Synopsis

Clinical Report Synopsis for Protocol 242-08-210
Eudra CT No. 2009-014944-13

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

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

Protocol Title: A Phase 2, Multi-center, Non-controlled, Open-label Dose Escalation Trial to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Orally Administered OPC-67683 Two Times Daily to Patients with Pulmonary Multidrug-resistant Tuberculosis Refractory to Conventional Treatment

Coordinating Investigator and Trial Sites: Coordinating Investigator: Andra Cirule, MD, State Agency "Infectology Center of Latvia," Clinic of Tuberculosis and Lung Diseases, Ceplisi Branch, Priezu Street 1, Tinuzi, Ogre District, LV 5015, Latvia. Conducted in 3 sites in Latvia and Lithuania.

Publications: None to date

Trial Period:

Date of first signed informed consent: 19 Feb 2010

Date of last trial observation: 12 May 2011

Clinical Phase/Trial Type: 2/Therapeutic exploratory

Objectives:
Primary:

- To evaluate the safety and tolerability of orally administered OPC-67683 2 times daily (BID) given in sequentially escalated doses for up to 196 days (28 weeks) at each dose to individual cohorts of multidrug-resistant tuberculosis (MDR-TB) patients refractory to treatment with optimized background regimen (OBR).
- To evaluate pharmacokinetic (PK) characteristics of orally administered OPC-67683 from 250 mg BID up to 400 mg BID.
- To determine the potential dose limiting factors and, potentially, the maximum tolerated dose (MTD) in patients treated with OPC-67683.

Secondary:

- To determine the proportion of patients with sputum culture conversion (SCC). Sputum culture conversion was defined to occur at the time of the collection of a sputum specimen with mycobacterial culture negative for growth of *Mycobacterium tuberculosis* (MTB) using the Mycobacteria Growth Indicator Tube® (MGIT) culture system followed by at least one additional sputum specimen negative for growth at least 28 days after the first specimen negative for

growth and not followed by any sputum specimens positive for growth of MTB during the remainder of the 280-day (40-week) trial period.

- To monitor development of in vitro resistance to OPC-67683 among enrolled patients over the 196-day (28-week) Treatment Period of the trial.

Methodology: This trial was designed as a phase 2, multicenter, noncontrolled, nonrandomized, open-label trial to assess safety, tolerability, and PK characteristics of delamanid and to explore potential efficacy in treating MDR-TB patients otherwise refractory to treatment, which was defined as those remaining sputum culture positive for MDR-TB after at least 270 days (9 months) of prior treatment with OBR for MDR-TB.

The number of patients planned for each cohort was 5; the maximum number of patients planned for this trial was 30.

The investigational medicinal product (IMP) for this trial, delamanid, was supplied by Otsuka as 50-mg tablets dosed orally BID with meals to optimize absorption. The starting dose was 500 mg/day (250 mg BID) in the first cohort of patients, with dose escalation in 100-mg daily increments (50 mg per BID dose) in subsequent cohorts of patients, up to a total daily dose of 800 mg (400 mg BID), depending on tolerability. If the 250-mg BID dose level was not tolerated by the first enrolled 5-patient cohort, 200 mg BID was to be evaluated as the next and final dosing level.

The duration of the trial per patient from Screening through Post-treatment Follow-up was approximately 292 days (42 weeks). The duration of the clinical conduct of this trial was 15 months.

The trial was conducted in 2 stages.

Stage 1 refers to the first 56 days (when metabolites of delamanid were projected to reach steady state) of the 196-day (28-week) Treatment Period for each patient during which patients were hospitalized for frequent safety monitoring, including clinical laboratory assessments and electrocardiograms (ECGs). The first 28 days of Stage 1 in the first 5-patient cohort constituted the period of evaluation for dose escalation (or de-escalation) for the subsequent cohort(s) enrolled.

Stage 2 refers to the remaining 140 days (20 weeks) of the Treatment Period for each patient during which ongoing monthly safety monitoring was performed, followed by an immediate 84-day (12-week) Post-treatment Period for each patient during which monthly sputum samples for microbiologic testing, recording of anti-tuberculosis (TB) medications, and assessments of adverse events (AEs) and immediately reportable events (IREs) were performed for 3 months; patients may have continued in Stage 2 as outpatients or under hospitalization at the discretion of the investigator.

