Report on the Deliberation Results

May 16, 2014

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Deltyba Tablets 50 mg
[Non-proprietary name]	Delamanid (JAN*)
[Applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	March 27, 2013

[Results of deliberation]
In the meeting held on April 30, 2014, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years. The drug substance and the drug product are both classified as powerful drugs, and the drug product is not classified as a biological product or a specified biological product.

[Conditions for approval]
Because of the extremely limited clinical experience with the product in Japanese patients, the applicant is required to conduct a drug use results survey, which covers all patients treated with the product, for a certain period of time after the market launch in order to understand the characteristics of patients treated with the product and collect safety and efficacy data on the product during the early post-marketing period, thereby taking necessary measures to facilitate the proper use of the product.

**Japanese Accepted Name (modified INN)*

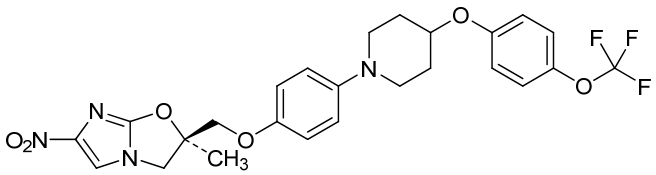
Review Report

April 18, 2014
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Deltyba Tablets 50 mg
[Non-proprietary name]	Delamanid
[Applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	March 27, 2013
[Dosage form/Strength]	Tablets: Each tablet contains 50 mg of Delamanid.
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{25}H_{25}F_3N_4O_6$
Molecular weight: 534.48
Chemical name:
(2*R*)-2-Methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]piperidin-1-yl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-*b*]oxazole

[Items warranting special mention]
Orphan drug (Designation No. [20 yaku] 205, Notification No. 0218001 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated February 18, 2008)

[Reviewing office] Office of New Drug IV

Review Results

April 18, 2014

[Brand name]	Deltyba Tablets 50 mg
[Non-proprietary name]	Delamanid
[Applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	March 27, 2013

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with multidrug-resistant pulmonary tuberculosis has been demonstrated and its safety is acceptable in view of its observed benefits. Given that there are extremely limited experiences of the product in Japanese patients, that the product prolongs QT intervals, and that the efficacy and safety of the product in long-term administration have not been investigated, these should be further investigated after the market launch. Also, since there are only very few therapeutic agents available for multidrug-resistant pulmonary tuberculosis, in order to prevent the emergence of resistance to the product, sufficient treatment should be given to appropriately selected patients. Thus, an appropriate use of Responsible Access Program (RAP) is critical.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration with the following conditions for approval.

[Indication]	Bacterial microorganisms: Delamanid-susceptible strains of *Mycobacterium tuberculosis* Disease: Multidrug-resistant pulmonary tuberculosis
[Dosage and administration]	The usual adult dosage of delamanid is 100 mg administered orally twice daily in the morning and in the evening after meals.
[Conditions for approval]	Because of the extremely limited clinical experience with the product in Japanese patients, the applicant is required to conduct a drug use results survey, which covers all patients treated with the product, for a certain period of time after the market launch in order to understand the characteristics of patients treated with the product and collect safety and efficacy data on the product during the early post-marketing period, thereby taking necessary measures to facilitate the proper use of the product.

Review Report (1)

March 31, 2014

I. Product Submitted for Registration

[Brand name]	Deltyba Tablets 50 mg
[Non-proprietary name]	Delamanid
[Applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	March 27, 2013
[Dosage form/Strength]	Tablets: Each tablet contains 50 mg of Delamanid.
[Proposed indication]	Bacterial microorganisms: Delamanid-susceptible strains of *Mycobacterium tuberculosis* Disease: Multidrug-resistant pulmonary tuberculosis
[Proposed dosage and administration]	The usual adult dosage of delamanid is 100 mg administered orally twice daily in the morning and in the evening after meals.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The data submitted in this application and the outline of review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Delamanid is a nitro-dihydroimidazo-oxazole derivative discovered by Otsuka Pharmaceutical Co., Ltd., and is considered to exhibit an anti-tuberculosis effect by inhibiting the biosynthesis of mycolic acid, a compound unique to mycobacteria. Delamanid shows an anti-tuberculosis effect against all clinical isolates of *Mycobacterium tuberculosis* (*M. tuberculosis*) that are susceptible or resistant to existing anti-tuberculosis drugs, and shows no cross-resistance with existing anti-tuberculosis drugs.

The standard treatment for tuberculosis is a 2-month intensive therapy with 4-drug regimen using rifampicin (RFP), isoniazid (INH), ethambutol (EB), and pyrazinamide (PZA), followed by a 4-month maintenance therapy with RFP and INH combined. The cure rate in patients with drug-susceptible tuberculosis is reported to be 90%.[1)] In contrast, in patients with multidrug-resistant pulmonary tuberculosis (tuberculosis caused by *M. tuberculosis* resistant at least to RFP and INH), the cure rate is reported to be 50% to 70% with a mortality rate of 25% even in patients receiving the best treatment program.[2)]

Since multidrug-resistant pulmonary tuberculosis is resistant to both RFP and INH, precluding the use of the standard therapy that contains these drugs, the guidelines published by the World Health Organization (WHO) in 2008 recommends the use of a 4-drug therapy consisting of the first-line drugs EB and PZA together with the second-line drugs, an injectable anti-tuberculosis drug (any one of kanamycin [KM], amikacin [AMK], capreomycin, and streptomycin [SM]) and a fluoroquinolone drug (any one of levofloxacin [LVFX], moxifloxacin [MFX], and ofloxacin).[3)]

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1) World Health Organization (WHO). Global Tuberculosis Control 2010. Geneva: WHO; 2010.
2) Orenstein EW et al, Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis*. 2009;9(3):153-161.
3) World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2008.402. Geneva: WHO; 2008.

If any of these 4 drugs cannot be used for reasons such as drug resistance or adverse drug reactions, addition of at least one of other second-line drugs (p-aminosalicylic acid [PAS], cycloserine [CS], terizidone, ethionamide [TH], or prothionamide) is recommended.[3] However, the options of available drugs are limited. Also, the multidrug-resistant pulmonary tuberculosis treatment should consist of at least 6 months of intensive therapy with anti-tuberculosis drugs including injectable agents and 18 months of treatment that is continued after the culture results have become negative.[3] In Japan, a guideline presented by the Treatment Committee of the Japanese Society for Tuberculosis in 2008 recommends combination therapy including at least one of injectable anti-tuberculosis drugs such as PZA, EB, and SM, and fluoroquinolone antibacterial drugs for the treatment of tuberculosis resistant to RFP and INH.[4]

In Japan, it is reported that 110 to 120 new cases of multidrug-resistant pulmonary tuberculosis emerge every year.[5] Another literature reports that, among all patients with multidrug-resistant pulmonary tuberculosis, the percentage of patients who have resistance to fluoroquinolone drugs and injectable anti-tuberculosis drugs such as KM in addition to the first-line drugs INH and RFP is higher in Japan than in other countries.[6]

The applicant conducted global phase II studies (Studies 242-[redacted]-204 and 242-[redacted]-208) involving patients with multidrug-resistant pulmonary tuberculosis. The applicant claims that the results demonstrated the efficacy of delamanid and an acceptable safety profile, and has been filed a marketing application for delamanid based on these results.

Delamanid was filed for approval in Europe in [redacted] but has not been approved in any country as of March 2014.

2. Data relating to quality

2.(1) Drug substance

2.(1).1) Characterization

The drug substance is white to pale yellow crystals or crystalline powder. The determined properties include specific optical rotation, dissociation constant, solubility, partition coefficient, hygroscopicity, melting point, thermal analysis, and X-ray powder diffraction.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry (MS), ultravioletvisible spectrophotometry (UV/VIS), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), and high performance liquid chromatography (HPLC).

2.(1).2) Manufacturing process

[redacted].

Mainly the following investigations were performed using the quality-by-design (QbD) approach.

- [redacted]
- Identification of critical process parameters (CPPs) based on quality risk assessment

4) The Treatment Committee of the Japanese Society for Tuberculosis, *Kekkaku*. 2008;83(7):529-535.
5) Mori T, et al, *Kekkaku*. 2012;87(9):565-575.
6) World Health Organization (WHO). Stop TB Department. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Geneva: WHO, 2010. and Toyota E, et al. *Kekkaku*. 2008;83(12):773-777.

[redacted].

2.(1).3) Control of drug substance

[redacted].

2.(1).4) Stability of drug substance

Table 1 shows the results of stability studies of the drug substance. The results of the photostability test showed the light stability of the drug substance.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 pilot-scale batches	30°C	65% RH	Double-layered polyethylene bag + fiber drum	48 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

Based on the above, a retest period of [redacted] years has been proposed for the drug substance when stored in a double-layered polyethylene bag placed within a fiber drum at room temperature, according to the "Guideline on Evaluation for Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing is scheduled to last up to [redacted] months.

2.(2) Drug product

2.(2).1) Description and composition of the drug product and formulation development

The drug product is a tablet containing 50 mg of the drug substance. The drug product also contains, as excipients, lactose hydrate, microcrystalline cellulose, sodium starch glycolate, carmellose calcium, hypromellose phthalate, light anhydrous silicic acid, povidone, tocopherol, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, talc, and yellow ferric oxide.

2.(2).2) Manufacturing process

[redacted].

Mainly the following investigations were performed using a QbD approach.

- [redacted]
- Identification of CPPs based on the quality risk assessment and on the design of experiments

2.(2).3) Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (HPLC), related substances (HPLC), uniformity of dosage unit (test for content uniformity), dissolution, and assay (HPLC).

2.(2).4) Stability of drug product

Table 2 shows the results of stability studies of the drug product. The results of the photostability test showed the light stability of the drug product.

Table 2. Stability studies on drug products

Study	Primary batches	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 pilot-scale batches	25°C	60% RH	PTP packages	48 months
Accelerated	3 pilot-scale batches	40°C	75% RH		6 months

From the above results, a shelf life of 48 months has been proposed for the drug product when stored in PTP (aluminum-laminated film/aluminum foil) packages at room temperature. The long-term testing is scheduled to last up to [redacted] months.

2.B Outline of the review by PMDA

Based on the submitted data and on the results of the following review, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

2.B.(1) Formation of related substances in the drug substance manufacturing process

Among the batches of the drug substance manufactured by the proposed manufacturing process, there were batches containing a high residual level of Related Substance I, an impurity in the manufacturing process. Therefore, PMDA asked the applicant to explain the reason for the difference in the residual level of Related Substance I among the batches and to explain the necessity of defining the acceptance criteria of Related Substance I separately from other related substances.

The applicant explained as follows:

[redacted].

PMDA considered that the above explanation of the applicant was acceptable.

2.B.(2) New excipients

[redacted].

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Outline of submitted data

In this application, the results from 43 primary pharmacodynamic studies and 8 safety pharmacology studies were submitted as evaluation data, and the results from 37 primary pharmacodynamic studies and 4 safety pharmacology studies were submitted as reference data.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* studies

(a) Anti-*M. tuberculosis* activity of delamanid at different inoculation sizes and at different medium pHs (4.2.1.1-01, 4.2.1.1-02)

The effects of the inoculation size and medium pH on the *in vitro* anti-*M. tuberculosis* activity of delamanid were investigated using the agar dilution method. Test bacterial strains (3 *M. tuberculosis* strains [H37Rv, Erdman, Kurono] and 2 *Mycobacterium bovis* (*M. bovis*) *Bacillus Calmette-Guérin* [BCG] strains [Pasteur, Tokyo]) were inoculated into agar plates containing serial 2-fold dilutions of delamanid and were then incubated at 37°C for 14 days, after which the minimum inhibitory concentration (MIC)[7)] was calculated. MIC of delamanid against the 5 bacterial strains (0.006 μg/mL in all strains) remained unchanged over the inoculation size from 10^5 to 10^7 colony forming units (CFU) per mL but increased at 10^8 CFU/mL (0.2-6.25 μg/mL). The study on the effect of pH using agar media of pH 6 to 8 showed that MIC of delamanid against 5 bacterial strains was 0.012 μg/mL both at pH 6 and at pH 7, while the MIC against 4 strains increased at pH 8 (0.024-0.78 μg/mL).

(b) Comparison of MIC between the agar dilution method and agar proportion method (4.2.1.1-03)

Anti-*M. tuberculosis* activity of delamanid was measured according to the agar proportion method of the Clinical and Laboratory Standards Institute (CLSI), and the results were compared with those of the agar dilution method. MICs of delamanid against 7 *M. tuberculosis* strains[8)]were 0.003 to 0.012 μg/mL by the agar proportion method and 0.006 to 0.012 μg/mL by the agar dilution method.

(c) Activity against *M. tuberculosis* strains and clinical isolates (4.2.1.1-04 to 4.2.1.1-15)

In vitro activities of test compounds against standard strains of *M. tuberculosis* and *M. bovis* BCG strain as well as against clinical isolates were investigated by the agar dilution method, aerobic liquid culture, and agar proportion method. The results were as shown in Table 3.

7) The minimum concentration of the test compound showing no growth visible to the naked eye

8) H37Rv, H37Rv RIF-R, H37Rv INH-R, H37Rv EMB-R, H37Rv SM-R, H37Rv PZA-R, and Kurono strains

Table 3. Susceptibility of *M. tuberculosis* strains and atypical mycobacteria to test compounds

Study	Species/strain, lineage	Susceptibility of *M. tuberculosis* complex and atypical mycobacteria		
		Test compound	MIC_{90} (μg/mL)	Range of MIC (μg/mL)
In vitro activity by agar dilution method	11 *M. tuberculosis* strains [a] and 4 *M. bovis* BCG strains (Pasteur, Montreal, Glaxo and Tokyo, NIHJ 1608)	Delamanid	0.012	0.006-0.024
		INH	12.5	0.05 to >100
		PA-824	0.2	0.05-0.78
		RFP	>100	0.05 to >100
		SM	6.25	0.39 to >100
		EB	12.5	1.56-50
		PZA	>6400	3200 to >6400
	67 Clinical isolates of *M. tuberculosis*	Delamanid	0.024	0.006-0.024
		INH	100	0.05 to >100
		RFP	>100	0.05 to >100
		SM	>100	0.39 to >100
		PA-824	0.2	0.05-0.78
		EB	12.5	0.78-25
	12 Strains of 10 atypical mycobacteria species	Delamanid	-	0.024-1.56
		RFP, SM, PA-824	-	0.024 to >100
		INH	-	0.39-100
		EB	-	0.39-12.5
	M. africanum ATCC 35711 strain[b] and 5 strains of 5 atypical mycobacteria species	Delamanid	-	>100
In vitro activity in aerobic liquid culture	*M. bovis* BCG Tokyo strain	Delamanid (0.016, 0.08, 0.4 μg/mL) and INH (0.4, 2.0 μg/mL) decreased CFU/mL after 3 and 7 days as compared with the vehicle control, whereas CFU/mL in the presence of MNZ (10-250 μg/mL) was similar to that observed in the presence of the vehicle control.		
In vitro activity by agar proportion method (*M. tuberculosis* complex)	*M. africanum*	Delamanid	-	≤0.0005
	M. bovis		-	0.004
	M. caprae		-	0.002
	M. pinnipedii		-	0.002
	M. microti		-	0.002
	M. tuberculosis H37Rv strain (ATCC 25618)	Delamanid	-	0.002

PA-824: (6S)-2-nitro-6-[4-(trifluoromethoxy)benzyloxy]-6,7-dihydro-*5H*-imidazo[2,1-*b*][1,3]oxazine, MTZ: Metronidazole
MIC_{90}: The minimum concentration that inhibits the growth of 90% of bacterial strains tested
MIC range: Minimum – maximum of MIC in bacterial strains tested (only a single value is given when only 1 strain was tested)

a) H37Ra, H37Rv, Erdman, Aoyama B, H37Rv-SM-R, H37Rv-INH-R, H37Rv-PZA-R, H37Rv-EMB-R, H37Rv-RIF-R, Kurono, and Tu-26 strains

b) It was found out that the *M. africanum* ATCC 35711 strain was contaminated by bacteria with spontaneous resistance to delamanid. Of 20 randomly isolated clones, 16 clones had MIC to delamanid of ≤0.002 μg/mL, and the frequency of emergence of clones with spontaneous resistance to delamanid was not significantly different from the frequency of the emergence of *M. tuberculosis* with spontaneous resistance. Based on the result, it is determined that *M. africanum* ATCC 35711 strain is susceptible to delamanid.

In addition, clinically isolated *M. tuberculosis* strains were classified as drug-susceptible, multi-drug resistant, and extensively drug-resistant, and their susceptibility to delamanid was determined. The results were as shown in Table 4.

