Synopsis

Clinical Report Synopsis for Protocol 242-07-208

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

Name of Product: Delamanid (OPC-67683)

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

Investigator(s) and Study Center(s): Multicenter (14 centers; multinational)

Publications: None to date.

Studied Period:

Date of first signed informed consent: 26 Mar 2009

Date of last study observation: 27 Oct 2011

Clinical Phase: 2

Objectives: The primary objective of this trial was to provide extended safety and tolerability data for longer-term exposure to delamanid for up to 6 additional months beyond any exposure patients had to delamanid in Trial 242-07-204 (hereafter, Trial 204).

The secondary objective of this trial was to evaluate the efficacy of delamanid at either 100 mg twice daily (BID) or 200 mg BID (if the patient was titrated to the higher dose) administered orally in combination with an optimized treatment regimen (OBR) (designed and administered according to World Health Organization [WHO] guidelines) for up to 6 months of exposure in patients who had completed Trial 204. Also, this trial was to provide additional access to delamanid for patients with the potential to receive clinical benefit from continued delamanid exposure or first time access (for patients who received placebo in Trial 204) for patients who might receive clinical benefit from delamanid exposure.

Methodology: This was a phase 2, multicenter, uncontrolled, open-label trial in patients with multi-drug resistant tuberculosis (MDR-TB). All 402 patients who completed Trial 204 were eligible for this trial if all inclusion criteria and no exclusion criteria were met.

Patients were treated with delamanid plus OBR for up to 6 months (26 weeks) beyond delamanid exposure in Trial 204 (which was 56 days for those patients randomized to active treatment). The 242-07-208 extension trial (hereafter, Trial 208) was comprised of the following periods:

- Pre-Treatment Period: Informed consent and screening began at each patient's Day 56 visit for Trial 204 or thereafter and continued until the patient was determined eligible for enrollment in this trial, or determined to be a screen failure. Baseline could have occurred no earlier than the day of the completion visit (Day 84) of Trial 204, no later than 30 days after the patient completed Day 84 of Trial 204, or 30 days (90 days for sites located within Peru or Philippines) after the patient's trial investigator's site was initiated to begin enrolling in this trial following national authority approval, whichever was later. Trial 204 completion visit procedures that matched baseline procedures in this trial were not repeated if the patient's Trial 208 baseline visit occurred within 7 days of the Trial 204 completion visit. Patients enrolling in this trial (who completed baseline procedures) more than 8 days after completion of the Day 84 visit of Trial 204 were required to complete all baseline procedures for this trial.
- Treatment Period: The treatment period began with the day of the first dose of delamanid and continued for 26 weeks (or until the point of delamanid discontinuation) of the remaining full treatment course of OBR. All patients started at the 100 mg BID dose of delamanid and either stayed at that dose or were titrated up to 200 mg BID at the investigator's discretion after 2 weeks of 100 mg BID dosing. All patients were hospitalized for at least 2 weeks from the time of initiation of dosing with delamanid for intensive safety monitoring; those who were titrated up to the 200 mg BID dose had an additional 2 weeks of hospitalization with the initiation of the higher dose. Following the 2- to 4-week titration period, Trial 208 was conducted primarily as an outpatient trial with no restrictions on diet or daily routine.
- Follow-up Period: Patients continued on OBR as prescribed by their physicians. A telephone or face-to-face contact to identify any adverse events (AEs) was conducted with each patient 28 to 32 days after the last dose of delamanid.

Efficacy (ie, sputum culture conversion [SCC]) was assessed by the Mycobacterial Growth Indicator Tubes (MGIT®) sputum culture system as well as by solid culture media. Sputum was collected at screening, baseline, and at Weeks 2, 4, 6, 10, 14, 18, 22, and 26. Blood was drawn for pharmacokinetic (PK) assessment of delamanid at baseline (before the first dose of delamanid) and at Week 2, Week 6, Week 10, Week 14, Week 18, Week 22, Early Termination (ET), and Week 26 immediately following electrocardiogram (ECG) assessment.

An independent Data Safety Monitoring Board (DSMB) was contracted by Otsuka to review safety and PK data during the conduct of the trial.