Microbiologic assessments of sputum culture status by both the MGIT system and solid media were performed weekly in Stage 1 of the trial, every 2 weeks in Stage 2 of the trial through Day 196 (28 weeks), and monthly thereafter for 3 months through Day 280 (40 weeks).

To determine tolerability, each patient in a given cohort was evaluated by a data monitoring committee (DMC) after 28 days of treatment. Dose-limiting toxicity (DLT) was determined based on laboratory, vital sign, and ECG assessments and reported AEs. Dose toleration in an

individual patient was defined as follows: during the course of the trial, the patient did not experience any untoward events or potentially clinically significant changes from baseline in laboratory values, vital signs, or ECGs that were assessed as possibly related to IMP and that were severe or serious, or that would have necessitated adjustment or discontinuation of IMP. For the overall evaluation of the cohort, a dose was judged to be tolerated if 4 out of 5 patients (80%) in a cohort tolerated the dose. Assessment of dose tolerability for a cohort was conducted after the first 4 patients enrolled in the cohort completed the first 28 days of treatment in Stage 1 of the Treatment Period. Based on these criteria, if the dose was determined to be tolerated by the cohort, a separate cohort of 5 patients was started on a dose 100 mg total daily (50 mg BID) higher than the previous tolerated dose.

Patients who did not tolerate a given dose would have been given the option of continuing in the trial and receiving a dose reduced by 100 mg total daily (50 mg BID) for the remaining time of the Treatment Period up to 196 total days, after review and approval by the medical monitor and the safety officer for this trial.

If any dose was not tolerated, the previous dose that was tolerated would have been identified as the MTD. If 250 mg BID, the initial dose tested, was not tolerated based on the criteria, a dose of 200 mg BID was to be evaluated as the next and final dose.

At the discretion of the sponsor, an additional separate cohort of 5 patients may have been tested to confirm the MTD.

Number of Patients: Up to 30 male or female patients with culture-positive pulmonary MDR-TB refractory to treatment with OBR were planned to be enrolled in this trial. Multidrug-resistant TB patients refractory to treatment were defined as those remaining sputum culture positive for MTB isolates resistant to isoniazid and rifampicin after 270 days (9 months) of prior treatment with an OBR for MDR-TB. A total of 10 patients were enrolled per the dose escalation (de-escalation) design described above (5 patients each in the delamanid 250 mg BID + OBR and delamanid 300 mg BID + OBR cohorts) and included in the safety and efficacy analyses.

The trial was terminated per protocol for lack of efficacy and for lack of increased concentrations of delamanid with increased dose, not for DLT. No further patient cohorts were enrolled after the first 2 cohorts because review of the data by the DMC revealed lack of sustained response in most patients. Further, at the time of data review by the DMC, the data from Trial 242-07-204 had recently been unblinded and it was observed that the higher dose in that trial (delamanid 200 mg BID + OBR) was not more effective than the lower dose (delamanid 100 mg BID + OBR), and that exposure in Trial 242-08-210 at doses of delamanid 250 mg BID + OBR and delamanid 300 mg BID + OBR did not exceed exposure observed at doses of delamanid 100 mg BID + OBR and delamanid 200 mg BID + OBR in patients with MDR-TB in Trial 242-07-204.

Diagnosis and Main Criteria for Inclusion: Male or female patients were between 18 and 64 years of age, inclusive. Patients had at least 3 sputum mycobacterial cultures positive for MTB with in vitro resistance to isoniazid and rifampicin collected at separate time points during the previous 270 days (9 months) despite treatment with first- and second-line anti-TB drugs. One of the cultures was within the previous 60 days prior to the date of Screening initiation. Sputum mycobacterial culture positive for MTB with in vitro susceptibility to at least one anti-TB medication was within the previous 60 days prior to the date of Screening initiation.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No: Delamanid was manufactured by Otsuka Pharmaceutical

Co., Ltd. (Japan) and supplied as 50-mg tablets (lots 09B87A050A, 07F91A050H, and 07F91A050I) and supplied in bottles. Lot 07F91A050I was not dispensed. Doses were given orally, BID, immediately following a meal for 196 days (28 weeks).