Table 4. Susceptibility of clinical isolates to delamanid

Testing method	Year (place) of isolation	Species/strain	Number of strains	MIC_{90} (μg/mL)	MIC range (μg/mL)	MIC (μg/mL) against H37Rv strain
Agar dilution method [a)]	Isolated in 1990 to 1994 (Japan), obtained in 1997 (overseas)	Drug-susceptible *M. tuberculosis*	34	0.024	0.006-0.024	Not tested
		Multidrug-resistant *M. tuberculosis*	33	0.024	0.006-0.024	
Proportion method [b)]	Unknown (South Africa)	Drug-susceptible *M. tuberculosis*	7	-	≤0.00625 to 0.0125	≤0.00625
		Multidrug-resistant *M. tuberculosis*	10	0.0125	≤0.00625 to 0.0125	
		Extensively drug-resistant *M. tuberculosis*	6	-	≤0.00625 to 0.0125	
Proportion method [c)]	2007 to 2012 (Japan)	Multidrug-resistant *M. tuberculosis*	37	0.008	0.002-0.008	0.004
		Extensively drug-resistant *M. tuberculosis*	8	-	0.002-0.004	
Proportion method [d)]	20[redacted] to 20[redacted] (Study 242-[redacted]-204)	Multidrug-resistant *M. tuberculosis* (Japanese origin)	290 (6)	0.008 (-)	0.001 to >8 (0.002-0.004)	0.002-0.008
		Extensively drug-resistant *M. tuberculosis* (Japanese origin)	21 (1)	0.008 (-)	0.002-0.031 (0.004)	

MIC_{90}: The minimum concentration that inhibits the growth of 90% of bacterial strains tested
MIC range and MIC against H37Rv strain: Minimum – maximum of MIC in bacterial strains tested (only a single value is given when only 1 strain was tested)

a) Strains resistant to both RFP and INH were classified as multidrug-resistant *M. tuberculosis* according to the CLSI criteria.
b) Classified as drug-susceptible *M. tuberculosis*, multidrug-resistant *M. tuberculosis* (strains resistant to both RFP and INH), or extensively drug-resistant *M. tuberculosis* (strains resistant to all of RFP, INH, ofloxacin, and KM).
c) Classified as multidrug-resistant *M .tuberculosis* (strains resistant to both RFP and INH) or extensively drug-resistant *M. tuberculosis* (strains resistant to all of RFP, INH, LVFX, and KM) according to the criteria of Policy Guideline on Drug Susceptibility Testing [DST] of second line antituberculosis drugs. World Health Organization Geneva, 2008.
d) As a rule, classified as multidrug-resistant *M. tuberculosis* (strains resistant to both RFP and INH) or extensively drug-resistant *M. tuberculosis* (among multidrug-resistant *M. tuberculosis* strains, those resistant to either one or more of KM, AMK, and capreomycin and to either one or more of ofloxacin, LVFX, and ciprofloxacin) according to the criteria of Policy Guideline on Drug Susceptibility Testing [DST] of second line antituberculosis drugs. World Health Organization Geneva, 2008.

(d) Antibacterial activity of delamanid against intracellular *M. tuberculosis* and intracellular *M. bovis* BCG strain (4.2.1.1-19, 4.2.1.1-20, 4.2.1.1-21, Reference data 4.2.2.1-22)

Given that *M. tuberculosis*, once infecting the lung, is thought to survive in host macrophages and prolong or cause the relapse of infection,[9)] the activity of delamanid against intracellular *M. tuberculosis* was evaluated. Cells of human acute myelomonocytic leukemia cell line (THP-1) were treated with 0.1 μg/mL of phorbol 12-myristate 13-acetate (PMA) and were differentiated into adhesive macrophage-like cells to be infected with *M. tuberculosis,* then the infected cells were treated with each test compound at 37°C for 72 hours. The infected THP-1 cells were lysed and smeared onto agar plates and, after incubation at 37°C for 15 days, bacterial colonies were counted and log-transformed CFU/well was calculated. Bactericidal activities (IC_{90} [95% confidence interval (CI)])[10)] of delamanid, INH, and PA-824 against intracellular *M. tuberculosis* H37Rv strain were 0.215 [0.178, 0.261] μg/mL, 0.123 [0.104, 0.146] μg/mL, and 0.535 [0.423, 0.677] μg/mL, respectively. RFP showed IC_{90} of >0.78 μg/mL, and EB, SM and PZA all had IC_{90} of >6.25 μg/mL. In a separate experiment, THP-1 cells intracellularly infected with *M. bovis* BCG strain were treated with serial 4-fold dilutions of each test compound for 24 hours, after which cells were lysed and counted for intracellular bacteria. IC_{90} values of EB, PZA, SM, and INH were all >25 μg/mL, whereas IC_{90} [95% CI] values of delamanid, RFP, and PA-824 were

9) Armstrong JA and Hart PD, *J Exp Med.* 1971;134(3 Pt 1):713-740, Parrish NM et al, *Trends Microbiol.* 1998;6(3):107-112.
10) The concentration of the drug that decreased the viable bacterial count by 1 $\log_{10}$ compared with the untreated control group (IC_{90}) was calculated using a linear regression analysis model.

0.199 [0.133, 0.298] μg/mL, 0.403 [0.345, 0.470] μg/mL, and 0.560 [0.350, 0.896] μg/mL, respectively.

Intracellular bactericidal activity of short-term exposure to delamanid, INH, PA-824, and RFP against *M. tuberculosis* within THP-1 cells was investigated. After PMA-induced differentiation, THP-1 cells were infected with *M. tuberculosis* H37Rv strain then treated with delamanid (0.1-1 μg/mL), PA-824 (0.1-1 μg/mL), INH (0.3-3 μg/mL), or RFP (0.3-3 μg/mL) for 2, 4, 8, or 24 hours and, at 72 hours after the removal of the drug, intracellular viable bacterial cells were counted by the standard method. At all concentrations and at all treatment periods, intracellular viable bacterial counts were decreased by treatment with delamanid as compared with the vehicle control group.

M. tuberculosis is reported to infect alveolar epithelial cells as well in the intrapulmonary environment.[11] Cells of human lung epithelial cell-derived cell line A549 and THP-1 cells were infected with *M. tuberculosis* H37Rv strain or *M. bovis* BCG strain, and intracellular bactericidal activities of delamanid and INH (0.39-6.25 μg/mL) and of PA-824 and RFP (0.39 and 1.56 μg/mL) were investigated. The anti-*M. tuberculosis* activity of each test compound tended to increase in a time-dependent manner both during 1 to 7 days and during 2 to 120 hours.

(e) *In vitro* activity of delamanid against dormant *M. bovis* (4.2.1.1-25, 4.2.1.1-26)

Within the pulmonary lesion of patients with tuberculosis,[12] dormant *M. tuberculosis* is resistant to existing anti-*M. tuberculosis* drugs, which is considered to be a cause for the intractability and relapse.[13] Therefore, bactericidal activity of delamanid against dormant *M. tuberculosis* was investigated.

The bactericidal activity of delamanid against dormant *M. bovis* BCG Tokyo strain was investigated using the culture method of Wayne under complete anaerobic conditions.[14] *M. bovis* cells were cultured under the anaerobic conditions generated by gradual depletion of oxygen, after which the cells were treated with delamanid (0.016-10 μg/mL), INH (0.4-10 μg/mL), metronidazole (2-50 μg/mL), or dimethyl sulfoxide (DMSO), the vehicle control, for 8 days. The culture fluid was then smeared onto agar gel plates and cells were incubated for 14 days so that viable bacterial cells were counted. The viable bacterial count decreased in a delamanid concentration-dependent manner (4.936-3.949 $\log_{10}$ CFU/mL) at ≥0.4 μg/mL as compared with the vehicle control (5.486 $\log_{10}$ CFU/mL). Metronidazole at 2 μg/mL exhibited bactericidal activity (4.861 $\log_{10}$ CFU/mL), whereas INH at 10 μg/mL did not have bactericidal activity (5.681 $\log_{10}$ CFU/mL).

(f) Frequency of the emergence of spontaneous resistant mutants of *M. tuberculosis* and of *M. bovis* BCG Tokyo strain (4.2.1.1-04, 4.2.1.1-27, 4.2.1.1-28)

A total of 10 colonies were isolated from *M. tuberculosis* H37Rv strain, and MICs of delamanid, RFP, and INH against the isolates were investigated by the agar dilution method. The bacterial fluids obtained by the growth of each colony were smeared onto agar plates containing delamanid (0.192 μg/mL, which is 16 times the MIC [0.012μg/mL]), RFP (0.8 or 1.6 μg/mL, which is 16 times the MIC [0.05 or 0.1 μg/mL]), or INH (1.6 μg/mL, which is 32 times the MIC [0.05 μg/mL]) and, after incubation at 37°C for 4 weeks, colonies of resistant bacteria on each plate were counted. The frequencies of the emergence of bacteria with spontaneous resistance[15] to delamanid, RFP,

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11) Bermudez LE and Goodman J, *Infect Immun*. 1996;64(4):1400-1406.

12) Within the pulmonary lesion of patients with tuberculosis, *M. tuberculosis* is considered to exist as an inhomogeneous population of active bacteria and non-growing bacteria including dormant type.

13) Sacchettini JC et al, *Nat Rev Microbiol*. 2008;6(1): 41-52, Yew WW et al, *Espert Opin Emerg Drugs*. 2011;16(1):1-21.

14) Wayne LG, *Am Rev Respir Dis*. 1976;114:807-811.

15) Each bacterial fluid of 10 isolated colonies was diluted 10^4, 10^5, and 10^6 fold and smeared onto agar plates in duplicate, and the number of colonies after incubation was counted. The number of colonies per inoculated bacteria was calculated, and the mean of the calculated values was defined as the frequency of emergence of spontaneous resistant mutants.

and INH were 6.44×10^{-6} to 4.19×10^{-5}, 1.77×10^{-8} to 4.26×10^{-6}, and 1.74×10^{-5} to 3.13×10^{-5}, respectively.

The fluids containing *M. tuberculosis* Kurono strain or *M. bovis* BCG Tokyo strain were smeared onto agar plates containing each test compound[16] at concentrations 4, 16, and 64 times the MIC, and incubated at 37°C for 27 or 28 days, and the frequency of emergence of spontaneous resistant mutants[17] of each bacterial strain to each test compound was calculated. The frequencies of emergence of spontaneous resistance[17]17[17] of the *M. tuberculosis* Kurono strain were 1.35×10^{-4} to 1.57×10^{-4} to delamanid, $<3.42 \times 10^{-9}$ to 1.03×10^{-8} to RFP, 1.20×10^{-5} to 1.16×10^{-4} to INH, $<3.42 \times 10^{-9}$ to 1.03×10^{-8} to MFX, and 1.18×10^{-4} to 2.82×10^{-4} to PA-824, and those of the *M. bovis* BCG Tokyo strain were 2.51×10^{-5} to 3.95×10^{-5} to delamanid, 8.66×10^{-10} to 3.46×10^{-9} to RFP, 1.06×10^{-5} to 1.46×10^{-5} to INH, $<8.66 \times 10^{-10}$ to 3.03×10^{-8} to MFX, and 3.05×10^{-5} to 5.04×10^{-5} to PA-824.

(g) Inhibitory effect of delamanid against mycolic acid synthesis (4.2.1.1-32)

Mycolic acid, a critical component of the cell wall of *M. tuberculosis*, is regarded as an important target for anti-tuberculosis drugs.[18] *M. bovis* BCG strain was allowed to grow for 30 to 60 minutes in a ^{14}C-labeled acetic acid-containing liquid medium supplemented with delamanid, INH, or vehicle (DMSO) to and the uptakes of ^{14}C into fatty acid and into mycolic acid subclasses were measured by thin-layer chromatography. Delamanid inhibited the synthesis of methoxy-mycolic acid, keto-mycolic acid, alpha-mycolic acid, and nonpolar fatty acid by *M. bovis* BCG strain with IC_{50}[19] values of 0.036, 0.021, >0.25, and >0.25 μg/mL, respectively, while IC_{50} values of INH against these substances were 0.685, 0.690, 1.851, and >4 μg/mL, respectively.

(h) Mechanism of resistance to delamanid (4.2.1.1-33 to 4.2.1.1-36)

Delamanid is known to exhibit an anti-*M. tuberculosis* effect by the bioreductive activity of the nitroaromatic group via coenzyme F_{420}.[20] When delamanid-resistant *M. bovis* BCG Tokyo strains (containing mutations in coenzyme F_{420}-related genes *fgd*, *Rv3547*, *fbiA*, *fbiB,* or *fbiC*) were introduced with each wild-type gene or with *fbiA* and *fbiB*, the range of MIC of delamanid against these transformants (0.006-0.024 μg/mL) was similar to that against susceptible strains and to strains transfected with the plasmid vector alone (0.006-0.012 μg/mL).

In the global phase II study (Study 242-[redacted]-208), delamanid-resistant strains[21] were isolated from 4 subjects. Among these clinical isolates, those that were confirmed to be resistant in the sensitivity study[22] were investigated for their mechanism of resistance. As a result, mutation of *fbiC* and dysfunction of *Rv3547* were confirmed.

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16) Concentrations of each test compound used in the test on *M. tuberculosis* Kurono strain: Delamanid (MIC 0.012 μg/mL), 0.05 to 0.7825 μg/mL; RFP (MIC 0.39 μg/mL) 1.5625 to 25 μg/mL; INH (MIC 0.1 μg/mL) 0.39 to 6.25 μg/mL; MFX (MIC 0.1 μg/mL) 0.39 to 6.25 μg/mL, and PA-824 (MIC 0.2 μg/mL) 0.7825 to 1.25 μg/mL. Concentrations of each test compound used in the test on *M. bovis* BCG Tokyo strain: Delamanid (MIC 0.012 μg/mL), 0.05 to 0.7825 μg/mL; RFP (MIC 0.2 μg/mL) 0.7825 to 12.5 μg/mL; INH (MIC 0.1 μg/mL), 0.39 to 6.25 μg/mL, MFX (MIC 0.2 μg/mL), 0.7825 to 12.5 μg/mL, and PA-824 (MIC 0.1 μg/mL) 0.39 to 6.25 μg/mL

17) The number of colonies that appeared after incubation on each agar plate smeared with bacterial suspension was counted, and the number of colonies per inoculated bacteria was defined as the frequency of emergence of spontaneous resistant mutants.

18) Brennan PJ and Nikaido H, *Annu Rev Biochem*. 1995;64:29-63, Rozwarski DA et al, *Science*. 1998;279(5347):98-102.

19) Radioactivity of nonpolar fatty acids and of each mycolic acid subclass isolated from *M. bovis* BCG strain was measured using image analysis software, and the percentage of radioactivity in each test sample relative to that of the vehicle control (DMSO) was calculated. IC_{50} was calculated using a linear regression analysis model.

20) Matsumoto M et al, *PLoS Med.* 2006;3(11):e466.

21) When the growth in the presence of 0.2 μg/mL delamanid exceeded 1% of the growth observed in the medium not containing delamanid, the strain was defined as a delamanid-resistant strain.

22) Isolated from 3 patients (strains isolated at 4, 6, and 14 weeks after treatment start, and at study discontinuation, strains isolated at 22 weeks after treatment start, strains isolated at 14 weeks after treatment start)

(i) Anti-*M. tuberculosis* activities of delamanid, its metabolites, and control compounds (4.2.1.1-38, 4.2.1.1-39, 4.2.2.2-03, 4.2.2.2-08, 4.2.2.4-10)

Anti-*M. tuberculosis* activities of delamanid, RFP, and the metabolites [(*R*)-DM-6701, (*R*)-DM-6702, (*R*)-DM-6703] identified in plasma of rats and dogs treated orally with delamanid against *M. tuberculosis*[23] were measured by the agar dilution method. The ranges of MICs were 0.006 to 0.012 with delamanid, 0.05 to 100 with RFP, 6.25 to 50 with (*R*)-DM-6701, 12.5 with (*R*)-DM-6702, and ≥50 μg/mL with (*R*)-DM-6703. Anti-*M. tuberculosis* activities of delamanid, RFP, and metabolites [(*S*)-DM-6717, (*S*)-DM-6718, (4*RS*, 5*S*)-DM-6720, (4*R*, 5*S*)-DM-6721, (4*S*, 5*S*)-DM-6722] identified in plasma of mice, rats, rabbits, and dogs treated with a delamanid-containing product obtained by the new manufacturing process were measured in a similar manner. The ranges of MICs were 0.003 to 0.012 with delamanid, 0.05 to 100 with RFP, 50 to 100 with (*S*)-DM-6717, 12.5 to >100 with (*S*)-DM-6718, 12.5 to 25 with (4*RS*, 5*S*)-DM-6720, 12.5 to 50 with (4*R*, 5*S*)-DM-6721, and 12.5 to 50 μg/mL with (4*S*, 5*S*)-DM-6722.

(j) Antibacterial activities of delamanid, its metabolites, and control compounds (4.2.1.1-40)

Approved anti-tuberculosis drugs cause gastrointestinal symptoms such as diarrhoea.[24] Therefore, antibacterial activities of delamanid and its metabolites [(*R*)-DM-6701, (*R*)-DM-6702, (*R*)-DM-6703], RFP, SM, and PA-824 against standard bacterial strains (24 aerobic bacterial strains,[25] 10 anaerobic bacterial strains[26]) including enteric bacteria, were measured by the agar dilution method. MIC of delamanid was >100 μg/mL against all of the bacterial strains tested. The ranges of MICs of metabolites (*R*)-DM-6701, (*R*)-DM-6702, and (*R*)-DM-6703 were 12.5 to >100, 6.25 to >100, and 50 to >100 μg/mL, respectively, and the ranges of MICs of RFP, SM, and PA-824 were ≤0.006 to 25, 1.56 to >100, and 6.25 to >100 μg/mL, respectively.

