Details describing Groups 3 and 4 will be included in an amendment to this protocol.~~	**The current Trial 242-12-233 (Trial 233) will be conducted sequentially in *4* groups of pediatric patients with MDR-TB.** • **Group 1 (ages 12 - 17 years, inclusive) will receive adult formulation delamanid 100 mg BID + OBR (n = 6)** • **Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)** • ***Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)*** • ***Group 4 (ages birth - 2 years, inclusive) will receive pediatric***

Location	Old Text	Updated Text
	~~Group 1 includes pediatric patients with MDR-TB age 12 to 17 years receiving OBR. Group 2 includes pediatric patients with MDR-TB age 6 to 11 years receiving OBR.~~ Patients will be assigned to one of two treatment groups based on age: Group 1 will receive delamanid 100 mg (2 x 50 mg tablets) (twice daily) BID orally (PO) plus OBR for 6 months (180 days). Group 2 will receive delamanid 50 mg (1 x 50 mg tablet) BID PO plus OBR for 6 months (180 days).	***formulation delamanid (dose to be determined) BID + OBR (n = 12)***
Synopsis (Trial Design)	Screening Period (Day -30 to -1): Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the 30-day period immediately after completion of Trial 232 as described in the Schedule of Assessments. Baseline (Day 0): Inclusion/exclusion criteria, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications. Treatment Outcome Follow-up (Day 730 (M24) ~~or until treatment for MDR-TB is completed or discontinued, whichever comes first)~~: Collection of treatment outcome information as routinely documented in the patient medical records or in a National TB Program.	Screening Period (Day −30 ***to −2***): Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the 30-day period immediately after completion of Trial 232 as described in the Schedule of Assessments. Baseline (***Day −1***): Inclusion/exclusion criteria, physical examination, and safety assessments, including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and electrocardiogram (ECG) as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications. Treatment Outcome Follow-up (Day 730 **[Month 24] + 2 months**: Collection of treatment outcome information as routinely documented in the patient medical records or in a national TB program.
Synopsis (Patient Population)	At least twelve male and female pediatric patients who have successfully completed Trial 232 will be enrolled in two sequential age groups, at least six each in Group 1 (ages 12 to 17 years) and in Group 2 (ages 6 to 11 years) who have confirmed or presumptive MDR-TB and are also receiving an OBR. Group 1 (ages 12 to 17 years) must contain at least two but no more than five females.	**At least 36 male and female MDR-TB patients ages birth to 17 years, inclusive, who meet all of the inclusion criteria and none of the exclusion criteria and who are also receiving OBR will be assigned to one of 4 treatment groups based on age. For Groups 1 and 2, a minimum of 6 patients will be included in each age group, and Group 1 (12 to 17 years, inclusive) must include at least 2 but no more than 5 females.** ***For Groups 3 and 4, a minimum of 12 patients will be included in each age group.***
Synopsis (Inclusion	Key Inclusion Criteria: • Patients enrolled in this Trial 233 must have successfully	Key Inclusion Criteria: • Successfully completed Trial 232

Location	Old Text	Updated Text
Criteria)	completed the previous Trial 232. • Male and female children • Negative urine pregnancy test for female patients who have reached menarche • Age 6 to 17 years In two sequential cohorts of 12 to 17 years (Group 1) and 6 to 11 years (Group 2) • Confirmed diagnosis of MDR-TB OR • Presumptive diagnosis of MDR-TB such that the treating physician has decided to treat the patient for MDR-TB who has one of the following: ~~Sputum smear positive for acid-fast bacilli (AFB)~~ - Clinical specimen (eg, cerebral spinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of turberculosis disease - Persistent cough lasting > 2 weeks - Fever, weight loss, and failure to thrive - Findings on recent chest radiograph consistent with TB AND - Household contact of a person with known MDR-TB or a person who died while appropriately taking drugs for sensitive TB OR - On first-line TB treatment but with no clinical improvement • Negative urine pregnancy test for female patients who have reached menarche • Trial-specific written informed consent/assent obtained from a parent(s) or guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol required procedures. In addition, the subject must provide informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time~~. All informed~~	• Male or female • **Age birth to 17 years, inclusive** • **Confirmed diagnosis of MDR-TB, ie,** ***culture positive for Mycobacterium tuberculosis (MTB) with isoniazid and rifampicin resistance on drug-susceptibility testing,*** or a positive rapid test demonstrating resistance to rifampicin alone or to rifampicin and isoniazid OR • Presumptive diagnosis of pulmonary ***or extrapulmonary*** MDR-TB such that the treating physician has decided to treat for MDR-TB the patient who has one of the following: • Clinical specimen (eg, cerebral spinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue specimen) suggestive of tuberculosis (TB) disease • Persistent cough lasting > 2 weeks • Fever, weight loss, and failure to thrive • Findings on recent chest radiograph ***or other imaging studies (prior to Visit 1)*** consistent with TB AND - Household contact of a person with known MDR TB or a person who died while appropriately taking drugs for drug-sensitive TB OR - On first-line TB treatment but with no clinical improvement • Negative urine pregnancy test for female patients who have reached menarche • Study-specific written informed consent/assent obtained from a parent(s) or guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol-required procedures. In addition, ***for patients in Groups 1 and 2 and as required by local laws,*** the patient must provide informed assent at screening and must be able to fully understand that he or she can withdraw from the study at

Location	Old Text	Updated Text
	~~consent/assent procedures must be in accordance with the trial center's institutional review board/ethics committee (IRB/EC) and local regulatory requirements~~	any time.
Synopsis (Exclusion Criteria)	• Patients who have not completed Trial 232 • Children with a positive test for human immunodeficiency virus (HIV) or who have been previously identified as having HIV or with laboratory evidence of hepatitis B or C • History of allergy to metronidazole and any disease or condition in which metronidazole is required • Use of amiodarone within 12 months of the first dose of investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within 30 days prior to the first dose of IMP • Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP • Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment) • Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds • A concomitant condition such as renal impairment characterized by serum creatinine levels >1.5 mg/dL, hepatic impairment (ALT or AST >3 x ULN), or hyperbilirubinemia characterized by total bilirubin > 2x ULN • Abnormalities in screening ECG (including atrioventricular [AV] block, bundle branch block [BBB] or hemi-block, QRS prolongation >120 msec, or QTcF >450 msec in both males and females) • Positive urine drug screen • Concurrent diagnosis of severe malnutrition or kwashiorkor • Lansky Play Performance Score < 50 or Karnofsky Score < 50	• Patients who have not completed Trial 232 • Children with a positive test result for human immunodeficiency virus (HIV) or who have been previously identified as having HIV or with laboratory evidence of ***active*** hepatitis B or C • History of allergy to metronidazole and any disease or condition in which metronidazole is required • Use of amiodarone within 12 months prior to the first dose of investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within 30 days prior to the first dose of IMP • Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment) • Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds • Abnormalities in screening electrocardiogram (ECG) (including atrioventricular block, bundle branch block or hemi-block, QRS prolongation > 120 msec, or QT interval corrected using Fridericia's method (QTcF) > 450 msec in both males and females) • A concomitant condition such as renal impairment characterized by serum creatinine levels > 1.5 mg/dL, hepatic impairment (alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of normal [ULN]), or hyperbilirubinemia characterized by total bilirubin > 2x ULN • Concurrent diagnosis of severe malnutrition or kwashiorkor • Positive urine drug screen ***(Groups 1 and 2 only)*** • Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP and/***or any prior or concurrent use bedaquiline*** • Lansky Play Performance Score < 50 or Karnofsky Score <

Location	Old Text	Updated Text
	• Administered an IMP within 1 month prior to Visit 1 other than delamanid given as IMP in Trial 232 • Pregnant, breast-feeding, or planning to conceive or father a child within the study timeframe described in the informed consent form	50 • Administered an IMP within 1 month prior to Visit 1 other than delamanid given as IMP in Trial 232 • Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form (Groups 1 and 2 only)
Investigational Medicinal Product, Dose, Dosage regimen, Formulation, Mode of Administration:	Delamanid 50 mg oral tablets provided in blister cards and administered orally. • Dose for Group 1 (ages 12 to 17 years) will be delamanid 100 mg BID PO with meals for 180 days. • Dose for Group 2 (ages 6 to 11 years) will be delamanid 50 mg BID PO with meals for 180 days. OBR is generally comprised of 4 classes or more of first-line (other than isoniazid [INH] and rifampicin) and second-line anti-TB medications to which the patient's strain of Mycobacterium tuberculosis (MTB) has confirmed or likely susceptibility based on previous treatment history and epidemiologic and clinical factors. 3) Fluoroquinolone class: preferred order of selection: levofloxacin, gatifloxacin > ofloxacin (Gatifloxacin to be used with caution, secondary to rare but severe side effect of dysglycemia; moxifloxacin causes QT interval prolongation and therefore will not be used in this trial; and ciprofloxacin is not recommended for use in this trial because of poor efficacy).	**Delamanid 50-mg adult formulation tablets administered orally for 6 months to Groups 1 and 2:** • **Group 1 (ages 12 to 17 years, inclusive) - 100 mg (2 x 50-mg tablet) BID** • **Group 2 (ages 6 to 11 years, inclusive) - 50 mg (1 x 50-mg tablet) BID** ***Delamanid pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension to Groups 3 and 4 for 6 months:*** • ***Group 3 (ages 3 to 5 years, inclusive) - 25 mg (1 x 25-mg tablet) BID*** • ***Group 4 (ages birth to 2 years, inclusive) - dose to be determined*** **OBR generally comprises 4 or more classes of first-line (other than isoniazid and rifampicin) and second-line anti-TB medications to which the patient's strain of MTB has suspected or documented susceptibility based on previous treatment history and epidemiologic and clinical factors.** **3) Fluoroquinolone class; preferred order of selection: moxifloxacin, levofloxacin, gatifloxacin > ofloxacin (gatifloxacin to be used with caution secondary to rare but severe side effect of dysglycemia; ciprofloxacin not recommended for use). Moxifloxacin causes QT interval prolongation and should not be used in this trial**

Location	Old Text	Updated Text
Synopsis (Criteria for Evaluation)	The secondary criteria for assessment in this trial are: • Pharmacokinetics/Phamacodynamics: ~~Time-matched~~ ECG and blood samples for PK/PD analysis for changes in QTc interval as a function of DM-6705 plasma concentrations • Efficacy: assessed by results of chest radiography (for patients with pulmonary disease); change in body weight and height measurements; and evaluation of TB symptoms. In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (or provide other biological specimens) for microbiological evaluation according to the requirements of the National TB Program.	The secondary criteria for evaluation in this trial are: • Pharmacokinetics/Pharmacodynamics: ECG and blood samples for PK/PD analysis for changes in QTc as a function of ***delamanid*** and DM-6705 plasma concentrations • Efficacy: evaluated on the basis of results of chest radiography (for patients with pulmonary disease); change in body weight and height measurements; and evaluation of TB symptoms. In addition, sputum culture conversion (for culture-positive patients) will be assessed in patients who are able to produce sputum (or provide other biological specimens) for microbiological evaluation according to the requirements of the national TB program • ***Palatability: The palatability of the delamanid pediatric formulation (Groups 3 and 4 only) will be assessed using an age-appropriate visual hedonic scale and clinical assessment***
Synopsis (Endpoints)	The secondary endpoints in this trial are: • Pharmacokinetics/Pharmacodynamics: PK/PD analysis for changes in QTc as a function of DM-6705 plasma concentrations.	The secondary endpoints in this trial are: • Pharmacokinetics/Pharmacodynamics: PK/PD analysis for changes in QTc as a function of ***delamanid and*** DM-6705 plasma concentrations.
Synopsis (Statistical Methods)	No power calculation was performed for this trial because of the limited number of patients expected to be enrolled in the population of interest (i.e. pediatrics). No formal statistical analysis is planned due to the small sample sizes; all statistical presentations will be descriptive. ~~The number of patients enrolled should be at least 6 per age and dose group.~~	No power calculation was performed for this trial because of the limited number of patients expected to be enrolled in the population of interest (ie, pediatrics). No formal statistical analysis is planned due to the small sample sizes; all statistical presentations will be descriptive.
Synopsis Trial Duration	The trial duration per patient (Screening, Baseline, Treatment, Post Treatment, and Follow-up Periods) will be 760 days including the following: 30-day Screening period, 182-day Treatment period, 56-day Post-treatment period, and a 492-day follow-up period (127-day from the last Post-treatment period, incorporating a 6 month post last delamanid dose follow-up visit and additional 365-day treatment outcome follow up period from the last follow up visit ~~or until treatment for MDR-TB is completed or discontinued, whichever comes first).~~	**The trial duration per patient will be up to 760 days including the following: 30-day screening period, 182-day treatment period, 56-day post-treatment period, additional follow-up period through Day 365 (ie, 6 months after the last delamanid dose), and treatment outcome follow-up *at Day 730 (Month 24) + 2 months* (ie, 1 year after the Day-365 follow-up visit).**
Section 1 through 1.4.2		Minor editorial and content updates, including references.

Location	Old Text	Updated Text
Section 1	Tuberculosis Incidence In 2011, the estimated global incidence was 8.8 million cases. Deaths among HIV negative persons were 1.1 million and among HIV infected persons were 0.35 million. It was estimated that Asia (55%) and Africa (30%) accounted for most cases of TB. This contrasts to the number of cases that were estimated to have occurred in the Eastern Mediterranean Region (7%); the European Region (4%); and in the Americas (3%). During that year, the 5 countries with the highest burden included: India (1.6 to 2.4 million), China (1.1 to 1.5 million), South Africa (0.40 to 0.59 million), Nigeria (0.37 to 0.55 million), and Indonesia (0.35 to 0.52 million).9 India and China alone accounted for 35% of estimated cases. Although the overall global incidence of TB is falling, the number of incident cases in the last few years has remained relatively stable due to population increases. Further, the overall annual incidence of TB in high income countries remains relatively low.	Tuberculosis Incidence **In 2012, the estimated global incidence of TB was 8.6 million cases. Deaths among HIV negative persons were 1.0 million and among HIV infected persons were 0.32 million. The majority of cases in 2012 were in Southeast Asia (29%), Africa (27%) and the Western Pacific Region (12%). India (26%) and China (12%) were the individual countries with the highest proportion of cases.{+WHO_TB_Global_Report_2013}**

Location	Old Text	Updated Text
Section 1	Multidrug-resistant and Extensively Drug-resistant Tuberculosis In addition to the effects of the global HIV epidemic, the emergence of MDR-TB or TB caused by strains of MTB resistant to at least INH and rifampicin, has further complicated global efforts to control the TB epidemic. Approximately 500,000 cases of MDR-TB occur in the world annually, representing nearly 5% of the world's annual TB burden.10 The estimated prevalence of MDR-TB is 1.5 million cases and the annual incidence is 500,000 cases (60% new cases, 40% retreatment). The 4 countries with the largest number of cases of MDR-TB in 2008 were China (100,000), India (99,000), the Russian Federation (38,000), and South Africa (13,000).9 In some countries, such as Latvia and Peru, where comprehensive TB control measures have been established, including the WHO-recommended DOTS strategy and program activities to address the diagnosis and treatment of MDR-TB, the prevalence of MDR-TB has decreased.11 However, the prevalence of MDR-TB continues to increase in many regions where these measures have not been implemented and in regions where the prevalence of HIV is high. Patients with MDR-TB require longer treatment, usually 18 to 24 months, compared with 6 to 8 months for patients with drug-susceptible tuberculosis (DS-TB). Moreover, and the so-called "second-line" drugs used to treat MDR-TB are less potent and more toxic than those for DS-TB.12 At least 4 medications from the various classes of second-line anti-TB drugs to which a given MDR-TB patient's disease is susceptible or likely to be susceptible should be used in combination for MDR TB treatment.12 Some data suggest that at least 5 different medications should be used to optimize the chance for a successful treatment	Multidrug-resistant and Extensively Drug-resistant Tuberculosis **In addition to the effects of the global HIV epidemic, the emergence of MDR-TB or TB caused by strains of MTB resistant to at least isoniazid and rifampicin has further complicated global efforts to control the TB epidemic. Approximately 450,000 people developed MDR-TB globally in 2012 and there were an estimated 170,000 deaths from MDR-TB. There were 94,000 MDR-TB patients detected in 2012; 84,000 of those were confirmed to have resistance to rifampicin and isoniazid and a further 10,000 were found to have rifampicin (RIF) resistance by GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA).{+WHO_TB_Global_Report_2013} The highest concentrations of MDR-TB are found in Eastern Europe and Central Asia where the percentage of new TB cases that are multidrug resistant (MDR) may reach 20% and the percentage of those previously treated for TB may reach 50%.{+WHO_TB_Global_Report_2013}**