Trial duration per patient (pre-treatment, treatment, and follow-up period) was approximately 30 weeks. The total duration of the trial was 30 months from first patient

enrolled in any participating trial site in any country until the last patient completed the follow-up period in any participating trial site in any country.

Number of Patients: 250 patients were planned, and 213 patients were enrolled. For the efficacy and safety analyses, patients were grouped according to the longest duration of delamanid dose administered during the trial (ie, either delamanid 100 mg BID + OBR or delamanid 200 mg BID + OBR). Of the 213 patients who enrolled, 137 (64.3%) were included in the delamanid 100 mg BID + OBR group, and 76 (35.7%) were titrated up in dose and included in the delamanid 200 mg BID + OBR group. A total of 205 patients (96.2%) (132 in the delamanid 100 mg BID + OBR group and 73 in the delamanid 200 mg BID + OBR group) were included in the Efficacy Analysis population, defined as all enrolled patients who had a baseline and a post-baseline measurement available for assessment of any efficacy endpoint. All 213 patients (100.0%) were included in the Safety population, defined as all enrolled patients treated with at least one dose or a partial dose of delamanid. Of the 213 patients considered for the pharmacokinetic/pharmacodynamic (PK/PD) analyses, 125 were assigned to the delamanid 100 mg BID + OBR dose group, 68 were assigned to the delamanid 200 mg BID + OBR dose group (titrated as per protocol), and 20 were assigned to a 'mixed' delamanid 100/200 mg BID + OBR dose group.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 to 64 years old, inclusive (at the time of enrollment into Trial 204) and who were judged to have potential clinical benefit from delamanid exposure were eligible to participate in this trial. Patients must have completed participation in Trial 204.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): Delamanid (Lot numbers: 07F91A050D, 07F91A050E, 07F91A050F, 08E85A050A, 08E85A050B, and 08E85A050C) was supplied as 50-mg tablets provided in bottles and administered orally (in the morning and evening with meals) as either 100 mg BID or 200 mg BID (if the patient was titrated to the higher dose). All patients started at the 100 mg BID dose and either stayed at that dose or were titrated up to 200 mg BID at the investigator's discretion after 2 weeks of 100 mg BID dosing.

Reference Product, Dose, Mode of Administration, Batch or Lot No(s): The OBR was provided for all patients by the investigational sites as per WHO guidelines for the treatment of MDR-TB and the investigator's best clinical judgment. The components of OBR generally include:

- Any remaining first-line anti-TB medications to which the patient's isolates of *Mycobacterium tuberculosis* (MTB) are susceptible – pyrazinamide, ethambutol
- An anti-TB medication given by injection; preferred order of selection → streptomycin > amikacin = kanamycin > capreomycin
- Fluoroquinolone class; preferred order of selection → levofloxacin (or gatifloxacin) > ofloxacin; gatifloxacin was to be used with caution because of the rare but severe side effect of dysglycemia. Ciprofloxacin was not recommended for use. Though moxifloxacin is a commonly used fluoroquinolone for MDR-TB treatment, it was a

prohibited medication for this trial because of moxifloxacin's known QT interval prolongation effects.

- Other medications include but are not limited to:
  - Ethionamide or prothionamide
  - Cycloserine
  - Para-amino salicylic acid

Criteria for Evaluation: Efficacy (ie, SCC) was evaluated by the MGIT sputum culture system as well as by solid culture media. Safety was assessed throughout the trial by physical examinations, vital signs (blood pressure, heart rate, body temperature, and weight), 12-lead ECG, clinical laboratory tests (hematology, serum chemistry, and urinalysis), audiometry, visual acuity, neurological and psychiatric assessments, coagulation (prothrombin time [PT] and activated partial thromboplastin time [aPTT]), adrenal function (cortisol), concomitant medications, and AEs.

Statistical Methods:
Demographic and Baseline Characteristics: Demographic characteristics, medical history, and other baseline data were summarized by descriptive statistics, as appropriate.