A 250-mg dose was given as 5 × 50-mg tablets.
A 300-mg dose was given as 6 × 50-mg tablets.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No: Use of anti-TB medications in treatment with IMP was provided for all patients by the investigators as per the World Health Organization's *Guidelines for the Programmatic Management of Drug-resistant Tuberculosis* and the investigator's best clinical judgment.

Trial Assessments:
Efficacy: Morning spot sputum collection for mycobacterial cultures to evaluate for growth of MTB using the MGIT liquid culture system and solid culture media, and drug susceptibility testing for delamanid.

Pharmacokinetics: Blood sampling for delamanid and metabolites plasma concentrations.

Safety: AE reporting, clinical laboratory assessments including hematology and serum chemistry, 12-lead ECGs, vital signs, and physical examinations.

Screening/Other: Diagnostic and treatment history for TB, other medical and medication history, urine drug screening, urine pregnancy test, chest x-ray, and audiometry.

Criteria for Evaluation:
Primary Endpoints:
Safety: Vital signs, ECGs, clinical laboratory assessments, audiometry, visual acuity, neurological assessments, coagulation, concomitant medication usage, AEs, and IREs were assessed for safety.

Pharmacokinetics: For delamanid, the following PK parameters were to be estimated: time to maximum (peak) plasma concentration (t_{max}), maximum (peak) plasma concentration (C_{max}), area under the concentration-time curve (AUC) from time zero to 24 hours ($AUC_{0\text{-}24h}$), and accumulation ratios for C_{max} and $AUC_{0\text{-}24h}$ ($R_{ac}[C_{max}]$ and R_{ac}[AUC] for Days 14, 28, 56, 112, or 196/Day 1).

Secondary Endpoints:
Pharmacokinetics: For delamanid metabolites, the following PK parameters were to be estimated: t_{max}, C_{max}, $AUC_{0\text{-}24h}$, and $R_{ac}(C_{max})$ and R_{ac}(AUC) for Days 14, 28, 56, 112, or 196/Day 1.

Efficacy: No inferential analysis was planned. The following descriptive analyses on microbiologic endpoints were to be performed:

- Proportion of patients with SCC at Day 168 evaluated with the MGIT culture system.
- Proportion of patients achieving SCC on solid mycobacterial culture media at Day 168.

- Change from baseline in time to culture positivity using the MGIT system.
- Area under the curve of change from baseline in time to culture positivity in the MGIT system.
- Proportion of patients whose sputum reverted to culture positive status after achieving an initial SCC using the MGIT system.
- Proportion of patients who never achieved SCC using the MGIT system.
- Proportion of patients who developed resistance to delamanid at Days 28, 56, 84, 112, 140, 168, and 196 while on treatment.
- Proportion with sputum mycobacterial culture negative for growth at Day 196 using the MGIT culture system.
- Proportion with sputum mycobacterial culture negative for growth at Day 196 on solid media.
- Slopes characterizing the changes in time to culture positivity in the MGIT system.

Statistical Methods: Because of the small sample size, no inferential statistical analysis was performed. As primarily an investigation of safety and PK, this trial was designed to explore whether higher total daily doses of delamanid were successful in increasing delamanid exposure with an acceptable safety profile.

The main focus in the efficacy analysis was on monitoring the sputum culture status of all the patients throughout the trial and providing descriptive statistics of 3 major microbiologic endpoints (ie, the first 3 efficacy endpoints listed above).

Analysis endpoints were descriptively listed by cohort with a given dose.

Pharmacokinetic/pharmacodynamic Methods:
Bioanalytical: Plasma concentrations of delamanid, DM-6704, DM-6705, and DM-6706 were quantified by a validated ultra performance liquid chromatographic assay utilizing tandem mass spectrometric detection.

Pharmacokinetics: Delamanid, DM-6704, DM-6705, and DM-6706 PK parameters were determined by noncompartmental methods. The present PK analysis slightly differed from the per protocol analysis for the estimation of 2 PK parameters: a) Estimation of PK parameters over a 12-hour dosing interval (τ) instead of over a 24-hour dosing interval, and b) $R_{ac}(C_{max})$ and $R_{ac}(AUC_{0\text{-}24h})$ for metabolites.