Location	Old Text	Updated Text
	outcome.13,14,15 Medications from the fluoroquinolone class of drugs and from the injectable classes – either an aminoglycoside or a cyclic peptide - as well as any remaining first-line medications to which a given patient's disease is susceptible are integral to an optimized treatment regimen for MDR TB.12,13,14,16 Under the best of programmatic conditions, the cure rates achievable for MDR-TB, as demonstrated by studies of treatment outcomes for patient cohorts, are in the range of only 60% to 70%.17,18 In contrast, cure rates for drug susceptible TB in well- performing programs often exceed 90%.19	
Section 1.3.2	In MDR-TB patients receiving delamanid 100 mg and 200 mg BID for 2 months, delamanid exposure reached steady-state after 2 weeks (38 hour t1/2), and metabolite exposure continued to increase. On Day 56, after the 200-mg BID and 200 mg BID doses, delamanid Cmax was 414 (39.9%) ng/mL and 611 (35.6%) ng/mL, respectively, and AUC0-24h was 7925 (37.5%) ng•h/mL and 11,837 (33.6%) ng•h/mL, respectively.	In MDR-TB patients in Trial 204 receiving delamanid 100 mg and 200 mg BID for 2 months, delamanid exposure reached steady state after 2 weeks (38 hour t1/2), and metabolite exposure continued to increase. On Day 56, after the ***100-mg*** BID and 200 mg BID doses, delamanid Cmax was 414 (39.9%) ng/mL and 611 (35.6%) ng/mL, respectively, and AUC0-24h was 7925 (37.5%) ng•h/mL and 11,837 (33.6%) ng•h/mL, respectively.
Section 1.3.2	Trial 242-07-208 demonstrated that in general, steady-state exposure was reached by 8 weeks of dosing for DM-6705 and by 8 to 14 weeks of dosing for the other metabolites. PK/PD analysis for QTc prolongation indicated that DM-6705, in agreement with human ether-à-go-go-(hERG) inhibition potential and exposure, contributed to the QTc prolonging effect. This analysis, conducted in all Phase 2 trials, allowed the estimation of the maximal QTc effect at DM-6705 Cmax. The most accurate PK/PD analysis (Trial 204) predicted a maximal QTc effect of 13.7 msec (14.9 msec upper bound) and 19.4 msec (20.9 msec upper bound) after doses of delamanid 100 mg BID and 200 mg BID plus OBR, respectively.111 From the EBA and clinical efficacy trials, it appears that the minimal exposure (AUC0 24h) of delamanid for efficacy is approximately 2500 ng•h/mL; the effect appears to be maximal at delamanid 100 mg BID exposure. Additional information may be found in the IB.1	Trial 208 demonstrated that, in general, steady-state exposure was reached by 8 weeks of dosing for DM-6705 and by 8 to 14 weeks of dosing for the other metabolites. PK/PD analysis of delamanid and DM-6705 plasma concentrations as a function of QTc changes were performed. The results indicated that the predicted changes were similar to the observed increases in QTc. Additional information may be found in the IB.{+IB_ed_10}
Section 1.4.1	As of 31 January 2012, 887 subjects and patients had been exposed to delamanid in clinical trials.3 Of these 887, 422 were healthy subjects, 60 were patients with uncomplicated	**As of 26 Mar 2014, 887 adult subjects have been exposed to oral doses of delamanid in 17 completed trials in Japan, China, South Africa, Peru, Korea, Philippines, Egypt, the**

Location	Old Text	Updated Text
	DS TB, 395 were patients with MDR-TB, and 10 were patients with MDR-TB refractory to conventional therapy. In total, 18 clinical trials involving delamanid have been carried out worldwide: 4 in multiple countries; 4 in the United States (US); 4 in the United Kingdom; 2 in Japan; 2 in China; and 2 in South Africa. One of the trials is currently ongoing in multiple countries. Also, one observational study (Trial 242-10-116) which follows patients for long-term outcomes who were enrolled in Trial 242 07-204 (also referred to as Trial 204)103, Trial 242-07-208 (also referred to as Trial 208)104, or Trial 242-08-210105 was completed. No safety data were collected and no delamanid was administered in Trial 242-10-116. In Trial 242-05-101, single oral doses of delamanid up to a maximum of 400 mg administered after a high-fat meal were well tolerated in healthy subjects.100 Similarly, 10 days of repeated dosing with delamanid after a standard meal was also well tolerated in healthy subjects.100 102 There were no serious or severe adverse events (AEs), and no subjects were withdrawn as a result of AEs. Of AEs reported in 3 or more subjects, only headache (12%) and abdominal pain (7%) occurred more frequently with delamanid than with placebo (there were no occurrences of either event with placebo). Headache (delamanid, 42%; placebo, 25%) and dizziness (delamanid, 14%; placebo, 0%) were among the most common AEs reported by subjects who received multiple doses of delamanid up to 400 mg daily for 10 days. There were no clinically significant changes in QTc interval duration.	**European Union, and the United States. Of these 887 adult subjects, 422 were healthy subjects, 60 were patients with uncomplicated DS-TB, 395 were patients with MDR-TB, and 10 were patients with MDR-TB refractory to treatment. Of these 887 adult subjects, 791 subjects (338 healthy subjects, 48 patients with uncomplicated DS-TB, 395 patients with MDR-TB, and 10 patients with MDR-TB refractory to treatment) have been exposed to oral doses of delamanid tablets (ie, the modified spray-dried tablet formulation). Delamanid is well tolerated by healthy adult subjects and adult patients with TB.{+IB ed 10} One observational study (Trial 242-10-116) also was conducted that follows long-term outcome patients who were enrolled in Trial 204, Trial 208, or Trial 210. No safety data was collected and no delamanid was administered in Trial 242-10-116.** **In Trial 242-05-101, single oral doses of delamanid up to a maximum of 400 mg administered after a high-fat meal were well tolerated in healthy subjects; delamanid was also well tolerated with 10 days of repeated dosing after a standard meal in healthy subjects.{+CSR 242 05 101} There were no serious adverse events (SAEs) and no severe adverse events (AEs), and no subjects were withdrawn as a result of AEs.**
Section 1.4.1	Results were similar for delamanid 200 mg BID + OBR compared with placebo + OBR for the incidence of QT interval prolongation (13.1% vs 3.8%), but the incidence of chest pain was not 5 percentage points greater than placebo + OBR (8.8% vs 4.4%).	**QT prolongation (13.1% vs 3.8%) was the only TEAE reported at an incidence of > 5 percentage points more in the delamanid 200 mg BID + OBR group than in the placebo + OBR group; the incidence of chest pain was similar between groups (8.8% vs 4.4%).**
Section 1.4.1	Drug exposure did not increase with these higher doses, apparently due to absorption and limited increases in concentration.	Drug exposure did not increase with these higher doses, apparently due to ***lack of further*** absorption and limited increases in concentration.

Location	Old Text	Updated Text
Section 1.4.1	As of 31 Jan 2012, in the phase 3 Trial 242-09-213, a randomized, double-blind, and placebo-controlled conducted in patients to determine the safety, PK, and efficacy of delamanid plus OBR versus placebo in patients with MDR-TB, there were no serious TEAEs, no TEAEs leading to discontinuation, and no deaths. This trial was conducted in patients with MDR-TB who had previously been treated in other delamanid trials.	***As of 31 Jan 2014 in Trial 242-09-213, the ongoing phase 3, randomized, double-blind, and placebo-controlled trial conducted in MDR-TB patients to determine the safety, PK, and efficacy of delamanid plus OBR versus placebo plus OBR, enrollment was complete and 511 patients had begun blinded treatment. Three deaths had been reported, 65 patients had reported SAEs, and 8 patients had discontinued IMP due to TEAEs.{+IB_ed_10}***
Section 1.4.2	The design of treatment regimens for MDR-TB is highly complex. Often it is empiric in the initial stages of treatment until full information on drug susceptibility testing is available on the MTB isolate to tailor a patient's regimen, the patient's previous treatment history for TB, information on drug resistance patterns of known MDR-TB patients with whom a given patient has been in close contact, and available information on HIV status. Treatment is generally divided into an initial intensive phase, which is focused on achieving sputum culture conversion (SCC) from positive growth of MTB to a negative culture as soon as possible. Thereafter, the continuation phase of treatment − the part more readily delivered in an ambulatory setting – ensues, and a full treatment course can last for 20 to 24 months; occasionally some patients are successfully treated for less than 18 months.	**The design of treatment regimens for MDR-TB is highly complex. Often it is empiric in the initial stages of treatment until full information on drug susceptibility testing of the clinical isolate is available to tailor a patient's regimen. Up until that point, the patient's previous treatment history for TB, information on drug resistance patterns of known MDR-TB patients with whom a given patient has been in close contact, and the patient's HIV status are used to guide the choice of anti-TB drugs. Treatment is generally divided into an initial intensive phase, which is focused on achieving sputum culture conversion (SCC) from positive growth of MTB to a negative culture as soon as possible.** **Thereafter, the continuation phase of treatment − the part more readily delivered in an ambulatory setting –ensues, and a full treatment course can last for 24 months.**
Section 1.4.2	Given the high proportion of patients with MDR-TB whose disease does not resolve with available treatment, and that many of them die, it is clear that new medications that have potent activity against MDR-TB are urgently needed to improve the outcome of this patient group and to reduce the risk of further global spread of MDR-TB.	Given the high proportion of patients with MDR-TB whose disease does not resolve with available treatment, and that many of them die, it is clear that new medications that have potent activity against MDR-TB are urgently needed to improve the outcome of this patient group and to reduce the risk of further global spread of MDR-TB***. With the advent of new medications for MDR-TB, new cotoxicities may be encountered. For example, delamanid, as well as bedaquiline, moxifloxacin, and clofazimine, have been associated with QT prolongation and, in most instances, the combined QTcF prolongation of 2 or more of these drugs has not yet been characterized.{+Sirturo_pkg_insert}{+Trial_213_MMP}***
Section 2.1	Delamanid has been extensively studied in healthy adults and in patients with both uncomplicated TB and with MDR-TB.	Delamanid has been extensively studied in healthy adults and in patients with both uncomplicated TB and with MDR-TB.

Location	Old Text	Updated Text
	Delamanid has shown low toxicity and good tolerability in all populations studied. For adults, marketing authorization in the European Union (EU) is being sought for the use of delamanid with OBR during the 6 month intensive phase of OBR treatment. However, until Trial 232, delamanid had not been studied in the pediatric population.	Delamanid has shown low toxicity and good tolerability in all populations studied. **For adults, marketing authorization has been obtained in the European Union, Japan, and Korea for the use of delamanid with OBR during the 6 month intensive phase of OBR treatment.** However, until Trial 232, delamanid had not been studied in the pediatric population.
Section 2.1	Both Trial 232 and this Trial 233 are age de-escalation trials designed to study the safety, tolerability, and PK of delamanid in four pediatric age groups: Group 1: Adolescents 12 to 17 years (100 mg BID) Group 2: Children 6 to 11 years (50 mg BID) Group 3: Children 3 to 5 years (25 mg BID and 50 mg BID) Group 4: Newborns and infants 0 to 2 years (5 mg BID and 25 mg BID) ~~The present protocol for Trial 233 outlines the trial specification in children and adolescents ages 6 to 17 years. Younger age groups (Group 3, [3 to 5 years] and Group 4, [0 to 2 years]) will be enrolled when the pediatric formulation becomes available. Details describing Groups 3 and 4 will be included in an amendment to this protocol.~~ Delamanid plasma concentrations in the pediatric population will be described by POPPK analysis of the data collected in trials 232 and 233. In addition, a PK/PD analysis will be performed for changes in QTc as a function of DM-6705 plasma concentrations throughout Trials 232 and 233. The safety and PK data from each dose group in Trial 232 will be analyzed before initiation of enrollment in the next younger group. The patients in each group will then be sequentially enrolled into this Trial 233 six-month treatment extension trial ~~to receive the dose determined from Trial 232 and~~ to evaluate the safety, tolerability, PK, and efficacy of delamanid during the extended time period planned in this trial for treatment of MDR-TB. To be eligible for Trial 233, all patients must rollover from Trial 232 within 30 days of completing that trial.	**Both Trial 232 and Trial 233 are age de-escalation trials in which pediatric patients will be enrolled in 4 age groups: adolescents ages 12 to 17 years, inclusive (Group 1); children ages 6 to 11 years, inclusive (Group 2); children ages 3 to 5 years (Group 3); and infants ages birth to 2 years (Group 4)** Delamanid plasma concentrations in the pediatric population will be analyzed using a population pharmacokinetics (POPPK) approach of the data collected in Trials 232 and 233. In addition, a PK/PD analysis will be performed for changes in QTc as a function of ***delamanid and*** DM-6705 plasma concentrations of the data collected in Trials 232 and 233. **Patients in each age group will be sequentially enrolled into this 6-month treatment extension trial (Trial 233) to evaluate the safety, tolerability, PK, and efficacy of delamanid during the extended time period planned in this trial for treatment of MDR-TB. To be eligible for Trial 233, all patients must rollover within 30 days of completing Trial 232.**

Location	Old Text	Updated Text
Section 2.2	Adolescents (ages 12 to 17 years) will be given delamanid at the adult dose, which will be delamanid 100 mg BID; children (ages 6 to 11 years) will be given half the adult dose, which will be delamanid 50 mg BID. Delamanid will be given as delamanid 50 mg tablets. Dosing in children younger than those in this trial will be defined based upon safety and PK findings in Trial 232.	**Children 6 to 17 years, inclusive, will receive the delamanid 50-mg tablet adult formulation. Adolescents (12 to 17 years) will be given delamanid at the adult dose, 100 mg BID, while children 6 to 11 years will be given one half of the adult dose, 50 mg BID.** **Younger children (ages birth to 5 years, inclusive) will be given pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension.** ***The delamanid dose for children ages 3 to 5 years, inclusive (Group 3) will be 25 mg BID.*** **The delamanid dose for children ages birth to 2 years, inclusive (Group 4) will be confirmed using the PK, safety, and tolerability findings in the older age groups and based on the bioavailability of the pediatric formulation.**
Section 2.3	The primary objectives of this trial are: • ~~Safety and tolerability~~: To evaluate the long-term safety and tolerability of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB for the age-specific delamanid doses determined in Trial 232. • ~~Pharmacokinetics:~~ To report delamanid and metabolite plasma concentrations at each visit day by age groups and to conduct POPPK of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR TB. The secondary objectives are: • To evaluate the PK/PD relationship of the metabolite DM-6705 plasma concentrations and QTc prolongation when delamanid is administered in combination with OBR during a 6 month treatment period in pediatric patients with MDR-TB • ~~Efficacy:~~ To evaluate the efficacy of delamanid when administered in combination with an OBR during a 6 month treatment period in pediatric patients with MDR-TB	The primary objectives of this trial are: • To evaluate the long-term safety and tolerability of delamanid and its metabolites in combination with an OBR during a 6-month treatment period in pediatric patients with MDR-TB for the age-specific delamanid doses determined in Trial 232 • To report delamanid and metabolite plasma concentrations at each visit day by age groups and to conduct **a population pharmacokinetics (POPPK) analysis** of delamanid when delamanid is administered in combination with an OBR during a 6-month treatment period in pediatric patients with MDR TB The secondary objectives are: • To evaluate the PK/PD relationship ***of delamanid*** and its metabolite DM-6705 plasma concentrations and **change in QTc** when delamanid is administered in combination with OBR during a 6 month treatment period in pediatric patients with MDR-TB • To evaluate the efficacy of delamanid when administered in combination with an OBR during a 6 month treatment period in pediatric patients with MDR-TB • ***To determine the palatability of the delamanid pediatric formulation***
Section 3.1	~~At least 12 male and female patients will be enrolled to obtain a minimum of 12 completed patients, at least 6 in each age group. Patients will be assigned to one of two treatment~~	***Delamanid will be administered twice daily for 182 days. The trial will be conducted sequentially in 4 groups of pediatric patients:***

