Synopsis

Clinical Report Synopsis for Protocol 242-07-204
Eudra CT No. 2007-005229-31

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)

Name of Investigational Medicinal Product: Delamanid (OPC-67683)

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

Coordinating Investigator and Trial Sites: The coordinating investigator for this trial was Maria Tarcela Gler, MD. This trial was conducted in 9 countries (the Philippines, Latvia, Estonia, South Korea, Peru, China, Japan, the United States [US], and Egypt) at 17 trial centers.

Publications: None to date.

Trial Period:

Date of first signed informed consent: 08 May 2008

Date of last trial observation: 11 Jun 2010

Clinical Phase/Trial Type: Phase 2

Objectives: The purpose of this trial was to evaluate the safety, efficacy, and pharmacokinetics (PK) of 2 doses of delamanid (100 mg twice daily [BID] and 200 mg BID) administered orally for 56 consecutive days in combination with an optimized background treatment regimen (OBR), compared with placebo in combination with OBR, to patients with pulmonary, sputum-culture-positive multidrug-resistant tuberculosis (MDR TB; tuberculosis [TB] resistant to at least the 2 first-line anti-TB drugs isoniazid and rifampicin). Specifically, this trial assessed the treatment effect of delamanid on sputum mycobacterial culture conversion (ie, SCC), and provided additional data to assist in the determination of the optimal dose and dosing regimen of delamanid by assessing the secondary efficacy endpoints, PK/pharmacodynamic (PD) relationships for safety and efficacy, and the safety profile for both dose levels. Sputum culture conversion (SCC) was defined to occur at the time of the collection of a sputum specimen with mycobacterial culture negative for growth of *Mycobacterium tuberculosis* (MTB) followed by at least one additional sputum specimen with mycobacterial culture negative for growth at least 27 days after the first negative specimen and not followed by any

sputum specimens with a mycobacterial culture positive for growth of MTB at any time point during the remainder of the 84-day trial.

Methodology: This trial was a phase 2, multicenter, double-blind, randomized, stratified, placebo-controlled clinical trial conducted in 3 parallel groups.
Patients were randomized to one of the following 3 treatment groups in a 1:1:1 ratio:

- Delamanid 100 mg BID + OBR,
- Delamanid 200 mg BID + OBR, or
- Placebo + OBR.

Treatment allocation was stratified by extent of pulmonary TB (ie, presence of cavitation versus no cavitation on chest radiograph at baseline); an equal number of patients with cavities visible on chest radiograph were allocated to each treatment group. The trial comprised the following periods:

- Pretreatment Period (Days −12 to −1) for screening and baseline safety assessments including electrocardiograms (ECGs), and for establishing baseline culture status.
- Treatment Period (Days 1 to 56) for randomization (Day 1), BID administration of either delamanid or placebo as the investigational medicinal product (IMP) in combination with OBR; periodic ECG assessments; periodic safety assessments, PK sampling, and weekly microbiologic assessments.
- Post-treatment Period (Days 57 to 84) for ongoing administration of OBR to all patients, and weekly PK sampling, safety assessments including ECGs, and weekly microbiologic assessments.

All patients were hospitalized for the duration of the Treatment Period. At the discretion of the investigator, patients could have been discharged from the hospital on Day 57. Trial duration per patient (pretreatment, treatment, and follow-up periods) was up to 96 days. The total duration of the trial was 104 weeks. Interim monitoring of safety data was performed by an independent Data and Safety Monitoring Board (DSMB) throughout the trial.

Number of Patients: A total of 430 eligible male or female patients were planned to be enrolled (approximately 140 patients per group). A total of 481 patients were randomized to 1 of the 3 treatment groups (161 in the delamanid 100 mg BID + OBR group, 160 in the delamanid 200 mg BID + OBR group, and 160 in the placebo + OBR group) and received at least one dose of IMP. A total of 31.2% were randomized in the Philippines, 27.2% in Peru, 22.0% in Northeast Asia, and 19.5% in other countries. Overall, a total of 434/481 (90%) patients completed the trial. The majority of patients, representing the Modified Intent-to-treat (MITT) population of the trial, were analyzed for efficacy using the Mycobacterial Growth Indicator Tube (MGIT) system (402/481, 83.6%) and using solid culture media (347/481, 72.1%). A total of 336/481 (69.9%) patients were analyzed in the per protocol (PP) data set for the MGIT system and 292/481 (60.7%) patients were analyzed in the PP data set for solid culture media. All of the 481 randomized patients were analyzed for safety. Data from 151 patients (delamanid 100 mg BID + OBR) and 154 patients (delamanid 200 mg BID + OBR) were used in the

PK analysis and data from 481 patients (delamanid 100 mg BID + OBR, delamanid 200 mg BID + OBR, and placebo BID + OBR) were used in the PK/PD analysis.

Diagnosis and Main Criteria for Inclusion: Male or female patients, 18 to 64 years of age (inclusive), with sputum-culture-positive, pulmonary MDR TB or with sputum smears positive for acid fast bacilli (AFB) and a positive rapid test for rifampicin resistance were randomized. Patients with AFB-positive smears and a positive rapid rifampicin resistance test were enrolled and presumed to have sputum-culture-positive MDR TB. If they were later found to have either a mycobacterial culture negative for growth of MTB, or a positive culture for MTB with susceptibility to rifampicin and/or isoniazid, they were continued in the trial at the discretion of the investigator.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch, or Lot No(s): Delamanid was supplied as 50-mg tablets (lot numbers 07F91A050A, 07F91A050B, 07F91A050C, 08E85A050H) provided in bottles and was administered orally as 100 mg BID and 200 mg BID for 56 consecutive days. Matching placebo tablets (lot numbers 07F91P050A, 07F91P050B, and 08E85P050A) were provided in bottles and were administered orally BID as required to maintain the blinded trial design. Delamanid and matching placebo were manufactured by Otsuka Pharmaceutical Co., Ltd.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No(s): The specific medications comprising OBR for each patient were selected by the principal investigator at each site, who was an MDR TB treatment and management expert. Selection and administration of the treatment medications were based on the World Health Organization's (WHO) *Guidelines for the Programmatic Management of Drug-resistant TB* and any existing national guidelines for a given setting. Each patient's OBR generally included at least 4 medications from the classes of anti-TB medications to which a given patient's TB was known or presumed to be susceptible.

The principal investigator for a site could change OBR for a patient as necessary based on patient tolerability or drug susceptibility testing (DST) results at any time during the trial. After completion of 56 days of delamanid BID + OBR at either of 2 dose levels, or placebo + OBR, all patients were to continue treatment with OBR as directed by the given investigator based on WHO guidelines and clinical judgment.

Criteria for Evaluation:

Primary Endpoints:

Efficacy: The primary efficacy endpoint was the proportion of patients who achieved SCC using the MGIT system, by Day 57 of treatment with IMP among patients with sputum culture positive for MTB identified as MDR TB at baseline (MITT population). Sputum culture conversion was defined to occur at the time of the collection of the first sputum specimen with mycobacterial culture negative for growth of MTB followed by at least one additional sputum specimen with mycobacterial culture negative for growth at least 27 days after the first negative specimen and not followed by any sputum specimens

with a mycobacterial culture positive for growth of MTB at any time point during the remainder of the 84-day trial. Missing culture data due to contamination and unknown results were handled by several methods, including microbiological confirmation, last observation carried forward (LOCF) method, and multiple imputation.