Efficacy Methods: All efficacy analyses were secondary objectives for the trial. The patients were classified for purposes of analysis based on sputum culture status and whether the patient had already achieved SCC at baseline. (The event of SCC for a patient under treatment was previously defined in Trial 204 as the time of the first sputum culture negative for MTB for a patient followed by an additional sputum culture negative for MTB at least 28 days later without subsequent sputum cultures positive for MTB, and this principle for defining SCC was carried forward for this trial.) A baseline negative sample was confirmed if the Week 2 sputum sample was negative as well. If the baseline sample was missing and the patient had 2 consecutive negative samples at Week 2 and Week 4, the patient was classified as having a negative sputum result at baseline. Applying these principles to the trial population, 4 groups were determined for the efficacy analysis:

- Sustained Converter - defined as a patient with SCC at baseline and without any positive culture result during the 26-week trial period;
- New Converter - defined as a patient without SCC at baseline who subsequently met the definition of SCC. A patient was classified as having achieved SCC if he/she achieved two consecutive sputum cultures negative for growth of MTB at least 28 days apart after his/her last sputum culture that was positive;
- Non-converter - defined as a patient without SCC at baseline who did not achieve SCC during the 26-week trial period; or
- Reverter - defined as a patient with SCC at baseline who then had at least one positive culture for MTB growth during the 26-week trial period.

Building on this classification of patients, a Treatment Responder was defined as a Sustained Converter or New Converter and a Treatment Non-responder was defined as a Non-converter or Reverter.

Frequency counts and proportion of Sustained Converter, New Converter, Non-converter, and Reverter patients determined by MGIT system and by solid culture media were summarized overall, by treatment group, and by cavitation strata (presence and absence of cavitations based on the chest radiograph from the baseline visit for Trial 208) for each analysis population.

Frequency counts and proportion of patients who developed resistance to delamanid while on treatment were provided for all visits with drug susceptibility testing (DST) for delamanid by treatment group and overall.

Safety Methods: Safety of long-term delamanid + OBR therapy was the primary focus of this trial. Safety was assessed qualitatively and quantitatively for the Safety population (ie, all enrolled patients that received at least one dose or a partial dose of delamanid) using descriptive statistics for AEs, vital signs, ECGs, and clinical laboratory tests.

Pharmacokinetic/pharmacodynamic Methods:
Single blood sampling for PK occurred at pre-dose (before first dose of delamanid), at Week 2, Week 6, Week 10, Week 14, Week 18, Week 22, Week 26, and at ET during delamanid 100 mg BID +OBR and delamanid 200 mg BID + OBR treatment to assess delamanid and metabolite plasma concentrations. Pharmacokinetic sampling occurred at any time of the visit day, and immediately after the ECG (pharmacodynamic [PD]) assessment; times for PK and PD measurements were recorded. In addition, the metabolite-to-parent (M/P) ratio of molar plasma concentration was calculated. Descriptive statistics of concentrations and M/P ratios were reported by dose and visit.

Mean and median delamanid, DM-6704, DM-6705, and DM-6720 plasma concentrations over time, together with the corresponding corrected QT interval (QTc), ie, using Fridericia's method (QTcF) and Bazett's method (QTcB) or change in QTc from baseline (ΔQTc), ie, ΔQTcF and ΔQTcB after delamanid 100 mg BID + OBR and delamanid 200 mg BID + OBR, were presented graphically.

Demographic and Baseline Characteristics:
The majority of patients enrolled in this trial were male (70.9%) and most were Asian (58.2%). The mean age was 36.9 years with a range of 18 to 64 years. The mean body mass index was 21.08 kg/m^2 with a range of 13.1 to 46.7 kg/m^2. Overall, 50.7% of the patients had cavitation present at baseline. A larger percentage of patients from Europe/Mediterranean region (69.4%, 34/49 patients) were included in the delamanid 200 mg BID + OBR group (ie, titrated up from 100 mg BID based on an investigator's discretion and had a longer duration at 200 mg BID than at 100 mg BID) than patients from any other region (North East Asia: 21.1%, 16/76 patients; South East Asia: 18.4%, 9/49 patients; and America: 43.6%, 17/39 patients). The delamanid 200 mg BID + OBR group had a larger percentage of patients with positive culture results at baseline (15.1%,

11/73, for MGIT and 12.3%, 9/73, for solid culture media) and a larger percentage of patients with cavitations at baseline (55.3%, 42/76) than did the delamanid 100 mg BID + OBR group (9.8%, 13/132, for MGIT positive cultures and 6.8%, 9/132 for solid culture media; 48.1%, 65/135 with cavitations). These findings indicate that patients in the delamanid 200 mg BID + OBR group may have had more extensive and severe disease compared with patients in the delamanid 100 mg BID + OBR group.