Location	Old Text	Updated Text
	~~groups based on age:~~ ~~Group 1 (patients with MDR-TB age 12 to 17 years)~~ ~~Delamanid 100 mg BID for 6 months plus OBR~~ ~~Group 2 (patients with MDR-TB age 6 to 11 years)~~ ~~Delamanid 50 mg BID for 6 months plus OBR~~	• ***Group 1 (ages 12 - 17 years, inclusive) will receive adult formulation delamanid 100 mg BID + OBR (n = 6)*** • ***Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)*** • ***Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)*** • ***Group 4 (ages birth - 2 years, inclusive) will receive pediatric formulation delamanid BID + OBR (n = 12) (dose will be determined after data from at least 6 subjects from Group 3 in Trial 232 is available)***
	Screening Period (Day -30 to -1): Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the post-Trial 232 thirty (30) - day screening period for Trial 233, as described in the Schedule of Assessments. **Baseline (Day 0):** Inclusion/exclusion criteria, physical examination and safety assessments including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications. **Treatment Outcome Follow-up (Day 730 (M24) or until treatment for MDR-TB is completed or discontinued, whichever comes first):** Collection of treatment outcome information as routinely documented in the patient medical records or in a National TB Program.	**Screening Period (Day −30 <u>to −2</u>):** Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the post-Trial 232 thirty (30)- day screening period for Trial 233, as described in the Schedule of Assessments **Baseline (<u>Day −1</u>):** Inclusion/exclusion criteria, physical examination, and safety assessments including laboratory tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications **<u>Treatment Outcome Follow-up (Day 730 [Month 24] + 2 months:</u>** Collection of treatment outcome information as routinely documented in the patient medical records or in a national TB program
Figure 3.1-1		Updated to include Groups 3 and 4

Location	Old Text	Updated Text
Section 3.2	Patients will be assigned by age group to receive one of the following treatments for 182 days. 1. Group 1 (ages 12 to 17 years): delamanid 100 mg (2 x 50 mg tablets) BID PO plus OBR 2. Group 2 (ages 6 to 11 years): delamanid 50 mg (1 x 50 mg tablet) BID PO plus OBR It should be noted that patient age group and dosing will be determined at the time of enrollment into Trial 232 and will not change during rollover into Trial 233.	Patients will be assigned by age group to receive one of the following treatments for 182 days: **7) Group 1 (12 to 17 years, inclusive): adult formulation delamanid 100 mg BID (administered as 2 x 50-mg tablets BID) + OBR** **8) Group 2 (6 to 11 years, inclusive): adult formulation delamanid 50 mg BID (administered as 1 x 50-mg tablet BID) + OBR** ***9) Group 3 (3 to 5 years, inclusive): pediatric formulation delamanid 25 mg BID (administered as 1 x 25-mg tablet BID) + OBR*** ***10) Group 4 (birth to 2 years, inclusive): pediatric formulation delamanid + OBR (dose will be determined after data from at least 6 subjects from Group 3 in Trial 232 are available)*** **Patient age group and dosing will be determined at the time of enrollment into Trial 232 and will not change during rollover into Trial 233.**
Section 3.2.1	All delamanid doses will be given PO as the appropriate number of 50 mg tablets depending on the age group, as described in Section 3.2. All Group 1 patients who complete screening will receive 100 mg delamanid (2 x 50 mg tablets) BID for 6 months. All Group 2 patients who complete screening will receive 50 mg delamanid (1 x 50 mg tablet) BID for 6 months. According to the country-specific DOT plan, one dose per day for a minimum of 5 days per week will be given under direct observation. It is recommended that all delamanid doses be administered under fed conditions in the morning and evening. It	**All doses for Groups 1 and 2 will be given orally as the appropriate number of 50-mg adult formulation delamanid tablets (Section 3.2). Adult formulation delamanid tablets should be taken with water. Children in Groups 3 and 4 will be given delamanid as an extemporaneous suspension using the delamanid pediatric dispersible tablet formulation.** According to the country-specific DOT plan, one dose per day for a minimum of 5 days per week will be given under direct observation. It is recommended that all delamanid doses be administered under fed conditions in the morning and evening. It is also recommended that delamanid be dosed within 30 minutes of the start of a meal, if possible. Optimally, OBR medications should be given at least 1 hour

Location	Old Text	Updated Text
	is also recommended that delamanid be dosed within 30 minutes of the start of a meal, if possible. ~~Each dose is to be taken with water.~~ Optimally, OBR medications should be given at least 1 hour prior to or 1 hour after dosing of delamanid. The time of dosing with delamanid following the meal will be documented when patients are in the hospital or clinic or for regularly scheduled assessments or for observation.	prior to or 1 hour after dosing of delamanid. The time of dosing with delamanid following the meal will be documented when patients are in the hospital or clinic or for regularly scheduled assessments or for observation.
Section 3.3.1	At least 12 male and female patients from 6 to 17 years of age, inclusive, who have successfully completed Trial 232, who are receiving OBR for confirmed or presumptive MDR-TB will be enrolled in two sequential age groups. These patients (and age groups) will be the same groups who successfully completed Trial 232: Group 1 (ages 12 to 17 years) will contain a minimum of six patients and must include at least two but no more than five females. Group 2 (ages 6 to 11 years) will also contain a minimum of six patients and will include both genders.	**At least 36 males and females ages birth to 17 years, inclusive, who have successfully completed Trial 232 and who are receiving OBR for confirmed or presumptive MDR-TB will be enrolled in 4 sequential age groups. These patients (and age groups) will be the same groups who successfully completed Trial 232: Group 1 (ages 12 to 17 years) will contain a minimum of 6 patients and must include at least 2 but no more than 5 females. Group 2 (ages 6 to 11 years, inclusive) will contain a minimum of 6 patients.** ***Group 3 (ages 3 to 5 years, inclusive) and Group 4 (ages birth to 2 years, inclusive) each will contain a minimum of 12 patients.*** **Groups 2, 3, and 4 will include both genders.**
Section 3.4.1	When a screening informed consent form (ICF) is used for general health assessment prior to identifying or consenting candidates for this specific trial, the screening ICF/assent will also become part of this study's file and the patient's chart. If any patient should turn 18 years of age (or the age of adulthood, as specified by local laws or regulations) within 4 weeks prior to entry into Trial 233 or during Trial 233 participation, an ICF must be signed by the patient. The patient shall be given a copy of the signed ICF and the original shall be kept on file by the investigator. In addition to the English version of the ICF, the document may also be translated into local languages for use in	When a screening informed consent form (ICF)/assent form is used for general health assessment prior to identifying or consenting candidates for this specific trial, the screening ICF/***assent form*** will also become part of this study's file and the patient's chart. If any patient should turn 18 years of age (or the age of adulthood as specified by local laws or regulations) within 4 weeks prior to entry into Trial 233 or during Trial 233 participation, an ICF must be signed by the patient. The patient shall be given a copy of the signed ICF/assent, and the original shall be kept on file by the investigator. ***A patient who turns age 18 (or the age of adulthood as specified by local laws or regulations) during the study must sign an appropriate***

Location	Old Text	Updated Text
	this trial. Translation with back-translation for confirmation will be utilized to ensure accuracy.	***ICF/assent form for himself/herself at that time.*** In addition to the English version of the ICF/assent form, the document may also be translated into local languages for use in this study. Translation with back-translation for confirmation will be used to ensure accuracy.
Table 3.4.2-1	1. Patient must have successfully completed Trial 232 and have and met all inclusion criteria for that trial 2. Male and female children 3. Age 6 to 17 years ~~4. In two sequential cohorts of 12 to 17 years (Group 1) and 6 to 11 years (Group 2)~~ 5. Confirmed diagnosis of MDR-TB OR Presumptive diagnosis of MDR-TB such that the treating physician has decided to treat the patient for MDR-TB who has one of the following: - Sputum smear positive for AFB - Clinical specimen (eg, CSF, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of tuberculosis disease - Persistent cough lasting > 2 weeks - Fever, weight loss, and failure to thrive - Findings on recent chest radiograph consistent with TB AND - Household contact with a person with known MDR-TB or with a person who died while appropriately taking drugs for sensitive TB OR - On first-line TB treatment but with no clinical improvement 6. Negative urine pregnancy test for female patients who have reached menarche 7. Trial-specific written informed consent/assent obtained from a parent(s) or guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol required procedures. In addition, the subject must provide informed assent at screening and must be able to understand that he or she can withdraw from the trial at any time~~. All informed consent/assent procedures must be in accordance with the trial IRB/EC and local regulatory requirements~~	1. Patient must have successfully completed Trial 232 and have and met all inclusion criteria for that trial 2. Male or female ***3. Age birth to 17 years, inclusive*** 4. Confirmed diagnosis of MDR-TB,a,b **ie, culture positive for MTB with isoniazid and rifampicin resistance on DST, or a positive rapid test demonstrating resistance to rifampicin alone or to rifampicin and isoniazid** OR Presumptive diagnosis of pulmonary ***or extrapulmonary*** MDR-TBb such that the treating physician has decided to treat the patient for MDR-TBa who has one of the following: -Clinical specimen (eg, cerebrospinal fluid, pleural fluid, ascitic fluid, lymph node aspirate, or other tissue) suggestive of tuberculosis disease -Persistent cough lasting > 2 weeks -Fever, weight loss, and failure to thrive -Findings on recent chest radiograph ***(prior to Visit 1)*** consistent with TB AND -Household contact with a person with known MDR-TB or with a person who died while appropriately taking drugs for sensitive TB OR -On first-line TB treatment but with no clinical improvement 5. Negative urine pregnancy test for female patients who have reached menarche 6. Study-specific written informed consent/assent obtained from a parent/guardian or legally acceptable representative, as applicable for local laws prior to the initiation of any protocol-required procedures. In addition, ***for patients in Groups 1 and 2 or as required by local***

Location	Old Text	Updated Text
	~~AFB = acid-fast bacilli; CSF = cerebral spinal fluid; EC = Ethics Committee; IRB = Institutional Review Board; MDR-TB = Multi-drug resistant tuberculosis; TB = tuberculosis.~~	***law***, **the patient must provide informed assent at screening and must be able to fully understand that he or she can withdraw from the study at any time.** ***a Patients should be on OBR for at least 2 weeks prior to baseline assessments.*** ***b Includes pre−XDR TB.***
Table 3.4.3-1	10. Positive urine drug screen 11. Use of rifampicin or moxifloxacin within 1 week prior to the first dose of IMP 14. Pregnant, breast-feeding, or planning to conceive or father a child within the study timeframe described in the informed consent form	10. Positive urine drug screen ***(Groups 1 and 2 only)*** 11. Use of rifampicin **and/or** moxifloxacin within 1 week prior to the first dose of IMP 14. Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form ***(Groups 1 and 2 only)***
Section 3.5.1.2	~~Delamanid and metabolite plasma concentrations will be measured during the treatment period at predose (0 hours) on Days 1, 56, 154, and 182; and during the post-treatment period on Day 210 at the theoretical predose time when delamanid would have been administered. Delamanid and metabolite plasma concentrations will be measured at any time point on Days 14, 98, 189, 196, 203, and 238. In addition, population PK (POPPK) analysis for delamanid plasma concentrations will be performed.~~	***PK parameters from the population pharmacokinetic analysis, using data from this trial and from the -232 trial, will be reported.***
Section 3.5.2.1	PK/PD analysis to determine the relationship between DM-6705 plasma concentrations and changes in QTc interval will be performed ~~using the paired PK/PD assessments~~.	PK/PD analysis to determine the relationship between ***delamanid and*** DM-6705 plasma concentrations and changes in QTc interval will be performed.
Section 3.5.2.3	New Section	***3.5.2.3 Palatability*** ***The palatability of the pediatric formulation will be assessed using an-age appropriate visual hedonic scale and clinical assessment.***
Section 3.7	Each patient will participate in the trial for up to 760 days. The trial will be comprised of the Screening Period (30 days); Baseline (Day 0); Treatment Period (182 days of delamanid plus OBR administration); Post-treatment Period (56 days with visits at Days 189, 196, 203, 210, and 238 [Day 238 corresponds to 2-months post last delamanid dose]); and a Follow-up Period with a visit at 6 months post last delamanid dose (Day 365) and additional 365-day treatment outcome follow up period from the last follow up visit ~~or until treatment for MDR-TB is completed or discontinued, whichever comes first)~~. Trial assessment time points are summarized in Table 3.7-1	Each patient will participate in the trial for up to 760 days. The trial will comprise the screening period **(29 days)**; baseline **(Day −1)**; treatment period (182 days of delamanid plus OBR administration); post-treatment period (56 days with visits at Days 189, 196, 203, 210, and 238 [Day 238 corresponds to 2 months post last delamanid dose]); and a follow-up period with a visit at 6 months after the last delamanid dose (Day 365) and an additional 365-day treatment outcome follow-up period from the last follow-up visit. Trial assessment time points are summarized in Table 3.7-1.
Table 3.7-1		Modified to correspond with changes to Section 3.7.1 Schedule of

Location	Old Text	Updated Text
		Assessments
Table 3.7-1 footnotes		Updated to correspond with changes to the table and to clarify table content.
Section 3.7.1.1	3.7.1.1 Visit 1, Screening/Enrollment (Days -30 to -1) For patients who elect to be rolled-over from Trial 232 into Trial 233, the following procedures will either be collected from screening data for Trial 232, from Day 10 data of Trial 232, or will be assessed/performed within 30 days prior to Trial 233: The following information will be taken from screening data of Trial 232 and used as screening data for this Trial 233: • Inclusion/exclusion criteria • Diagnosis of MDR-TB, confirmed or suspected • Demographic data • Signs and symptoms of TB • Audiometry and visual assessments • Chest radiograph for confirmation of radiological picture compatible with TB. Final official interpretation must be available prior to enrollment • Laboratory assessments including HIV, hepatitis B surface antigen (HBsAG), anti hepatitis C virus (HCV) antibody, adrenocorticotropic hormone (ACTH), adrenal function (cortisol), thyroid function tests (T4 and thyroid stimulating hormone [TSH]), and C reactive protein testing The following information will be taken from Day 10 data of Trial 232 and used as screening data for this Trial 233: ~~• Complete physical examination~~ • 12-lead ECG ~~• Safety lab assessments including urinalysis, hematology and coagulation, and serum chemistry~~ The following information will be obtained during the screening period of this Trial 233 between Days -30 and -1: • Informed consent/assent (may be completed prior to Day -30) • Medical history • Vital sign assessments (blood pressure [BP], HR, respiratory rate [RR], and body temperature) after the subject has been supine for ≥ 3 minutes • ~~Height,weight,~~ and BMI	3.7.1.1 Visit 1, Screening/Enrollment **(Days −30 to −2)** For patients who elect to be rolled over from Trial 232 into Trial 233, the following procedures will either be collected from screening data for Trial 232 or from Day 10 data of Trial 232, or will be assessed/performed within 30 days prior to Trial 233. The following information will be taken from the screening data of Trial 232 and used as screening data for this Trial 233: • Inclusion/exclusion criteria • Diagnosis of MDR-TB, confirmed or suspected • Demographic data • ***Complete physical examination*** • Signs and symptoms of TB • Audiometry and visual assessments • Chest radiograph for confirmation of radiological picture compatible with TB • **Laboratory assessments including serum chemistry, hematology and coagulation, urinalysis, HIV, hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), adrenocorticotropic hormone (ACTH), adrenal function (cortisol), C-reactive protein (Groups 1 and 2 only), and thyroid function tests (T4 and thyroid stimulating hormone [TSH])** The following information will be taken from Day 10 data of Trial 232 and used as screening data for this Trial 233: • 12-lead ECG The following information will be obtained during the screening period of this Trial 233 between Days −30 and −2: • Informed consent/assent (may be completed prior to Day −30) • Medical history • Vital signs assessments (blood pressure, heart rate, respiratory rate, and body temperature) after the subject has been in a supine ***or semi-recumbent position*** for ≥ 3 minutes ***(as possible for Groups 3 and 4)***; ***height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)***