1) The only PK sampling times at 12 and 24 hours after the delamanid evening dose did not allow for an accurate estimation of PK parameters over that observation period, resulting in a considerable underestimation of AUC from 12 to 24 hours ($AUC_{12\text{-}24h}$). A more accurate estimation of $AUC_{0\text{-}24h}$ was therefore obtained using 2 × AUC from time zero to 12 hours ($AUC_{0\text{-}12h}$) values.
2) Limited metabolite exposure on Day 1 did not allow for estimation of R_{ac} for metabolites. Instead, ratios for $AUC_{0\text{-}12h}$ with respect to Day 14 values were calculated on Days 28, 56, 112, and 196.

Pharmacokinetics/pharmacodynamics: Linear mixed effects modeling was applied to quantify the relationship between corrected QT interval (QTc; using Fridericia's formula [QTcF]) change from time-matched baseline values (ΔQTcF) (pharmacodynamic [PD]) versus DM-6705 plasma concentrations (PK). DM-6705 mainly contributes to the QTc prolongation observed with delamanid administration. All individual-paired, PK/PD data on Days 1, 14, 28, 56, 112, and 196 from 10 patients receiving delamanid (250 mg BID or 300 mg BID) with OBR were considered in the PK/PD analysis for QTc prolongation.

Statistics: Delamanid, DM-6704, DM-6705, and DM-6706 plasma concentrations, PK parameters, and QTc measurements for the PK/PD analysis are presented as individual values with descriptive statistics by day and treatment group.

Efficacy Results: Overall, 2/10 patients achieved SCC during the trial period. In the delamanid 300 mg BID + OBR cohort, 1/5 (20.0%) patients achieved SCC at Day 168 using either the MGIT system or solid culture. Beginning on Days 56 and 70, the patient had sustained negative culture results using solid culture and the MGIT system, respectively. This patient's MTB specimen had unexpected susceptibility to rifampicin at baseline (but not to isoniazid) and therefore received treatment with 3 bactericidal agents (rifampicin, delamanid, and amikacin) during the trial's treatment period.

No patients achieved SCC at Day 168 in the delamanid 250 mg BID + OBR cohort; however, one patient achieved SCC starting on Days 49 and 56 using solid culture and the MGIT system, respectively, through Day 84 and again at Day 252 through the end of the trial (Day 280).

Overall, 7/10 (70.0%) patients had MTB specimens that developed resistance to delamanid during the trial. Of the 7 patients whose MTB specimens developed resistance to delamanid, 5 patients had XDR-TB and were essentially treated with delamanid as a single bactericidal agent with only bacteriostatic agents to which the patient's isolates may or may not have been susceptible. This finding was not unexpected based on reports in the literature from the time when streptomycin was introduced as the first antimicrobial treatment agent for TB initially administered as monotherapy.

Pharmacokinetic/pharmacodynamic Results: A summary of the PK parameters for delamanid, DM-6704, DM-6705, and DM-6706 following administration of delamanid 250 mg BID + OBR or delamanid 300 mg BID + OBR to patients with MDR-TB refractory to conventional treatment is presented in the following tables:

Mean (%CV) Delamanid Pharmacokinetic Parameters in Patients With MDR-TB Refractory to Conventional Treatment

Trial Day	PK Parameter	Delamanid 250 mg BID + OBR (n = 5)	Delamanid 300 mg BID + OBR (n = 5)
Day 1	C_{max} (ng/mL)	142 (48.1)	192 (48.6)
	t_{max} (h)[a]	2.95 (2.95, 12.15)	3.20 (3.00, 11.88)
	AUC_{0-24h} (h·ng/mL)[b]	2020 (35.0)	2650 (48.2)
	R_{ac}(AUC)	ND	ND
	R_{ac}(C_{max})	ND	ND
Day 14	C_{max} (ng/mL)	521 (25.4)	514 (19.3)
	t_{max} (h)[a]	2.95 (0.00, 3.27)	3.02 (2.53, 3.05)