Overall, as only those with positive sputum cultures at baseline could be evaluated with DST, 13.6% (29/213) patients had baseline DST for anti-TB medications performed: 12.4%, 17/137 in the delamanid 100 mg BID + OBR group and 15.8% (12/76) in the delamanid 200 mg BID + OBR group. Overall, 55% of patients were resistant to at least one fluoroquinolone and 35% of patients were resistant to at least one injectable anti-TB medication.

Efficacy Results:
Overall, 99.1% (211/213) patients had compliance data available and were at least 80% compliant with delamanid dosing in this primarily outpatient trial. The compliance rate could not be calculated for Patients [redacted] and [redacted] in the delamanid 100 mg BID + OBR group due to the missing number of tablets returned at the last visit (Week 22 for Patient [redacted] and Week 4 for Patient [redacted]).

Overall, 205/213 patients were included in the efficacy analysis population, defined as all enrolled patients who had a baseline and a post-baseline measurement available for assessment of any efficacy endpoint. Based on the MGIT system, 78.0% (160/205) of patients were Treatment Responders, including 69.8% (143/205) of patients who were Sustained Converters and 8.3% (17/205) of patients who were New Converters, and 22.0% (45/205) of patients were Non-responders, including 11.7% (24/205) of patients who were Reverters and 10.2% (21/205) of patients who were Non-converters. The percentage of Treatment Responders was similar between the delamanid 100 mg BID + OBR group and the delamanid 200 mg BID + OBR group (79.5%, 105/132 vs 75.3%, 55/73, respectively).

Based on solid culture media, 82.0% (168/205) of patients were Treatment Responders, including 73.7% (151/205) of patients who were Sustained Converters and 8.3% (17/205) of patients who were New Converters, and 18.0% (37/205) of patients were Non-responders, including 10.2% (21/205) of patients who were Reverters and 7.8% (16/205) of patients who were Non-converters. The percentage of Treatment Responders was similar between the delamanid 100 mg BID + OBR group and the delamanid 200 mg BID + OBR group (81.8%, 108/132 vs 82.2%, 60/73, respectively).

Because of the large number of negative cultures at baseline, 86.4% of patients did not undergo baseline DST for first- or second-line anti-TB drugs and 89.2% of patients did not undergo baseline DST for delamanid. At baseline, none of the patients who had DST for delamanid demonstrated resistance. During the trial, 4 (2.0%) of the 205 patients in the efficacy analysis population demonstrated resistance to delamanid; one of these patients was withdrawn from the trial because of the delamanid resistance, which was a

protocol criterion for withdrawal under the protocol amendment applicable to this patient at the time resistance was determined. Each of the 4 delamanid-resistant patients had confirmed sensitivity to no more than 2 of the drugs included in their OBR.

Pharmacokinetic/pharmacodynamic Results:

Median (% coefficient of variation [%CV]) time of PK sample collection time post dose ranged from 3.68 h (94%) to 13.92 h (62%) in the delamanid 100 mg BID + OBR group and from 1.62 h (123%) to 5.77 h (81%) in the delamanid 200 mg BID + OBR group. Median (%CV) delamanid and metabolite plasma concentrations during the 26 weeks of delamanid 100 mg BID or delamanid 200 mg BID administration to patients with MDR-TB on OBR therapy are presented in the tables below. Plasma concentrations essentially reached a plateau by Week 6 for DM-6704, DM-6705, and DM-6706 and by Week 14 for DM-6717, DM-6718, DM-6720, DM-6721, and DM-6722.