Location	Old Text	Updated Text
	• Date of birth and gender • ~~Percentiles for age~~ • Urine pregnancy test for all female subjects who have reached menarche • Urine drug screen (as per Table 3.7-1) • Record prior concomitant medications including prior concomitant anti-TB medications. (Note: Patients will have been on OBR in Trial 232 for at least two weeks prior to baseline assessments) • Record start date of menstrual period and/or date of last menstrual period (LMP)	• **BMI and percentiles for age** • Date of birth and gender • Urine pregnancy test for all female subjects who have reached menarche • ***For Groups 1 and 2 only***, urine drug screen (as per Table 3.7-1) • Record prior concomitant medications including prior concomitant anti-TB medications. (Note: Patients will have been on OBR in Trial 232 for at least 2 weeks prior to baseline assessments) • ***Groups 1 and 2 only,*** record date of ***menarche and/or*** date of last menstrual period
Section 3.7.1.2	3.7.1.2 Visit 2, Baseline, (Day 0) For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Baseline (Day 0): • Review of inclusion/exclusion criteria • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • ~~Height,weight, and BMI~~ • ~~Percentiles for age~~ • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Signs and symptoms of TB • Audiometry and visual assessments • Three consecutive 12-lead ECGs. • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and full urinalysis • OBR administration, as prescribed by investigator • Record concomitant medications including concomitant anti TB medications.	3.7.1.2 Visit 2, Baseline **(Day −1)** For all treatment groups the following procedures will be conducted and/or recorded in the patient's electronic case report form (eCRF) for **Baseline (Day −1):** • Review of inclusion/exclusion criteria • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • **Vital signs assessments (blood pressure, heart rate, respiratory rate, and body temperature) after the subject has been in a supine** ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Three consecutive 12-lead ECGs ***after the patient has been in a supine or semi recumbent position and at rest for ≥ 10 minutes (as possible for Groups 3 and 4)*** • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • OBR administration, as prescribed by investigator • Record concomitant medications including concomitant anti TB medications
Section 3.7.1.3	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 1: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature)	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 1: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital signs assessments **(BP, HR, RR, and body temperature)**

Location	Old Text	Updated Text
	after the subject has been supine for ≥3 minutes • Three consecutive 12-lead ECGs prior to blood draw for PK. Sequence should be ECG assessment, then blood draw for PK, then administration of delamanid • Blood draw ~~(3 mL)~~ for PK at predose (0 hours). • Delamanid dispensed, ~~if needed~~ (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti TB medications.	**after the subject has been in a supine** ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4). Note: height and weight do not need to be measured at this visit*** • Three consecutive 12-lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4)*** prior to blood draw for PK. Sequence should be ECG assessment, then blood draw for PK, then administration of delamanid • Blood draw for PK at predose (0 hours) (see Section 3.7.4) • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • ***Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)*** • Record AEs and IREs • Record concomitant medications including concomitant anti TB medications
Section 3.7.1.4	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 14: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • ~~Height,weight, and BMI~~ • Blood draw ~~(3 mL)~~ for PK at any time point. • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 14: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • **Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine** ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Blood draw for PK at any time point (see Section 3.7.4) • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • ***Groups 1 and 2 only***, record date of ***menarche and*****/or date of LMP**
Section 3.7.1.5	For all treatment groups the following procedures will be	For all treatment groups the following procedures will be conducted

Location	Old Text	Updated Text
	conducted and/or recorded in the patient's eCRF for Day 28: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • Three consecutive 12-lead ECGs. Sequence should be ECG assessment then administration of delamanid. • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications.	and/or recorded in the patient's eCRF for Day 28: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • Three consecutive 12-lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4).*** Sequence should be ECG assessment then administration of delamanid • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • ***Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)*** • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications
Section 3.7.1.6	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 42: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • ~~Height,weight, and BMI~~ • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications.	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 42: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) ***after the subject has been in a supine or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening)

Location	Old Text	Updated Text
	• Record start date of menstrual period and/or date of LMP	• Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, record date of ***menarche and***/or date of LMP
Section 3.7.1.7	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 56: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • Three consecutive 12-lead ECGs. Sequence should be ECG assessment then PK blood draw followed by administration of delamanid. • Blood draw ~~(3 mL)~~ for PK at predose (0 hours). • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications.	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 56: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • Three consecutive 12-lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4).*** Sequence should be ECG assessment then PK blood draw followed by administration of delamanid • Blood draw for PK at predose (0 hours) (see Section 3.7.4) • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • ***Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)*** • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications
Section 3.7.1.8	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 70: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • ~~Height, weight, and BMI~~	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 70: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages***

Location	Old Text	Updated Text
	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	***birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, **record date of menarche and/or date of LMP**
Section 3.7.1.9	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 84: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • Blood draw for thyroid function tests (T4 and ~~thyroid stimulating hormone~~ [TSH]) for patients taking ethionamide or PAS. • Three consecutive 12-Lead ECGs. Sequence should be ECG assessment then administration of delamanid. • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications.	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 84: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • Blood draw for thyroid function tests (T4 and TSH) for patients taking ethionamide or PAS • Three consecutive 12-lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4).*** Sequence should be ECG assessment then administration of delamanid • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications
Section 3.7.1.10	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 98: • Complete physical examination. Please refer to the trial	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 98: • Complete physical examination. Please refer to the trial Operations

Location	Old Text	Updated Text
	Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes ~~• Height, weight, and BMI~~ • Blood draw ~~(3 mL)~~ for PK at any time point • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Blood draw for PK at any time point ***(see Section 3.7.4)*** • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, **record date of menarche and/or date of LMP**
Section 3.7.1.11	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 126: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Height, weight, and BMI • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • Three consecutive 12-Lead ECGs. Sequence should be ECG assessment then administration of delamanid. • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 126: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • Three consecutive 12-lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4).*** Sequence should be ECG assessment then administration of delamanid • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening)

Location	Old Text	Updated Text
		• Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, **record date of menarche and/or date of LMP**
Section 3.7.1.12	The following procedures will be conducted and/or recorded in the patient's eCRF for Day 154: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Height, weight, and BMI • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • Three consecutive 12-Lead ECGs prior to blood draw for PK. Sequence should be ECG assessment, then blood draw for PK, then administration of delamanid. • Blood draw ~~(3 mL)~~ for PK at predose (0 hours). • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	The following procedures will be conducted and/or recorded in the patient's eCRF for Day 154: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • Three consecutive 12-Lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4) and*** prior to blood draw for PK. Sequence should be ECG assessment, then blood draw for PK, then administration of delamanid. • Blood draw for PK at predose (0 hours) (see Section 3.7.4) • Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening) • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only*****, record date of menarche and/or date of LMP**
Section 3.7.1.13	Note: Day 182 is the last day of delamanid dosing. For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 182: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed.	Note: Day 182 is the last day of delamanid dosing. For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 182: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed

Location	Old Text	Updated Text
	• Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Height, weight, and BMI • Percentiles for age • Signs and symptoms of TB • Chest radiograph • Audiometry and visual assessments • Urine pregnancy test for all female subjects who have reached menarche • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, C reactive protein testing and ~~full~~ urinalysis • Blood draw for adrenocorticotropic hormone (ACTH), and adrenal function (cortisol) • Blood draw for thyroid function tests (T4 and thyroid stimulating hormone [TSH]) for patients taking ethionamide or PAS. • Three consecutive 12-lead ECGs. Sequence should be ECG assessment then PK blood draw followed by administration of delamanid. • Blood draw ~~(3 mL)~~ for PK at predose (0 hours). • Delamanid dispensed, if needed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). NOTE: This is the last day of delamanid dosing. • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	• Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine or ***semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Chest radiograph • Audiometry and visual assessments • Urine pregnancy test for all female subjects who have reached menarche • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, C-reactive protein ***(Groups 1 and 2 only)*** testing and urinalysis • Blood draw for ACTH and adrenal function (cortisol) • Blood draw for thyroid function tests (T4 and TSH) for patients taking ethionamide or PAS • Three consecutive 12-lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4).*** Sequence should be ECG assessment then PK blood draw followed by administration of delamanid • Blood draw for PK at predose (0 hours) ***(see Section 3.7.4)*** • Delamanid dispensed, if needed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). NOTE: This is the last day of delamanid dosing • ***Groups 3 and 4 only, palatability assessment of the delamanid pediatric formulation within 25 - 30 minutes postdose (see trial operations manual for details)*** • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, **record date of menarche and/or date of LMP**
Section 3.7.1.14	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 189: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed.	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 189: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after

Location	Old Text	Updated Text
	• Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Blood draw ~~(3 mL)~~ for PK at any time point • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications.	the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight*** • ***BMI and percentiles for age*** • Blood draw for PK at any time point ***(see Section 3.7.4)*** • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications
Section 3.7.1.15	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 196: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Blood draw ~~(3 mL)~~ for PK at any time point • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications.	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 196: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight*** • ***BMI and percentiles for age*** • Blood draw for PK at any time point ***(see Section 3.7.4)*** • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications

Location	Old Text	Updated Text
3.7.1.16	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 203: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Blood draw ~~(3 mL)~~ for PK at any time point • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications.	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 203: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight*** • ***BMI and percentiles for age*** • Blood draw for PK at any time point ***(see Section 3.7.4)*** • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications
3.7.1.17	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 210: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Height, weight, and BMI • Signs and symptoms of TB • Audiometry and visual assessments • Clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • Three consecutive 12-lead ECGs. Sequence should be ECG assessment then PK blood draw at the theoretical predose. • Blood draw ~~(3 mL)~~ for PK at theoretical predose (0 hours). • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 210: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • Three consecutive 12-lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4).*** Sequence should be ECG assessment then PK blood draw at the theoretical predose • Blood draw for PK at theoretical predose (0 hours) ***(see Section 3.7.4)*** • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, **record date of menarche and/or date of LMP**

Location	Old Text	Updated Text
3.7.1.18	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 238: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • Blood draw ~~(3 mL)~~ for PK at any time point. • ~~Height, weight, and BMI~~ • ~~Percentiles for age~~ • Signs and symptoms of TB • Audiometry and visual assessments • Thyroid function tests for those patients taking ethionamide or PAS • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 238: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • Blood draw for PK at any time point ***(see Section 3.7.4)*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Thyroid function tests for those patients taking ethionamide or PAS • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, **record date of menarche and/or date of LMP**
3.7.1.19	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 365: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • ~~Height, weight, and BMI~~ • ~~Percentiles for age~~ • Signs and symptoms of TB • Audiometry and visual assessments • Thyroid function tests for those patients taking ethionamide or PAS • Chest radiograph • Clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-	For all treatment groups the following procedures will be conducted and/or recorded in the patient's eCRF for Day 365: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Signs and symptoms of TB • Audiometry and visual assessments • Thyroid function tests for those patients taking ethionamide or PAS • Chest radiograph • Clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB

Location	Old Text	Updated Text
	TB medications.	medications
Section 3.7.1.20	**3.7.1.20 Treatment Outcome Follow-up (Day 730 (M24) ~~or until treatment for MDR-TB is completed or discontinued, whichever comes first)~~** Treatment outcome information will be collected as routinely documented in the patient medical records or in a National TB Program.	**3.7.1.20 Treatment Outcome Follow-up (Day 730 [Month 24] + *2 Months)*** ***All patients who complete the study will come into the clinic or be contacted by telephone on Day 730 (Month 24) + 2 months for clinical assessment.*** Treatment outcome ***and microbiology*** information will be collected as routinely documented in the patient medical records or in a National TB Program.

Location	Old Text	Updated Text
Section 3.7.1.21	For all patients who early terminate from the trial, the following procedures will be conducted and/or recorded in the eCRF: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed. • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been supine for ≥3 minutes • ~~Height, weight, and BMI~~ • ~~Percentiles for age~~ • Blood draw (3 mL) for PK • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and ~~full~~ urinalysis • Three consecutive 12-Lead ECGs. • Urine pregnancy test for all female subjects who have reached menarche • OBR administration, as prescribed by investigator. • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications. • Record start date of menstrual period and/or date of LMP • Patients who terminate early from Trial 233 prior to their last scheduled visit will have a follow-up contact (phone call or visit) 28 to 32 days after the Early Termination Visit to assess for AEs and IREs. All patients will continue treatment with OBR as prescribed by the investigator according to WHO guidelines.	For all patients who terminate early from the trial, the following procedures will be conducted and/or recorded in the eCRF: • Complete physical examination. Please refer to the trial Operations Manual for details on the assessments to be performed • Vital sign assessments (BP, HR, RR, and body temperature) after the subject has been in a supine ***or semi-recumbent position for ≥ 3 minutes (as possible for Groups 3 and 4); height and weight; and measurement of head circumference for children in Group 4 (ages birth - 2 years, inclusive)*** • ***BMI and percentiles for age*** • Blood draw for PK ***(see Section 3.7.4)*** • Blood draw for clinical laboratory assessments (as per Table 3.7-1): serum chemistry, hematology, coagulation, and urinalysis • Three consecutive 12-Lead ECGs ***after the subject has been in a supine or semi-recumbent position for ≥ 10 minutes (as possible for Groups 3 and 4)*** • Urine pregnancy test for all female subjects who have reached menarche • ***Groups 3 and 4 only and only if prior to Day 182 and within 25 - 30 minutes postdose, palatability assessment of the delamanid pediatric formulation (see trial operations manual for details)*** • OBR administration, as prescribed by investigator • Record AEs and IREs • Record concomitant medications including concomitant anti-TB medications • ***Groups 1 and 2 only***, **record date of menarche and/or date of LMP** • Patients who terminate early from Trial 233 prior to their last scheduled visit will have a follow-up contact (phone call or visit) 28 to 32 days after the Early Termination Visit to assess for AEs and IREs. All patients will continue treatment with OBR as prescribed by the investigator according to WHO guidelines
Section 3.7.1.22	The last dose of delamanid will be given on Day 182. Patients will continue on OBR, as prescribed by the investigator, and have post-delamanid treatment visits on Days 189, 196, 203, 210, 238 (2-month post last dose), Day 365 (6-month post last dose), treatment outcome follow-up on (Day 730 (M24) ~~or until treatment for MDR-TB is completed or discontinued, whichever comes first).~~	The last dose of delamanid will be given on Day 182. Patients will continue on OBR, as prescribed by the investigator, and have post-delamanid treatment visits on Days 189, 196, 203, 210, 238 (2-month post last dose), **and 365 (6-month post last dose), and a treatment outcome follow-up on Day 730 (Month 24)** ***+ 2 months.***