(k) *In vitro* combined effect of delamanid and the first-line anti-tuberculosis drugs (4.2.1.4-01 to 4.2.1.4-04)

In vitro combined effect of delamanid and the first-line anti-tuberculosis drugs[27] against 27 clinically isolated *M. tuberculosis* strains was investigated by the checkerboard method using agar dilution.[28] FIC indexes[29] were calculated based on MIC values measured by the combination of delamanid (0.0002-0.1 μg/mL) with INH (0.0015-0.39 μg/mL), RFP (0.0015-1.56 μg/mL), SM (0.012-6.25 μg/mL), or EB (0.024-12.5 μg/mL). Table 5 is the results, showing no competition.

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23) A total of 10 *M. tuberculosis* strains including those resistant to existing anti-tuberculosis drugs (H37Ra, H37Rv, Erdman, Kurono, Aoyama B, H37Rv-SM-R, H37Rv-INH-R, H37Rv-PZA-R, H37Rv-EMB-R, and H37Rv-RIF-R strains)

24) Iseman MD, *A Clinician's Guide to Tuberculosis 1st ed*, 2000, Rom WN Garay S, editors, *Tuberculosis 1st ed*, 1996

25) *Staphylococcus aureus* ATCC 29213, *S. aureus* ATCC 43300, *Staphylococcus epidermidis* ATCC 12228, *Staphylococcus haemolyticus* ATCC 29970, *Streptococcus pyogenes* ATCC 12351, *Streptococcus pneumoniae* ATCC 49619, *Enterococcus faecalis* ATCC 29212, *Enterococcus faecium* ATCC 49224, *Bacillus subtilis* ATCC 6633, *Micrococcus luteus* ATCC 7468, *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, *Klebsiella oxytoca* ATCC 15764, *Serratia marcescens* ATCC 14756, *Proteus mirabilis* ATCC 4630, *Enterobacter aerogrnes* ATCC 13048, *Enterobacter cloacae* ATCC 13047, *Acinetobacter lwoffii* ATCC 15309, *Stenotrophomonas maltophylia* ATCC 13637, *Pseudomonas aeruginosa* ATCC 27853, *Burkholderia cepacia* ATCC 25416, *Haemophilis influenzae* ATCC 49247, and *Neisseria gonorrhoeae* ATCC 49226

26) *Propionibacterium acnes* ATCC 6919, *Clostridium perfringens* ATCC 13124, *Eubacterium lentum* ATCC 43055, *Lactobacillus acidophilus* JCM 1028, *Anaerococcus hydrogenalis* JCM 7635, *Bifidobacterium befidum* JCM 7004, *Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, *Bateroides caccae* JCM 9498, and *Prevotella melaninogenica* JCM 6325

27) Laurenzi M et al, *Infect Disord Drug Targets.* 2007;7(2):105-119.

28) Martin SJ et al, *Antimicrob Agents Chemother*. 1996;40(6):1419-1420.

29) FIC of drug A: MIC of concomitant use with drug A/MIC of drug A alone, FIC of drug B: MIC of concomitant use with drug B/MIC of drug B alone, FIC index: FIC of drug A + FIC of drug B
FIC index ≤0.5, synergy; 0.5< FIC index ≤0.75, partial synergy; 0.75< FIC index ≤1.0, additive effect; 1.0< FIC index ≤4.0, indifference; 4.0< FIC index, antagonism [Martin SJ et al, *Antimicrob Agents Chemother.* 1996;40(6):1419-1421]

Table 5. *In vitro* combined effect of delamanid and the first-line anti-tuberculosis drugs against 27 clinically isolated *M. tuberculosis* strains (FIC index)

Co-administered compound	Number (%) of strains classified by each FIC index [a]				
	Synergy	Partially synergy	Additive effect	Indifference	Antagonism
EB	3 (11.1)	21 (77.8)	3 (11.1)	0	0
INH	0	12 (44.4)	5 (18.5)	10 (37.0)	0
RFP	1 (3.7)	24 (88.9)	2 (7.4)	0	0
SM	0	7 (25.9)	10 (37.0)	10 (37.0)	0

a) A FIX index was calculated based on concentration of 2 drugs concomitantly used, and the lowest value was adopted.

3.(i).A.(1).2) *In vivo* studies

(a) Treatment effect of each test drug in a mouse model of chronic tuberculosis (4.2.1.1-41)

A mouse model of chronic tuberculosis was generated by infecting Slc:ICR mice with *M. tuberculosis* Kurono strain (inoculation size, 8.6×10^4 CFU) by inoculation into the caudal vein. To these mice, vehicle (5% gum arabic or physiological saline), delamanid (0.156-40 mg/kg/day), EB (20-160 mg/kg/day), PZA (40-320 mg/kg/day), INH (1.25-20 mg/kg/day), RFP (1.25-20 mg/kg/day), or PA-824 (1.25-40 mg/kg/day) was administered by oral gavage, or SM (20-160 mg/kg/day) was administered subcutaneously, once daily (QD) for 4 weeks. The number of viable bacterial cells in the lung was counted at the end of the treatment in each treatment group. The viable bacterial counts in the lung were low in animals treated with ≥0.313 mg/kg/day of delamanid, ≥160 mg/kg/day of EB, ≥80 mg/kg/day of PZA, ≥2.5 mg/kg/day of INH, ≥3.5 mg/kg/day of RFP, ≥20 mg/kg/day of PA-824, or ≥20 mg/kg/day of SM, as compared with the vehicle control group.

(b) Treatment effect of test drugs in a mouse model of immunodeficiency (4.2.1.1-50)

Immunodeficient BALB/c nude mice and immunocompetent BALB/c mice were infected with *M. tuberculosis* Kurono strain (inoculation size, unknown) by inoculation into the caudal vein. Delamanid (0.313-10 mg/kg/day) was orally administered QD for 10 days to these mice starting from 1 day after infection. The viable bacterial counts decreased in the lung, liver, and spleen in a dose-dependent manner in all mice receiving doses of ≥0.625 mg/kg/day and in the liver of immunodeficient mice and in the lung of immune competent mice at the dose of ≥0.313 mg/kg/day.

(c) Effect in a mouse model of tuberculosis generated by multidrug-resistant *M. tuberculosis* (Reference data 4.2.1.1-54, Reference data 4.2.1.1-55, Reference data 4.2.1.1-56)

A mouse model of acute tuberculosis was generated by infecting BALB/c mice with a strongly pathogenic multidrug-resistant *M. tuberculosis* strain 0308-0783 or 0306-0206 (inoculation size, 5×10^5 CFU) by inoculation into the caudal vein. Delamanid, INH, or RFP (0.03125-0.5 mg/mouse) was orally administered to these mice for 30 days. The bacterial counts decreased by 3 to 4 $\log_{10}$ CFU in the spleen, lung, and liver in mice receiving 0.03125 mg/mouse of delamanid, while the extent of the decrease in animals treated with INH or RFP was less than approximately 1 $\log_{10}$ CFU.

A mouse model of tuberculosis was generated by transtracheal infection of BALB/c mice with multidrug-resistant *M. tuberculosis* strain QR-9 (inoculation size, approximately 10^6 CFU). Starting from 8 days after the infection, delamanid (0.156-5 mg/kg/day), INH (2.5-10 mg/kg/day), PA-824 (5-20 mg/kg/day), or RFP (5-20 mg/kg/day) was orally administered to these mice for 10 days. The mean survival times after infection were 73.1 to 151.2 days in animals receiving ≥0.313 mg/kg/day of delamanid, whereas all animals in the untreated group, all INH dose groups, all RFP dose groups, and the delamanid 0.156 mg/kg/day group died within 5 days after the end of the

administration. In a separate study conducted under the same experimental conditions,[30] the bacterial count in the lung at the end of administration was below the level at the start of administration (7.21 $\log_{10}$ CFU) only in the delamanid ≥1.25 mg/kg/day groups.

(d) Early bactericidal activities of test drugs in a mouse model of chronic tuberculosis (4.2.1.1-57 to 4.2.1.1-59)

The early bacterial activity (EBA) of an anti-tuberculosis drug is defined as a decrease in CFU of *M. tuberculosis* in the sputum from the level on the first day of administration.[31] A mouse model of chronic tuberculosis was generated by intratracheal inoculation of *M. tuberculosis* Kurono strain (inoculation size, 375-2000 CFU) to Slc:ICR mice. Delamanid, INH, MFX, PZA, RFP, or vehicle (5% gum arabic solution) was orally administered to the mice QD for 7 days starting from 21 days after infection. The number of viable bacterial cells in the bronchoalveolar lavage fluid was counted on Day 1 (vehicle control group only), 3, 5, 7, and 8, and the decrease per day averaged during the period from Day 1 to Day 3 ($\log_{10}$ CFU/mL/day) was defined as EBA. EBA values of delamanid (0.625-10 mg/kg/day) were 0.355 to 0.648 $\log_{10}$ CFU/mL/day, INH (2.5-10 mg/kg/day) 0.352 to 0.514 $\log_{10}$ CFU/mL/day, and RFP (2.5-10 mg/kg/day) 0.165 to 0.371 $\log_{10}$ CFU/mL/day.

(e) Intrapulmonary and plasma concentrations, pharmacokinetic and pharmacodynamic (PK/PD) study of delamanid in mice (4.2.1.1-62, 4.2.1.1-70)

Delamanid (0.156-40 mg/kg) was orally administered to Slc:ICR mice in a single dose at each pre-set time point, and intrapulmonary and plasma concentrations were measured using HPLC. C_{max} and $AUC_{0\text{-}24h}$ increased in a dose-dependent manner. In animals receiving delamanid at 0.625 mg/kg,[32] C_{max} of delamanid was 0.1004 μg/mL in plasma and was 0.273 μg/mL in the lung. C_{max} values of a metabolite DM-6702 in the lung were 77.3% to 114.6% of that of delamanid. The dose of 0.625 mg/kg was considered as the effective dose in the study on treatment effect in a mouse model of chronic tuberculosis (4.2.1.1-41).

A mouse model of chronic tuberculosis was generated by intravenous inoculation of *M. tuberculosis* Kurono strain (inoculation size, 1.2×10^3 CFU) to ICR mice. To these mice, delamanid (0.625-10 mg/kg QD 7 days/week, 2.5 mg/kg twice daily [BID] 7 days/week, 2.5-10 mg/kg QD 1 or 3 days/week) was orally administered for a total of 28 days. In all treatment groups, intrapulmonary bacterial counts decreased by ≥1.672 $\log_{10}$ CFU (approximately 98%). The viable bacterial counts in the lung decreased by ≥2 $\log_{10}$ CFU (99%) in the groups receiving ≥2.5 mg/kg/dose and in groups receiving a total dose of 30, 70, 120, 140, or 280 mg/kg.

(f) *In vivo* combined effect of delamanid and the first-line drugs (4.2.1.4-06)

A mouse model of chronic tuberculosis (4 animals/group) was generated by intratracheal inoculation of *M. tuberculosis* Kurono strain (inoculation size, 455 CFU) to Slc:ICR mice. Delamanid (0.313-2.5 mg/kg/day) was orally administered QD for 4 weeks alone or in combination with INH or RFP (2.5 or 5 mg/kg/day, respectively), EB or PZA (80 or 320 mg/kg/day, respectively), or SM (40 or 160 mg/kg/day, subcutaneous administration). Animals in the vehicle control group received 5% gum arabic solution (10 mL/kg) orally alone or in combination with physiological saline (subcutaneous injection). After administration, the viable bacterial counts in the lung was calculated as logarithmic value/lung ($\log_{10}$ CFU). In each combined administration group, the viable bacterial count in the lung decreased in a delamanid dose-dependent manner. The viable bacterial count in the vehicle (5% gum arabic solution)

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30) INH at 1.25 mg/kg/day was also investigated.

31) Hafner R et al, *Am J Respir Crit Care Med*. 1997;156:918-923.

32) Treatment effect of delamanid (0.156, 0.313, 0.625, 1.25, 2.5, 5, 10, 20, 40 mg/kg/day) was investigated in a mice model of chronic tuberculosis (4.2.1.1-41). The viable bacterial count in the lung was lower in the ≥0.313 mg/kg/day groups as compared with the vehicle control group, and the dose of delamanid showing the effect equivalent to that of RFP (3.5 mg/kg/day) was estimated to be 0.52 mg/kg/day (by linear regression analysis model). Based on these results, the effective dose of delamanid was determined to be 0.625 mg/kg.

control group was 7.157 log_{10} CFU, whereas that was 5.037 log_{10} CFU in the delamanid 2.5 mg/kg/day monotherapy group, 4.322 log_{10} CFU in the EB (320 mg/kg/day) co-administration group, 4.693 log_{10} CFU in the INH (5 mg/kg/day) co-administration group, 2.497 log_{10} CFU in the PZA (320 mg/kg/day) co-administration group, 4.114 log_{10} CFU in the RFP (5 mg/kg/day) co-administration group, and 3.868 log_{10} CFU in the SM (160 mg/kg/day) co-administration group.

(g) Effects of combination therapies in a mouse model of chronic tuberculosis

i) Effects of combination therapies on viable bacterial counts in the lung in a mouse model of chronic tuberculosis (4.2.1.4-10, 4.2.1.4-11)

Using a mouse model of chronic tuberculosis generated by intratracheal inoculation of *M. tuberculosis* Kurono strain (inoculation size; 205, 350 CFU) into BALB/c mice, the effects of combination therapies containing delamanid on the viable bacterial counts in the lung were investigated. The results were as shown in Table 6.

Table 6. Viable bacterial count in the lung following combination therapy in a mouse model of chronic tuberculosis

Administration method [a)] (intensive therapy period/maintenance therapy period[b)])	Viable bacterial count in the lung (log_{10} CFU)	Timing of evaluation	Evaluation model (bacterial strain, time from inoculation to start of administration)
INH + PZA + RFP (2 months)/INH + RFP (3 months)	1.68 ± 0.26	Month 2	Kurono strain, 2 weeks
Delamanid + PZA + RFP (2 months)/ delamanid + RFP (3 months)	0.60 ± 0.70		
INH + PZA + RFP (2 months)/INH + RFP (2 months)	0.28 ± 0.45	Month 2	Kurono strain, 2 weeks
Delamanid + AMK + MFX + PZA (2 months)/ delamanid + MFX (2 months)	0.01 ± 0.02		
Delamanid + AMK + LVFX + PZA (2 months)/ delamanid + LVFX (2 months)	0.03 ± 0.02		

a) Dose of each test drug: Delamanid 2.5 mg/kg/day, RFP 10 mg/kg/day, INH 25 mg/kg/day, PZA 150 mg/kg/day, MFX 100 mg/kg/day, LVFX 300 mg/kg/day (p.o.), AMK 150 mg/kg/day (sc)

b) The administration period consisted of a 2-month intensive therapy period and a 2- or 3-month maintenance therapy period. Data are expressed as a mean ± standard deviation (SD) of 5 animals.

ii) Effects of combination therapies assessed by relapse rates in a mouse model of chronic tuberculosis (4.2.1.4-10, 4.2.1.4-11)

Using a mouse model of chronic tuberculosis generated by intratracheal or trans-airway inoculation of *M. tuberculosis* Kurono strain (inoculation size; 205, 350 CFU) to BALB/c mice, relapse rates at Week 12 after the end of administration were investigated. The lung homogenate was incubated and tested for *M. tuberculosis*, and the relapse rates were expressed in percentages of *M. tuberculosis*-positive animals. The results were as shown in Table 7.

Table 7. Relapse rate of tuberculosis after concomitant use of delamanid with other drugs in mice

Administration method [a] (intensive therapy period/maintenance therapy period[b])	Number of animals with relapse (relapse rate)	
	Treatment duration	
	4 months	5 months
INH + PZA + RFP (2 months)/INH + RFP (2 or 3 months)	2/14 (14.3%)	0/14 (0%)
PZA + RFP (2 months)/RFP (2 or 3 months)	15/15 (100%)	10/15 (66.7%)
Delamanid + INH + PZA + RFP (2 months)/delamanid + INH + RFP (2 or 3 months)	3/15 (20%)	0/15 (0%)
Delamanid + PZA + RFP (2 months)/delamanid + RFP (2 or 3 months)	0/15 (0%)	0/15 (0%)
Delamanid + INH + RFP (2 months)/INH + RFP (2 or 3 months)	12/15 (80%)	4/15 (26.7%)
Delamanid + INH + RFP (4 or 5 months)	9/15 (60%)	3/15 (20%)
	13 weeks [c]	16 weeks [c]
INH + PZA + RFP (8 weeks)/INH + RFP (5 or 8 weeks)	3/20 (15%)	0/20 (0%)
Delamanid + AMK + MFX + PZA (8 weeks)/delamanid + MFX (5 or 8 weeks)	3/19 (15.8%)	1/18 (5.6%)
Delamanid + AMK + LVFX + PZA (8 weeks)/delamanid + LVFX (5 or 8 weeks)	9/18 (50%)	3/18 (16.7%)
Delamanid + AMK + TH + MFX + PZA (8 weeks)/delamanid + MFX (5 or 8 weeks)	4/18 (22.2%)	1/19 (5.3%)
Delamanid + AMK + TH + LVFX + PZA (8 weeks)/delamanid + LVFX (5 or 8 weeks)	11/18 (61.1%)	5/18 (27.8%)

a) Dose of each test drug: Delamanid 2.5 mg/kg/day, RFP 10 mg/kg/day, INH 25 mg/kg/day, PZA 150 mg/kg/day, TH 50 mg/kg/day, MFX 100 mg/kg/day, LVFX 300 mg/kg/day (p.o.), AMK 150 mg/kg (s.c.)

b) The administration period consisted of a 2-month intensive therapy period and a 2- or 3-month maintenance therapy period. Combination therapy of delamanid + INH + RFP for 4 or 5 months also was given.

c) The study protocol had planned 2-month intensive therapy and 4-month maintenance therapy, 6 months in total. However, because of the low level of the viable bacterial count in the lung at 2 months after treatment start, the maintenance therapy period was reduced to 2 months (8 weeks), resulting in the administration period of 4 months (16 weeks) at the maximum. The relapse rate was evaluated at 12 weeks after 13- and 16-week administration instead of after 4- and 6-month administration originally planned.