Mean (%CV) Delamanid Pharmacokinetic Parameters in Patients With MDR-TB Refractory to Conventional Treatment			
Trial Day	**PK Parameter**	**Delamanid 250 mg BID + OBR (n = 5)**	**Delamanid 300 mg BID + OBR (n = 5)**
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	9580 (29.1)	10400 (18.7)
	$R_{ac}(AUC)$	4.85 (19.3)	5.45 (80.4)
	$R_{ac}(C_{max})$	4.01 (30.3)	3.76 (83.3)
Day 28	C_{max} (ng/mL)	558 (20.3)	573 (20.4)
	t_{max} (h)[a]	2.95 (2.95, 3.00)	3.03 (3.00, 8.92)
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	9840 (31.4)	11200 (21.9)
	$R_{ac}(AUC)$	4.92 (14.2)	5.66 (73.9)
	$R_{ac}(C_{max})$	4.33 (30.3)	4.01 (70.9)
Day 56	C_{max} (ng/mL)	558 (42.9)	503 (25.1)
	t_{max} (h)[a]	2.95 (0.00, 8.95)	3.00 (3.00, 8.97)
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	10500 (42.9)	9720 (24.7)
	$R_{ac}(AUC)$	5.13 (14.8)	4.55 (54.0)
	$R_{ac}(C_{max})$	4.04 (16.3)	3.24 (52.8)
Day 112	C_{max} (ng/mL)	441 (64.9)	427 (26.7)[c]
	t_{max} (h)[a]	2.95 (0.00, 3.00)	3.03 (3.00, 3.05)[c]
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	8020 (68.3)	8470 (36.4)[c]
	$R_{ac}(AUC)$	3.74 (39.4)	2.85 (44.8)[c]
	$R_{ac}(C_{max})$	3.07 (40.7)	1.89 (25.6)[c]
Day 196	C_{max} (ng/mL)	494 (26.2)	499 (48.4)[d]
	t_{max} (h)[a]	2.95 (0.00, 8.95)	3.00 (3.00, 3.00)[d]
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	9420 (24.8)	8640 (33.4)[d]
	$R_{ac}(AUC)$	4.79 (16.7)	2.29 (16.0)[d]
	$R_{ac}(C_{max})$	3.80 (33.0)	1.93 (21.7)[d]

%CV = percent coefficient of variation; ND = not determined.

[a]Median (minimum, maximum).

[b]$AUC_{0\text{-}24h}$ is calculated as $2 \times AUC_{0\text{-}12h}$.

[c]n = 4.

[d]n = 2.

Mean (%CV) DM-6704 Pharmacokinetic Parameters in Patients With MDR-TB Refractory to Conventional Treatment			
Trial Day	**PK Parameter**	**Delamanid 250 mg BID + OBR (n = 5)**	**Delamanid 300 mg BID + OBR (n = 5)**
Day 56	C_{max} (ng/mL)	59.9 (37.4)	119 (67.1)
	t_{max} (h)[a]	5.95 (0.00, 8.95)	3.00 (0.00, 9.00)
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	1280 (38.9)	2610 (67.6)

Mean (%CV) DM-6704 Pharmacokinetic Parameters in Patients With MDR-TB Refractory to Conventional Treatment			
Trial Day	**PK Parameter**	**Delamanid 250 mg BID + OBR (n = 5)**	**Delamanid 300 mg BID + OBR (n = 5)**
	Day 56/14 Ratio $AUC_{0\text{-}12h}$	1.62 (36.7)	1.44 (51.2)
Day 196	C_{max} (ng/mL)	71.2 (12.4)	99.3 (105.0)[c]
	t_{max} (h)[a]	2.95 (0.00, 8.95)	3.00 (3.00, 3.00)[c]
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	1550 (11.4)	2130 (104.4)[c]
	Day 196/14 Ratio $AUC_{0\text{-}12h}$	2.40 (67.1)	0.988 (83.3)[c]

%CV = percent coefficient of variation; ND = Not determined.

[a]Median (minimum, maximum).

[b]$AUC_{0\text{-}24h}$ is calculated as 2 × $AUC_{0\text{-}12h}$.

[c]n = 2.

Mean (%CV) DM-6705 Pharmacokinetic Parameters in Patients With MDR-TB Refractory to Conventional Treatment			
Trial Day	**PK Parameter**	**Delamanid 250 mg BID + OBR (n = 5)**	**Delamanid 300 mg BID + OBR (n = 5)**
Day 56	C_{max} (ng/mL)	140 (45.9)	142 (35.4)
	t_{max} (h)[a]	5.95 (2.95, 9.00)	8.97 (0.00, 12.00)
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	3100 (47.8)	3150 (35.9)
	Day 56/14 Ratio $AUC_{0\text{-}12h}$	1.84 (19.9)	1.56 (26.8)
Day 196	C_{max} (ng/mL)	135 (46.7)	154 (83.3)[c]
	t_{max} (h)[a]	5.95 (2.95, 12.00)	7.49 (6.00, 8.98)[c]
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	3060 (46.2)	3440 (84.1)[c]
	Day 196/14 Ratio $AUC_{0\text{-}12h}$	1.86 (25.1)	1.40 (91.9)[c]

%CV = percent coefficient of variation; ND = not determined.