Location	Old Text	Updated Text
Table 3.7.4.1-1	Updated table to indicate which tests are group/cohort specific	Triglycerides (Groups 1 and 2 only) Cholesterol (Groups 1 and 2 only) Urine pregnancy test (for female patients who have reached menarche) C-reactive protein (Groups 1 and 2 only) Drug screen (Groups 1 and 2 only)
Section 3.7.2.2	Complete physical examinations of the head, eyes, ears, nose and throat (HEENT), thorax, abdomen, skin and mucosae, lymph nodes, extremities, BMI and neurological, including body weight and height will be performed and vital signs obtained at the times indicated in Table 3.7-1. The principal investigator or appointed medical doctor (MD) designee is primarily responsible for performing the physical examination. Whenever possible, the same individual should perform all physical examinations for each subject. If the appointed MD designee is to perform the physical examination, he or she must be permitted by local regulations and his/her name must be included on the FDA Form 1572. Any clinically significant condition present at the post treatment examination that was not present at the baseline examination should be documented as an AE and followed to satisfactory conclusion. Vital sign assessments include BP, HR, respiration rate, and body temperature. Vital signs are to be recorded after the subject has remained in a supine position and at rest for ≥3 minutes. When vital signs and safety ECGs are scheduled for the same nominal time, vital sign assessments should be obtained prior to the ECG.	**A complete medical history will be taken at the screening visit, and physical examinations and vital signs measurements will be performed according to the schedule provided in Table 3.7-1.** **A complete physical examination will include examination of the head, eyes, ears, nose, throat, thorax, abdomen, skin and mucosae, lymph nodes, extremities, and urogenital** ***(for Groups 3 and 4, required only at screening and subsequently at the discretion of the investigator)*** **systems.** ***The physical examination will also include a neurological examination and a psychiatric assessment (Groups 1 and 2 only) as described in the trial operations manual.*** The principal investigator or appointed medical doctor designee is primarily responsible for performing the physical examination. Whenever possible, the same individual should perform all physical examinations for each patient. If the appointed medical doctor designee is to perform the physical examination, he or she must be permitted by local regulations and his or her name must be included on FDA Form 1572. Any clinically significant condition present at the post-treatment examination that was not present at the baseline examination should be documented as an AE and followed to satisfactory conclusion. Vital signs assessments include ***head circumference for patients in Group 4 (ages birth - 2 years, inclusive),*** blood pressure, heart rate, respiration rate, and body temperature. Vital signs are to be recorded after the patient has remained in a supine ***or semi-recumbent position and at rest for ≥ 3 minutes (as possible for Groups 3 and 4).*** When vital signs and safety ECGs are scheduled for the same nominal time, vital signs assessments should be obtained prior to the ECG. ***Body weight and height, BMI, and age percentiles will also be recorded.***
Section 3.7.3.3	Twelve-lead ECGs will be recorded with the subject supine and at rest for ≥10 minutes.	Twelve-lead ECGs will be recorded with the subject in a supine ***or semi-recumbent position*** and at rest for ≥ 10 minutes ***(as possible for Groups 3 and 4).***

Location	Old Text	Updated Text
Section 3.7.4	~~Minimal blood volume will be collected at optimal sparse PK sampling times.~~ Approximately 3 mL of blood will be collected per PK sample in the 12 to 17 year old group and 1.5 mL to 3 mL per PK sample in the 6 to 11 year old group. Delamanid data from this trial are to be combined with PK data from Trial 232 for the POPPK analysis.	Approximately 3 mL of blood will be collected per PK sample in the 12- to 17-year-old group (Group 1) ***and 2 mL per PK sample for children ages 11 years and younger (Groups 2, 3, and 4).*** Delamanid data from this trial are to be combined with PK data from Trial 232 for the POPPK analysis.
Section 3.7.4.1	~~Blood will be collected for PK as per the Schedule of Assessments in Table 3.7-1.~~ When blood collection for PK is paired with ECGs, the ECG will be performed first, followed by the PK blood draw, and then, dosing with delamanid. ~~Optimized PK sampling times and volumes will vary according to age/weight group as the trial progresses to younger age groups according to standards put forth in the PIP, applicable norms and standards in the local region, and modified according to findings in the older age groups during the trial, as appropriate.~~	***Blood collection for PK will occur on Days 1 to 2 and 10 to 11. Blood draws will occur at predose (0 hours during treatment) paired with the 12-lead ECGs on Days 1, 56, 154, and 182. A PK blood sample will be obtained on Day 210 paired with the 12-lead ECG at the theoretical predose. Additional PK blood samples will be drawn on Days 14, 98, 189, 196, 203, and 238. A PK blood draw will be collected at ET.*** When blood collection for PK is paired with ECGs, the ECG will be performed first, followed by the PK blood draw, and then ***dosing with delamanid***.
Section 3.7.5	Time-matched ECGs and PK measurements for determination of delamanid and DM 6705 plasma concentrations will be ~~analyzed~~ (see Section 3.7) ~~to determine the relationship of DM-6705 levels to any changes in QTc interval.~~	ECGs and PK measurements for determination of delamanid and DM 6705 plasma concentrations will be ***collected*** (see Section 3.7). ***These assessments should be time-matched if possible.***
Section 3.7.6	~~3.7.6 End of Trial~~ ~~The End of Trial Date is defined as the last Date of Contact or the Date of Final Contact Attempt from the Post-treatment Follow-up eCRF page for the last subject completing or withdrawing from the trial.~~	***3.7.6 Other Assessments*** ***The palatability of the delamanid pediatric formulation will be assessed (Groups 3 and 4 only) within 25 - 30 minutes after the morning dose on Days 1, 28, 56, 182, and ET if prior to Day 182 using an age-appropriate visual hedonic scale and clinical assesssment. See the trial operations manual for details.***
Section 3.7.7	3.7.7 Safety Monitoring Committee To provide trial oversight for the monitoring of patient safety, an independent Safety Monitoring Committee (SMC) will be established. Patient care will be in accordance with the pediatric guidelines for TB in the local region.	3.7.7 End of Trial The end-of-trial date is defined as the last date of contact or the date of the final contact attempt from the post-treatment follow-up eCRF for the last subject completing or withdrawing from the trial.
Section 3.7.8	3.7.7 Safety Monitoring Committee ~~To provide trial oversight for the monitoring of patient safety, an independent Safety Monitoring Committee (SMC) will be established. Patient care will be in accordance with the pediatric guidelines for TB in the local region.~~	3.7.8 Safety Monitoring CommitteeA safety monitoring committee (SMC) composed of external consultants with expertise in pediatric TB and pediatric cardiology will review safety and laboratory test results during the conduct of the trial. The SMC will comprise not less than 2 members who are not involved with enrolling patients into the trial. The SMC will convene and operate based on the availability of patient safety information. The SMC will seek additional independent

Location	Old Text	Updated Text
		expertise, if needed. The primary responsibility of the SMC will be to monitor safety and to determine whether or not the safety concerns merit stopping the trial.
Section 3.8.2	New section	3.8.2 Individual Site The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IRB/IEC at the site. A particular site may be terminated from the trial at the discretion of the investigator, sponsor, or IRB/IEC, eg, for nonenrollment of subjects or noncompliance with the protocol.
Section 3.11	Patients who cannot be contacted on or before the scheduled ~~discharge~~ visit and who do not have a known reason for discontinuation (eg, withdrew consent or AE, etc.) will be classified as "lost to follow-up" as the reason for discontinuation. The site will make 3 attempts to contact the patient/parent or guardian by telephone; in the event the site is unable to reach the patient or parent/guardian by telephone, the site will attempt to contact the patient/parent or guardian via certified mail or an alternative similar method, where appropriate.	Patients who cannot be contacted on or before the scheduled ***M24*** follow-up visit and who do not have a known reason for discontinuation (eg, withdrew consent or AE) will be classified as "lost to follow-up" as the reason for discontinuation. The site will make 3 attempts to contact the patient or parent/guardian***/ legal representative*** by telephone and in the event the site is unable to reach the patient or parent/guardian***/ legal representative*** by telephone, the site will attempt to contact the patient or parent/guardian/***legal representative*** via certified mail or an alternative similar method, as appropriate.
Table 4.1-1		added bedaquiline as an other medication
Section 5.1	•Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate delamanid discontinuation and must be reported on an IRE form to ~~Otsuka Frankfurt Research Institute~~ Pharmacovigilance Region Europe (OFRI PVRE; See also Section 5.4). Pregnancy will only be documented on the AE-eCRF if there is an abnormality or complication.	•Pregnancies are also defined as IREs; although a normal pregnancy is not an adverse event, it will mandate delamanid discontinuation and must be reported on an IRE form to ***Otsuka Europe Development and Commercialisation Ltd (OEDC)*** Pharmacovigilance Region Europe (PVRE) (See also Section 5.4). ***This includes pregnancies occurring in the female partner of a male patient.*** Pregnancy will only be documented on the AE CRF if there is an abnormality or complication
Section 5.1	If this laboratory value is determined by the investigator to be an abnormal change from baseline for that subject, it is considered an AE.	If this laboratory value is determined by the investigator to ***be a clinically significant*** abnormal change from baseline for that patient, it is considered an AE.
Section 5.4	Pregnancy testing will be performed during the screening period prior to trial enrollment and at the ~~end of the treatment period~~ according to the Schedule of Assessments for FOCBP who have reached menarche. If pregnancy is suspected while the patient is taking delamanid during the trial, delamanid must be withheld immediately and if pregnancy is confirmed, the delamanid will be permanently discontinued.	Pregnancy testing will be performed during the screening period prior to study enrollment and at ***the end of the trial*** according to the schedule of assessments for all female patients who have reached menarche. **If pregnancy is suspected while the patient is taking delamanid during the trial, delamanid must be withheld immediately. If pregnancy is confirmed, the delamanid will be permanently discontinued** ***but the patient will not be automatically withdrawn from the trial.***

Location	Old Text	Updated Text
Section 6.1	Delamanid and metabolite plasma concentrations will be reported with descriptive statistics at each visit day per age and dose group. In addition, delamanid plasma ~~concentrations will be included in a delamanid population PK (POPPK) model.~~	Delamanid and metabolite plasma concentrations will be reported with descriptive statistics at each visit day per age group. In addition, delamanid plasma concentrations ***will be analyzed using a POPPK approach.***
Section 6.2	PK/PD relationship analysis will be conducted for DM-6705 plasma concentrations and QTcF prolongation.	Pharmacokinetic/pharmacodynamic relationship analysis will be conducted for ***delamanid and*** DM-6705 plasma concentrations and QTcF prolongation.
Sections 7.4 and 7.5	~~7.4 Pharmacokinetics~~ ~~Descriptive statistics of delamanid and metabolite plasma concentrations will include N, mean, SD, minimum, median, maximum, and % coefficient of variation and will be provided in the clinical study report (CSR). The POPPK analysis, when completed, will be provided together with the data analysis plan (DAP) in a separate report.~~ ~~7.5 Pharmacokinetic/Pharmacodynamic Relationships~~ ~~A PK/PD relationship analysis of DM-6705 plasma concentrations and QTcF prolongation will be conducted using regression analysis. Changes in QTc from baseline will be estimated using the ECG baseline assessment on Day -1 (at theoretical pre-dose time) in Trial 232. The maximal change in QTcF prolongation (with one-sided upper 95% CI] will be reported at the observed mean maximal DM-6705 plasma concentrations.~~	7.4 Efficacy Analyses Because of the small sample sizes per group, large-sample-based statistical methods cannot be used. Exact methods, if available, will be pursued. All statistical presentations will be descriptive. ***7.5 Palatability Analysis*** ***The palatability of the delamanid pediatric formulation will be assessed (Groups 3 and 4 only) using an age-appropriate visual hedonic scale and clinical assessment. The data will be summarized by descriptive statistics (mean, SD, min, max).***
Section 8.1	Trial drugs will be provided to the investigator(s) by the sponsor (or designated agent). ~~Delamanid will be supplied as 50 mg tablets packaged in blister packs.~~ Each blister packs used in the dosing period will be labeled to clearly disclose the compound identification (ID), protocol number, the sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements (see Section 8.1.1).	Investigational medicinal product will be provided to the investigator(s) by the sponsor (or designated agent). ***The IMP will be packaged in blister cards.*** Each blister ***card*** used in the dosing period will be labeled to clearly disclose the compound ID, protocol number, sponsor's name and address, instructions for use, route of administration, and appropriate precautionary statements (see Section 8.1.1).
Section 8.1.1	~~Delamanid will be supplied as 50 mg tablets packaged in blister packs.~~ Each blister pack of delamanid <u>50-mg</u> used during the 182-day dosing period will be labeled to clearly disclose the following information: • Trial/protocol number • Compound ID • Patient ID number or initials (to be filled in by the investigator designee ~~of the trial site(to be filled in by the investigator~~ when delamanid is assigned and/or dispensed to the patient)	Each blister card of delamanid used during the 182-day dosing period will be labeled to clearly disclose the following information: • Trial/protocol number • Compound ID • Patient ID number and/or initials (to be filled in by the investigator/designee when delamanid is assigned and/or dispensed to the patient)

Location	Old Text	Updated Text
Section 11	At a minimum, the IRB/IEC should be supplied with the following documents: trial protocol(s)/amendment(s), written ICFs and ~~consent form~~ updates that the investigators propose for use in the trial, patient recruitment procedures (for example, advertisements), written information to be provided to participants, IB, additional available safety information, information about payments and compensation available to participants, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents the IRB/IEC may need to fulfill its responsibilities.	At a minimum, the IRB/IEC should be supplied with the following documents: trial protocol(s)/amendment(s), written ICFs and ***IFC/assent*** form updates that the investigators propose for use in the trial, patient recruitment procedures (for example, advertisements), written information to be provided to participants, IB, additional available safety information, information about payments and compensation available to participants, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfill its responsibilities.
Section 14		Updated reference list to match updated citations.
Appendix 1	Report Immediately Reportable Events (serious adverse events, liver enzyme elevation cases, pregnancies, and adverse events requiring discontinuation of trial drug) to: Otsuka Europe Development and Commercialisation, Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) Zweigniederlassung Frankfurt am Main Europa-Allee 52 60327 Frankfurt am Main Germany Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry) E-mail: [redacted]	Report Immediately Reportable Events to: Otsuka Europe Development and Commercialisation, Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry) E-mail: [redacted]
Appendix 3	Blood (1.5-3 mL) will be collected into green-top Vacutainer tubes containing sodium heparin anticoagulant.	Blood ***(2 -*** 3 mL) will be collected into green-top Vacutainer® tubes containing sodium heparin anticoagulant.
Appendix 4		Added Amendment 3

ADDITIONAL RISK TO THE SUBJECT:
This amendment will not affect the safety of patients, the scope of the investigation, or the scientific quality of the trial.

Amendment Number: 4

Issue Date: 04 October 2016

PURPOSE: The purpose of this amendment is to add information for Group 4 including weight based computation of dosage, dose adjustment if needed based on weight change during specific visits, to modify the schedule of laboratory assessments in order to meet the required blood volume for younger age groups as mandated by the applicable regulatory authorities, to add and to modify the exclusion criteria, to add holter monitoring in the safety assessments, to reduce the blood volume requirement for PK samples, to add the occurrence of proarryhthmic events in the stopping rule and immediately reportable events, to make minor editorial changes to the text, to make minor content and editorial changes to the Introduction and references, and to update sponsor representative information.

BACKGROUND: In the previous version of the protocol, delamanid pediatric formulation dosing for Group 4 was not yet included, and HIV patients were excluded from the trial. Also, due to the maximum blood volumes allowed to be drawn within a specified time period for pediatric patients of certain weights, the schedule of blood extractions for safety assessments during screening period need to be modified to comply with regulatory guidelines.