(h) Effects of concomitant use of delamanid with other anti-tuberculosis drugs in a guinea pig model of chronic tuberculosis (4.2.1.1-62, 4.2.1.4-18, Reference data 4.2.1.4-19)

A guinea pig model of chronic tuberculosis was generated by intratracheal inoculation of *M. tuberculosis* Kurono strain (inoculation size, 4.34×10^2 or 6.04×10^2 CFU) to Hartley guinea pigs, followed by maintenance for 28 or 33 days. Delamanid (10 or 100 mg/kg/day[33]), INH, RFP, delamanid (10 or 100 mg/kg/day) + PZA + RFP, AMK + TH + LVFX + PZA, delamanid (100 mg/kg/day) + AMK + TH + LVFX + PZA, or INH + PZA + RFP (the standard therapy) was orally administered 5 days/week (AMK was subcutaneously administered) to these animals, and viable bacterial counts ($\log_{10}$ CFU) in the lung were determined after 4 and 8 weeks of administration. The vehicle control group received 5% gum arabic solution. The viable bacterial counts in the lung were as shown in Table 8.

33) In a preliminary pharmacokinetic study, plasma delamanid concentration was compared between guinea pigs and mice. The results showed that the pharmacokinetic values were similar in guinea pigs receiving 100 mg/kg of delamanid and in mice receiving 2.5 mg/kg of delamanid.

Table 8. Viable bacterial counts in the lung following concomitant use of delamanid with other anti-tuberculosis drugs

Administration method [a)]	Dose of delamanid (mg/kg)	Viable bacterial count in the lung (log_{10} CFU)	
		After 4 weeks	After 8 weeks
Delamanid	10	4.025 ± 0.181	3.214, 3.368[b)]
Delamanid	100	2.040 ± 1.774	0
INH	0	4.407, 4.858[b)]	3.014 ± 0.181
RFP	0	4.195 ± 0.145	-[e)]
Delamanid + PZA + RFP	10	2.410 ± 0.902	0
Delamanid + PZA + RFP	100	0	0
AMK + TH + LVFX + PZA	0	1.915 ± 1.798	0
Delamanid + AMK + TH + LVFX + PZA	100	0	0
INH + PZA + RFP	0	2.410 ± 0.437[c)], 2.989 ± 0.544[d)]	0

Mean ± SD

a) Dose of control compounds: INH 25 mg/kg, RFP 25 mg/kg, PZA 150 mg/kg, AMK 150 mg/kg, TH 50 mg/kg, LVFX 50 mg/kg
b) Data show the results with 2 animals in which the viable bacterial count in the lung was determined. In the remaining 1 animal negative for colonies in agar plate culture, the viable bacterial count in the lung is considered to be below the detection limit (1.919 in animal receiving 10 mg/kg of delamanid, 2.871 in animal receiving INH).
c) The viable bacterial count in the lung in the INH + PZA + RFP group in the study evaluating the effect of delamanid 10 mg/kg, INH, RFP, and delamanid 10 mg/kg+PZA+RFP
d) The viable bacterial count in the lung in the INH＋PZA + RFP group in the study evaluating the effect of delamanid 100 mg/kg, delamanid 100 mg/kg+PZA + RFP, AMK + TH + LVFX + PZA, and delamanid 100 mg/kg + AMK + TH + LVFX + PZA
e) One animal died during the treatment period. The remaining 2 animals were negative for colonies in agar plate culture, which suggested that the viable bacterial count in the lung might be below the detection limit (1.894, 1.911).

3.(i).A.(2) Secondary pharmacodynamics (4.2.1.2-01)

The inhibitory effects of delamanid against binding of specific ligands to 53 types of receptors, 5 types of ion channels, and 3 types of transporters were investigated. The inhibitory rates of delamanid (3 μmol/L) were <50% against all the ligands.

3.(i).A.(3) Safety pharmacology (4.2.1.3-04, 4.2.1.3-06 to 4.2.1.3-12)

In this application, the following safety pharmacology studies were conducted: the effects of delamanid on hERG current, the active potential of right ventricular papillary muscles isolated from guinea pigs, and the central nervous system (general symptoms, behavior), respiratory system, and cardiovascular system. The results were as shown in Table 9.

Table 9. Safety pharmacology

Test parameter		Animal species (sex, number/group)	Route of administration	Dose (mg/kg)	Noteworthy findings
Central nervous system (general symptoms, behavior)	General symptoms and behavior	Rats (male, 6)	p.o.	10, 100, 1000	10 mg/kg: No effect 100 mg/kg: Soft feces (8 hr after administration in 1/6 animal) 1000 mg/kg: White soft feces (4, 6, and 8 hr after administration in 2/6, 5/6, and 6/6 animals, respectively)
	General conditions	Conscious dogs (male, 5[a)])	p.o.	50, 150, 450	No effect
Respiratory and cardiovascular systems	Respiratory and cardiovascular systems	Conscious dogs (male, 5[a)])	p.o.	50, 150, 450	No effect
	hERG current	hERG channel-expressing cells	*in vitro*	0.03, 0.1, 0.3, 1, 3 μmol/L	19.6%, 21.7%, 21.8%, 23.2%, and 35.4% inhibition at 0.03, 0.1, 0.3, 1, and 3 μmol/L, respectively
	hERG current	hERG channel-expressing cells	*in vitro*	8 types of metabolites	(*R*)-DM-6702: IC_{50} = 0.0822 μmol/L (*R*)-DM-6701: IC_{50} = 1.60 μmol/L (*4RS, 5S*)-DM-6720: Inhibited hERG current by 54.9% at 1 μmol/L
	Action potential	Right ventricular papillary muscle	*in vitro*	3 μmol/L	No effect

Test parameter		Animal species (sex, number/group)	Route of administration	Dose (mg/kg)	Noteworthy findings
		isolated from guinea pigs			

a) Each dose was administered to all 5 animals at intervals of 6 to 8 days.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Anti-*M. tuberculosis* activity of delamanid and the susceptibility to delamanid of multidrug-resistant *M. tuberculosis* in Japan and other countries

Based on the submitted data, PMDA confirmed that the susceptibility to delamanid of multidrug-resistant *M. tuberculosis* (37 strains) and of extensively drug-resistant *M. tuberculosis* (8 strains) that were clinically isolated in Japan from 2007 through 2012 (ranges of MICs are 0.002-0.008 μg/mL and 0.002-0.004 μg/mL, respectively) was within the ranges of the sensitivity to delamanid of multidrug-resistant *M. tuberculosis* (290 strains) and extensively drug-resistant *M. tuberculosis* (21 strains) that were clinically isolated in the global phase II study (Study 242-[redacted]-204) (ranges of MICs are 0.001 to >8 and 0.002 to 0.031 μg/mL, respectively).

Based on the above, PMDA considers that there is no significant difference in the sensitivities of multidrug-resistant or extensively drug-resistant *M. tuberculosis* to delamanid between strains isolated in Japan and those isolated in foreign countries, and that there is no clinically significant problem in the anti-*M. tuberculosis* activity of delamanid against multidrug-resistant *M. tuberculosis* (including extensively drug-resistant *M. tuberculosis*).

3.(i).B.(2) Mechanism of action of delamanid

According to the submitted data, delamanid inhibits the biosynthesis of mycolic acid. Given the fact that INH, which also inhibits the biosynthesis of mycolic acid, does not act on dormant *M. tuberculosis*, PMDA asked the applicant to explain the detailed mechanism of the action of delamanid.

The applicant explained as follows:
According to a report, INH is metabolized by the enzyme KatG in *M. tuberculosis* and binds to NAD thereby inhibiting the enzyme InhA that plays an important role in mycolic acid synthesis pathway, resulting in the inhibition of all the subclasses of mycolic acid (alpha, methoxy, keto).[34)] In contrast, delamanid inhibited the production of methoxy mycolic acid and keto mycolic acid but did not inhibit the synthesis of either alpha mycolic acid or non-polar fatty acids. Therefore, delamanid inhibits the synthesis of mycolic acid at a different site of action from that of INH. Delamanid-induced accumulation of hydroxy mycolic acid, an intermediate in the mycolic acid synthesis pathway, suggests that delamanid inhibits the reaction of MmaA3 (Rv0643c) that catalyzes the biosynthesis of methoxy mycolic acid from hydroxyl mycolic acid and the reaction of an unidentified enzyme that catalyzes the biosynthesis of keto mycolic acid from hydroxyl mycolic acid.

The activity of KatG is known to be oxygen-dependent.[35)] KatG expression level is reduced in *M. tuberculosis* within the caseous necrosis layer (anaerobic region) of lung tissue derived from patients with tuberculosis as shown by the gene expression analysis of *M. tuberculosis*.[36)] Because of these findings, it is assumed that metabolism of INH by KatG is reduced in *M. tuberculosis* within the anaerobic caseous necrosis layer, and the inactive INH does not exhibit activity against *M. tuberculosis* in the dormant state. In contrast, the enzyme required for activating delamanid is

34) Vilcheze C and Jacobs WR, *Annu Rev Microbiol.* 2007;61:35-50.
35) Zabinski RF and Blanchard JS, *Journal of the American Chemical Society*. 1997;119(9):2331-2332.
36) Helmy Rachman et al, *Infection and Immunity*. 2006;74(2):1233-1242.

thought to be an oxygen-independent enzyme Rv3547, as demonstrated by the studies on the mechanism of resistance to delamanid (4.2.1.1-33 to 4.2.1.1-36), and delamanid is therefore expected to be active even in dormant *M. tuberculosis* cells, thereby exhibiting an effect on dormant bacteria as well.

PMDA considers that the applicant's explanation concerning the mechanism of action of delamanid is appropriate, well-supported by the available scientific evidence and therefore is acceptable, despite some details remaining unclear for now.

3.(i).B.(3) Emergence of resistance to delamanid

According to the submitted data, the frequency of the emergence of spontaneous, drug-resistant mutants of *M. tuberculosis* H37Rv strain[15)] was 6.44×10^{-6} to 4.19×10^{-5} for delamanid, 1.77×10^{-8} to 4.26×10^{-6} for RFP, and 1.74×10^{-5} to 3.13×10^{-5} for INH. The frequency of the emergence of spontaneous, drug-resistant mutants of *M. tuberculosis* Kurono strain[17)] was 1.35×10^{-4} to 1.57×10^{-4} for delamanid, $<3.42 \times 10^{-9}$ to 1.03×10^{-8} for RFP, 1.20×10^{-5} to 1.16×10^{-4} for INH, $<3.42 \times 10^{-9}$ to 1.03×10^{-8} for MFX, and 1.18×10^{-4} to 2.82×10^{-4} for PA-824. The frequency of the emergence of spontaneous, drug-resistant mutants of *M. bovis* BCG Tokyo strain was 2.51×10^{-5} to 3.95×10^{-5} for delamanid, 8.66×10^{-10} to 3.46×10^{-9} for RFP, 1.06×10^{-5} to 1.46×10^{-5} for INH, $<8.66 \times 10^{-10}$ to 3.03×10^{-8} for MFX, and 3.05×10^{-5} to 5.04×10^{-5} for PA-824. PMDA confirmed that the frequency of emergence of spontaneous mutants resistant to delamanid was within the range of the frequencies observed for other test compounds. In the global phase II study (Study 242-[redacted]-208), delamanid-resistant strains[21)] were isolated from 4 subjects. Taking account of the fact that no study was conducted on the emergence of resistant strains after the long-term treatment of delamanid exceeding 26 weeks, information on the emergence of delamanid-resistant strains needs to be further collected.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

For this regulatory submission, studies were conducted on the pharmacokinetics of ^{14}C-labeled and unlabeled delamanid (product produced by the old manufacturing process, product produced by the new manufacturing process[37)]) in mice, rats, rabbits, and dogs. Concentrations of delamanid and metabolites in plasma of mice, rats, rabbits, and dogs, in the homogenate of mouse lung, and in the cell culture fluid containing rat liver supernatant (S9) were measured by liquid chromatography/tandem mass spectrometry (LS/MS/MS).[38)]

Pharmacokinetic parameter values are expressed as mean or mean ± standard deviation (SD), unless specified otherwise.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single oral administration in mice, rats, rabbits, and dogs (4.2.2.2-03, 4.2.2.2-06 to 4.2.2.2-08, 4.2.2.2-13, reference data 4.2.2.2-01, reference data 4.2.2.2-04, reference data 4.2.2.2-09)

Delamanid (0.3-1000 mg/kg) produced by the old manufacturing process was administered to 3 male ICR mice, 3 male SD rats, and 4 male beagle dogs, delamanid (10 mg/kg) produced by the new manufacturing process was administered to 3 male SD rats and 4 male beagle dogs, and ^{14}C-labeled delamanid (3-10 mg/kg) was administered to 3 each of male and female SD rats, 3 female

37) During the early stage of the development of delamanid, tablets produced by the old manufacturing process were used. Subsequently, a new manufacturing process was developed to manufacture delamanid with improved bioavailability.

38) Lower limit of quantitation
Concentration in mouse plasma, 6 ng/mL for both delamanid and metabolites; concentration in mouse liver homogenate, 10 ng/mL for both delamanid and metabolites; concentration in rat plasma, 3 ng/mL for both delamanid and metabolites; concentration in cell culture fluid containing rat liver S9, 10 ng/mL for both delamanid and metabolites; concentration in rabbit plasma, 3 ng/mL for both delamanid and metabolites; concentration in dog plasma, 3 ng/mL and 6 ng/mL for delamanid and metabolites, respectively

NZW rabbits, and 3 male beagle dogs, all orally in a single dose under fed or fasted conditions. Plasma pharmacokinetic parameters were as shown in Tables 10 to 12. The maximum concentration (C_{max}) and the area under the concentration-time curve from time 0 to the time of the last measurable concentration (AUC_t) were non-linear in all cases, and no sex difference was observed in rats.

Table 10. Pharmacokinetic parameters of delamanid following a single oral dose of delamanid produced by the old manufacturing process to mice, rats, and dogs

Animal species	Feeding condition	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_t (ng·h/mL)	$t_{1/2}$ (h)
Male mice	Fed	0.3	54.4	2.0	497.9	4.5
		1	155.3	2.0	1783.1	5.2
		3	430.6	4.0	5673.3	5.9
		10	820.2	4.0	10,852.4	6.8
		30	1198.6	4.0	21,975.7	5.8
Male rats	Fed	3	493.5	6.0	7475.1	6.4
		10	982.6	6.0	13,698.6	8.2
		30	1468.7	4.0	19,671.9	7.5
		100	1619.3	8.0	27,163.0	6.9
		1000	1974.7	12.0	37,266.1	7.2
	Fasted	10	894.6	8.0	13,997.6	7.0
Female rats	Fed	10	1060.0	6.0	12,659.4	6.8
Male dogs	Fed	3	324.8 ± 151.6	9.5 ± 3.0	8313.0 ± 3256.7	17.0 ± 3.6
		10	296.9 ± 85.2	16.0 ± 9.8	10,047.7 ± 4675.3	20.6 ± 6.5
		30	505.6 ± 148.3	14.0 ± 6.9	14,059.4 ± 3241.1	17.3 ± 2.8
		100	493.0 ± 139.5	17.5 ± 20.4	17,517.2 ± 3955.3	14.3 ± 0.8
		1000	1184.6 ± 163.1	18.0 ± 6.9	51,016.4 ± 10,628.7	20.7 ± 4.7
	Fasted	10	74.6 ± 28.4	14.8 ± 10.9	1644.7 ± 891.0	14.5 ± 2.7

t_{max}: Time to maximum concentration, $t_{1/2}$: Elimination half-life
Mice and rats: Values are expressed as a mean of 3 animals. Dogs: Values are expressed as a mean ± SD of 4 animals.

Table 11. Pharmacokinetic parameters of delamanid following a single oral dose of delamanid produced by the new manufacturing process to rats and dogs

Animal species	Feeding condition	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_t (ng·h/mL)	$t_{1/2}$ (h)
Male rats	Fed	10	2173.1	8.0	19,518.9	9.0
	Fasted	10	1139.1	4.0	19,815.3	5.7
Male dogs	Fed	10	898.8 ± 344.3	9.5 ± 3.0	20,200.2 ± 5779.2	15.5 ± 5.0
	Fasted	10	337.3 ± 313.1	11.0 ± 14.1	6432.6 ± 5107.4	12.0 ± 2.6

Rats: Values are expressed as a mean of 3 animals. Dogs: Values are expressed as a mean ± SD of 4 animals.