[a]Median (minimum, maximum).

[b]$AUC_{0\text{-}24h}$ is calculated as 2 × $AUC_{0\text{-}12h}$.

[c]n = 2.

Mean (%CV) DM-6706 Pharmacokinetic Parameters in Patients With MDR-TB Refractory to Conventional Treatment			
Trial Day	**PK Parameter**	**Delamanid 250 mg BID + OBR (n = 5)**	**Delamanid 300 mg BID + OBR (n = 5)**
Day 56	C_{max} (ng/mL)	77.6 (36.6)	103 (70.2)
	t_{max} (h)[a]	5.95 (0.00, 8.95)	0.00 (0.00, 9.00)
	$AUC_{0\text{-}24h}$ (h·ng/mL)[b]	1670 (36.5)	2290 (72.2)
	Day 56/14 Ratio $AUC_{0\text{-}12h}$	1.93 (33.6)	1.38 (53.4)
Day 196	C_{max} (ng/mL)	81.7 (7.8)	94.9 (97.1)[c]
	t_{max} (h)[a]	8.95 (2.95, 8.98)	6.01 (3.00, 9.02)[c]

Mean (%CV) DM-6706 Pharmacokinetic Parameters in Patients With MDR-TB Refractory to Conventional Treatment			
Trial Day	**PK Parameter**	**Delamanid 250 mg BID + OBR (n = 5)**	**Delamanid 300 mg BID + OBR (n = 5)**
	AUC_{0-24h} (h·ng/mL)[b]	1820 (10.3)	2060 (99.9)[c]
	Day 196/14 Ratio AUC_{0-12h}	2.43 (53.6)	1.12 (77.2)[c]

%CV = percent coefficient of variation; ND = not determined.

[a] Median (minimum, maximum).

[b] AUC_{0-24h} is calculated as $2 \times AUC_{0-12h}$.

[c] n = 2.

Pharmacokinetic/pharmacodynamic Results: Mean (and upper one-sided 95% confidence intervals [CIs] for the mean) ΔQTcF values estimated from the linear regression line at DM-6705 C_{max} for each delamanid treatment are presented in the table below:

Predicted QTcF Change From Baseline at DM-6705 C_{max}			
Delamanid Dose + OBR (mg BID)	**DM-6705 C_{max} (ng/mL)**	**ΔQTcF**	
		$\mu_{\Delta QTcF}$ (msec)	**Upper 95% CI (msec)**
250	140	16.03	20.35
300	154	17.63	22.38

$\mu_{\Delta QTcF}$ = mean changed from time-matched baseline in QTcF.

Safety Results: A total of 10 patients received at least one dose of IMP in this trial and were 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. Five patients each were administered delamanid 250 or 300 mg BID (500 or 600 mg/day, respectively) + OBR. Overall, 7/10 (70.0%) patients completed the trial. No DLT was observed and an MTD was not identified. Two of 10 (20.0%) patients discontinued early due to AEs (see below) and 1/10 (10.0%) patients discontinued early due to a protocol deviation (taking prohibited concomitant medication).

Based on medical and treatment history and drug resistance data, this group of patients had extensive disease that had been heavily treated. All patients had cavitation and 60% had bilateral cavitations, an indicator of more extensive disease. The majority of patients had hearing loss, indicative of extensive previous treatment with injectable anti-TB agents, which have ototoxicity as a common side effect from longer term use.

The most frequently reported treatment-emergent adverse events (TEAEs; incidence ≥ 4 patients overall) included hyperglycemia, TB (progressive or worsening TB), viral upper respiratory tract infection, and nausea.