MODIFICATIONS TO PROTOCOL:

Bold and underlined text: Changed Text

~~**Bold and strike through text**~~: Deleted Text

Bold and italicized text: Added Text

Global Changes:

- Corrected minor typographical, grammatical, and formatting errors.
- Made minor content and editorial changes and corrections to the Introduction.
- Modified the exclusion criteria.
- Added the weight based computation of delamanid pediatric formulation for Group 4.
- Added holter monitoring in the safety assessments
- Reduce the blood volume requirement for PK sample collection
- Updated the schedule of assessments.
- Added the occurrence of proarryhthmic events in the stopping rule and immediately reportable events.

Sectional Revisions:

Location	Old Text	Updated Text
Title Page	Otsuka Europe Development and Commercialisation Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) Grüneburgweg 102 60323 Frankfurt am Main Germany Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry)	Otsuka Europe Development and Commercialisation Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) Grüneburgweg 102 60323 Frankfurt am Main Germany Fax: [redacted] ***E-mail:*** [redacted] ~~**Phone:** [redacted] **(24h/7d PVRE Blackberry)**~~
Title Page	Added text	***Amendment 4 Issue Date 04 October 2016***

Synopsis (Trial Design)	This is a phase 2, open-label, multiple-dose, multicenter trial to assess the safety, tolerability, PK, and efficacy of delamanid in pediatric patients with MDR-TB over a 6-month treatment period. This long-term trial, an extension of Trial 242-12-232 (Trial 232), will be conducted in patients who have completed Trial 232. The current Trial 242-12-233 (Trial 233) will be conducted sequentially in 4 groups of pediatric patients with MDR-TB.
	
	• Group 1 (ages 12 - 17 years, inclusive) will receive adult formulation delamanid 100 mg BID + OBR (n = 6)
	• Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)
	• Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)
	• Group 4 (ages birth - 2 years, inclusive) will receive pediatric formulation delamanid (dose to be determined) BID + OBR (n = 12)
		This is a phase 2, open-label, multiple-dose, multicenter trial to assess the safety, tolerability, PK, and efficacy of delamanid in pediatric patients with MDR-TB over a 6-month treatment period. This long-term trial, an extension of Trial 242-12-232 (Trial 232), will be conducted in patients who have completed Trial 232. The current Trial 242-12-233 (Trial 233) will be conducted sequentially in 4 groups of pediatric patients with MDR-TB.
		
		• Group 1 (ages 12 - 17 years, inclusive) will receive adult formulation delamanid 100 mg BID + OBR (n = 6)
		• Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)
		• Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)
		• Group 4 (ages birth - 2 years, inclusive) will receive **the following delamanid pediatric formulation (DPF) dose based on patient's body weight during baseline visit** (n = 12)**:**
		  • ***Patient > 10 kg will receive DPF 10 mg BID + OBR***
		  • ***Patient > 8 and ≤ 10 kg will receive DPF 5 mg BID + OBR***

Location	Old Text	Updated Text
		• ***Patient ≤ 8 kg will receive DPF 5 mg QD + OBR*** • ***Delamanid dose will be adjusted as needed for Group 4 patients based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).***
Synopsis (Trial Design (continued))	The trial will comprise the following periods: **Screening Period (Day −30 to −2):** Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the 30-day period immediately after completion of Trial 232 as described in the Schedule of Assessments. **Baseline (Day −1):** Inclusion/exclusion criteria, physical examination, and safety assessments, including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and electrocardiogram (ECG) as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications. **Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination, and other safety assessments, including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly, and collection of adverse events (AEs) and immediately reportable events (IREs), and concomitant medications. **Post-treatment Period (Days 183 to 238):** Physical examination, vital signs, ECGs, safety labs, and sparse blood draws for PK at visits and times described in the Schedule of Assessments. OBR dosing and collection of AEs/IREs, and concomitant medications. **Follow-up Period (Days 239 to 365) Six Month Post Last Delamanid Dose:** Physical examination, height and weight, BMI, percentiles for age, vital signs, signs and symptoms of TB,	The trial will comprise the following periods: **Screening Period (Day −30 to −2):** Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the 30-day period immediately after completion of Trial 232 as described in the Schedule of Assessments. **Baseline (Day −1):** Inclusion/exclusion criteria, physical examination, and safety assessments, including lab tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, ***head circumference (Group 4 only)***, percentiles for age, body mass index (BMI), and electrocardiogram (ECG) as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications. **Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid with meal. OBR administration as prescribed by investigator. Sparse blood draws for PK as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination, and other safety assessments, including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. ***Vital signs, head circumference (Group 4 only)***, **height, weight, and BMI beginning at Week 2,** and collection of adverse events (AEs) and immediately reportable events (IREs), and concomitant medications. **Post-treatment Period (Days 183 to 238):** Physical examination, vital signs, ECGs, safety labs, and sparse blood draws for PK at visits and times described in the Schedule of Assessments. ***Head circumference (Group 4 only), height, weight, signs and symptoms of TB, audiometry and visual assessments, thyroid function tests (for patients taking ethionamide or para-aminosalicylic acid),*** OBR administration, and collection of AEs/IREs and concomitant medications. **Follow-up Period (Days 239 to 365) Six Month Post Last Delamanid Dose:** Physical examination, height and weight, BMI,

Location	Old Text	Updated Text
	chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or para-aminosalicylic acid, OBR administration, and collection of AEs/IREs and concomitant medications. **Treatment Outcome Follow-up (Day 730 [Month 24] + 2 months):** Collection of treatment outcome information as routinely documented in the patient medical records or in a national TB program.	percentiles for age, vital signs, ***head circumference (Group 4 only), height, weight,*** signs and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or para-aminosalicylic acid), OBR administration, and collection of AEs/IREs and concomitant medications. **Treatment Outcome Follow-up (Day 730 [Month 24] + 2 months):** All patients will either visit the clinic or be contacted by telephone for clinical assessment. Collection of treatment outcome information as routinely documented in the patient medical records or in a national TB program.
Synopsis (InclusionExclusion Criteria)	Key Exclusion Criteria: • Patients who have not completed Trial 232 • Children with a positive test result for human immunodeficiency virus (HIV) or who have been previously identified as having HIV or with laboratory evidence of active hepatitis B or C • History of allergy to metronidazole and any disease or condition in which metronidazole is required • Use of amiodarone within 12 months prior to the first dose of investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within 30 days prior to the first dose of IMP • Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment) • Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds • Abnormalities in screening electrocardiogram (ECG) (including atrioventricular block, bundle branch block or hemi-block, QRS prolongation > 120 msec, or QT interval corrected using Fridericia's method (QTcF) > 450 msec in both males and females) • A concomitant condition such as renal impairment	Key Exclusion Criteria: • Patients who have not completed Trial 232 • **<u>Children with laboratory evidence of active hepatitis B or C</u>** • ***Children with body weight < 5.5 kg.*** • ***For patients with HIV co-infection, CD4 cell count ≤ 1000/mm^3 for children 1-5 years old, and ≤ 1500/mm^3 for children less than 1 year old*** • History of allergy to metronidazole and any disease or condition in which metronidazole is required • Use of amiodarone within 12 months prior to the first dose of investigational medicinal product (IMP) or use of other predefined antiarrhythmic medications within 30 days prior to the first dose of IMP • Serious concomitant conditions (cardiovascular disorders, severe respiratory disease, severe diarrheal disease, renal, hepatic, or neurological impairment) • Preexisting cardiac conditions including but not limited to structural cardiac disease including suspected TB involvement of the heart on clinical or radiographic grounds • Abnormalities in screening electrocardiogram (ECG) (including atrioventricular block, bundle branch block or hemi-block, QRS prolongation > 120 msec, or QT interval corrected using Fridericia's method (QTcF) > 450 msec in both males

Location	Old Text	Updated Text
	characterized by serum creatinine levels > 1.5 mg/dL, hepatic impairment (alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of normal [ULN]), or hyperbilirubinemia characterized by total bilirubin > 2x ULN • Concurrent diagnosis of severe malnutrition or kwashiorkor • Positive urine drug screen (Groups 1 and 2 only) • Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP and/or any prior or concurrent use bedaquiline • Lansky Play Performance Score < 50 or Karnofsky Score < 50 • Administered an IMP within 1 month prior to Visit 1 other than delamanid given as IMP in Trial 232 Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form (Groups 1 and 2 only)	and females) • A concomitant condition such as renal impairment characterized by serum creatinine levels > 1.5 mg/dL, hepatic impairment (alanine aminotransferase or aspartate aminotransferase > 3 times the upper limit of normal [ULN]), or hyperbilirubinemia characterized by total bilirubin > 2x ULN • Concurrent diagnosis of severe malnutrition or kwashiorkor • Positive urine drug screen (Groups 1 and 2 only) • Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP and/or any prior or concurrent use ***of*** bedaquiline • Lansky Play Performance Score < 50 ***(not applicable for children < 1 year old)*** or Karnofsky Score < 50 • Administered an IMP within 1 month prior to Visit 1 other than delamanid given as IMP in Trial 232 • Pregnant, breast-feeding, or planning to conceive or father a child within the timeframe described in the informed consent form (Groups 1 and 2 only)
Synopsis (Investigational Medicinal Product, Dose, Formulation, Mode of Administration:	Delamanid pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension to Groups 3 and 4 for 6 months: • Group 3 (ages 3 to 5 years, inclusive) - 25 mg (1 x 25-mg tablet) BID • Group 4 (ages birth to 2 years, inclusive) - dose to be determined	Delamanid pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension to Groups 3 and 4 for 6 months: • Group 3 (ages 3 to 5 years, inclusive) - 25 mg (1 x 25-mg tablet) BID • Group 4 (ages birth to 2 years, inclusive) - **<u>will receive the following dose depending on patient's weight:</u>** • ***Patient > 10 kg will receive pediatric formulation delamanid 10 mg BID + OBR*** • ***Patient > 8 and ≤ 10 kg will receive pediatric formulation delamanid 5 mg BID + OBR*** • ***Patient ≤ 8 kg will receive pediatric formulation delamanid 5 mg QD + OBR***

Location	Old Text	Updated Text
Synopsis (Criteria for Evaluation)	The primary criteria for evaluation in this trial are: • Safety and Tolerability: assessed by physical examination, vital signs, treatment-emergent adverse events (TEAEs), ECGs, and clinical laboratory tests • Pharmacokinetics: Delamanid and metabolite plasma concentrations at each visit day per age and dose group	The primary criteria for evaluation in this trial are: • Safety and Tolerability: assessed by physical examination, vital signs, treatment-emergent adverse events (TEAEs), ECGs, ***Holter monitoring (if applicable),*** and clinical laboratory tests • Pharmacokinetics: Delamanid and metabolite plasma concentrations at each visit day per age and dose group
Synopsis (Endpoints)	The primary endpoints in this trial are: • Safety and tolerability: Changes in physical examination including visual testing and audiometry during screening, TEAEs, vital signs, ECGs, and clinical laboratory tests	The primary endpoints in this trial are: • Safety and tolerability: Changes in physical examination including visual testing and audiometry during screening, TEAEs, vital signs, ECGs, ***holter monitoring (if applicable),*** and clinical laboratory tests
List of Abbreviations and Definitions of Terms	Added text	Abbreviation — Defintion ***CD4 cell*** — ***Cluster of differentiation 4 (helper/inducer T-lymphocyte)***
Section 1	Justification for Exclusion of HIV Co-infected Patients Tuberculosis and HIV/AIDS constitute the main burden of infectious disease in resource-limited countries.[45] Tuberculosis remains the most common opportunistic infection and is the most common cause of death in HIV-infected patients.[46] In HIV-affected communities, the highest TB incidence rates now occur among men and women in their reproductive years (ages 20 to 45 years) who are likely to be parents of young and vulnerable children.[30] However, HIV coinfected children will be excluded from this trial because the diagnosis, management, and treatment of TB in the presence of HIV coinfection are complicated by the following factors[28]: • The tuberculin skin test is much less sensitive in HIV-infected children than in those without HIV. • Smear microscopy is less sensitive in HIV-infected individuals who are more likely to have smear-negative	~~**Justification for Exclusion of HIV Co-infected Patients**~~ ~~**Tuberculosis and HIV/AIDS constitute the main burden of infectious disease in resource-limited countries.[45] Tuberculosis remains the most common opportunistic infection and is the most common cause of death in HIV-infected patients.[46] In HIV-affected communities, the highest TB incidence rates now occur among men and women in their reproductive years (ages 20 to 45 years) who are likely to be parents of young and vulnerable children.[30] However, HIV coinfected children will be excluded from this trial because the diagnosis, management, and treatment of TB in the presence of HIV coinfection are complicated by the following factors[28]:**~~ ~~• **The tuberculin skin test is much less sensitive in HIV-infected children than in those without HIV.**~~ ~~• **Smear microscopy is less sensitive in HIV-infected individuals who are more likely to have smear-negative disease.**~~

Location	Old Text	Updated Text
	disease. • Chronic pulmonary symptoms may be related to HIV-related conditions, such as gastroesophageal reflux disease, bronchiectasis, and other opportunistic infections that reduce the specificity of symptom-based diagnostic approaches. • Weight loss or failure to thrive are typical characteristics of both TB and HIV infections. • Rapid TB progression is more likely to occur in HIV-infected children, reducing the sensitivity of diagnostic and treatment approaches that focus on persistent, nonremitting symptoms.[6] • Interpretation of chest radiographs is complicated by HIV-associated comorbidities, such as bacterial pneumonia, lymphocytic interstitial pneumonitis, bronchiectasis, pulmonary Kaposi sarcoma, and the atypical presentation of TB.[35] • Treatment of both HIV and TB are complicated by overlapping side effects, the immune reconstitution inflammatory syndrome, drug-drug interactions, and high pill burden, all with the potential to complicate adherence.	~~• Chronic pulmonary symptoms may be related to HIV-related conditions, such as gastroesophageal reflux disease, bronchiectasis, and other opportunistic infections that reduce the specificity of symptom-based diagnostic approaches.~~ ~~• Weight loss or failure to thrive are typical characteristics of both TB and HIV infections.~~ ~~• Rapid TB progression is more likely to occur in HIV-infected children, reducing the sensitivity of diagnostic and treatment approaches that focus on persistent, nonremitting symptoms.[6]~~ ~~• Interpretation of chest radiographs is complicated by HIV-associated comorbidities, such as bacterial pneumonia, lymphocytic interstitial pneumonitis, bronchiectasis, pulmonary Kaposi sarcoma, and the atypical presentation of TB.[35]~~ ~~• Treatment of both HIV and TB are complicated by overlapping side effects, the immune reconstitution inflammatory syndrome, drug-drug interactions, and high pill burden, all with the potential to complicate adherence.~~
Section 1.3.1 through 1.3.2		Minor editorial and content updates.
Section 1.4.1	As of 26 Mar 2014, 887 adult subjects have been exposed to oral doses of delamanid in 17 completed trials in Japan, China, South Africa, Peru, Korea, Philippines, Egypt, the European Union, and the United States. Of these 887 adult subjects, 422 were healthy subjects, 60 were patients with uncomplicated DS-TB, 395 were patients with MDR-TB, and 10 were patients with MDR-TB refractory to treatment. Of these 887 adult subjects, 791 subjects (338 healthy subjects, 48 patients with uncomplicated DS-TB, 395 patients with MDR-TB, and 10 patients with MDR-TB refractory to treatment) have been exposed to oral doses of delamanid tablets (ie, the modified spray-dried tablet formulation).	**As of 31 Jan 2016, a total of 949 adult subjects (484 healthy adult subjects, 60 adult patients with uncomplicated DS-TB, 395 adult patients with MDR-TB, 10 adult patients with MDR-TB refractory to treatment) have been exposed to oral doses of delamanid in 19 completed trials.** **In addition, a total of 22 healthy adult subjects and 511 adult subjects with MDR-TB have been exposed to either delamanid or placebo (trial is still blinded) in ongoing trials (Trials 242-201-00001 and 242-09-213, respectively).** **Fourteen children (ages 3 - 17 years) with MDR-TB have also been exposed to oral doses of delamanid in 2 ongoing, open-label,**