Table 12. Pharmacokinetic parameters of delamanid following a single oral dose of ^{14}C-labeled delamanid to rats, rabbits, and dogs

Animal species	Feeding condition	Dose (mg/kg)	Sample	C_{max} (ng·eq/mL)	t_{max} (h)	AUC_t (ng·eq·h/mL)	$t_{1/2}$ (h)
Male rats	Fed	3	Blood	582 ± 285	8.0 ± 0.0	19,400 ± 5100	82.3 ± 17.1
	Fasted	3	Blood	735 ± 96	6.3 ± 3.5	19,600 ± 1400	49.5 ± 1.9
Female rats	Fed	3	Blood	643 ± 307	8.0 ± 0.0	20,300 ± 2700	57.2 ± 3.7
	Fasted	3	Blood	815 ± 283	5.0 ± 1.7	19,700 ± 4000	59.8 ± 7.3
Female rabbits	Fed	3	Plasma	692 ± 116	48 ± 0	91,697 ± 11,035	142 ± 35
Male dogs	Fed	10	Blood	891.5 ± 308.2	18.7 ± 9.2	97,515.6 ± 24,756.6	148.1 ± 27.2
	Fed	10	Plasma	1162.2 ± 429.7	18.7 ± 9.2	116,168.9 ± 29,888.1	158.7 ± 6.7

Values are expressed as a mean ± SD of 3 animals.

3.(ii).A.(1).2) Single intravenous administration in mice, rats, and dogs (4.2.2.2-03, 4.2.2.2-06, 4.2.2.2-08, reference data 4.2.2.2-01)

Delamanid (3 mg/kg) produced by the old manufacturing process was intravenously administered in a single dose to 3 male ICR mice, 3 male SD rats, 3 female SD rats, and 4 male beagle dogs.

As a result, $t_{1/2}$ values of delamanid in plasma were 6.3, 9.2, 8.8, and 17.6 hours, respectively, total body clearances (CL) were 222.4, 139.1, 161.9, and 215.1 mL/h/kg, respectively, and distribution volumes in the terminal phase (V_z) were 2025.8, 1841.4, 2055.5, and 5387.9 mL/kg, respectively. No sex difference was observed in CL and V_z in rats.

3.(ii).A.(1).3) Repeated oral administration in mice, rats, rabbits, and dogs (4.2.3.2-02, 4.2.3.2-04, 4.2.3.2-14, 4.2.3.7.3-06, 4.2.3.7.3-09, 4.2.2.2-14)

In a toxicokinetics study, delamanid (1-300 mg/kg/day) produced by the new manufacturing process was orally administered QD for 2 to 39 weeks[39] to 3 each of male and female ICR mice, 3 each of male and female SD rats, 3 to 8 male and 5 female NZW rabbits, and 4 each of male and female beagle dogs. Pharmacokinetic parameters of delamanid in plasma were as shown in Table 13. C_{max} of delamanid in plasma and the area under plasma concentration-time curve from time 0 to 24 hours after administration ($AUC_{0\text{-}24h}$) in the first and last doses were non-linear and did not show differences between males and females.

Table 13. Pharmacokinetic parameters of delamanid produced by the new manufacturing process in repeated oral dose of delamanid produced by the new manufacturing process to rats and dogs

Animal species	Treatment duration	Dose (mg/kg/day)	C_{max} (ng/mL)		$AUC_{0\text{-}24h}$ (ng·h/mL)	
			Male	Female	Male	Female
Mice	1 day	3	559.6	693.6	6511.8	8955.5
		30	2314.1	3675.7	35,840.3	38,700.5
		300	4710.6	4764.1	72,054.2	76,057.5
	13 weeks	3	1004.7	782.0	13,268.0	10,071.6
		30	2920.9	2780.5	36,509.4	45,126.5
		300	5603.1	4144.8	82,002.5	70,916.9
Rats	1 day	3	835.8	650.2	8860.1	9994.7
		30	2695.3	2377.7	36,639.7	24,998.1
		300	2977.3	3840.5	42,086.3	58,009.0
	26 weeks	3	1076.3	2202.6	17,691.4	29,736.9
		30	1799.2	4669.5	34,237.9	80,352.6
		300	2727.8	6835.3	54,163.9	132,737.5
Rabbits	1 day	5	246 ± 53	225 ± 34	2775 ± 513	2699 ± 294
		10	NE	401 ± 63	NE	4889 ± 733
		30	637 ± 175	553 ± 71	9707 ± 2535	9229 ± 1227
	2 weeks	5	408 ± 69	281 ± 34	4565 ± 1143	3759 ± 518
		10	NE	446 ± 79	NE	6238 ± 490
		30	1048 ± 544	1018 ± 578	19,459 ± 12,000	19,737 ± 12,609
Dogs	1 day	1	97.5 ± 43.9 a)	60.9 ± 16.5 a)	-	-
		3	237.9 ± 155.0 a)	83.4 ± 50.0 a)	-	-
		30	383.1 ± 414.2 a)	340.5 ± 270.8 a)	-	-
	39 weeks	1	269.3 ± 71.6	274.9 ± 126.4	3878.2 ± 849.6	4355.4 ± 1647.3
		3	586.1 ± 70.2	453.4 ± 260.4	10,456.6 ± 1212.7	7284.4 ± 4546.6
		30	1400.7 ± 326.9	2130.5 ± 859.7	21,769.2 ± 6884.2	36,333.6 ± 10,519.3

Mice and rats, mean of 3 animals; male rabbits, mean ± SD of 3 animals (5 mg/kg) or 7 to 8 animals (30 mg/kg); female rabbits, mean ± SD of 5 animals; dogs, mean ± SD of 4 animals
NE: Not examined, -: Not evaluated because of too few measuring time points
a) Value at 2 or 6 hours after administration

In a separate experiment, ^{14}C-labeled delamanid (3 mg/kg/day) was orally administered QD for 21 days to male SD rats. Blood radioactivity concentration increased with the number of doses and was 1.74 times higher 8 hours after the last dose and 2.68 times higher 24 hours after the last

[39] Delamanid was administered at 3 to 300 mg/kg/day for 13 weeks to male and female mice, at 3 to 300 mg/kg/day for 26 weeks to male and female rats, at 5 to 30 mg/kg/day for 2 weeks to male and female rabbits, and at 1 to 30 mg/kg/day for 39 weeks to male and female dogs.

dose as compared with the level achieved after a single-dose administration.[40] Radioactivity was eliminated only gradually ($t_{1/2}$, 370 hours).

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution following single oral administration in rats (4.2.2.3-01 to 4.2.2.3-03)

^{14}C-labeled delamanid (3 mg/kg) was orally administered in a single dose to 1 female and 3 male SD rats to investigate tissue radioactivity concentration[41]. Radioactivity concentrations reached C_{max} in almost all tissues examined 8 hours after administration. High radioactivity concentrations were observed in the liver, adrenal gland, Harderian gland, brown fat, spleen, kidney, and fat in the decreasing order. Relatively high radioactivity was detected in the lung as well.[42] Radioactivity concentrations in most of the tissues were higher than that in blood.[43] Radioactivity was eliminated from the tissues only gradually and was detected even 168 hours after administration. No clear sex difference was observed in tissue distribution of radioactivity.

In a separate experiment, ^{14}C-labeled delamanid (3 mg/kg) was orally administered in a single dose to 3 pigmented male Long-Evans rats. Radioactivity in the eye, which is a melanin-containing tissues, reached C_{max} (915.1 ng·eq./g tissue) 24 hours after administration, which was higher than C_{max} (264.0 ng·eq./g tissue) observed in white male rats. The half-life ($t_{1/2}$) of radioactivity in the eye was 1073 hours.

3.(ii).A.(2).2) Tissue distribution in repeated oral administration in rats (4.2.2.2-14, 4.2.2.4-12)

^{14}C-labeled delamanid (3 mg/kg) was orally administered QD for 21 days to 3 male SD rats. Tissue radioactivity concentration reached C_{max} at 8 hours after the last dose. In many tissues, radioactivity concentrations after the last dose was higher than that after a single dose administration, with the ratios being 5.19 in the testis, 4.72 in the medulla oblongata, 4.20 in the adrenal gland, 3.04 to 3.69 in the kidney, cerebrum, cerebellum, heart, and spleen, 1.91 in the lung, and 0.87 to 2.77 in other tissues. After repeated oral administration, radioactivity was detectable in all these tissues even 672 hours after the last dose.

^{14}C-labeled delamanid (3 mg/kg) was orally administered QD for 21 days to 3 male SD rats, and the state of the radioactivity in tissues (whether it was bound covalently) was investigated. The results suggested that delamanid-derived radioactivity was tightly bound to tissues.[44] The amount of covalently-bound radioactivity decreased over time in each tissue.

3.(ii).A.(2).3) Distribution in blood cells (4.2.2.3-01, 4.2.2.2-13 to 4.2.2.2-14, 5.3.4.1-01)

^{14}C-labeled delamanid (3 mg/kg in rats, 10 mg/kg in dogs) was orally administered in a single dose to 3 each of male and female SD rats and to 3 male beagle dogs. The distribution rate of

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[40] 556.6 ± 168.8 ng·eq./mL at 8 hours after single-dose administration, 224.0 ± 61.2 ng·eq./mL at 24 hours after single-dose administration, 968.1 ± 51.2 ng·eq./mL at 8 hours after the last dose, 599.5 ± 51.5 ng·eq./mL at 24 hours after the last dose

[41] Measured by whole body autoradiography at 2, 8, 72, and 168 hours after administration, and by tissue counting at 2, 8, 24, 72, and 168 hours after administration.

[42] Liver, 5193.7 ng·eq./g tissue (male), 3035.0 ng·eq./g tissue (female); adrenals, 3232.9 ng·eq./g tissue (male), 2365.6 ng·eq./g tissue (female); kidney, 2033.9 ng·eq./g tissue (male), 1419.8 ng·eq./g tissue (female); spleen, 2087.6 ng·eq./g tissue (male), 1457.8 ng·eq./g tissue (female); Harderian gland, 2910.1 ng·eq./g tissue (male), 1952.3 ng·eq./g tissue (female); brown fat 2395.2 ng·eq./g tissue (male), 1425.6 ng·eq./g tissue (female); lung, 1563.2 ng·eq./g tissue (male), 2184.9 ng·eq./g tissue (female). All values were obtained at 8 hours after administration.

[43] Radioactivity concentration in blood at 8 hours after administration was 403.0 ng·eq./mL in males and 294.0 ng·eq./mL in females.

[44] The amount of delamanid covalently bound to each tissue (pmol eq./mg protein) was calculated based on the tissue radioactivity measured by liquid scintillation counter and on the protein concentration measured by spectrophotometry, according to the following equation.
"Amount of covalently bound delamanid (pmol eq./mg protein) = tissue concentration of covalently bound delamanid (pmol/mL)/tissue protein concentration (mg/mL)"
Amount of covalently bound delamanid was 13.76 to 48.96 pmol eq./mg protein in cerebrum, 8.84 to 18.38 pmol eq./mg protein in heart, 5.56 to 13.75 pmol eq./mg protein in lung, 1.91 to 46.64 pmol eq./mg protein in liver, 3.16 to 29.40 pmol eq./mg protein in kidney, and 9.06 to 9.77 pmol eq./mg protein in testis.

delamanid in blood cells increased over time in rats,[45] whereas no time-course increase was observed in dogs.[46] When ^{14}C-labeled delamanid (3 mg/kg/day) was orally administered QD for 21 days to 3 male SD rats, the distribution rate of delamanid in blood cells increased over time, reaching 36.7% at 2 hours after the last dose and 94.2% at 336 hours after administration. The distribution rates of radioactivity in blood cells in humans were 5.2% to 25.8%.[47]

3.(ii).A.(2).4) Serum protein binding (4.2.2.3-04, 4.2.2.3-05, 4.2.2.3-08, 4.2.2.3-09)

In mice, rats, rabbits, dogs, and humans, the binding rates of ^{14}C-labeled delamanid (500, 5000 ng/mL) to serum protein were all ≥99.3%. The protein binding rates of ^{14}C-labeled delamanid[48] in human serum were 97.4% to 98.5% for serum albumin (40 mg/mL), 97.3% for very-low-density lipoprotein (1 mg/mL), 97.6% for low-density lipoprotein (4 mg/mL), 97.8% for high-density lipoprotein (3 mg/mL), 68.7% to 87.9% for α_1-acid glycoprotein (1 mg/mL), and 77.6% to 97.1% for γ-globulin (12 mg/mL). The results revealed the high rates of binding to serum albumin and lipoproteins.

The binding rates of the metabolites of delamanid ((*R*)-DM-6701, (*R*)-DM-6702, (*R*)-DM-6703) to rat, rabbit, dog, and human serum protein were ≥97.4% at the concentrations tested (500, 5000 ng/mL).

3.(ii).A.(2).5) Placental and fetal transfer following a single oral administration in pregnant rats (4.2.2.3-03, 4.2.2.3-10)

^{14}C-labeled delamanid (3 mg/kg) was orally administered in a single dose to pregnant SD rats (1 rat on Gestation day 16, 3 rats on Gestation day 17), and tissue radioactivity in maternal animals and in fetuses was measured.[49] Radioactivity levels in fetal tissues reached C_{max} at 8 hours post-dose, with the maximum concentration observed in the liver (725.9 ng·eq./g tissue). In fetal tissues, radioactivity levels were higher than plasma radioactivity levels in the maternal animals after 24 hours post-dose. In the maternal animals, radioactivity levels in tissues (except blood, eye, femur, amniotic fluid, and cerebrospinal fluid) at 8 hours post-dose were higher than plasma radioactivity levels and were relatively high in the ovary, uterus, and placenta as well.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) Possible metabolic pathway

Figure 1 shows the possible metabolic pathway of delamanid in mice, rats, rabbits, dogs, monkeys, and humans. A total of 8 metabolites of delamanid (DM-6701, DM-6702, DM-6703, DM-6717, DM-6718, DM-6720, DM-6721, DM-6722) were identified. Delamanid is an optically active compound with *R* configuration, but no optical isomer was detected.

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[45] The distribution rate in male rats was 4% at 2 hours post dose, 13% at 8 hours post dose, 22% at 24 hours post dose, 49% at 72 hours post dose, and 76% at 168 hours post dose. The distribution rate in female rats was 10% at 2 hours post dose, 12% at 8 hours post dose, 9% at 24 hours post dose, 32% at 72 hours post dose, and 60% at 168 hours post dose.

[46] The distribution rate was 35.2% at 4 hours post dose, 26.2% at 8 hours post dose, 23.8% at 12 hours post dose, 27.5% at 24 hours post dose, 32.8% at 32 hours post dose, 26.6% at 48 hours post dose, and 32.0% at 72 hours post dose.

[47] Calculated using plasma radioactivity concentrations, blood radioactivity concentrations, and hematocrit values measured in the mass balance study [Study 242-[redacted]-102; see "4.(i).A.(2).4) Mass balance study in foreign healthy adult subjects conducted in the UK"]

[48] 50 to 5000 ng/mL for human serum albumin, α_1-acid glycoprotein, and γ-globulin, and 500 ng/mL for very-low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein

[49] Measured by whole body autoradiography at 2, 8, and 24 hours after administration and by tissue counting at 2, 8, 24, 48, and 72 hours after administration.

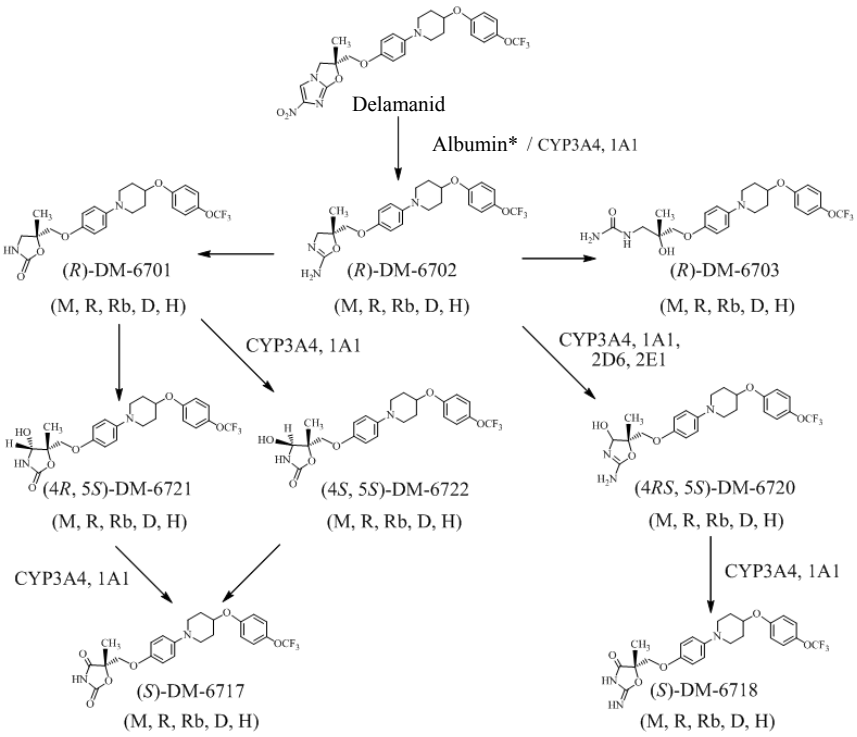

Figure 1. Possible metabolic pathway of delamanid in animals and humans
M: Mice, R: Rats, Rb: Rabbits, D: Dogs, H: Humans
*: There were no metabolites formed by NADH/NADPH-dependent catalysis by CYP3A4 or CYP1A1

3.(ii).A.(3).2) Metabolites in plasma and tissues (4.2.2.4-02 to 4.2.2.4-14, 4.2.3.2-02, 4.2.3.2-04, 4.2.3.2-14, 4.2.3.7.3-06, 4.2.3.7.3-09, Reference data 4.2.2.2-01)

Delamanid produced by the new manufacturing process was orally administered repeatedly to male and female ICR mice, male and female SD rats, male and female NZW rabbits, and male and female beagle dogs.[50)] Delamanid concentration was the highest in plasma from mice, rats, and dogs,[51)] whereas concentrations of metabolites were low as compared with delamanid. In contrast, DM-6717 was detected at the highest concentration in rabbit plasma.