Pharmacokinetic: Full PK profiles (at predose, and at 2, 3 ,4, 10, 12, 13, 14, and 24h postdose) were measured on visit Days 1, 14, 28, and 56 after the initiation of delamanid dosing. Plasma concentrations of all analytes were analyzed by noncompartmental methods. The following PK parameters were to be determined for delamanid as the data permitted: maximum (peak) plasma concentration following the first daily dose (C_{max1}), maximum (peak) plasma concentration following the second daily dose (C_{max2}), time to C_{max1} (t_{max1}), time to C_{max2} (t_{max2}), and area under the concentration-time curve from time zero to 24 hours (AUC_{0-24h}) on Days 1, 14, 28, and 56, when possible. Apparent clearance of drug from plasma after extravascular administration (CL/F) was calculated on Days 14, 28, and 56. Elimination half-life ($t_{1/2}$) was calculated on Day 56. Observed plasma concentrations at predose (C_{0h}) and at 10 hours (C_{10h}) and 24 hours (C_{24h}) postdose were determined on Days 1, 14, 28 and 56 by visual inspection of the concentration data. Time to reach 90% (steady state) of the Day 56 delamanid plasma concentration values was assessed using a t-test analysis on the log-transformed ratios of the AUC_{0-24h} on Day 14 and Day 28 to that on Day 56, namely AUC_{0-24h} D14/D56 and AUC_{0-24h} D28/D56, respectively. Steady state was defined to be achieved when the AUC_{0-24h} reached or exceeded 90% of that observed on Day 56, namely when the mean ratio of AUC_{0-24h} (with 2-sided 90% confidence interval [CI]) was equal to or exceeded 0.90. The accumulation ratios for C_{max1} ($R_{ac}[C_{max1}]$), accumulation ratios for C_{max2} ($R_{ac}[C_{max2}]$), accumulation ratios for AUC_{0-24h} ($R_{ac}[AUC_{0-24h}]$), and accumulation ratios for C_{24h} ($R_{ac}[C_{24h}]$) were also calculated for delamanid on Days 14, 28, and 56 with respect to Day 1.

The following PK parameters were to be determined for DM-6704, DM-6705, DM-6706, DM-6717, DM-6718, DM-6720, DM-6721, and DM-6722 as the data permitted: maximum (peak) plasma concentration (C_{max}) over the 24-hour dosing interval, time to C_{max} (t_{max}) over the 24-hour dosing interval, and AUC_{0-24h} on Days 14, 28, and 56. Elimination half-life ($t_{1/2}$) was calculated on Day 56. Observed plasma concentrations (C_{0h} and C_{24h}) were determined on Days 1, 14, 28, and 56 by visual inspection of the concentration data. Limited metabolite exposure on Day 1 did not allow for accumulation ratios (R_{ac}) to be estimated. Hence, ratios for AUC_{0-24h} and C_{24h} on Days 28 and 56 with respect to Day 14 (Ratio AUC_{0-24h} D56/D14, Ratio AUC_{0-24h} D28/D14, Ratio C_{24h} D56/D14, and Ratio C_{24h} D28/D14), were calculated instead for metabolites. Metabolite-to-parent ratios (M/P ratio) of AUC_{0-24h} (expressed as μM*h) were calculated on Days 14, 28, and 56.

Secondary Endpoints:

Efficacy: Secondary efficacy variables included the following:

1) Proportion of patients with a positive culture on solid media at baseline (Day −1 or Day 1) achieving SCC using solid culture media. A patient achieving SCC using solid culture media was defined as one with sputum culture negative for growth of MTB on Day 57, and (a) not followed by a positive culture at any time point thereafter, and (b) confirmed by at least one additional negative sputum culture at Day 84.
2) Change from baseline in time to culture positivity (ie, time to detection [of MTB growth] [TTD]) using the MGIT system.
3) Area under the curve (AUC) of change from baseline in time to culture positivity (ie, TTD) using the MGIT system.
4) Proportion of patients with sputum mycobacterial culture negative for growth at Day 57 using the MGIT system, without consideration of subsequent culture results.
5) Proportion of patients with sputum mycobacterial culture negative for growth at Day 57 using the MGIT system confirmed with another culture negative for growth at Day 84 using the MGIT system, without consideration of interim culture results.
6) Proportion of patients with sputum mycobacterial culture negative for growth at Day 57 using solid culture media, without consideration of subsequent culture results.
7) Proportion of patients with sputum mycobacterial culture negative for growth at Day 57 using solid culture media confirmed by another culture negative for growth at Day 84 using solid culture media, without consideration of interim culture results.
8) Dose response in the proportion of patients achieving SCC using the MGIT system.
9) Time to initial SCC from baseline using the MGIT system.
10) Time to initial SCC using solid culture media.
11) Time to final SCC (sustained SCC achieved by Day 57) using the MGIT system and solid culture media.

The analyses in items 5, 7, and 10 above were included in the statistical analysis plan prior to breaking the blind and database lock. For item 11, time to final SCC using the MGIT system was a secondary endpoint outlined in the protocol; however, time to final SCC using solid culture media was considered exploratory, as it was not included in the protocol or the statistical analysis plan. .

Safety: Safety parameters included: physical examination (including vision and neuropsychiatric assessments); vital signs (blood pressure, pulse rate, body temperature, and body weight); standard 12-lead ECG; clinical laboratory tests (hematology, clinical chemistry, urinalysis); audiometry; thyroid hormones (thyroid stimulating hormone [TSH], free thyroxine [T4]); adrenal hormone (cortisol); coagulation (prothrombin time

[PT] and activated partial thromboplastin time [aPTT]); concomitant medication usage; adverse events (AEs), and immediately reportable events (IREs).

Primary ECG Analysis: The primary ECG parameter was time-matched change from baseline (Day −1) in QT interval corrected by Fridericia's formula (QTcF) at Day 56.

Secondary ECG Analyses: The following parameters were defined using the available ECG data: changes from mean baseline in QTcF, QT interval corrected by Bazett's formula (QTcB), heart rate (HR), PR interval, QRS interval, QT interval, and ECG morphological pattern. These data were obtained on Days 1, 14, 28, and 56, as well as on other treatment days when ECGs were collected.

Statistical Methods:

Efficacy Data: The primary efficacy analysis was performed on the MITT population defined as all randomized patients having a positive sputum culture for MDR TB at baseline (Day −1 and/or Day 1) using the MGIT system. The primary efficacy endpoint was selected and the trial powered to ascertain whether delamanid at either of 2 dosages was superior to placebo when given with OBR during early treatment. This was assessed by comparing the proportion of patients with SCC at Day 57 in each of the delamanid BID + OBR groups (100 mg BID and 200 mg BID) with that of the group receiving placebo + OBR. The trial was not powered to compare the 2 doses of delamanid BID + OBR to one another. For the primary analysis, the proportion of patients with SCC in each of the delamanid groups (100 mg BID and 200 mg BID + OBR) was compared with that of the placebo + OBR group using the Cochran-Mantel-Haenszel (CMH) test stratified by randomization strata (cavitation/no cavitation). The overall nominal significance level for testing the 2 comparisons was maintained at 0.05 (2-sided) by the Hochberg multiple testing procedure. In addition, 95% confidence intervals (CI) for the ratio of proportion of SCC regarding the treatment effect size differences (delamanid relative to placebo) were constructed for each stratum.