Location	Old Text	Updated Text
		pediatric trials (Trials 242-12-232 and 242-12-233).
Section 1.4.1	As of 31 Jan 2014 in Trial 242-09-213, the ongoing phase 3, randomized, double-blind, and placebo-controlled trial conducted in MDR-TB patients to determine the safety, PK, and efficacy of delamanid plus OBR versus placebo plus OBR, enrollment was complete and 511 patients had begun blinded treatment. Three deaths had been reported, 65 patients had reported SAEs, and 8 patients had discontinued IMP due to TEAEs.[1] Refer to the IB for additional information on the delamanid safety profile.[1]	As of 31 Jan **2016** in Trial 242-09-213, the ongoing phase 3, randomized, double-blind, and placebo-controlled trial conducted in MDR-TB patients to determine the safety, PK, and efficacy of delamanid plus OBR versus placebo plus OBR, enrollment was complete and 511 patients had begun blinded treatment. ~~**Three deaths had been reported, 65 patients had reported SAEs, and 8 patients had discontinued IMP due to TEAEs.**~~[1] ***A total of 238 serious TEAEs occurred. The most frequently reported serious TEAEs were hypokalaemia (12 [2.3%]), tuberculosis (14 [2.7%]), deafness bilateral (8 [1.6%]), acute kidney injury (8 [1.6%]), electrocardiogram QT prolonged (7 [1.4%]), haemoptysis (5 [1.0%]), and hepatotoxicity (5 [1.0%]). Nineteen deaths (19/511; [3.7%]) were reported for patients with MDR-TB. Two patients died due to acute respiratory failure (one of these patients also had worsening of MDR TB), 2 patients died due to haemoptysis, 2 patients died due to disseminated tuberculosis and sepsis, one due to cardiac arrest and pneumonia, and one patient each died of cardiopulmonary failure, myocardial ischemia, pulmonary edema, pulmonary embolism, respiratory failure, acute myocardial infarction, hypothermia, metastatic neoplasm of unknown primary site, squamous cell carcinoma of lung, renal impairment, lung adenocarcinoma metastatic, and completed suicide. All of these events were considered by the investigator as unrelated or unlikely related to IMP.***[1] ***In the ongoing trials in pediatric patients with MDR TB (Trials 242-12-232 and 242-12-233), there was 1 serious TEAE of non-Hodgkin's lymphoma reported as of the cutoff date of 31 Jan 2016.***[1]
Section 2.1	Trial 232 was designed to define the pediatric dose that will result in a delamanid systemic exposure (AUC) equivalent to that observed in the pivotal adult trials where efficacy against MDR-TB has been demonstrated.	Trial 232 was designed to define the pediatric dose ***in patients between 0-17 years of age*** that will result in a delamanid systemic exposure (AUC) equivalent to that observed in the pivotal adult trials where efficacy against MDR-TB has been demonstrated.
Section 2.1	Patients in each age group will be sequentially enrolled into this 6-month treatment extension trial (Trial 233) to evaluate the	Patients in each age group will be sequentially enrolled into this 6-month treatment extension trial (Trial 233) to evaluate the safety,

Location	Old Text	Updated Text
	safety, tolerability, PK, and efficacy of delamanid during the extended time period planned in this trial for treatment of MDR-TB. To be eligible for Trial 233, all patients must rollover within 30 days of completing Trial 232.	tolerability, PK, efficacy, ***and palatability*** of delamanid during the extended time period planned in this trial for treatment of MDR-TB. To be eligible for Trial 233, all patients must rollover within 30 days of completing Trial 232.
Section 2.2	Delamanid will be administered to pediatric MDR-TB patients on OBR therapy. Children will be given delamanid BID in agreement with the delamanid dosing regimen for adult MDR-TB patients, which is BID treatment for 6 months.	Delamanid will be administered to pediatric MDR-TB patients on OBR therapy. Children will be given delamanid BID ***(except for the 5.5-8 kg group who will receive a QD dose)*** in agreement with the delamanid dosing regimen for adult MDR-TB patients, which is BID treatment for 6 months.
Section 2.2	Younger children (ages birth to 5 years, inclusive) will be given 25-mg pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension. The delamanid dose for children ages 3 to 5 years, inclusive (Group 3) will be 25 mg BID. The delamanid dose for children ages birth to 2 years, inclusive (Group 4), will be confirmed using the PK, safety, and tolerability findings in the older age groups and based on the bioavailability of the pediatric formulation.	Younger children (ages birth to 5 years, inclusive) will be given pediatric dispersible tablets admixed with water and administered orally as an extemporaneous suspension. Children ages 3 to 5 years, inclusive (Group 3) will be given pediatric delamanid formulation 25 mg BID. ***The delamanid dose for children ages birth to 2 years, inclusive (Group 4), will be determined based on body weight during baseline visit. Children with weight > 10 kg will be given delamanid pediatric formulation (DPF) , 10 mg BID, those with weight > 8 and ≤ 10 kg will be given DPF 5 mg BID, while children with weight ≤ 8 kg will receive DPF 5 mg QD. Delamanid dose will be adjusted as needed for Group 4 patients based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).*** **Delamanid doses in younger children were** confirmed using the PK, safety, and tolerability findings in the older age groups and based on the bioavailability of the pediatric formulation.
Section 3.1	Delamanid will be administered twice daily for 182 days. The trial will be conducted sequentially in 4 groups of pediatric patients: • Group 1 (ages 12 - 17 years, inclusive) will receive adult	**Delamanid will be administered for 182 days.** The trial will be conducted sequentially in 4 groups of pediatric patients: • Group 1 (ages 12 - 17 years, inclusive) will receive adult formulation delamanid 100 mg BID + OBR (n = 6)

Location	Old Text	Updated Text

	formulation delamanid 100 mg BID + OBR (n = 6)
	• Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)
	• Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)
	• Group 4 (ages birth - 2 years, inclusive) will receive pediatric formulation delamanid BID + OBR (n = 12) (dose will be determined after data from at least 6 subjects from Group 3 in Trial 232 is available)
	The trial will comprise the following periods:
	• **Screening Period (Day −30 to −2):** Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the post-Trial 232 thirty (30)-day screening period for Trial 233, as described in the Schedule of Assessments
	• **Baseline (Day −1):** Inclusion/exclusion criteria, physical examination, and safety assessments including laboratory tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications
	• **Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid. PK sampling every 2 weeks through Week 14 at 0 hours predose, then as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination, and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. Height, weight, and BMI beginning at Week 2 and assessed monthly. OBR administration as prescribed by the investigator and collection of AEs, immediately reportable events (IREs), and concomitant medications
		• Group 2 (ages 6 - 11 years, inclusive) will receive adult formulation delamanid 50 mg BID + OBR (n = 6)
		• Group 3 (ages 3 - 5 years, inclusive) will receive pediatric formulation delamanid 25 mg BID + OBR (n = 12)
		• Group 4 (ages birth - 2 years, inclusive) will receive ***the following delamanid pediatric formulation (DPF) dose based on body weight during baseline visit.(n = 12):***
		  • ***Patient > 10 kg will receive DPF 10 mg BID + OBR***
		  • ***Patient > 8 and ≤ 10 kg will receive DPF 5 mg BID + OBR***
		  • ***Patient ≤ 8 kg will receive DPF5 mg QD + OBR***
		Delamanid dose will be adjusted as needed for Group 4 patients based on the weight measurement at specified study visits (Visits 5, 7, 9, 11 and 12).
		The trial will comprise the following periods:
		• **Screening Period (Day −30 to −2):** Study data will either be taken from screening or Day 10 of Trial 232 or will be performed during the post-Trial 232 thirty (30)- day screening period for Trial 233, as described in the Schedule of Assessments
		• **Baseline (Day −1):** Inclusion/exclusion criteria, physical examination, and safety assessments including laboratory tests, signs and symptoms of tuberculosis (TB), audiometry and visual assessments, vital signs, height, weight, ***head circumference (Group 4 only),*** percentiles for age, body mass index (BMI), and ECG as described in the Schedule of Assessments. OBR administration as prescribed by investigator, and recording of concomitant medications
		• **Treatment Period (Days 1 to 182):** Morning and evening dosing of delamanid. PK sampling every 2 weeks through Week 14 at 0 hours predose, then as described in the Schedule of Assessments. Signs and symptoms of TB, physical examination, and other safety assessments including safety lab tests. Audiometry and visual assessments, and ECG at weeks and times shown in the Schedule of Assessments. ***Vital signs, head circumference (Group 4 only),*** **height, weight, and**

Location	Old Text	Updated Text
	• **Post-treatment Period (Days 183 to 238):** Physical examination, vital signs, ECGs, safety labs, blood draws for PK at visits and times described in the Schedule of Assessments. OBR administration as prescribed by the investigator and collection of AEs/IREs, and concomitant medications • **Follow-up Period (Days 239 to 365, 6 month Post Last Delamanid Dose Visit):** Physical examination, height and weight, BMI, percentiles for age, vital signs, signs and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or para aminosalicylic acid), OBR administration as prescribed by the investigator and collection of AEs/IREs and concomitant medications • **Treatment Outcome Follow-up (Day 730 [Month 24] + 2 months:** Collection of treatment outcome information as routinely documented in the patient medical records or in a national TB program	**BMI beginning at Week 2.** OBR administration as prescribed by the investigator and collection of AEs, immediately reportable events (IREs), and concomitant medications • **Post-treatment Period (Days 183 to 238):** Physical examination, vital signs, ECGs, safety labs, blood draws for PK at visits and times described in the Schedule of Assessments. ***Head circumference (Group 4 only), height, weight, signs and symptoms of TB, audiometry and visual assessments, thyroid function tests (for patients taking ethionamide or para-aminosalicylic acid),*** OBR administration as prescribed by the investigator and collection of AEs/IREs, and concomitant medications • **Follow-up Period (Days 239 to 365, 6 month Post Last Delamanid Dose Visit):** Physical examination, height and weight, BMI, percentiles for age, vital signs, ***head circumference (Group 4 only), height, weight,*** signs and symptoms of TB, chest radiograph, audiometry and visual assessments, safety labs, thyroid function tests (for patients taking ethionamide or para aminosalicylic acid), OBR administration as prescribed by the investigator and collection of AEs/IREs and concomitant medications • **Treatment Outcome Follow-up (Day 730 [Month 24] + 2 months:** ***All patients will either visit the clinic or be contacted by telephone for clinical assessment.*** Collection of treatment outcome information as routinely documented in the patient medical records or in a national TB program
Figure 3.1-1	Delamanid BID + OBR Safety, PK, Efficacy Evaluations	Delamanid BID***/QD*** + OBR Safety, PK, Efficacy Evaluations
Section 3.2	Patients will be assigned by age group to receive one of the following treatments for 182 days: 1) Group 1 (12 to 17 years, inclusive): adult formulation delamanid 100 mg BID (administered as 2 x 50-mg tablets BID) + OBR	Patients will be assigned by age group to receive one of the following treatments for 182 days: 1) Group 1 (12 to 17 years, inclusive): adult formulation delamanid 100 mg BID (administered as 2 x 50-mg tablets BID) + OBR

Location	Old Text	Updated Text
	2) Group 2 (6 to 11 years, inclusive): adult formulation delamanid 50 mg BID (administered as 1 x 50-mg tablet BID) + OBR 3) Group 3 (3 to 5 years, inclusive): pediatric formulation delamanid 25 mg BID (administered as 1 x 25-mg tablet BID) + OBR 4) Group 4 (birth to 2 years, inclusive): pediatric formulation delamanid + OBR (dose will be determined after data from at least 6 subjects from Group 3 in Trial 232 are available) Patient age group and dosing will be determined at the time of enrollment into Trial 232 and will not change during rollover into Trial 233	2) Group 2 (6 to 11 years, inclusive): adult formulation delamanid 50 mg BID (administered as 1 x 50-mg tablet BID) + OBR 3) Group 3 (3 to 5 years, inclusive): pediatric formulation delamanid 25 mg BID (administered as 1 x 25-mg tablet BID) + OBR ***4)*** Group 4 (birth to 2 years, inclusive): ***pediatric formulation delamanid based on body weight + OBR. Children with weight > 10 kg will be given delamanid pediatric formulation (DPF) 10 mg BID (administered as 2 x 5-mg dispersible tablet) + OBR; Children with weight > 8 and ≤ 10 kg will be given DPF 5 mg BID (administered as 1 x 5-mg dispersible tablet) + OBR, and children with weight ≤ 8 kg will be given DPF delamanid 5 mg QD (administered as 1 x 5-mg dispersible tablet) + OBR.*** **Patient age group and dosing *(Groups 1, 2 and 3)* will be determined at the time of enrollment into Trial 232 and will not change during rollover into Trial 233.** ***Dosing for Group 4 will be determined during baseline visit and will be adjusted based on weight measurement during specific study visits (Visits 5, 7, 9, 11 and 12).***
Table 3.4.3-1	2. Children with a positive test for HIV or who have been previously identified as having HIV or with laboratory evidence of hepatitis B or C	2.Children with ~~**a positive test for HIV or who have been previously identified as having HIV or with**~~ laboratory evidence of hepatitis B or C ***3. Children with body weight < 5.5 kg.*** ***4. For patients with HIV co-infection, CD4 cell count ≤ 1000/mm3 for children 1-5 years old, and ≤ 1500/mm3 for children less than 1 year old.***
Table 3.4.3-1		Minor revisions on number sequence.
Table 3.4.3-1	Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP	Use of rifampicin and/or moxifloxacin within 1 week prior to the first dose of IMP ***and/or any prior concurrent use of bedaquiline***

Location	Old Text	Updated Text
Table 3.4.3-1	Lansky Play Performance Score < 50 or Karnofsky Score < 50	Lansky Play Performance Score < 50 ***(not applicable for children < 1 year old)*** or Karnofsky Score < 50
Section 3.4.3	Patients ages 12 to 17 years excluded for a positive drug/alcohol screen are not eligible to be rescreened for participation in the trial.	Patients ages **6** to 17 years excluded for a positive drug/alcohol screen are not eligible to be rescreened for participation in the trial.
Section 3.5.1.1	Safety and tolerability of delamanid will be assessed by the following variables: • Reported TEAEs • Physical examination including visual testing and audiometry • Vital signs • ECGs • Clinical laboratory assessments (hematology, serum chemistry, urinalysis, and other laboratory tests [see Table 3.7.3.1-1])	Safety and tolerability of delamanid will be assessed by the following variables: • Reported TEAEs • Physical examination including visual testing and audiometry • Vital signs • ECGs • ***Holter monitoring (if applicable)*** • Clinical laboratory assessments (hematology, serum chemistry, urinalysis, and other laboratory tests [see Table 3.7.3.1-1])
Section 3.5.2.3	The palatability of the pediatric formulation will be assessed using an-age appropriate visual hedonic scale and clinical assessment.	The palatability of the pediatric formulation will be assessed using an-age appropriate visual hedonic scale and clinical assessment ***(Groups 3 and 4 only).***
Section 3.7	Delamanid will be administered twice daily with a standard meal for the duration of the trial. OBR will be administered as prescribed, under the DOTS guidelines of the WHO.	Delamanid will be administered **~~twice daily~~** with a standard meal for the duration of the trial. OBR will be administered as prescribed, under the DOTS guidelines of the WHO.
Table 3.7.1	Numerous updates to assessments and schedule	**Updates include:** - **ACTH test, Adrenal function and Thyroid function in Visit 13 was moved to Visit 14.** - **Minor revisions in reference to footnote**
Table 3.7.1	Additional footnotes	***t For Group 4 only, delamanid dose will be adjusted based on the subject's weight measurement during study visit*** ***" Twenty-four-hour Holter monitor tracing if QTcF > 490 msec.*** ***v Not required if patient had a documented HIV test and result within 1 year prior to the screening visit AND there is no known exposure to HIV.***

Location	Old Text	Updated Text
		w Screening CD4 cell count test will only be performed for patients with positive HIV test results unless the patient has documented CD4 cell count test and results within 3 months prior to screening visit.
Section 3.7.1.1	• Laboratory assessments including serum chemistry, hematology and coagulation, urinalysis, HIV, hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), adrenocorticotropic hormone (ACTH), adrenal function (cortisol), C-reactive protein (Groups 1 and 2 only), and thyroid function tests (T4 and thyroid stimulating hormone [TSH])	• Laboratory assessments including serum chemistry, hematology and coagulation, urinalysis, HIV, ***CD4 cell count (if HIV test is positive)***, hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), adrenocorticotropic hormone (ACTH), adrenal function (cortisol), C-reactive protein (Groups 1 and 2 only), and thyroid function tests (T4 and thyroid stimulating hormone [TSH])
Section 3.7.1.3	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening)	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~ ***For Group 4, delamanid dosing will be determined based on weight measurement during baseline visit.***
Section 3.7.1.3	Added text	• ***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec following the first dosing of delamanid pediatric formulation.***
Section 3.7.1.4	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening).	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~
Section 3.7.1.5	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening)	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~ ***For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.***
Section 3.7.1.5	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***
Section 3.7.1.6	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator).