Delamanid (0.3-30 mg/kg) produced by the old manufacturing process was orally administered in a single dose to male ICR mice, and concentrations of delamanid, DM-6701, DM-6702, and DM-6703 in the lung were measured. Delamanid and DM-6702 were detected at quantifiable levels, and DM-6702 concentration in the lung was higher than delamanid concentration in the lung. ^{14}C-labeled delamanid (3 mg/kg) was orally administered repeatedly to male SD rats, and radioactivity levels in the lung, cerebrum, liver, kidney, heart, and testis were measured. Delamanid was the main compound detected in all the tissues, and (*R*)-DM-6702 was detected in the lung, cerebrum, liver, kidney, and testis.

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50) Administered to male and female mice at 3 to 300 mg/kg/day for 13 weeks, to male and female rats at 3 to 300 mg/kg/day for 26 weeks, to male and female rabbits at 5 to 30 mg/kg/day for 2 weeks, and to male and female dogs at 1 to 100 mg/kg/day for 39 weeks.

51) C_{max} in mice, 2920.9 ng/mL (male) and 2780.5 ng/mL (female); $AUC_{0\text{-}24h}$ in mice, 36,509.4 ng·h/mL (male) and 45,126.5 ng·h/mL (female); C_{max} in rats, 1799.2 ng/mL (male) and 4669.5 ng/mL (female); $AUC_{0\text{-}24h}$ in rats, 34,237.9 ng·h/mL (male) and 80,352.6 ng·h/mL (female); C_{max} in dogs, 1400.7 ± 326.9 ng/mL (male) and 2130.5 ± 859.7 ng/mL (female); $AUC_{0\text{-}24h}$ in dogs, 21,769.2 ± 6884.2 ng·h/mL (male) and 36,333.6 ± 10,519.3 ng·h/mL (female). In all animal species, values are those observed at the dose of 30 mg/kg.

^{14}C-labeled delamanid (3 mg/kg in rats, 10 mg/kg in dogs) was orally administered in a single dose to male and female SD rats and male beagle dogs, and radioactivity levels in urine, feces, and bile (rats only) were measured. DM-6702 was detected in rat urine, whereas in rat feces, delamanid was the main compound detected and DM-6701, DM-6702, and DM-6703 were also detected. In rat bile, DM-6702 and DM-6703 were detected. In dog urine, neither delamanid nor known metabolites were detected. In dog feces, delamanid was the main compound detected and DM-6701 and DM-6702 were also detected.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Excretion in urine and feces (4.2.2.2-13 to 4.2.2.2-14, 4.2.2.3-01)

^{14}C-labeled delamanid (3 mg/kg in rats, 10 mg/kg in dogs) was orally administered in a single dose to male and female SD rats and male beagle dogs. In rats, 91.6% to 92.2% of the administered radioactivity was excreted in feces and 6.3% to 6.5% in urine within 168 hours after administration. In dogs, 89.8% of the administered radioactivity was excreted in feces and 3.0% in urine within 168 hours after administration. When ^{14}C-labeled delamanid (3 mg/kg) was orally administered QD for 21 days to male rats, the cumulative excretion rates in urine and feces within 336 hours after the last dose were 4.9% and 90.1% of the administered dose, respectively.

3.(ii).A.(4).2) Biliary excretion and enterohepatic circulation (4.2.2.5-01)

^{14}C-labeled delamanid (3 mg/kg) was orally administered in a single dose to male and female SD rats. The cumulative biliary excretion rates within 72 hours after administration were 34.1% to 36.9%. When collected bile was administered into the duodenum of other male rats, 10.5% of the administered radioactivity underwent enterohepatic circulation.

3.(ii).A.(4).3) Excretion in milk (4.2.2.3-10)

^{14}C-labeled delamanid (3 mg/kg) was orally administered in a single dose to SD rats on Postpartum day 10. C_{max} of radioactivity in milk was 1739.8 ng eq./mL and the area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) was 32,800 ng eq.·h/mL. The ratios to those in blood (C_{max}, 411.5 ng eq./mL; $AUC_{0-\infty}$, 15,400 ng eq.·h/mL) were 4.2 and 2.1, respectively.

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1) CYP inhibition (4.2.2.4-27 to 4.2.2.4-30)

The inhibitory effects of delamanid and its metabolites against CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) were investigated using human liver microsomes. As a result, 50% inhibitory concentrations (IC_{50}) of delamanid ranged from several tens to >100 μmol/L against all CYP isoforms, showing no inhibitory effect, whereas the metabolites inhibited CYP isoforms.

3.(ii).A.(5).2) CYP-inducing effect (4.2.2.4-31, reference data 4.2.2.4-32)

The activity of delamanid (0.1, 1, 10 μmol/L) to induce CYP isoforms (CYP1A2, CYP2B6, CYP2C9, CYP3A4/5) was investigated using human liver cells. Delamanid had no effect on enzymatic activities of CYP1A2, CYP2C9, or CYP3A4/5, nor on mRNA levels of CYP1A2, CYP2B6, CYP2C9, or CYP3A4 and therefore delamanid was considered not to have the activity to induce these CYP isoforms.

3.(ii).A.(5).3) Potential to serve as a substrate for human drug transporters (4.2.2.7-01, reference data 4.2.2.7-03)

Transport or uptake of delamanid (5 μmol/L) was investigated using multidrug resistance (MDR) 1-expressing LLC-PK1 cells (P-glycoprotein [P-gp]-mediated) and cells expressing breast cancer resistance protein (BCRP), organic cation transporter (OCT) 1, organic anion transporting

polypeptide (OATP) 1B1, or OATP1B3[52]. The results showed that delamanid did not serve as a substrate for P-gp or any other transporters.

3.(ii).A.(5).4) Inhibition of human drug transporters (4.2.2.7-01 to 4.2.2.7-02)

Using cells or vesicles expressing MDR1, BCRP, organic anion transporter (OAT) 1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or bile salt export pump (BSEP), the inhibitory effects of delamanid, (*R*)-DM-6701, (*R*)-DM-6702, (*S*)-DM-6718, and (4*RS*,5*S*)-DM-6720 against the substrate-transporting activity of human drug transporters were investigated. Delamanid did not inhibit the substrate transport by any of the transporters, whereas (*R*)-DM-6702 and (4*RS*,5*S*)-DM-6720 inhibited MDR1 and BCRP-mediated substrate transport.[53]

3.(ii).A.(5).5) Drug interaction with other anti-tuberculosis drugs in dogs (4.2.2.6-01, 4.2.2.6-03, 4.2.2.6-04)

After RFP (150 mg) was orally administered for 7 days to dogs, liver microsomes were isolated and ^{14}C-labeled delamanid was incubated with the microsomes in the presence of NADH/NADPH. As a result, hepatic intrinsic clearance (CL_{int}) increased 2.1 fold as compared with the value obtained in the microsomes from RFP-untreated dogs, demonstrating the enhanced delamanid metabolism in the liver after the administration of RFP.

Delamanid (50 mg) and anti-tuberculosis drugs (RFP [120 mg], INH [50 mg], PZA [300 mg], EB [200 mg]) were orally administered for 8 days to male and female beagle dogs to assess the effects of anti-tuberculosis drugs on the plasma pharmacokinetics of delamanid and metabolites. After the last dose, C_{max} and AUC_t of delamanid in plasma were 835.8 ± 340.3 ng/mL and 13,970 ± 5607 ng·h/mL, respectively, in the anti-tuberculosis drugs combination therapy group, showing decreases in C_{max} to 63.5% and in AUC_t to 70.2% as compared with the delamanid monotherapy group (C_{max}, 1315.8 ± 338.8 ng/mL; AUC_t, 19,900 ± 5996 ng·h/mL). Plasma (*R*)-DM-6702 concentrations were similar between the anti-tuberculosis drugs combination therapy group and the delamanid monotherapy group, whereas plasma (*R*)-DM-6701 and (*R*)-DM-6703 concentrations decreased in the combination therapy group as compared with the delamanid monotherapy group. The results of the study on the plasma pharmacokinetics of delamanid and metabolites following repeated oral dose of delamanid/RFP or delamanid/INH/PZA/EB[54] indicated that RFP was a likely contributory factor for decreased plasma delamanid concentration in the concomitant use with anti-tuberculosis drugs.

3.(ii).A.(5).6) Drug interactions with other anti-tuberculosis drugs in mice (4.2.2.6-07)

Delamanid (2.5 mg/kg) and other anti-tuberculosis drugs (RFP [10 mg/kg], TH [50 mg/kg], CS [60 mg/kg], MFX [100 mg/kg], AMK [150 mg/kg], PZA [150 mg/kg], PAS [1000 mg/kg]) were orally administered (or subcutaneously [AMK]) in a single dose to female Slc-BALB/c Cr mice, and the effects of anti-tuberculosis drugs on the plasma pharmacokinetics of delamanid and the effect of delamanid on the plasma pharmacokinetics of co-administered drugs were investigated. In the delamanid/PAS/CS group, C_{max} values of delamanid and CS in plasma were 0.195 and 26.0 μg/mL, respectively, and $AUC_{0-\infty}$ values were 1.75 and 47.8 ng·h/mL, showing decreases as compared with those in the delamanid monotherapy group (C_{max}, 0.234 μg/mL;

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52) In humans, the urinary excretion rate of delamanid-derived radioactivity was only approximately 3% [Study 242-[redacted]-102; see "4.(i).A.(2).4) Mass balance study in foreign healthy adult subjects conducted in the UK"], suggesting that renal transporters (OAT1, OAT3, OCT2) are not significantly involved in the pharmacokinetics of delamanid. Therefore, whether or not delamanid served as a substrate for these transporters was not investigated.

53) IC_{50} of (*R*)-DM-6702 against MDR1, 4.65 μmol/mL; IC_{50} of (*R*)-DM-6702 against BCRP, 5.71 μmol/mL; IC_{50} of (4*RS*,5S)-DM-6720 against MDR1, 7.80 μmol/mL; IC_{50} of (4*RS*,5*S*)-DM-6720 against BCRP, 6.02 μmol/mL.

54) When delamanid (50 mg) was orally administered with RFP (150 mg), INH (50 mg), PZA (300 mg), or EB (200 mg) for 8 days, C_{max} and AUC_t of delamanid in plasma in the RFP co-administration group after the last dose were 729.7 ng/mL and 11,710 ng·h/mL, respectively, showing decreases to 50.3% and 52.3%, respectively, compared with the delamanid monotherapy group (C_{max}, 1451.8 ng/mL; AUC_t, 22,370 ng·h/mL). In the INH/PZA/EB group, in contrast, C_{max} and AUC_t of delamanid in plasma were 848.8 ng/mL and 14,420 ng·h/mL, respectively, which were similar to those observed in the delamanid monotherapy group (C_{max}, 1123.0 ng/mL; AUC_t, 16,570 ng·h/mL).

$AUC_{0-\infty}$, 2.49 ng·h/mL) and the CS monotherapy group (C_{max}, 54.0 μg/mL; $AUC_{0-\infty}$, 58.6 ng·h/mL).[55)]

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Delamanid metabolism by serum albumin

The applicant explained the metabolism of delamanid by serum albumin as follows:
In vitro metabolism of delamanid to (*R*)-DM-6702 was investigated using ^{14}C-labeled delamanid (5 μg/mL, approximately 9.3 μmol/L), human plasma, purified serum protein, and recombinant human serum albumin. The results showed that metabolism of delamanid to (*R*)-DM-6702 was temperature- and pH- dependent, that the reaction occurred in the plasma albumin fraction, purified serum albumin, and recombinant human serum albumin, and that the pharmacokinetic parameters observed in the presence of plasma were similar to those observed in the presence of the purified serum albumin. Based on these findings, the applicant considered that serum albumin was involved in the metabolism of delamanid to (*R*)-DM-6702 (4.2.2.4-22, 4.2.2.3-05).

Taking account of the facts that serum albumin is involved in the metabolism of delamanid and that both delamanid and the metabolite have a high binding rate to serum protein, PMDA asked the applicant to explain whether or not there is a possibility that displacement of delamanid bound to serum albumin by metabolites may affect the pharmacokinetics of delamanid.

The applicant explained as follows:
In the *in vitro* study in which protein binding of delamanid was investigated, protein binding of delamanid and its binding site were investigated when albumin concentration was 1 mg/mL, one fortieth of that in *in vivo* plasma concentration. No saturation of protein binding was observed even at the high delamanid concentration of 30 μmol/L (approximately 16,000 ng/mL). Also, no decrease in the protein binding of delamanid was observed in the displacement test of delamanid using warfarin (site I), diazepam (site II), or digitoxin (site III). Based on these results, the applicant considers that delamanid does not have specific binding sites on an albumin molecule and the metabolite is unlikely to cause competitive displacement on the same site. In addition, delamanid binds to many proteins other than albumin in plasma (very-low-density lipoprotein, low-density lipoprotein, high-density lipoprotein, α_1-acid glycoprotein, γ-globulin) (4.2.2.3-05, 4.2.2.3-07, 4.2.2.3-09) showing no saturation up to 5000 ng/mL. Therefore, displacement of serum albumin-bound delamanid by the metabolite is unlikely to affect the pharmacokinetics of delamanid.

Furthermore, in the phase I single-dose and multiple-dose administration study in Japanese subjects (Study 242-[redacted]-001 [5.3.3.1-03]), comparison of C_{max} and AUC_{0-24h} of delamanid and the metabolites between a single oral dose of delamanid 400 mg and 10-day multiple oral doses of delamanid 400 mg QD showed that the accumulation rate of each metabolite was higher than that of delamanid after multiple oral administration, resulting in an increase in the percentage of metabolites relative to delamanid as compared to that after single oral administration. However, there was no clear difference in the total body clearance or distribution volume of delamanid between single oral administration and multiple oral administrations. Therefore, the applicant considers that metabolites generated are unlikely to affect the pharmacokinetics of delamanid.

In the *in vitro* study which investigated the protein binding of delamanid and the binding site on albumin, the phase I single-dose and multiple-dose study in Japanese subjects, and the phase II study in patients with multidrug-resistant pulmonary tuberculosis [see "4.(i).A.(3).2) Phase II studies in patients with multidrug-resistant pulmonary tuberculosis"], the concentration of each

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55) No significant difference was observed in C_{max} or AUC_{∞} in the comparison between each single-drug group and delamanid/AMK, delamanid/TH, delamanid/PAS, delamanid/CS, or delamanid/RFP group, or in the comparison between the delamanid/MFX/TH/PZA/AMK group and the delamanid alone group or the MFX/TH/PZA/AMK group.

metabolite in the long-term administration in humans was less than the maximum concentration that showed no saturation of protein binding. Taking account of these findings, PMDA accepted the explanation of the applicant that the generated metabolites are unlikely to affect the pharmacokinetics of delamanid.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The results from the following toxicity studies were submitted: single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (study on the mechanism of toxicity, study in juvenile animals, phototoxicity study). Also, the results of a genotoxicity study and reproductive and developmental toxicity studies of metabolites were submitted.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1-01, 4.2.3.1-02, reference data 4.2.3.1-03, reference data 4.2.3.1-04)

As data of single-dose toxicity studies, the results of oral administration studies in rats and dogs using delamanid produced by the new manufacturing process were submitted. The approximate lethal dose was determined to be >1000 mg/kg in rats and >900 mg/kg in dogs. Decreased food intake was seen in dogs but no clear toxic findings were observed after administration.

3.(iii).A.(2) Repeat-dose toxicity (4.2.3.2-01 to 4.2.3.2-04, reference data 4.2.3.2-05 to 4.2.3.2-13)

As data of main repeat-dose toxicity studies, the results of oral administration studies in rats (4 and 26 weeks) and in dogs (13 and 39 weeks) were submitted. Major delamanid-related findings were changes in blood parameters such as decreased hematocrit, hemoglobin, and red blood cell count, and increased reticulocyte ratios both in rats and dogs; changes in blood coagulation parameters such as prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT), and decreased thrombo-test (TTO) in rats; and prolonged QT and QTc, lipofuscin deposition in the liver, and appearance of foam cells in the lymphatic tissues, etc. in dogs.

In the 26-week oral administration study of delamanid in rats, the exposure level was high in animals receiving delamanid at the no observed adverse effect level (NOAEL) (30 mg/kg/day in male, 300 mg/kg/day in female) as compared with the exposure level[56)] observed at steady state after the administration of delamanid 100 mg BID (the recommended clinical dosage) for 2 month, with C_{max} being 4.3 times (male) and 16.5 times (female) higher and $AUC_{0\text{-}24h}$ being 4.3 times (male) and 16.7 times (female) higher. In a similar comparison in the 39-week oral administration study of delamanid in dogs, the exposure level was high at the NOAEL (1 mg/kg/day in male, 3 mg/kg/day in female) with C_{max} being 0.7 times (male) and 1.1 times (female) and $AUC_{0\text{-}24h}$ being 0.5 times (male) and 0.9 times (female) those at steady state after the administration of delamanid at the recommended clinical dosage.