In the secondary efficacy analyses, pairwise comparisons were made for delamanid 100 mg BID + OBR versus placebo + OBR and for delamanid 200 mg BID + OBR versus placebo + OBR. Statistical significance for each comparison was evaluated at a type I-error rate of 0.05 (2-sided), and no adjustments in levels of significance were made for multiple comparisons.

Safety Data: Safety analyses were conducted on the Intent-to-treat (ITT) population (defined as all randomized patients who received any amount of IMP, regardless of any protocol deviation or violation). All safety variables were listed and, where appropriate, summarized by treatment group with descriptive statistics (eg, mean changes in clinical laboratory measurement, frequency of AEs, etc). No inferential statistical analyses were performed. In addition, the ECG analyses were performed on patients in the ITT population who had at least one baseline and one on-treatment ECG.

Pharmacokinetic/pharmacodynamic Methods for ECG Analyses: All individual pairs of plasma concentrations (PK data) and QTc measurements (PD data) collected at each time point on Days 1, 14, 28, and 56 from patients receiving placebo (PK concentrations set to zero) or delamanid (100 mg BID or 200 mg BID) with OBR were considered in the PK/PD analysis. The PK/PD relationship between QTc interval (QTcF and QTcB) change from baseline (ΔQTc) versus delamanid, DM-6704, DM-6705, and DM-6720 concentrations, possibly contributing to the QTc prolongation was investigated using linear mixed effects modeling. Based on the models, the mean (and upper one-sided 95% CIs for the mean) placebo-adjusted QTc change from baseline (ΔQTc) was computed at C_{max} of delamanid, DM-6704, DM-6705, and DM-6720 following administration of delamanid 100 mg BID + OBR and delamanid 200 mg BID + OBR.

Efficacy Results:
The data set of the MITT population was the data set for the primary efficacy analysis. Demographic and baseline characteristics were similar in the ITT and MITT populations, as well as across all 3 of the treatment groups in both populations.

Primary Efficacy Variable:
Proportion of Patients Achieving SCC at Day 57 Using the MGIT System
Statistically significantly higher proportions of patients treated with delamanid BID + OBR achieved SCC (MGIT system) than patients treated with placebo + OBR. The proportions of patients achieving SCC in the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups, respectively, were 45.4% ($p = 0.0083$) and 41.9% ($p = 0.0393$) compared with placebo + OBR at 29.6%. For patients with cavitation, the proportions achieving SCC were also statistically significantly higher for delamanid BID + OBR than for placebo + OBR (46.0% for the delamanid 100 mg BID + OBR group [$p = 0.0155$] and 44.2% for the delamanid 200 mg BID + OBR group [$p = 0.0311$] compared with 28.7% for placebo + OBR). For patients without cavitation, the sample sizes were small and although not statistically significant, positive directions in effect sizes in favor of delamanid were observed. Sensitivity analysis results based on LOCF, observed cases (OC), and PP data sets for the MGIT system results were consistent with the results from the MITT data sets.

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

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

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

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

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

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

Key Secondary Efficacy Variables:

Proportion of Patients Achieving SCC at Day 57 Using Solid Culture Media

Using solid culture media, statistically significantly higher proportions of patients treated with delaminid + OBR achieved SCC than patients treated with placebo + OBR, regardless of the presence or absence of cavitation. The proportions of patients achieving SCC in the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups were 53.8% ($p = 0.0021$) and 65.2% ($p < 0.0001$), respectively, compared with placebo + OBR at 33.6%. For patients with cavitation, the proportions of patients achieving SCC in the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups were 51.8% ($p = 0.0259$) and 63.9% ($p = 0.0002$), respectively, compared with placebo + OBR at 34.6%. For patients without cavitation, the proportions of patients achieving SCC in the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups were 58.8% ($p = 0.0257$) and 68.8% ($p = 0.0029$), respectively, compared with placebo + OBR at 31.3%. Sensitivity analyses results based on LOCF, OC, and PP data sets for solid culture media supported the results from the MITT data sets.

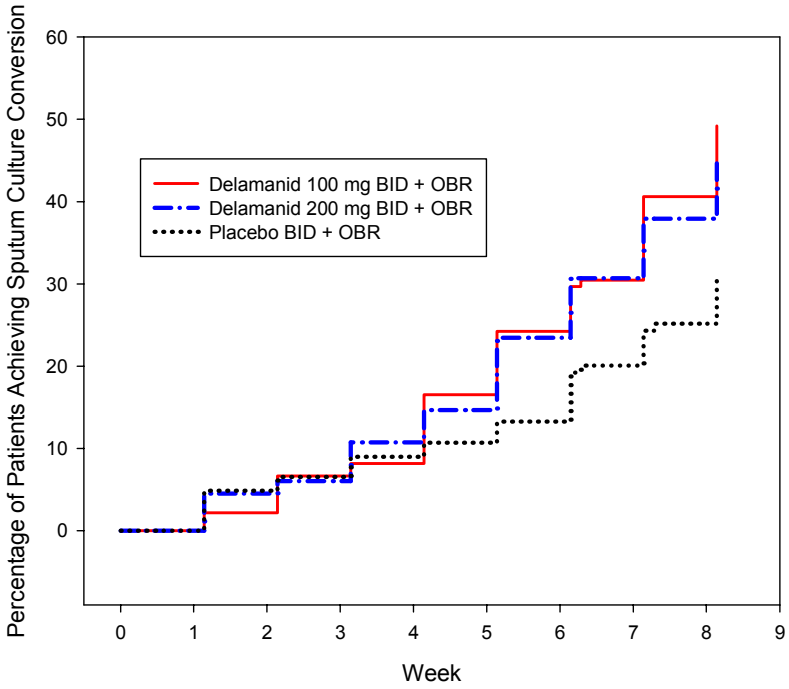
Multiple Logistic Regression Analysis of SCC

From the series of multiple regression analyses performed on the heterogeneous patient population included in this trial to identify independent factors associated with SCC, exposure to delamanid was consistently associated with at least a 1.3-fold higher likelihood of a patient achieving SCC by Day 57. These findings are consistent across the primary efficacy analysis and multiple secondary efficacy analyses and are consistent across both culture media types (MGIT and solid). The comparisons of delamanid 100 mg BID + OBR versus placebo + OBR were statistically significant using the MGIT

system and solid culture media ($p < 0.05$), and the comparison of delamanid 200 mg BID + OBR versus placebo + OBR was statistically significant using solid culture media ($p < 0.0001$). Other factors that were independently associated with a higher likelihood of achieving SCC included a longer time to positivity (ie, TTD) using the MGIT system at baseline (MGIT and solid culture media) and moderate previous anti-TB treatment (ie, any treatment with anti-TB medications for ≥ 90 days up to 6 months total and only within 6 months prior to randomization among otherwise treatment-naive patients) (using the MGIT system). The use of a later generation fluoroquinolone demonstrated an increased likelihood that patients would achieve SCC (solid culture media), with a trend toward significance ($p = 0.0594$). Risk factors negatively associated with achieving SCC included baseline resistance to at least one fluoroquinolone agent and one of the injectable anti-TB agents (ie, extensively drug-resistant TB [XDR TB]) (MGIT and solid culture media), increasing age (using the MGIT system), and by region, being from the Americas, almost entirely represented by Peru (solid culture media). The presence of cavitation, either unilateral or bilateral, was not statistically associated with achieving SCC at Day 57.