Median (%CV) Delamanid Plasma Concentrations Over Time (Weeks) in Patients With MDR-TB

Delamanid Dose[a] (mg BID)	Week 2	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26
100	342 (44)	393 (42)	365 (37)	408 (43)	373 (45)	376 (50)	366 (54)
200	284 (33)	482 (51)	428 (47)	540 (42)	446 (42)	378 (54)	433 (53)

BID = twice daily; CV = coefficient of variation; MDR-TB = multidrug-resistant tuberculosis; OBR = optimized background regimen.

[a]Patients on delamanid 200 mg BID + OBR received delamanid 100 mg BID + OBR for 2 weeks, followed by delamanid 200 mg BID + OBR as per protocol.

Median (%CV) Metabolite Plasma Concentrations Over Time (Weeks) in Patients With MDR-TB

Metabolite	Delamanid Dose[a] (mg BID)	Week 2	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26
DM-6704 Conc[b]	100	29.5 (58)	49.7 (57)	52.5 (51)	58.9 (62)	52.4 (66)	56.6 (57)	50.3 (68)
	200	35.4 (59)	72.6 (63)	84.1 (58)	87.1 (59)	87.4 (63)	90.0 (58)	88.0 (64)
DM-6705 Conc[b]	100	90.3 (53)	154 (40)	180 (42)	190 (47)	177 (47)	175 (51)	166 (57)
	200	54.2 (38)	155 (40)	149 (48)	170 (45)	155 (49)	164 (52)	149 (58)
DM-6706 Conc[b]	100	30.1 (42)	50.2 (53)	57.3 (43)	59.7 (44)	57.7 (46)	56.4 (45)	55.9 (53)
	200	36.1 (46)	74.5 (47)	71.9 (53)	87.0 (51)	87.5 (52)	89.5 (45)	90.5 (56)
DM-6717 Conc[b]	100	4.56 (106)	26.8 (58)	33.9 (60)	44.1 (57)	46.1 (62)	44.5 (69)	46.7 (76)
	200	5.84 (80)	35.9 (54)	49.4 (58)	68.7 (52)	60.7 (55)	75.1 (64)	70.5 (60)

Metabolite	Delamanid Dose[a] (mg BID)	Week 2	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26
DM-6718 Conc[b]	100	21.0 (78)	79.9 (51)	101 (46)	117 (46)	114 (51)	119 (53)	118 (61)
	200	25.1 (69)	98.8 (46)	133 (42)	135 (48)	118 (37)	144 (45)	144 (39)
DM-6720 Conc[b]	100	20.7 (55)	51.7 (41)	59.2 (39)	66.3 (42)	63.8 (44)	66.2 (49)	70.8 (54)
	200	20.4 (50)	60.9 (37)	70.8 (38)	77.1 (40)	71.5 (37)	80.1 (39)	81.3 (40)
DM-6721 Conc[b]	100	2.17 (67)	4.34 (68)	4.81 (70)	5.42 (68.1)	5.30 (65)	5.76 (68)	5.89 (70)
	200	2.70 (57)	7.14 (61)	9.19 (68)	9.88 (63)	9.40 (61)	10.4 (62)	10.5 (79)
DM-6722 Conc[b]	100	16.1 (68)	25.6 (71)	25.7 (67)	28.8 (70)	29.6 (64)	30.1 (64)	30.2 (69)
	200	18.0 (59)	41.3 (61)	49.1 (69)	55.2 (65)	53.2 (66)	53.9 (64)	55.5 (87)

BID = twice daily; Conc = concentration (in ng/mL); CV = coefficient of variation; MDR-TB = multidrug-resistant tuberculosis; M/P = Metabolite-to-parent plasma concentration ratio; OBR = optimized background treatment regimen.

[a]Patients on delamanid 200 mg BID + OBR received delamanid 100 mg BID + OBR for 2 weeks, followed by delamanid 200 mg BID + OBR as per protocol.

[b]Conc = concentration in ng/mL.

Among the analytes possibly involved (delamanid, DM-6704, DM-6705, DM-6720), DM-6705 was identified as the best correlate for QTc prolongation. DM-6705 and ΔQTc remained essentially unchanged beginning at Week 10, when the DM-6705 concentrations reached a plateau.