Metabolites (*R*)-DM-6702 and DM-6718 account for more than 10% of the total exposure level in humans. $AUC_{0\text{-}24h}$ values of (*R*)-DM-6702 at the NOAEL as compared with that at the recommended dosage regimen[57)] were 0.2 (male) and 0.9 (female) times in rats and 0.4 (male) and 1.1 (female) times in dogs, and of DM-6718 0.9 (male) and 2.0 (female) times in dogs.[58)]

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56) C_{max}, 414 ng/mL; $AUC_{0\text{-}24h}$, 7925 ng·h/mL (global phase II study [Study 242-[redacted]-204]) [see "4.(i).A.(3).2) Phase II studies in patients with multidrug-resistant pulmonary tuberculosis"]

57) $AUC_{0\text{-}24h}$ of (*R*)-DM-6702 and DM-6718 in the global phase II study (Study 242-[redacted]-204) (3207 ng·h/mL and 2959 ng·h/mL, respectively)

58 $AUC_{0\text{-}24h}$ was not calculated in rats because DM-6718 was below the lower limit of quantitation in all animals

3.(iii).A.(2).1) Four-week repeat oral dose toxicity study in rats (4.2.3.2-01)

Placebo (Excipient II) or delamanid (produced by the new manufacturing process; 3, 30, 300 mg/kg/day) was orally administered for 4 weeks to male and female SD rats (n = 10/sex/group). Increased urinary Na excretion was observed in females in the ≥30 mg/kg/day groups. Chronic inflammation of the cecum and retinal rosettes were observed in male and female rats in the 300 mg/kg/day group. Increased urinary Na excretion was not considered to be a toxic change because no change was observed in blood Na level. Chronic inflammation of the cecum and retinal rosettes are lesions that occur spontaneously, which were infrequent and mild in severity in this study. Therefore, they were not considered as changes caused by delamanid. Based on the result, the NOAEL was determined to be 300 mg/kg/day.

3.(iii).A.(2).2) Twenty six-week repeat oral dose toxicity study in rats (4.2.3.2-02)

[redacted]. Death occurred in 1 female in the 30 mg/kg/day group and in 1 male in the 300 mg/kg/day group. The causes of the deaths were considered angiosarcoma of the Harderian gland and an error in administration, respectively. Findings were decreased hematocrit in males in the ≥30 mg/kg/day groups, prolonged APTT in males and females in the 300 mg/kg/day group, and decreased hemoglobin, decreased red blood cell count, increased reticulocyte ratio, tendency of increased reticulocyte count, prolonged PT, and decreased TTO in males in the 300 mg/kg/day group. A decrease in hematocrit observed in males in the 30 mg/kg/day group was very slight, and prolonged APTT observed in females in the 300 mg/kg/day group was not accompanied by a change in TTO. Therefore, these findings were not considered to be toxic changes. Based on the result, the NOAEL was determined to be 30 mg/kg/day in males and 300 mg/kg/day in females.

3.(iii).A.(2).3) Thirteen-week repeat oral dose toxicity study in dogs (4.2.3.2-03)

Placebo (Excipient II) or gelatin-encapsulated delamanid (produced by the new manufacturing process; 3, 10, 30, 100 mg/kg/day) was orally administered for 13 weeks to male and female beagle dogs (n = 3/sex/group). Findings in the ≥10 mg/kg/day groups were lymphoid follicles in the mandibular lymph node, mesenteric lymph node, medial retropharyngeal lymph node, stomach, ileum, and cecum, and foam cells in the splenic white pulp in males and females; prolonged QT and QTc in males, and pale feces in males and females. Findings in the ≥30 mg/kg/day groups were thymic atrophy in males and females, increased alanine aminotransferase (ALT) in males of the 30 mg/kg/day group, and reduced body weight gain, prolonged QT and QTc, and decreased α_1-globulin in females. Findings observed in males in the 100 mg/kg/day group were reduced body weight gain, increased mean cell hemoglobin and mean cell hemoglobin concentration, decreased platelet count, decreased white blood cell count, decreased red blood cell count, decreased hemoglobin, decreased hematocrit, enhanced myelopoiesis, extramedullary hemopoiesis in the spleen, liver, and kidney, increased relative liver weight, and atrophy of lymphoid nodules in ileum, and ALT increased in females. Except increased relative liver weight, all other changes were reversible after a 4-week recovery period. Based on the result, the NOAEL was determined to be 3 mg/kg/day.

3.(iii).A.(2).4) Thirty nine-week repeat oral dose toxicity study in dogs (4.2.3.2-04)

[redacted]. Findings in the ≥1 mg/kg/day groups were lipofuscin deposition in centrilobular hepatocytes, lipofuscin deposition in bile duct epithelial cells and mucosal epithelial cells of the gallbladder, and small granuloma in the liver in males and females, and unilateral localized atrophy of seminiferous tubules in males. Findings in the ≥3 mg/kg/day groups were reduced body weight gain, prolonged QT and QTc, foam cells in follicles of medial retropharyngeal lymph nodes, and bilateral localized atrophy of

seminiferous tubules in males. Findings in the 30 mg/kg/day group were foam cells in medial retropharyngeal lymph nodes, mesenteric lymph node, and Peyer's patch follicles in males and females, lacrimation and spermostasis in males, and reduced body weight gain, prolonged QT and QTc, ST segment depression, foam cells in splenic white pulp and mandibular lymph node follicles in females. The applicant considered that lipofuscin deposition, small granuloma, and increased frequency and intensity of aggregation of foam cells caused by delamanid were changes of no toxicological significance for the following reasons: (i) although the mechanism of these changes induced by delamanid is unknown, a histopathological examination did not show degeneration or necrotic changes in hepatocytes or mucosal epithelial cells of gallbladder, (ii) an electron microscopic examination did not show changes in organelles of hepatocytes, and (iii) no changes were observed in laboratory test values related to liver and biliary duct such as ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin. Also, atrophy of the seminiferous tubules and spermostasis are spontaneous lesions, and the changes observed in this study were mild in severity and did not show a dose-response relationship. Therefore the applicant considered that the changes were not associated with delamanid. Based on the result, the NOAEL was determined to be 1 mg/kg/day in males and 3 mg/kg/day in females.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-01 to 4.2.3.3.1-04, 4.2.3.3.1-07 to 4.2.3.3.1-09, 4.2.3.3.2-01 to 4.2.3.3.2-03, reference data 4.2.3.3.1-05 to 4.2.3.3.1-06, reference data 4.2.3.3.2-04 to 4.2.3.3.2-06)

Data of the following genotoxicity studies on delamanid were submitted: a reverse mutation assay using bacteria (*Salmonella typhimurium*), a forward mutation assay using cultured mammalian cells (murine lymphoma cells), and a micronucleus assay in rats. For (*R*)-DM-6702 and DM-6718, metabolites accounting for more than 10% of the total exposure level in humans, and other metabolites (*R*)-DM-6701 and (*R*)-DM-6703,[59] results of a reverse mutation assay using bacteria (*Salmonella typhimurium*) and a micronucleus assay in rats were submitted. Neither delamanid nor the metabolites showed genotoxicity in any of the studies.

3.(iii).A.(4) Carcinogenicity (4.2.3.4.1-01 to 4.2.3.4.1-03)

Data of oral dose carcinogenicity studies in mice and rats were submitted. No delamanid-related changes in proliferative or neoplastic changes were observed in mice or rats. DM-6718, a metabolite accounting for more than 10% of the total exposure level in humans, is present only in a low exposure level in mice and rats. Therefore, carcinogenicity of DM-6718 was not evaluated in these studies.

3.(iii).A.(4).1) A 104-week repeat oral dose carcinogenicity study in mice (4.2.3.4.1-01 to 4.2.3.4.1-02)

[redacted]. In males in the 300 mg/kg/day group, the survival rate decreased from Week 52 of administration, and therefore the study in these animals was terminated prematurely at Week 67 of administration. The survival rate at the study termination was 50.9% (28 of 55 animals). In males in the placebo control group and in females in the vehicle control group, the administration of delamanid was terminated at Week 92 because of the decreased number of surviving animals. In all the treatment groups, animals were necropsied at Week 100 (males) or at Week 93 (female) of administration. The survival rates of males at necropsy were 42.6% (23 of 55 males) in the vehicle control group, 37.7% (20 of 55 males) in the placebo control group, 40.7% (22 of 55 males) in the delamanid 3 mg/kg/day group, and 29.6% (16 of 55 males) in the delamanid 30 mg/kg/day group. The survival rates of females at

[59] (*R*)-DM-6701 and (*R*)-DM-6703 had been suspected to be major metabolites accounting for more than 10% of the total exposure level in humans before the information on metabolites in humans became available. Therefore, genotoxicity studies were conducted on these metabolites.

necropsy were 36.4% (20 of 55 females) in the vehicle control group, 64.8% (35 of 55 females) in the placebo control group, 50.9% (28 of 55 females) in the delamanid 3 mg/kg/day group, 69.1% (38 of 55 females) in the delamanid 30 mg/kg/day group, and 50.9% (28 of 55 females) in the delamanid 300 mg/kg/day group. The decreases in the number of surviving animals in males in the placebo control group and in females in the vehicle control group were less than or comparable to the lowest level of the background data of the control group in the laboratory (male, 41% at Week 100 of administration; female, 36% at Week 93 of administration). However, there were no causes of death which were more frequently observed than in other treatment groups, and all the deaths were considered to be accidental events. The applicant considered that the deaths and sacrificed moribund in males in the delamanid 300 mg/kg/day group were caused by abnormalities in the blood coagulation system due to decreased activity in vitamin K-dependent blood coagulation factors, based on the findings that hemorrhage, myocardial necrosis, infiltration of polymorphonuclear leukocytes, hemosiderin pigment deposition, and PT and APTT prolongation accompanied by decreased TTO were observed in the heart, and on results of the study on the mechanism of action [see "3.(iii).A.(7) Other toxicity studies"]. Male rats fed with vitamin K-deficient diet are reported to present with hemorrhage or to have hemorrhagic lesions in the heart earlier than female rats,[60)] and these are the factors of the higher mortality rate of male rats. Therefore, the applicant considered that the higher mortality rate in male mice was also due to their higher sensitivity to vitamin K deficiency, as with male rats, and was not caused by the action mechanism of delamanid. No delamanid-related increase in the frequency of tumor growth was observed. Based on these outcomes, the applicant determined that delamanid was not carcinogenic in mice.

Except for a mild decrease in TTO and prolongation of PT in females in the delamanid 300 mg/kg/day group, no other delamanid-related non-neoplastic lesions were observed either in males or females.

3.(iii).A.(4).2) A 104-week repeat oral dose carcinogenicity study in rats (4.2.3.4.1-03)

[redacted]. In males in the placebo control group and in females in the vehicle control group, the number of surviving animals decreased to 20. Therefore, surviving male animals were necropsied at Week 100 of administration (treatment duration, 99 weeks) and surviving female animals at Week 97 (treatment duration, 96 weeks). The survival rates in males at necropsy were 50.9% (28 of 55 males) in the vehicle control group, 36.4% (20 of 55 males) in the placebo control group, 60.0% (33 of 55 males) in the delamanid 3 mg/kg/day group, 40.0% (22 of 55 males) in the delamanid 30 mg/kg/day group, and 50.9% (28 of 55 males) in the delamanid 300 mg/kg/day group. The survival rates in females at necropsy were 36.4% (20 of 55 females) in the vehicle control group, 47.3% (26 of 55 females) in the placebo control group, 38.2% (21 of 55 females) in the delamanid 3 mg/kg/day group, 49.1% (27 of 55 females) in the delamanid 30 mg/kg/day group, and 50.9% (28 of 55 females) in the delamanid 300 mg/kg/day group. The survival rates of males in the placebo control group and females in the vehicle control group were below the lowest level in the historical data for the control in the laboratory (male, 41.7% at Week 100 of treatment; female, 41.7% at Week 97 of treatment). However, there were no causes of death which were more frequently observed than in other treatment groups including the delamanid groups, and all deaths were therefore considered accidental events. Since no delamanid-related increase was observed in the frequency of tumor growth, the applicant determined that delamanid was not carcinogenic in rats.

Non-neoplastic changes observed in the delamanid ≥30 mg/kg/day groups were lipofuscin pigment deposition in adrenal cortical cells and diffuse hypertrophy of cortical cells in males and

60) Metta VC, *J Nutr*. 1960;72:455-458, Mellette SJ, *Am J Clin Nutr*. 1961;9:109-116.

females, increased ratio and number of reticulocytes in females, and those in the delamanid 300 mg/kg/day group were decreased body weight in males and females and a decrease in hematocrit levels in females. The applicant considered that the diffuse hypertrophy of adrenocortical cells was a secondary change due to the stress of administration, based on the tendency of decreased body weight observed in the delamanid ≥30 mg/kg/day groups.

3.(iii).A.(5) Reproductive and developmental toxicity (4.2.3.5.1-01, 4.2.3.5.2-01 to 4.2.3.5.2-04, 4.2.3.5.3-01, 4.2.3.5.4-01, Reference data 4.2.3.5.2-05 to 4.2.3.5.2-08, Reference data 4.2.3.5.4-02)

Data from the following reproductive and developmental toxicity studies were submitted: a study of fertility and early embryonic development to implantation in rats, studies on embryo-fetal development in rats and rabbits, and a study for effects on pre- and postnatal development, including maternal function in rats. Also, data of studies were submitted on the effects of metabolites (*R*)-DM-6702 and (*S*)-DM-6718 that account for more than 10% of the total exposure level in humans on embryo-fetal development in rats. Delamanid caused increases in early resorption of embryos in rabbits, and (*R*)-DM-6702 and (*S*)-DM-6718 caused systemic oedema, visceral variation, skeletal variation, etc. The ratios of the exposure levels at the NOAELs to those at the recommended clinical dosage[56)] in embryos and fetuses were 13 in rats and 1 in rabbits for delamanid (NOAEL; 300 mg/kg/day in rats, 5 mg/kg/day in rabbits), 3.8 in rats for (*R*)-DM-6702 (NOAEL, 10 mg/kg/day in rats), and 0.9 in rats for (*S*)-DM-6718 (NOAEL, 0.5 mg/kg/day in rats). In rats, delamanid was shown to be transferred through the placenta and excreted in milk [see "3.(ii).A.(4).3) Excretion in milk"].

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation (4.2.3.5.1-01)

[redacted]. Delamanid had no effect on the general conditions, fertility, or early embryonic development to implantation in parental animals. The NOAEL was determined to be 300 mg/kg/day for the general conditions, fertility, and early embryonic development in parental animals.

3.(iii).A.(5).2) Studies on embryo-fetal development

(a) Study on the effect of delamanid on embryo-fetal development in rats (4.2.3.5.2-01)

Placebo (Excipient II) or delamanid (produced by the new manufacturing process; 3, 30, 300 mg/kg/day) was orally administered to pregnant SD rats (n = 20/group) from Gestation day 7 to 17. Delamanid had no effect in maternal animals, showing no effect on the numbers of luteal bodies, implantations, dead/resorbed embryos, dead fetuses and the number of live fetuses, sex ratio, morphology of fetuses, etc. Based on the result, the NOAEL was determined to be 300 mg/kg/day for general toxicity in maternal animals, reproduction (maintenance of pregnancy), and embryofetal development.

(b) Study for effects of delamanid on embryo-fetal development in rabbits (4.2.3.5.2-04)

Placebo (Excipient II) or delamanid (produced by the new manufacturing process; 1, 5, 10 mg/kg/day) was administered orally to pregnant NZW rabbits (n = 20/group) from Gestation day 6 to 18. Vaginal hemorrhage, decreased food intake, and reduced body weight gain were observed in maternal animals in the delamanid 10 mg/kg/day group. The result of the dose-finding study on delamanid (Reference data 4.2.3.5.2-08) showed decreased body weight, decreased food intake, hemorrhage in the lung, subcutaneous tissue, and uterus, and abortion in the delamanid 10 mg/kg/day group, and death in the delamanid 20 and 30 mg/kg/day groups. In fetuses, increases in the number and incidence of early resorption of embryos, decreased sex ratio (male/female) of surviving fetuses, myeloschisis, and skeletal anomalies (unarticulated 7th costal cartilage and

sternum) were observed in the delamanid 10 mg/kg/day group. The low sex ratio (male/female) in the surviving fetuses was within the laboratory historical data, no morphological abnormalities were observed in the reproductive system, and the incidences of myeloschisis and skeletal anomalies (unarticulated 7th costal cartilage and sternum) were also within the range of the laboratory historical data. The applicant therefore considered these events were of spontaneous changes and were not delamanid-related. Based on the above, the NOAEL was determined to be 5 mg/kg/day for the general toxicity in maternal animals and for embryofetal development.