Time to Final SCC Using the MGIT System

Although the median time to final SCC (sustained SCC achieved by Day 57) could not be calculated because fewer than 50% of patients in each group met the criteria, the Kaplan-Meier curves for time to final SCC using the MGIT system showed clear separation between each delamanid BID + OBR group and the placebo + OBR group from Day 36 to Day 57 (Weeks 5 to 8). The Kaplan-Meier estimates of the proportions of SCC are as follows: By Day 36 (actual day), 24% and 23% of patients in the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups, respectively, achieved SCC compared with 13% of patients in the placebo + OBR group. By Day 44 (actual day), 30% and 31% of patients in the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups, respectively, achieved SCC compared with 20% of patients in the placebo + OBR group. By Day 50 (actual day), 41% and 38% of patients in the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups, respectively, achieved SCC compared with 24% of patients in the placebo + OBR group.



Number of Patients Not Achieving Sputum Culture Conversion by Week:

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

Time to Final Sputum Culture Conversion Using the MGIT System, Modified Intent-to-treat Population

BID = twice daily; OBR = optimized background treatment regimen.

The benefit ratios (ratio of likelihoods that patients treated with either dose of delamanid BID + OBR would achieve SCC more rapidly than patients treated with placebo + OBR) for patients achieving SCC are summarized for the MGIT system and solid culture media below.

Benefit Ratios for Patients Achieving Sputum Culture Conversion, Modified Intent-to-treat Population

Comparison	MGIT System		Solid Culture Media	
	Hazard Ratio[a], Mean (95% CI)	p-value[b]	Hazard Ratio[a], Mean (95% CI)	p-value[b]
Delamanid 100 mg BID + OBR vs placebo + OBR	1.727 (1.152, 2.591)	0.0056	1.846 (1.235, 2.759)	0.0016
Delamanid 200 mg BID + OBR vs placebo + OBR	1.585 (1.048, 2.399)	0.0232	2.301 (1.555, 3.405)	< 0.0001

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

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

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

With the MGIT system, the likelihood that a patient would achieve final SCC by Day 57 was 73% and 59% higher for the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups, respectively, compared with placebo + OBR ($p < 0.05$). The benefit ratios were higher with solid culture media; the probability that a patient would achieve final SCC by Day 57 was 85% and 130% higher for the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups, respectively, compared with placebo + OBR ($p < 0.01$). Results of the sensitivity analyses (LOCF, OC, and PP data sets) were consistent with those of the MITT data set using both the MGIT system and solid culture media.

Pharmacokinetic Results:

A summary of the PK parameters for delamanid and of the most relevant PK parameters for the metabolites DM-6704, DM-6705, DM-6706, DM-6717, DM-6718, DM-6720, DM-6721, and DM-6722 following administration of delamanid 100 mg BID + OBR or delamanid 200 mg BID + OBR to patients with MDR TB is presented in the tables below. Delamanid plasma concentrations were 50% higher after 200 mg BID + OBR as compared to 100 mg BID + OBR. On Day 56, mean (%CV) delamanid C_{max} values were 414 (39.9) ng/mL and 611 (35.6) ng/mL and $AUC_{0\text{-}24h}$ values were 7,925 (37.5) h*ng/mL and 11,837 (33.6) h*ng/mL, after delamanid 100 mg BID + OBR and delamanid 200 mg BID + OBR, respectively. Metabolites formed slowly and increased progressively until Day 56. DM-6705 concentrations were used as surrogate marker for QTc prolongation. On Day 56, they reached C_{max} (%CV) values of 151 (44.6) ng/mL and 233 (40.6) ng/mL after delamanid 100 mg BID + OBR and delamanid 200 mg BID + OBR, respectively.

Mean (%CV) Delamanid Pharmacokinetic Parameters in Patients With MDR TB

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

AUC_{0-24h} = area under the plasma concentration-time curve from time zero to 24 hours; BID = twice daily; C_{0h} = observed plasma concentration at predose; CL/F = apparent clearance of drug from plasma after extravascular administration; C_{max1} = maximum (peak) plasma concentration following the first daily dose; C_{max2} = maximum (peak) plasma concentration following the second daily dose; CV = coefficient of variation; MDR TB = multidrug resistant tuberculosis; ND = Not determined; OBR = optimized background treatment regimen; PK = pharmacokinetic; R_{ac}(AUC) = accumulation ratio for AUC; $t_{1/2}$ = elimination half-life.

Mean (%CV) Metabolite Main Pharmacokinetic Parameters on Day 56 in Patients With MDR TB

Analyte	PK Parameter Day 56	Delamanid 100 mg BID + OBR (n = 116 to 150)	Delamanid 200 mg BID + OBR (n = 127 to 153)
DM-6704	C_{max} (ng/mL)	60.6 (62.2)	90.3 (64.8)
	C_{0h} (ng/mL)	56.2 (63.6)	83.3 (62.5)
	AUC_{0-24h} (h·ng/mL)	1251 (61.2)	1902 (65.8)
	M/P AUC_{0-24h}	0.170 (70.0)	0.171 (71.1)
	$t_{1/2}$ (h)	195 (59.0)	191 (35.1)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	1.75 (55.1) vs 1.32 (33.0)	1.74 (37.9) vs 1.43 (27.4)
DM-6705	C_{max} (ng/mL)	151 (44.6)	233 (40.6)
	C_{0h} (ng/mL)	128 (47.6)	196 (41.6)
	AUC_{0-24h} (h·ng/mL)	3125 (44.7)	4907 (40.5)
	M/P AUC_{0-24h}	0.403 (34.8)	0.428 (31.8)
	$t_{1/2}$ (h)	231 (36.7)	233 (37.7)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	1.99 (26.8) vs 1.57 (20.1)	1.98 (28.2) vs 1.55 (15.6)
DM-6706	C_{max} (ng/mL)	59.2 (51.5)	84.3 (49.2)
	C_{0h} (ng/mL)	55.0 (50.5)	77.6 (47.4)
	AUC_{0-24h} (h·ng/mL)	1256 (51.2)	1796 (48.4)
	M/P AUC_{0-24h}	0.173 (60.6)	0.165 (53.1)
	$t_{1/2}$ (h)	180 (23.9)	184 (21.9)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	1.92 (36.3) vs 1.51 (20.7)	1.90 (31.2) vs 1.54 (18.3)
DM-6717	C_{max} (ng/mL)	34.7 (59.1)	53.4 (56.8)
	C_{0h} (ng/mL)	32.2 (59.3)	49.4 (57.0)
	AUC_{0-24h} (h·ng/mL)	720 (60.6)	1112 (56.0)
	M/P AUC_{0-24h}	0.0952 (52.9)	0.102 (63.6)
	$t_{1/2}$ (h)	265 (37.1)	265 (43.4)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	7.87 (44.3) vs 3.60 (30.9)	8.35 (41.3) vs 3.59 (24.1)