Fatal TEAEs were reported for one patient (delamanid 300 mg BID + OBR) 14 days following discontinuation of delamanid therapy and included acute myocardial infarction, coronary artery disease, TB (worsening of MDR-TB), and alcohol abuse. Nonfatal serious TEAEs were reported for 4 patients and included anemia, atrial fibrillation, TB (progressive or worsening TB), post procedural hemorrhage, prolonged ECG QT interval, lung lobectomy, and pneumonectomy.

Overall, 2 patients discontinued IMP due to nonfatal TEAEs (delamanid 300 mg BID); one patient each had a TEAE of atrial fibrillation and TB (progressive TB).

The mean changes from baseline in clinical laboratory and vital sign parameters were not clinically relevant and were generally similar between the dose groups.

The most frequently reported TEAEs related to serum chemistry abnormalities (incidence ≥ 2 patients overall) were hyperglycemia and hyperkalemia. Treatment-emergent AEs related to hematology abnormalities of anemia were reported for 2 patients and increased reticulocyte count was reported for one patient. One incidence of anemia was classified as serious. A TEAE related to a urinalysis abnormality of proteinuria was reported for one patient.

The most frequently reported potentially clinically significant abnormalities in vital signs (incidence ≥ 2 patients overall) included decrease of ≥ 5% in body weight, heart rate ≤ 60 bpm and a decrease of ≥ 15 bpm, and systolic blood pressure ≤ 90 mmHg and a decrease of ≥ 20 mmHg. Decreased weight was reported as a TEAE in 2/10 (20.0%) patients.

The most frequently reported categorical changes in ECGs included change in QTcF between ≥ 30 and ≤ 60 msec and new abnormal rhythm (reported for 7/10 patients each). The TEAEs related to ECG abnormalities included a serious TEAE of prolonged ECG QT interval (> 500 msec) and a nonserious TEAE of ECG ST-T change. Both TEAEs related to ECG abnormalities were reported for a single patient in the delamanid 300 mg BID + OBR cohort and were determined by the investigator to be potentially drug-related. An ECG showed QTc prolongation (QTcF 503 msec) the day after starting amiodarone therapy (suspected to be responsible for the QT prolongation) and 2 days after delamanid and other anti-TB medications were discontinued for this patient.

Conclusions:

- Six of the 10 patients enrolled in the trial with a 9-month or longer history of previous treatment with second-line drugs for MDR-TB had extensively drug-resistant TB at baseline, greatly limiting options for anti-TB drugs to use in combination with delamanid.
- No DLT was observed in this trial. The most frequently reported TEAEs included hyperglycemia, TB (progressive or worsening of TB), viral upper respiratory tract infection, and nausea.
- One patient in the delamanid 300 mg BID + OBR cohort died 14 days after the end of delamanid therapy due to acute myocardial infarction, coronary artery disease, TB (worsening of MDR-TB), and alcohol abuse.
- Due to the small sample size, no clinically meaningful changes from baseline in clinical laboratory or vital sign parameters were observed and the dose groups were generally similar.
- In patients with MDR-TB refractory to conventional treatment on delamanid 250 mg BID + OBR or delamanid 300 mg BID + OBR, delamanid steady-state plasma exposure ($AUC_{0\text{-}24h}$) was similar at both doses and ranged between 8,020 and 11,200 ng·h/mL.
- Predicted mean ΔQTcF values (upper one-sided 95% CI) at observed DM-6705 C_{max} were 16.03 (20.35) msec (C_{max} of 140 ng/mL) and 17.63 (22.38) msec (C_{max}

of 154 ng/mL), after delamanid 250 mg BID + OBR and delamanid 300 mg BID + OBR, respectively.

- Two patients achieved a sustained SCC during this trial. One patient achieved SCC beginning on Day 70 (MGIT) through the end of the trial and one patient achieved SCC during the 3-month follow-up period (beginning on Day 252). The patient achieving SCC at Day 70 had an MTB specimen with unexpected susceptibility to rifampicin at baseline (but not to isoniazid) and therefore received treatment with 3 bactericidal agents (rifampicin, delamanid, and amikacin) during the trial's treatment period.
- Overall, 7/10 (70.0%) patients had MTB specimens that developed resistance to delamanid during the trial. As was previously documented with the introduction of streptomycin as the first anti-TB drug initially administered as monotherapy, resistance to delamanid emerged among 6 of the 7 patients receiving delamanid as a single bactericidal agent.