Safety Results:

A total of 213 patients were exposed to delamanid in this trial, with 70% of patients exposed for ≥ 182 days. The mean duration of exposure was 170.5 days (range, 6 to 186 days). Exposure to delamanid occurred primarily on an outpatient basis, 68.8% of the patients received delamanid + OBR treatment as outpatients for ≥ 150 days [5 months] of the total 182-days [6-month] treatment period). The patients had no restrictions on diet or routine during outpatient treatment.

Overall, 93.9% (200/213) patients experienced a treatment-emergent adverse event (TEAE). The most frequently reported TEAEs overall (occurring at ≥ 10% in the overall population) were headache (25.4%), insomnia (23.5%), nausea (16.4%), vomiting and arthralgia (13.6% each), abdominal pain upper (11.7%), nasopharyngitis (11.3%), and dizziness (10.3%). Variability between treatment groups was observed in the incidence of TEAEs overall and by individual preferred term. TEAEs were reported by 92.0% (126/137) of patients in the delamanid 100 mg BID + OBR group and 97.4% (74/76) of patients in the delamanid 200 mg BID + OBR group. Individual TEAEs with a difference between groups of > 5 percentage points included palpitations, tinnitus, abdominal pain upper, vomiting, blood cortisol increased, hypokalaemia, myalgia,

dizziness, headache, tremor, throat irritation, rash papular, and hot flush with a higher incidence in the delamanid 100 mg BID + OBR group and nausea, nasopharyngitis, and alcohol abuse with a higher incidence in the delamanid 200 mg BID + OBR group. Most of these differences likely reflect the imbalance in the size of the groups as well as differences in the individual use of anti-TB medications. Most TEAEs were mild or moderate in intensity.

Overall, 53.5% (114/213) of patients reported a potentially drug-related TEAE during this trial. A difference in the incidence of potentially drug-related TEAEs was observed between the delamanid 100 mg BID + OBR group (64.2%, 88/137 patients) and the delamanid 200 mg BID + OBR group (34.2%, 26/76 patients); however, the incidences of the most frequently reported potentially drug-related TEAEs were generally similar between groups (less than 5 percentage points difference between groups), with the exception of palpitations, upper abdominal pain, and headache, each of which occurred in a larger percentage of patients in the delamanid 100 mg BID + OBR group.

One death was reported in this trial. A 25-year-old male with MDR-TB who received delamanid 100 mg BID + OBR, died of a TEAE of right ventricular failure 62 days after delamanid discontinuation and withdrawal from Trial 208 on Day 9 of the treatment period. The investigator considered the right ventricular failure possibly related to delamanid.

Overall, 11.7% (25/213) of patients reported a total of 30 serious adverse events (SAEs). Although a difference in the incidence of SAEs was observed between the delamanid 100 mg BID + OBR group (13.9%, 19/137) and the delamanid 200 mg BID + OBR group (7.9%, 6/76), the incidence of individual SAEs was similar between treatment groups. SAEs reported by more than one patient overall were hyperbilirubinaemia and tuberculosis each in 3 (1.4%) patients and prolonged ECG QT interval and haemoptysis each in 2 (0.9%) patients. The SAEs of hyperbilirubinaemia were reported from a single site (Site 001 in the Philippines) and consisted of 4 episodes in a total of 3 patients (Patient [redacted] [2 episodes], Patient [redacted], and Patient [redacted]). The hyperbilirubinaemia in these 4 SAEs did not result in discontinuation of medications and was not accompanied by clinically significant abnormality of alkaline phosphatase, direct bilirubin (see narratives in Section 16.2) GGT, ALT, or AST. The patients with SAEs of tuberculosis included 2 patients who had a planned hospitalization to switch OBR medications and one patient who had worsening MDR-TB.

Overall, 3.3% (7/213) of patients discontinued delamanid because of TEAEs (including the patient who died); 3/137 patients in the delamanid 100 mg BID + OBR group (right ventricular failure, electrocardiogram QT prolonged, incomplete abortion) and 4/76 patients in the delamanid 200 mg BID + OBR group (electrocardiogram QT prolonged, acute hepatitis, lip and oral cavity cancer, suicide attempt). Prolonged ECG QT interval was the only TEAE that led to discontinuation of more than 1 patient; 2 patients, one in each treatment group, were discontinued due to prolonged ECG QT interval (QTcF > 500 ms). All of the TEAEs leading to discontinuation were reported as serious.