Analyte	PK Parameter Day 56	Delamanid 100 mg BID + OBR (n = 116 to 150)	Delamanid 200 mg BID + OBR (n = 127 to 153)
DM-6718	C_{max} (ng/mL)	107 (43.4)	138 (34.7)
	C_{0h} (ng/mL)	100 (44.3)	130 (35.8)
	AUC_{0-24h} (h·ng/mL)	2285 (43.4)	2954 (33.6)
	M/P AUC_{0-24h}	0.318 (48.8)	0.289 (65.0)
	$t_{1/2}$ (h)	302 (43.8)	305 (43.0)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	5.18 (39.2) vs 3.01 (28.6)	5.04 (36.6) vs 2.86 (25.5)
DM-6720	C_{max} (ng/mL)	57.4 (39.4)	79.3 (33.2)
	C_{0h} (ng/mL)	48.0 (40.2)	64.9 (32.9)
	AUC_{0-24h} (h·ng/mL)	1206 (39.3)	1668 (32.9)
	M/P AUC_{0-24h}	0.166 (45.7)	0.155 (46.5)
	$t_{1/2}$ (h)	394 (40.1)	424 (45.3)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	3.32 (35.9) vs 2.19 (25.1)	3.33 (33.7) vs 2.15 (23.7)
DM-6721	C_{max} (ng/mL)	6.38 (88.4)	9.92 (71.0)
	C_{0h} (ng/mL)	5.82 (90.6)	9.15 (72.9)
	AUC_{0-24h} (h·ng/mL)	132 (89.5)	210 (73.3)
	M/P AUC_{0-24h}	0.0171 (87.1)	0.0183 (71.3)
	$t_{1/2}$ (h)	168 (29.5)	153 (34.8)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	2.48 (97.7) vs 1.76 (35.1)	2.70 (49.9) vs 1.94 (32.4)
DM-6722	C_{max} (ng/mL)	33.3 (69.2)	56.1 (70.8)
	C_{0h} (ng/mL)	30.6 (69.4)	51.8 (71.4)
	AUC_{0-24h} (h·ng/mL)	699 (69.9)	1191 (72.4)
	M/P AUC_{0-24h}	0.0930 (76.6)	0.106 (73.9)
	$t_{1/2}$ (h)	134 (63.6)	148 (40.6)
	Ratio AUC_{0-24h} Day56/14 vs Day28/14	1.94 (91.2) vs 1.49 (55.8)	2.00 (51.8) vs 1.55 (33.2)

AUC_{0-24h} = area under the plasma concentration-time curve from time zero to 24 hours; BID = twice daily; C_{0h} = observed plasma concentration at predose; C_{max} = maximum (peak) plasma concentration; CV = coefficient of variation; M/P = metabolite-to-parent ratio; DM = drug metabolite; MDR TB = Multidrug resistant tuberculosis; OBR = optimized background treatment regimen; PK = pharmacokinetic; ; $t_{1/2}$ = elimination half-life.

Pharmacokinetic/pharmacodynamic Results:

Based on the linear regression analysis, the mean (and upper one-sided 95% CIs of the mean) predictions of mean placebo-adjusted ΔQTc at C_{max} of each delamanid treatment arm was calculated for each analyte. The results for mean placebo-adjusted ΔQTcF are

tabulated below for the full data set (n = 481) and for the restricted dataset (excluding sites 015 and 016, n = 414). The results for mean placebo-adjusted QTcB and QTcB change from baseline (ΔQTcB) are presented in the QTc PK/PD report. The highest predictions of mean placebo-adjusted ΔQTcF [upper 95% CI] on Day 56 at maximal DM-6705 plasma exposure, were 14.24 [15.39] ms (C_{max} of 151 ng/mL) and 21.98 [23.75] ms (C_{max} of 233 ng/mL) after delamanid 100 mg BID + OBR and 200 mg BID + OBR, respectively. These values were slightly higher in the restricted data set (414 patients excluding Sites 015 and 016 in Peru versus 481 patients), namely 15.63 [16.92] ms (C_{max} of 160 ng/mL) and 24.03 [26.01] ms (C_{max} of 246 ng/mL), respectively (see below regarding the restricted data set for ECG analyses).

Predicted Placebo-adjusted ΔQTcF at Cmax in the Full Data Set (n = 481 Patients)

Analyte	Delamanid Dose (mg BID)	C_{max} on Day 56 (ng/mL)	Placebo-adjusted ΔQTcF	
			μΔQTcF (ms)	Upper 95%CI (ms)
Delamanid	100	414	12.67	13.77
Delamanid	200	611	18.71	20.32
DM-6704	100	60.6	14.57	16.05
DM-6704	200	90.3	21.71	23.91
DM-6705	100	151	14.24	15.39
DM-6705	200	233	21.98	23.75
DM-6720	100	57.4	14.28	15.62
DM-6720	200	79.3	19.73	21.58

BID = twice daily; CI = confidence interval; C_{max} = maximum (peak) plasma concentration; DM = drug metabolite; ΔQTcF = QTcF change from baseline; μΔQTcF = mean placebo-adjusted ΔQTcF; QTcF = QT interval corrected by Fridericia's formula.

Predicted Placebo-adjusted ΔQTcF at Cmax in the Restricted Data Set (n = 414 Patients Excluding Sites 015 and 016)

Analyte	Delamanid Dose (mg BID)	C_{max} on Day 56 (ng/mL)	Placebo-adjusted ΔQTcF	
			μΔQTcF (ms)	Upper 95%CI (ms)
Delamanid	100	435	13.81	15.05
Delamanid	200	641	20.35	22.18
DM-6704	100	65.1	16.01	17.61
DM-6704	200	96.7	23.79	26.16
DM-6705	100	160	15.63	16.92
DM-6705	200	246	24.03	26.01
DM-6720	100	59.1	15.81	17.3
DM-6720	200	81.1	21.7	23.73

BID = twice daily; CI = confidence interval; C_{max} = maximum (peak) plasma concentration; DM = drug metabolite; ΔQTcF = QTcF change from baseline; μΔQTcF = mean placebo-adjusted ΔQTcF; QTcF = QT interval corrected by Fridericia's formula.

Safety Results:

A total of 481 patients (representing the ITT population) were exposed to IMP during the trial: 161 in the delamanid 100 mg BID + OBR group, 160 in the delamanid 200 mg BID + OBR group, and 160 in the placebo + OBR group. Overall, 437/481 (90.9%) patients received IMP for ≥ 56 days and duration of exposure was evenly distributed among the 3 treatment groups.