Location	Old Text	Updated Text
	investigator). Delamanid will be administered twice daily (morning and evening).	~~Delamanid will be administered twice daily (morning and evening).~~
Section 3.7.1.7	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening).	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~ ***For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.***
Section 3.7.1.7	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***
Section 3.7.1.8	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening).	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~
Section 3.7.1.9	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening).	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ***For Group 4 Delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.***
Section 3.7.1.9	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***
Section 3.7.1.10	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening).	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~
Section 3.7.1.11	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily	Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~

Location	Old Text	Updated Text
	(morning and evening)	***For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.***
Section 3.7.1.11	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***
Section 3.7.1.12	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening)	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~ ***For Group 4 only, delamanid dosing will be adjusted as needed based on weight measurement during this visit. Study personnel must determine whether or not delamanid dosing will be adjusted prior to IWRS drug dispensation.***
Section 3.7.1.12	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***
Section 3.7.1.13	• Delamanid dispensed (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). Delamanid will be administered twice daily (morning and evening). NOTE: This is the last day of delamanid dosing	• Delamanid ***dosing*** (plus OBR administration either one hour before or one hour after delamanid dosing, as prescribed by investigator). ~~**Delamanid will be administered twice daily (morning and evening).**~~ NOTE: This is the last day of delamanid dosing
Section 3.7.1.13	Deleted text	~~• Blood draw for ACTH and adrenal function (cortisol)~~ ~~• Blood draw for thyroid function tests (T4 and TSH) for patients taking ethionamide or PAS~~
Section 3.7.1.13	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***
Section 3.7.1.14	Added text	• ***Blood draw for ACTH and adrenal function (cortisol)*** • ***Blood draw for thyroid function tests (T4 and TSH) for patients taking ethionamide or PAS***
Section 3.7.1.17	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***
Section 3.7.1.19	Added text	***Obtain twenty-four-hour Holter monitor tracing if QTcF > 490 msec***

Location	Old Text	Updated Text
Table 3.7.3.1-1	Other Laboratory Tests Morning cortisol Thyroid function tests (serum thyroid stimulating hormone and free T4) Urine pregnancy test (for female patients who have reached menarche) Adrenocorticotropic (screening only) HIV (screening only) Hepatitis B surface antigen (screening HBsAg only) Antibody to hepatitis C virus (screening only) C-reactive protein (Groups 1 and 2 only	Other Laboratory Tests - Morning cortisol - Thyroid function tests (serum thyroid stimulating hormone and free T4) - Urine pregnancy test (for female patients who have reached menarche) - Adrencorticotropic ***hormone*** ~~**(screening only)**~~ - HIV (screening only[a]) - ***CD4 cell count (screening only[b])*** - Hepatitis B surface antigen (screening HBsAg only) - Antibody to hepatitis C virus (screening only) - C-reactive protein (Groups 1 and 2 only) ***[a] Not required if patient had a documented HIV test and result within 1 year prior to the screening visit AND there is no known exposure to HIV.*** ***[b] Screening CD4 cell count test will only be performed for patients with positive HIV test results unless the patient has documented CD4 cell count test and results within 3 months prior to screening visit.***
Section 3.7.4	Approximately 3 mL of blood will be collected per PK sample in the 12- to 17-year-old group (Group 1) and 2 mL per PK sample for children ages 11 years and younger (Groups 2, 3, and 4). Delamanid data from this trial are to be combined with PK data from Trial 232 for the POPPK analysis.	Approximately 3 mL of blood will be collected per PK sample in the 12- to 17-year-old group (Group 1); **2 mL per PK sample for in the 3- to 11-year-old children** (Groups 2 and 3) and ***0.6 mL per PK sample for children ages 2 years and (Group 4).*** Delamanid data from this trial are to be combined with PK data from Trial 232 for the POPPK analysis.
Section 3.8.1	2. Occurrence of QTcF > 500 msec	2. Occurrence of QTcF > 500 msec ***or occurrence of proarrhythmic events***
Section 4.1	Table 4.1-1 List of Medications Prohibited Prior to and During the Treatment Period of the Trial Anti-Arrhythmic medications with potential for QT interval prolongation 1. Quinidine 2. Procainamide 3. Disopyramide 4. Encainide	Table 4.1-1 List of Medications Prohibited Prior to and During the Treatment Period of the Trial Anti-Arrhythmic medications with potential for QT interval prolongation 1. Quinidine 2. Procainamide 3. Disopyramide 4. Encainide

Location	Old Text	Updated Text
	5. Flecainide 6. Sotalol 7. Amiodarone 8. Digitalis Other Medications With Potential For QT Interval Prolongation 1. Moxifloxacin Other Medications 1. Antiretroviral Medications 2. Rifampicin 3. Bedaquiline	5. Flecainide 6. Sotalol 7. Amiodarone 8. Digitalis Other Medications With Potential For QT Interval Prolongation 1. Moxifloxacin Other Medications **1. Rifampicin** **2. Bedaquiline**
Section 5.1	QTcF interval prolongation > 500 msec	QTcF interval prolongation > 500 msec ***or occurrence of proarrhythmic event***
Section 5.2.3	QTcF interval prolongation > 500 msec	QTcF interval prolongation > 500 msec ***or occurrence of proarrhythmic event***
Section 5.2.3	E-mail: [redacted] Fax: [redacted] Phone: [redacted] (PVRE Blackberry 24h/7d)	E-mail: [redacted] Fax: [redacted] ~~Phone: [redacted] (PVRE Blackberry 24h/7d)~~
Section 6.2	Pharmacokinetic/pharmacodynamic relationship analysis will be conducted for delamanid and DM-6705 plasma concentrations and QTcF prolongation.	**Delamanid and DM-6705 plasma concentrations will be examined in conjunction with QTcF data to explore if there is a PK/PD correlation.**
Section 7.3.2	The quantitative change in clinical chemistry, hematology, coagulation, and urinalysis assessment results will be calculated relative to baseline. Baseline is defined as the last measurement before the first administration of delamanid. Thyroid function tests and ACTH will be measured at baseline only. Summary statistics for quantitative laboratory assessment results will be presented by treatment (age) group and visit for the change from baseline (Day −1) will be provided. Shift tables will be produced for assessing changes from baseline in clinical laboratory measurements.	The quantitative change in clinical chemistry, hematology, coagulation, and urinalysis assessment results will be calculated relative to baseline. Baseline is defined as the last measurement before the first administration of delamanid. ~~**Thyroid function tests and ACTH will be measured at baseline only.**~~ Summary statistics for quantitative laboratory assessment results will be presented by treatment (age) group and visit for the change from baseline (Day −1) will be provided. Shift tables will be produced for assessing changes from baseline in clinical laboratory measurements.
Section 14	Otsuka Maryland Research Institute. OPC-67683 Investigator's	**Otsuka Maryland Research Institute. OPC-67683 Investigator's**

Location	Old Text	Updated Text
	Drug Brochure, edition 10. Otsuka Report, issued May 2014.	**Drug Brochure, edition 12. Otsuka Report, issued April 2016.**
References	[45] Pawlowski A, Johnson M, Skold M, Rottenberg ME, Kallenius G. Tuberculosis and HIV co-infection. PLoS Path. 1012;8:1-5. [46] Reid A, Scano F, Getahun H, et al. Towards universal access to HIV prevention, treatment, care, and support: the role of TB/HIV collaboration. Lancet Infect Dis 2006; 6:483-95. [127] World Health Organization (WHO). Global tuberculosis control - surveillance, planning, financing. WHO Document, 2008, Geneva, Switzerland. WHO/HTM/TB/2008.393. [130] Salazar-Vergara RML, Sia IG, Tupasi TE, Alcneses MR, et al. Tuberculosis infection and disease in children living in households of Filipino patients with tuberculosis: a preliminary report. Int J Tuberc Lung Dis. 2003;7:S494-S500. [131] Schaaf H, Vermuelen H, Gie R, Beyers N, Donald P. Evaluation of young children in household contact with adult multidrug-resistant pulmonary tuberculosis cases. Pediatr Infect Dis. 1999;18:494-500	Removed references 45- 46, 129-131. Revised the number sequence. ~~[45] Pawlowski A, Johnson M, Skold M, Rottenberg ME, Kallenius G. Tuberculosis and HIV co-infection. PLoS Path. 1012;8:1-5.~~ ~~[46] Reid A, Scano F, Getahun H, et al. Towards universal access to HIV prevention, treatment, care, and support: the role of TB/HIV collaboration. Lancet Infect Dis 2006; 6:483-95.~~ ~~[127] World Health Organization (WHO). Global tuberculosis control - surveillance, planning, financing. WHO Document, 2008, Geneva, Switzerland. WHO/HTM/TB/2008.393.~~ ~~[130] Salazar-Vergara RML, Sia IG, Tupasi TE, Alcneses MR, et al. Tuberculosis infection and disease in children living in households of Filipino patients with tuberculosis: a preliminary report. Int J Tuberc Lung Dis. 2003;7:S494-S500.~~ ~~[131] Schaaf H, Vermuelen H, Gie R, Beyers N, Donald P. Evaluation of young children in household contact with adult multidrug-resistant pulmonary tuberculosis cases. Pediatr Infect Dis. 1999;18:494-500~~
Appendix 1	Report Immediately Reportable Events to: Otsuka Europe Development and Commercialisation, Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) Fax: [redacted] Phone: [redacted] (24h/7d PVRE Blackberry) E-mail: [redacted]	**Report Immediately Reportable Events to:** Otsuka Europe Development and Commercialisation, Ltd (OEDC) Pharmacovigilance Region Europe (PVRE) Fax: [redacted] ~~Phone: [redacted] (24h/7d PVRE Blackberry)~~ E-mail: [redacted]
Appendix 1	Deleted text	~~**For Medical Emergencies in the Philippines**~~ [redacted] ~~**Otsuka (Philippines) Pharmaceutical Inc.**~~ ~~**3F King's Court II Building**~~ ~~**2126 Chino Roces Avenue**~~ ~~**Makati City, Philippines**~~ ~~**Phone:** [redacted]~~

Location	Old Text	Updated Text
		~~**Fax:** [redacted]~~ ~~**E-mail:** [redacted]~~
Appendix 3	Blood (2 - 3 mL) will be collected into green-top Vacutainer® tubes containing sodium heparin anticoagulant. The tubes must be gently inverted 3 to 4 times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from each tube should then be divided equally between the 2 barcode-labeled polypropylene tubes. The PK sample must be stored at −65°C or below. One PK tube (primary sample) will be shipped on dry ice to the central lab. Following confirmation that the first tube arrived safely, the second tubes (backup samples) can also be shipped to the central lab.	Blood (**0.6** - 3 mL) will be collected into green-top Vacutainer® tubes containing sodium heparin/***lithium heparin*** anticoagulant. The tubes must be gently inverted 3 to 4 times and then centrifuged at 2500 rpm for at least 10 minutes at 4°C. The separated plasma from each tube should then be divided equally between the 2 barcode-labeled polypropylene tubes (Groups 1-3). ***For Group 4, the separated plasma should be transferred to a single barcode-labeled polypropylene tube.*** The PK sample must be stored at −65°C or below. One PK tube (primary sample) will be shipped on dry ice to the central lab ***(Groups 1-4).*** Following confirmation that the first tube arrived safely, the second tubes (backup samples) can also be shipped to the central lab ***(Groups 1-3). There will be no backup samples for Group 4.***

ADDITIONAL RISK TO THE SUBJECT:
This amendment will not affect the safety of patients, the scope of the investigation, or the scientific quality of the trial.

Amendment Number: 5

Issue Date: 28 February 2019

PURPOSE: The purpose of this amendment is to add an interim analysis to the protocol.

BACKGROUND: In the previous protocol, no interim analysis was included and now it has been added. To get preliminary safety information about the adult formulation of delamanid in children 6 to 17 years of age the interim analysis is focusing on those groups (Groups 1 and 2) treated with the adult formulation.

MODIFICATIONS TO PROTOCOL:

Bold and underlined text:	Changed Text
~~**Bold and strike through text**~~:	Deleted Text
Bold and italicized text:	Added Text

Global Changes:

- Corrected minor typographical, grammatical, and formatting errors.
- Added an interim analysis in children 6 to 17 years of age treated with the adult formulation of delamanid.

Sectional Revisions:

Location	Old Text	Updated Text
Title Page	Added text.	***Amendment 5 Issue Date 28 February 2019***
Synopsis	Statistical Methods: No power calculation was performed for this trial because of the limited number of patients expected to be enrolled in the population of interest (ie, pediatrics). No formal statistical analysis is planned due to the small sample sizes; all statistical presentations will be descriptive.	Statistical Methods: No power calculation was performed for this trial because of the limited number of patients expected to be enrolled in the population of interest (ie, pediatrics). No formal statistical analysis is planned due to the small sample sizes; all statistical presentations will be descriptive. ***An interim analysis review of safety, tolerability, PK, and efficacy of delamanid will be conducted with complete follow-up data in children 6 to 17 years of age.***
Section 7.6	Added text	***7.6 Interim Analysis*** ***An interim analysis of safety, tolerability, PK, and efficacy of delamanid in children 6 to 17 years of age is planned in the 1st quarter of 2019.***

ADDITIONAL RISK TO THE SUBJECT:
This amendment will not affect the safety of patients, the scope of the investigation, or the scientific quality of the trial.

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Research Agreement.

I will provide copies of the protocol to all physicians, nurses and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, delamanid (OPC-67683), the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where delamanid (OPC-67683) will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in Paragraph I of the sponsor's Clinical Research Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB- or IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on case report forms by me and my staff will be utilized by the sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any protocol amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB/IEC within 5 working days. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Research Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and sub-investigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication prior to publication of efficacy and safety results on an individual basis.

_____

Principal or Coordinating Investigator Signature and Date

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SIGNATURE PAGE

Document Name: Protocol_242-12-233_Amendment 5

Document Number: 0000843868

Document Version: 12.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
[redacted]	Clinical Approval	02-Mar-2019 01:44:10
[redacted]	Clinical Pharmacology Approval	01-Mar-2019 15:58:11
[redacted]	Biostatistics Approval	28-Feb-2019 23:21:58