The mean QTcF interval stabilized after Week 6; differences from time point to time point were minor and not clinically relevant. A total of 8/213 (3.8%) patients (4 patients in each group) had a change in QTcF of > 60 ms. One patient in each group had a new onset QTcF > 500 ms.

There were no clinically meaningful changes in laboratory assessments. The proportions of patients with clinically significant serum cortisol levels that met the prespecified criteria for clinical significance (defined as ≥ 26 μg/dL) was slightly higher in the delamanid 100 mg BID + OBR group (32.4%, 44/136) versus the delamanid 200 mg BID + OBR group (25.0%, 19/76); no clinical manifestations from elevated cortisol levels were observed.

There were no clinically meaningful changes in physical examination results, vital signs, or visual acuity.

Conclusions:

- Demographic and Baseline Characteristics:
    - The delamanid 100 mg BID and 200 mg BID groups were different in size, regional origin, and extent and severity of disease. Though all sites adhered to the principles of MDR-TB treatment as outlined by WHO treatment guidelines, differences between the groups reflected variations in clinical practice across regions.
        - 137 patients were included in the 100 mg group; 76 patients were included in the 200 mg group (treatment group assignment for efficacy and safety analysis was based on an individual patient's longest duration at either dose).
        - A much greater proportion of patients from the Europe/Mediterranean region were titrated to 200 mg BID (69.4%) compared with the America (43.6%), North East Asia (21.1%), and South East Asia (18.4%) regions.
        - The delamanid 200 mg BID group had a larger percentage of patients with positive sputum culture results at baseline (15.1% vs 9.8%), with any cavitation at baseline (55.3% vs 48.1%), and with bilateral cavitations at baseline (40.5% vs 29.2%) than did the delamanid 100 mg BID group.
    - Few patients had positive sputum cultures for MDR-TB at baseline; therefore only a small proportion of patients had baseline DST performed.

- Efficacy:
    - Compliance with delamanid dosing in Trial 208 was very high even with the trial's conduct being largely outpatient; 99.1% (211/213) of patients were at least 80% compliant with dosing, an important milestone of longer-term adherence for TB treatment more broadly.
    - Treatment Responders on MGIT comprised 78% of patients and on solid comprised 82% of patients.

        - The percentage of Treatment Responders was similar between the delamanid 100 mg BID + OBR group and the delamanid 200 mg BID + OBR group.
        - The rate of reversion was lower in Trial 208 (11.7% on MGIT, 10.2% on solid) than reported in a large meta-analysis of MDR-TB treatment cohorts (18% predominantly measured on solid).
    - The treatment response and reversion rates observed in this trial likely predict those that would occur outside the clinical trial setting, as patients were treated primarily on an outpatient basis with no restrictions to their normal diet or routine.

- Safety: 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 compared with previous trials.

- Resistance:
    - None of the patients who had DST performed for delamanid demonstrated resistance at baseline despite many of the patients having been treated with delamanid for 56 days in the parent trial (242-07-204).
    - Four (2.0%) of the 205 patients in the efficacy analysis population demonstrated post-baseline resistance to delamanid.
    - Delamanid resistance emerged in patients with confirmed sensitivity to no more than 2 of the drugs included in their OBR.
    - Overall, 55% of patients demonstrated resistant to at least one fluoroquinolone and 35% of patients were resistant to at least one injectable anti-TB medication.

- Pharmacokinetics:
    - Over the 26-week administration period and from Week 6 on, delamanid median plasma concentrations collected at various times post-dose (1.6 to 13.9 hours) varied between 365 and 408 ng/mL after delamanid 100 mg BID + OBR and between 378 and 540 ng/mL after delamanid 200 mg BID + OBR.
    - Metabolite plasma concentrations essentially reached a plateau by Week 6 for DM-6704, DM-6705, and DM-6706 and by Week 14 for DM-6717, DM-6718, DM-6720, DM-6721, and DM-6722.
    - In agreement with DM-6705 plasma concentration-time profiles, ΔQTc remained essentially unchanged beginning at Week 10.