The percentage of patients who experienced at least one treatment-emergent adverse event (TEAE) overall was similar between the total delamanid BID + OBR group (294/321, 91.6%) and the placebo + OBR group (149/160, 93.1%), and between the delamanid 100 mg BID + OBR group (145/161, 90.1%) and the 200 mg BID + OBR group (149/160, 93.1%). The incidences of the most frequently reported TEAEs were generally similar for delamanid BID + OBR and placebo + OBR (less than 5% difference between groups), with the exception of nausea (123/321, 38.3% versus 53/160, 33.1%); vomiting (106/321, 33.0% versus 44/160, 27.5%); headache (77/321, 24.0% versus 30/160, 18.8%); and prolonged ECG QT (37/321, 11.5% versus 6/160, 3.8%). The incidences of the most frequently reported TEAEs were also generally similar between the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups (less than 5% difference between groups), with the following exceptions of greater incidence in the delamanid 200 mg BID + OBR group: dyspepsia (6/161, 3.7% versus 14/160, 8.8%; vomiting (48/161, 29.8% versus 58/160, 36.3%); anorexia (23/161, 14.3% versus 34/160, 21.3%); hypokalaemia (20/161, 12.4% versus 31/160, 19.4%); depression (4/161, 2.5% versus 13/160, 8.1%); insomnia (42/161, 26.1% versus 51/160, 31.9%); and hyperhidrosis (9/161, 5.6% versus 17/160, 10.6%). The incidence of psychotic disorder was low (≤ 5%) and was similar in both the delamanid BID + OBR and placebo + OBR treatment groups. In addition, the TEAEs of hypokalaemia, hypoaesthesia, paraesthesia, and tremor are known side effects of OBR, which was administered to all patients in the trial, and each of these TEAEs occurred at similar incidences in the total delamanid BID + OBR and placebo + OBR groups, with incidences ranging from 5% to 16%. Reticulocytosis also occurred at a similar incidence in the delamanid and placebo groups (12% to 11%, respectively) and is likely an indicator of a response to anemia, a common condition in patients with TB, especially at the time of diagnosis and in the early stages of treatment.

Most TEAEs were mild or moderate in intensity. The most frequently reported TEAEs (by 3% or greater incidence in the total delamanid BID + OBR group and greater than placebo + OBR) are presented below.

Most Frequently Reported Treatment-emergent Adverse Events by 3% or Greater Incidence in the Total Delamanid BID + OBR Group and Greater Than Placebo + OBR

System Organ Class and MedDRA Preferred Term	Delamanid 100 mg BID + OBR (N = 161) n (%)[a]	Delamanid 200 mg BID + OBR (N = 160) n (%)[a]	Total Delamanid BID + OBR (N = 321) n (%)[a]	Placebo + OBR (N = 160) n (%)[a]	Total (N = 481) n (%)[a]
Patients with any TEAE[b]	145 (90.1)	149 (93.1)	294 (91.6)	149 (93.1)	443 (92.1)
Blood and Lymphatic System Disorders					
Reticulocytosis	19 (11.8)	20 (12.5)	39 (12.1)	17 (10.6)	56 (11.6)
Cardiac Disorders					
Palpitations	13 (8.1)	20 (12.5)	33 (10.3)	10 (6.3)	43 (8.9)
Ear and Labyrinth Disorders					
Tinnitus	16 (9.9)	22 (13.8)	38 (11.8)	12 (7.5)	50 (10.4)
Eye Disorders					
Vision blurred	12 (7.5)	15 (9.4)	27 (8.4)	9 (5.6)	36 (7.5)
Gastrointestinal Disorders					
Abdominal discomfort	7 (4.3)	8 (5.0)	15 (4.7)	5 (3.1)	20 (4.2)
Abdominal distension	5 (3.1)	9 (5.6)	14 (4.4)	5 (3.1)	19 (4.0)
Abdominal pain	16 (9.9)	12 (7.5)	28 (8.7)	11 (6.9)	39 (8.1)
Abdominal pain lower	4 (2.5)	11 (6.9)	15 (4.7)	7 (4.4)	22 (4.6)
Abdominal pain upper	41 (25.5)	36 (22.5)	77 (24.0)	38 (23.8)	115 (23.9)
Dyspepsia	6 (3.7)	14 (8.8)	20 (6.2)	6 (3.8)	26 (5.4)
Nausea	58 (36.0)	65 (40.6)	123 (38.3)	53 (33.1)	176 (36.6)
Stomach discomfort	3 (1.9)	7 (4.4)	10 (3.1)	3 (1.9)	13 (2.7)
Vomiting	48 (29.8)	58 (36.3)	106 (33.0)	44 (27.5)	150 (31.2)
General Disorders and Administration Site Conditions					
Asthenia	20 (12.4)	27 (16.9)	47 (14.6)	20 (12.5)	67 (13.9)
Chest pain	16 (9.9)	13 (8.1)	29 (9.0)	7 (4.4)	36 (7.5)
Malaise	12 (7.5)	16 (10.0)	28 (8.7)	12 (7.5)	40 (8.3)
Investigations					
Breath sounds abnormal	7 (4.3)	5 (3.1)	12 (3.7)	5 (3.1)	17 (3.5)
Electrocardiogram QT prolonged	16 (9.9)	21 (13.1)	37 (11.5)	6 (3.8)	43 (8.9)
Metabolism and Nutrition Disorders					
Anorexia	23 (14.3)	34 (21.3)	57 (17.8)	24 (15.0)	81 (16.8)
Hypokalaemia	20 (12.4)	31 (19.4)	51 (15.9)	24 (15.0)	75 (15.6)
Nervous System Disorders					
Headache	36 (22.4)	41 (25.6)	77 (24.0)	30 (18.8)	107 (22.2)
Hypoaesthesia	12 (7.5)	7 (4.4)	19 (5.9)	8 (5.0)	27 (5.6)
Paraesthesia	17 (10.6)	20 (12.5)	37 (11.5)	12 (7.5)	49 (10.2)
Tremor	19 (11.8)	16 (10.0)	35 (10.9)	13 (8.1)	48 (10.0)

System Organ Class and MedDRA Preferred Term	Delamanid 100 mg BID + OBR (N = 161) n (%)[a]	Delamanid 200 mg BID + OBR (N = 160) n (%)[a]	Total Delamanid BID + OBR (N = 321) n (%)[a]	Placebo + OBR (N = 160) n (%)[a]	Total (N = 481) n (%)[a]
Psychiatric Disorders					
Anxiety	9 (5.6)	12 (7.5)	21 (6.5)	5 (3.1)	26 (5.4)
Depression	4 (2.5)	13 (8.1)	17 (5.3)	5 (3.1)	22 (4.6)
Insomnia	42 (26.1)	51 (31.9)	93 (29.0)	42 (26.3)	135 (28.1)
Psychotic disorder	6 (3.7)	8 (5.0)	14 (4.4)	4 (2.5)	18 (3.7)
Restlessness	8 (5.0)	5 (3.1)	13 (4.0)	4 (2.5)	17 (3.5)
Respiratory, Thoracic, and Mediastinal Disorders					
Cough	8 (5.0)	8 (5.0)	16 (5.0)	7 (4.4)	23 (4.8)
Dyspnoea	3 (1.9)	8 (5.0)	11 (3.4)	5 (3.1)	16 (3.3)
Oropharyngeal pain	5 (3.1)	9 (5.6)	14 (4.4)	6 (3.8)	20 (4.2)
Throat irritation	5 (3.1)	8 (5.0)	13 (4.0)	0 (0.0)	13 (2.7)
Skin and Subcutaneous Tissue Disorders					
Hyperhidrosis	9 (5.6)	17 (10.6)	26 (8.1)	8 (5.0)	34 (7.1)

BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; OBR = optimized background treatment regimen; TEAE = treatment-emergent adverse event.

Patients are counted once, per term, for the most severe of multiple occurrences of a specific MedDRA preferred term.

[a]Percentages were based on the number of treated patients.

[b]Patients with AEs in multiple system organ classes were counted only once towards the total.

One death due to a TEAE occurred in this trial. A 50-year-old Asian female who received delamanid 200 mg BID + OBR died of respiratory failure on Day 8 of the treatment period. The investigator considered this to be unrelated to the IMP.

The percentages of patients with serious adverse events (SAEs) were slightly higher for the total delamanid BID + OBR group (36/321, 11.2%) compared with the placebo + OBR group (14/160, 8.8%), and for the delamanid 200 mg BID + OBR group (20/160, 12.5%) compared with the 100 mg BID + OBR group (16/161, 9.9%). The incidences of the individual SAEs were generally similar for the total delamanid BID + OBR and placebo + OBR groups (ie, incidences did not differ by more than 1%), with the exception of prolonged ECG QT (16/321, 5.0% and 3/160, 1.9%, respectively). The SAEs of prolonged ECG QT were considered by the investigator as possibly related to the IMP for 9 of the 16 patients treated with delamanid BID + OBR. The incidence of SAEs of prolonged ECG QT appeared to increase with increasing dose of delamanid: 7/161 (4.3%) for the delamanid 100 mg BID + OBR group and 9/160 (5.6%) for the delamanid 200 mg BID + OBR group. In this trial, guidance was provided to investigators for determination of QT/corrected QT interval (QTc) SAEs and the criteria changed over the course of the trial. As of 01 Jul 08, events of QTcB or QTcF > 500 ms, or changes from baseline of > 60 ms, or any increases associated with clinical symptoms were to be reported as SAEs; as of 05 Dec 08, any events of QTcB or QTcF > 500 ms, or any increases in QTcB or QTcF associated with clinical symptoms were to be reported as SAEs; and as of 04 Mar 09, within the SAE definition, “medically important” was expanded to include QTcF > 500 ms, or QTcF prolonged compared to baseline and accompanied by clinical symptoms. Of note, none of the SAEs pertaining to QTc

prolongation were actually accompanied by clinical symptoms. The effects of delamanid on ECG QT interval duration are further discussed below. Serious adverse events of hypokalaemia were reported for 2 patients in the delamanid 200 mg BID + OBR group. The potassium levels for these patients decreased to was 1.9 mEq/L for one patient, who later died due to respiratory failure, and 3.0 mEq/L for the other. Neither event was considered by the investigator to be related to the IMP. No SAEs of hypokalaemia were reported in the delamanid 100 mg BID + OBR group or the placebo + OBR group.

The percentage of patients who discontinued due to AEs was low (14/481, 2.9%) and similar among the 3 treatment groups (4/161, 2.5% in the delamanid 100 mg BID + OBR group; 6/160, 3.8% in the delamanid 200 mg BID + OBR group; and 4/160, 2.5% in the placebo + OBR group). None of the TEAEs resulting in discontinuation of IMP were reported for more than one patient with the exception of psychotic disorder, which was reported for 3 patients (2 in the delamanid 200 mg BID + OBR group and 1 in the placebo + OBR group).

Coadministration of delamanid with OBR in this trial did not adversely affect clinical laboratory values or vital signs when compared with OBR alone. Delamanid BID + OBR exposure was not associated with an increase in hepatotoxicity. No apparent safety signal of effect of delamanid BID + OBR exposure on prolongation of PT or aPTT was observed.

The effect of delamanid on cardiac repolarization using the measurement of the QTcF interval as the assessment showed a dose-response relationship, in which a progressive increase in QTcF duration occurred from Day 1 (first dose) to Day 56 (last dose). Using the time-matched analysis for the QTcF endpoint, patients with exposure to delamanid showed a progressive increase in the QTcF duration from Days 14 to Day 56. The upper CIs for the delamanid 100 and 200 mg BID + OBR groups increased, respectively, from 11 and 14 ms at Day 14, to 12 and 17 ms at Day 28, and then to 16 and 19 ms at Day 56. The greatest magnitude of effect at Day 56 was a 13 ms (10 to 16 ms) change for the delamanid 100 mg BID + OBR group and a 16 ms (12 to 19 ms) change for the delamanid 200 mg BID + OBR group. The placebo + OBR effect alone at Day 56 was −1 to +5 ms across the time points.

An analysis of the ECG data excluding data from Sites 015 and 016 (restricted data set) was conducted to assess the impact of Good Clinical Practice (GCP) issues at these sites relating to performing the ECGs. The analysis of QTcF on the restricted data set showed that the overall change from baseline in QTcF at Day 56 increased by about 2 ms for both of the delamanid BID + OBR groups compared with the analysis on the full data set. A comparison of the analysis of QTcF data in the full data set and the restricted data set is presented below.

Analyses of QTcF Data at Day 56 in the Full Data Set Compared With the Restricted Data Set (Excluding Sites 015 and 016)

ECG Parameter (ms)	Delamanid 100 mg BID + OBR		Delamanid 200 mg BID + OBR	
	Full Data Set (N = 161)	Restricted Data Set (N = 137)	Full Data Set (N = 160)	Restricted Data Set (N = 137)
	Mean (90% CI)	Mean (90% CI)	Mean (90% CI)	Mean (90% CI)
Maximum time-matched difference in QTcF, Day 56[a]	13.1 (10.14, 16.14)	14.8 (11.61, 18.03)	15.6 (12.45, 18.76)	17.5 (14.05, 20.97)
Categorical changes in QTcF from Days 0 to 56 (n/N, %)				
New onset > 500	0/161 (0.0)	0/137 (0.0)	0/160 (0.0)	0/137 (0.0)
New onset > 480	0/161 (0.0)	0/137 (0.0)	5/160 (3.1)	5/137 (3.6)
New onset > 450	25/161 (15.5)	24/137 (17.5)	22/160 (13.7)	22137 (16.0)
Change ≥ 30, ≤ 60	58/161 (36.0)	53/137 (38.6)	71/160 (44.3)	68/137 (49.6)
Change > 60	5/161 (3.1)	5/137 (3.6)	6/160 (3.7)	6/137 (4.3)

BID = twice daily; CI = confidence interval; OBR = optimized background treatment regimen; QTcF = QT interval corrected by Fridericia's formula.

[a]Maximum time-matched difference 3 hours postdose for the delamanid 100 mg BID + OBR group and 2 hours post dose for the delamanid 200 mg BID + OBR group.

Treatment with delamanid showed no signal of any effects on HR, AV conduction, or cardiac depolarization as measured by the PR and QRS interval durations. There were clinically relevant morphological changes in ST-T wave alterations related most likely to the observed changes in cardiac repolarization.

Conclusions:

- Statistically significantly higher proportions of patients treated with delamanid BID + OBR achieved SCC by Day 57 using the MGIT system than patients treated with placebo + OBR (45.4% versus 29.6% for the delamanid 100 mg BID + OBR group; p = 0.0083, and 41.9% versus 29.6% for the delamanid 200 mg BID + OBR group; p = 0.0393). These results represent a 42% to 53% increase in SCC as a result of treatment with delamanid.
- The results of the proportions of patients achieving SCC by Day 57 using solid culture media supported those of the primary analysis using the MGIT system. Using solid culture media, 53.8% of patients in the delamanid 100 mg BID + OBR group and 65.2% of patients in the delamanid 200 mg BID + OBR group achieved SCC compared with 33.6% for the placebo + OBR group; p < 0.01 for both comparisons.
- From the multiple regression analyses performed on the heterogeneous patient population included in this trial, exposure to delamanid, longer time to sputum culture positivity (ie, TTD) at baseline (with both MGIT and solid), and treatment of otherwise treatment-naïve patients with anti-TB medications (OBR) for > 90 days prior to randomization were independently associated with patients achieving SCC by Day 57. Use of a later generation fluoroquinolone as part of OBR demonstrated a

trend toward significance (p = 0.0594) for SCC. Patients with resistance to at least one fluoroquinolone agent and one of the injectable anti-TB agents at baseline (ie, XDR TB) (with both media types), older age (using the MGIT system), and originating from the Americas (Peru) were independently associated with not achieving SCC by Day 57. Presence of cavitation, either unilateral or bilateral, was not associated with a lower likelihood of SCC at Day 57.

- Time to sputum culture positivity at baseline using the MGIT system was similar for all 3 treatment groups. At all time points assessed after initiation of IMP, time to culture positivity using the MGIT system was longer for both the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups relative to placebo + OBR, suggesting that the use of delamanid at both doses + OBR led to greater reduction of MTB organism burden in sputum beyond that achieved with placebo + OBR.
- Median time to final SCC (sustained SCC achieved by Day 57) could not be calculated because fewer than 50% of patients in each group met the criteria; however, the Kaplan-Meier curves for time to final SCC using the MGIT system showed clear separation between each delamanid + OBR group and the placebo + OBR group. With the MGIT system, the likelihood that a patient would achieve final SCC by Day 57 was 73% and 59% higher for the delamanid 100 mg BID + OBR and delamanid 200 mg BID + OBR treatments, respectively, compared with placebo + OBR ($p < 0.05$).
- After oral administration of delamanid (100 mg BID and 200 mg BID) with food, at 10 and 14 hours dosing interval, in MDR TB patients on OBR therapy, delamanid mean (%CV) values for C_{max1} (at 4h post dose) on Day 56 were 414 (39.9) ng/mL and 611 (35.6) ng/mL; those for $AUC_{0\text{-}24h}$ were 7,925 (37.5) and 11,837 (33.6) h·ng/mL, respectively. Delamanid plasma AUC after the 200 mg BID + OBR dose was 50% higher than after the 100 mg BID + OBR dose. Delamanid $t_{1/2}$ was 38 hours. Delamanid steady state was reached by Day 14; upon BID dosing, R_{ac} at steady state was 3.4 to 3.5.
- Delamanid metabolites formed slowly and were also eliminated slowly ($t_{1/2}$ 124 to 425 h), resulting in flat concentration-time profiles that continuously increased over time. Metabolite exposure increased progressively. Hence steady state achievement of metabolites could not be estimated over the 2-month administration period in this trial.
- DM-6705 plasma concentrations predicted the highest placebo-adjusted ΔQTc value and were identified as surrogate marker for QTc prolongation after delamanid + OBR administration. The highest predictions of mean placebo-adjusted ΔQTcF [upper 95% CI] on Day 56 at maximal DM-6705 plasma exposure, were 14.24 [15.39] ms (C_{max} of 151 ng/mL) and 21.98 [23.75] ms (C_{max} of 233 ng/mL) after delamanid 100 mg BID + OBR and 200 mg BID + OBR, respectively.

- The incidences of the most frequently reported TEAEs were generally similar for delamanid BID + OBR and placebo + OBR, with the exception of the following events with a greater incidence in the delamanid BID + OBR group: nausea, vomiting, headache, and prolonged ECG QT. For all of these events, the incidences were greater in the delamanid 200 mg BID + OBR group than in the delamanid 100 mg BID + OBR group.
- The incidences of the most frequently reported TEAEs were also generally similar between the delamanid 100 mg BID + OBR and 200 mg BID + OBR groups, with the exception of the following events with a greater incidence in the delamanid 200 mg BID + OBR group: dyspepsia, vomiting, anorexia, hypokalaemia, depression, insomnia, and hyperhidrosis.
- One death due to a TEAE occurred in this trial. A 50-year-old female who received delamanid 200 mg BID + OBR died of respiratory failure on Day 8 of the treatment period. The investigator considered this to be unrelated to the IMP.
- The overall incidence of SAEs was slightly higher for the total delamanid BID + OBR group compared with the placebo + OBR group. The incidences of the individual SAEs were generally similar between these groups (ie, incidences did not differ by more than 1%), with the exception of prolonged ECG QT (16/321, 5.0% and 3/160, 1.9%, respectively). In the delamanid BID + OBR groups, the incidence of prolonged ECG QT also appeared to be dose-dependant: 7/161 (4.3%) for the 100 mg BID + OBR group and 9/160 (5.6%) for the 200 mg BID + OBR group.
- The percentages of patients who discontinued IMP due to TEAEs were similar in the total delamanid BID + OBR and placebo + OBR groups (10/321, 3.1% and 4/160, 2.5%, respectively). None of the TEAEs resulting in discontinuation of IMP were reported for more than one patient with the exception of psychotic disorder, which was reported for 3 patients: 2 patients who received delamanid 200 mg BID + OBR and 1 patient who received placebo + OBR.
- Coadministration of delamanid BID + OBR in this trial did not adversely affect clinical laboratory values or vital signs when compared with placebo + OBR. Delamanid BID + OBR exposure was not associated with an increase in hepatotoxicity.
- The effect of delamanid on cardiac repolarization using the measurement of the QTcF interval as the assessment showed a dose-response relationship, in which a progressive increase in QTcF duration occurred from Day 1 (first dose) to Day 56 (last dose). The greatest magnitude of effect at Day 56 for the delamanid 100 mg BID + OBR dose using the time-matched analysis showed a mean change in QTcF of 13 ms (10 to 16 ms). For the delamanid 200 mg BID + OBR dose, the mean change in QTcF was 16 ms (12 to 19 ms). While this is a potentially meaningful change from baseline in QTcF duration, its risk has to be weighed in light of the benefit of delamanid in treating MDR TB, a life-threatening condition.
- Treatment with delamanid showed no signal of any effects on HR, AV conduction or cardiac depolarization as measured by the PR and QRS interval durations. There were clinically relevant morphological changes in ST-T wave alterations related most likely to the observed changes in cardiac repolarization.