(c) Study for effects of (*R*)-DM-6702 on embryo-fetal development in rats (4.2.3.5.2-02)
Vehicle (5% gum arabic solution) or (*R*)-DM-6702 (5, 10, 30 mg/kg/day) was administered orally to pregnant SD rats (n = 20/group) from Gestation days 7 to 17. Reduced body weight gain and decreased food intake were observed in maternal animals in the 30 mg/kg/day group, and external anomaly (systemic oedema), visceral variation (thymic remnant in neck), and skeletal variations (dumbbell-shaped thoracic vertebrae, dichotomous ossification of thoracic vertebral bodies) were observed in fetuses in the 30 mg/kg/day group. Based on the result, the NOAEL was determined to be 10 mg/kg/day for the general toxicity in maternal animals and for embryofetal development.

(d) Study for effects of (*S*)-DM-6718 on embryo-fetal development in rats (4.2.3.5.2-03)
Vehicle (5% gum arabic solution) or (*S*)-DM-6718 (0.5, 1, 3 mg/kg/day) was administered orally to pregnant SD rats (n = 20/group) from Gestation days 7 to 17. No toxicity was observed in maternal animals, whereas an external anomaly (systemic edema) was observed in fetuses in the ≥1 mg/kg/day groups. Based on the result, the NOAEL was determined to be 3 mg/kg/day for the general toxicity in maternal animals and 0.5 mg/kg/day for embryofetal development.

3.(iii).A.(5).3) Study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3-01)

[redacted]. No effect of delamanid was observed in maternal animals. In pups, decreased frequency of open eyelid was observed in the delamanid 3 mg/kg/day and 300 mg/kg/day groups and decreased frequency of incisor eruption in the lower jaw was observed in the delamanid 300 mg/kg/day group. The frequencies of these observations were within the range shown in the laboratory historical data and were not dose-correlated, and no effect of delamanid was observed on the body weight of pups. The applicant therefore considered that these changes were not caused by delamanid. Based on the above, the NOAEL was determined to be 300 mg/kg/day both for the general toxicity in maternal animals and for reproduction and development of the offspring.

3.(iii).A.(6) Local tolerance (4.2.3.6-01 to 4.2.3.6-02)
As part of the safety assessment during the manufacture of delamanid, an acute skin irritation test and an acute eye irritation test were conducted in rabbits to evaluate the local tolerance of delamanid. Delamanid caused neither skin irritation nor eye irritation.

3.(iii).A.(7) Other toxicity studies
3.(iii).A.(7).1) Study on the mechanism of hemorrhage in mice (4.2.3.7.3-01)
In the carcinogenicity study in male mice, hemorrhagic changes were observed in dead animals and in moribund-sacrificed animals, and changes in blood coagulation system were observed in animals with premature study termination. Therefore, a study was conducted to investigate the mechanism of blood coagulation in mice.

Vehicle (5% gum arabic solution) or delamanid (300 mg/kg/day) was administered orally to male ICR mice (n = 20/group) for 24 weeks. In a separate experiment, vehicle (5% gum arabic solution) or delamanid (300 mg/kg/day) was administered orally to male ICR mice (n = 10/group) for 24

weeks and followed by vitamin K_1 (15 mg/kg/day) administered subcutaneously from Week 21 (vitamin K_1 co-administration group). Prolonged PT, tendency of prolonged APTT, and decreased TTO were observed in the 300 mg/kg/day group, whereas no effect on these blood coagulation parameters was observed in the vitamin K_1 co-administration group. The changes observed in the 300 mg/kg/day group were reversible at the end of the 4-week recovery period after the end of delamanid administration. Measurement of vitamin K_1 and vitamin K_2 concentrations in the liver of animals in the 300 mg/kg/day group showed that the concentrations were 87.9% and 70.5%, respectively, of those in the control group at the end of the administration period and 114.3% and 109.7%, respectively, at the end of the recovery period. Based on these, the applicant considered that the effect of delamanid on blood coagulation parameters in mice was related to vitamin K deficiency.

3.(iii).A.(7).2) Repeat-dose toxicity study on hemorrhage in rabbits (4.2.3.7.3-05, 4.2.3.7.3-06)

Placebo (Excipient II) or delamanid (produced by the new manufacturing process; 5, 30, 100 mg/kg/day) was administered orally for 2 weeks to male and female NZW rabbits (n = 5/sex/group). Three each of males and females were added to the placebo and the delamanid 100 mg/kg/day groups as the recovery groups. In the delamanid 100 mg/kg/day group, because of the extremely aggravated conditions observed after the start of treatment, administration was discontinued after 8 days in males and after 10 days in females. As a result, 1 male and 1 female in the delamanid 30 mg/kg/day group and 1 male and 2 females in the delamanid 100 mg/kg/day group died during the administration period. After the discontinuation of treatment, 1 male and 3 females in the delamanid 100 mg/kg/day group died or were moribund-sacrificed. The dead animals were shown to have pallor in palpebral conjunctiva, decreased body weight, decreased food intake, prolonged PT and APTT, decreased hematocrit, decreased hemoglobin, decreased red blood cell count, visceral hemorrhage, increased ratio of hematopoietic parenchyma in the bone marrow, necrosis and fatty degeneration of centrilobular hepatocytes in the liver, vacuolization of proximal tubular epithelium in the kidney, necrosis of the smooth muscle of the aorta, swelling of glomerulosa cells in adrenals, etc. In the delamanid ≥30 mg/kg/day groups. Surviving males and females showed decreased body weight, reduced body weight gain, and decreased food intake, and the surviving males showed pallor in palpebral conjunctiva. In the delamanid 100 mg/kg/day group, males and females had soft feces, prolonged PT and APTT, decreased hematocrit, decreased hemoglobin, decreased red blood cell count, increased reticulocyte count, visceral hemorrhage, fatty degeneration of centrilobular and marginal hepatocytes in the liver, vacuolization of proximal tubular epithelium in the kidney, necrosis of the smooth muscle of the aorta, and increased ratio of hematopoietic parenchyma in the bone marrow; males showed increased creatinine, decreased urea nitrogen, inorganic phosphorus, potassium, and calcium, and prolonged QT; while females showed discoloration foci in palpebral conjunctiva and nictitating membrane, hemosiderin deposition in the spleen, swelling and necrosis of glomerulosa cells in adrenals, localized infiltration of mononuclear cells, swelling of the zona fasciculate and the zona reticularis of adrenal cortex, and vacuolization of cells in the adrenal medulla. Based on these, the NOAEL was determined to be 5 mg/kg/day both in males and in females.

3.(iii).A.(7).3) Study on the mechanism of hemorrhage in rabbits (4.2.3.7.3-04 to 4.2.3.7.3-14)

The result of the 2-week repeat-dose toxicity study on hemorrhage in rabbits (4.2.3.7.3-05 to 4.2.3.7.3-06) suggested that delamanid affected vitamin K-dependent blood coagulation parameters. Therefore, the following studies were conducted to further investigate the effect. Based on the following study results, the applicant considered that the effect of delamanid on the blood coagulation parameter in rabbits (prolongation of blood coagulation time) was due to decreased activities of vitamin K-dependent blood coagulation factors and it was primarily attributable to the metabolite (*S*)-DM-6717 that inhibits vitamin K_1 epoxide reductase activity. In

the context of the decreased activity of vitamin K-independent coagulation factors (factor VIII, factor XII), the applicant considered that the decrease in the activities of vitamin K-independent factors are mild as compared with the changes in the activities of vitamin K-dependent factors and are therefore of no toxicological significance for the body.

(a) Time of onset of the effect on blood coagulation and recovery (4.2.3.7.3-07)

Placebo (Excipient II) or delamanid (produced by the new manufacturing process; 100 mg/kg/day) was administered orally in a single dose or repeatedly for 4 days to female NZW rabbits (n = 4/group). Following the single-dose administration, animals showed reduced body weight gain, decreased food intake, tendency of PT prolongation, and decreased activity of blood coagulation factors II, VII, VIII, IX, and X, but recovered from these changes after the 7-day recovery period. In the 4-day repeated administration, 2 animals in the delamanid group died and surviving animals showed decreased body weight, reduced body weight gain, decreased food intake, prolonged PT and APTT, and decreased activity of blood coagulation factors II, VII, VIII, IX, X, and XII, but recovered from these changes except those of factors II and VII by the end of the 10-day recovery period.

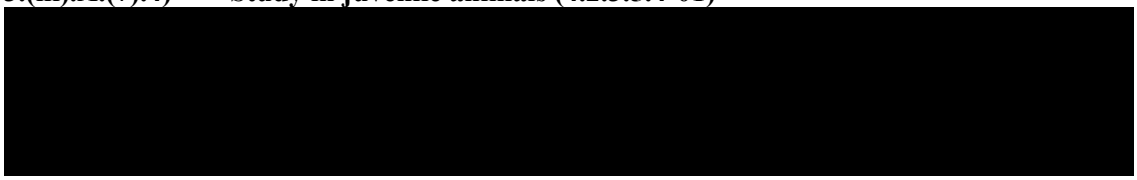
(b) Effect of supplementary administration of vitamin K_1 (4.2.3.7.3-08)

Placebo (excipient II) or delamanid (produced by the new manufacturing process; 100 mg/kg/day), or a combination of delamanid (p.o.)/vitamin K_1 (i.v.) (100/0.5 mg/kg/day or 100/5 mg/kg/day) was administered in a single dose or repeatedly for 3 days to female NZW rabbits (n = 4/group). After a single-dose administration, the following findings were observed in animals: in the delamanid 100 mg/kg/day group, prolonged PT and decreased activity of blood coagulation factors II, VII, IX, and X; in the delamanid 100 mg/vitamin K_1 0.5 mg/kg/day group, decreased activity of blood coagulation factors II, VII, IX, and X; in the delamanid 100 mg/vitamin K_1 5 mg/kg/day group, slightly decreased activity of blood coagulation factor II, decreased activity of factor VII. In 3-day repeated oral administration, animals in the delamanid monotherapy group showed reduced body weight gain, decreased food intake, prolonged PT, and decreased activity of blood coagulation factors II, VII, IX, and X even after the end of the 4-day recovery period, whereas animals in the delamanid 100 mg/vitamin K_1 5 mg/day group showed decreased activity of blood coagulation factors II, VII, IX, and X but recovered from these changes during the 4-day recovery period.

(c) *In vitro* study on the effect of metabolites on blood coagulation in rabbits (4.2.3.7.3-04)

Liver microsomes prepared from female rabbits were incubated in the presence of 0, 1, 10, or 100 μmol/L of delamanid or either of metabolites (*R*)-DM-6701, (*R*)-DM-6702, (*R*)-DM-6703, (*S*)-DM-6717, (*S*)-DM-6718, (4*RS*, 5*S*)-DM-6720, (4*RS*, 5*S*)-DM-6721, and (4*RS*, 5*S*)-DM-6722, and the amount of vitamin K_1 produced from vitamin K_1 epoxide was measured to evaluate the inhibitory effect of these compounds against the activity of vitamin K_1 epoxide reductase. (*S*)-DM-6717, (*R*)-DM-6701, and (*S*)-DM-6718 inhibited the formation of vitamin K_1. In particular, (*S*)-DM-6717 inhibited the activity of vitamin K_1 epoxide reductase by ≥50% with IC_{50} of 76 μmol/L. (*R*)-DM-6701 and (*S*)-DM-6718 at 100 μmol/L inhibited the enzyme by 29.9% and 38.0%, respectively. When each of these metabolites was administered orally to rabbits and the effects on blood coagulation factors and on plasma concentrations were investigated, (*S*)-DM-6717 was found to markedly decrease PT and the activity of blood coagulation factor VII.

3.(iii).A.(7).4) Study in juvenile animals (4.2.3.5.4-01)



[redacted]. During the lactation period, 1 male in the placebo group and 1 male and 2 females in the delamanid 300 mg/kg group died. There were no histopathological or necropsy findings allowing the presumption of the cause of the death in animals in the delamanid 300 mg/kg group, precluding the identification of the cause of death. Males in the delamanid ≥30 mg/kg/day groups showed decreased food intake and reduced body weight gain, males and females in the delamanid 300 mg/kg/day group showed prolonged PT and APTT, and females in the same group showed enhanced activities, and mating animals in the delamanid 300 mg/kg/day group showed a decreased number of luteal bodies. The decreased number of luteal bodies was observed in only 2 of 10 animals in the 300 mg/kg/day group, and no abnormality in the estrous cycle was observed in any of the animals in the 300 mg/kg/day group. In addition, no changes in the number of luteal bodies were observed in fertility studies or in pre- and post-natal studies in rats. Based on these results, the applicant considered that the decreases in the number of luteal bodies were incidental findings.

3.(iii).A.(7).5) Phototoxicity studies (4.2.3.7.7-01)

Mouse-derived BALB/3T3 fibroblasts were irradiated with UVA (5 J/cm^2) in the presence of delamanid (2.13-31.6 μg/mL). UVA irradiation did not affect the viability of the cells.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Effect on blood coagulation system

Delamanid was shown to affect the blood coagulation system in mice, rats, and rabbits. The effect was considered due to the decreased vitamin K in the liver in rodents (mice, rats) and the decreased activity in vitamin K-dependent coagulation factors in rabbits. Therefore, PMDA asked the applicant to explain the safety in humans.

The applicant explained as follows:

The cause of the decreased vitamin K in the liver of rodents was not identified in the study on the mechanism of hemorrhage in mice (4.2.3.7.3-01), which did not show any effect of delamanid on food intake, indicating that there is no significant difference in the intake of food-derived vitamin K between the delamanid-treated group and the untreated group. Taking account of the profiles of metabolites in mice [see "3.(ii).A.(3).2) Metabolites in plasma and tissues"] and the *in vitro* inhibitory effect of each metabolite against vitamin K epoxide reductase (4.2.3.7.3-04), the exposure to DM-6717, which is considered to be the causative substance of hemorrhagic tendency in rabbits, is extremely low in rodents. Therefore, the blood coagulation system was unlikely to have been affected by any specific metabolite but it was rather affected by delamanid per se. The safety margins of delamanid in the effect on blood coagulation system observed in rodents were 1.7 (male) and 6.7 (female) times in mice (in 13-week repeat-dose administration) and 4.3 (male) and 16.7 (female) times in rats (in 26-week repeat-dose administration), with the effect on blood coagulation system being more marked in males than in females. Male rodents are known to be highly susceptible to vitamin K deficiency.[61)]

In rabbits, decreased activities of vitamin K-dependent blood coagulation factors II, VII, IX, and X are considered to affect blood coagulation and were caused by the high exposure to (*S*)-DM-6717 that inhibits vitamin K epoxide reductase. However, in humans, $AUC_{0\text{-}24h}$ of DM-6717 is 1142 ng·h/mL with a safety margin of 26.4 times as compared with $AUC_{0\text{-}24h}$ of DM-6717 (30,116 ng·h/mL) at the NOAEL in rabbits (10 mg/kg/day, Study 018762), and this safety margin is considered sufficient.

Also the results of clinical studies (Study 242-[redacted]-204, Study 242-[redacted]-208) did not show any clear effect of delamanid on PT or APTT, and the frequencies of bleeding tendency-related adverse

61) Metta VC and Jonson BC, *J.Nutr.* 1960;72:455-458. Mellette SJ, *Am J Clin Nutr.* 1961;9:109-116.

events (e.g., anaemia, haematuria, haemoptysis, haemorrhage subcutaneous, or haematuria) after the administration of delamanid were low, showing no significant difference between the delamanid group and the placebo group. Based on these results, the applicant considered that the blood coagulation system-related toxicity observed in animals is unlikely to occur in humans.

PMDA considers as follows:
In light of the results of clinical studies, the findings on the blood coagulation system observed in toxicity studies are unlikely to pose a serious risk in the clinical use of delamanid. However, the mechanism of a delamanid-induced decrease in vitamin K in rodents remains unclear, and the comparison of the exposure levels at the recommended clinical dosage did not fully establish a sufficient safety margin. Therefore, information on hemorrhage in rodents due to a decreased level of vitamin K associated with the use of delamanid should be provided in the package insert. Since there were no cases of concomitant use of delamanid with vitamin K inhibitors such as warfarin in clinical studies, the effect of concomitant use is currently unknown. Therefore, information on the concomitant use with vitamin K inhibitors such as warfarin should be collected in an appropriate manner in post-marketing surveillance, etc.

3.(iii).B.(2) Carcinogenicity of metabolites
The metabolite DM-6718 is detected at a level exceeding 10% of total delamanid dose, and its exposure level in carcinogenicity studies in mice and rats ($AUC_{0\text{-}24h}$; 31.2-171.0 ng·h/mL in mice, 29.2 ng·h/mL in rats) is below the exposure level at the recommended clinical dosage ($AUC_{0\text{-}24h}$ 2959 ng·h/mL[57)]). Based on these findings, PMDA asked the applicant to explain the carcinogenicity of DM-6718.

The applicant explained as follows:
As genotoxicity studies on (*S*)-DM-6718, a reverse mutation assay in *Salmonella typhimurium* and a bone-marrow micronucleus assay in male rats were conducted. In the reverse mutation assay in *Salmonella typhimurium*, (*S*)-DM-6718 did not induce gene mutation until 5000 μg/mL. In the bone-marrow micronucleus assay in male rats, (*S*)-DM-6718 did not induce chromosomal injury, and $AUC_{0\text{-}24h}$ in the group receiving the maximum dose of 8 mg/kg/day was 58,850 ng·h/mL, which was 19.9 times $AUC_{0\text{-}24h}$[57)] observed at the recommended clinical dosage. Moreover, an *in silico* assessment of DM-6718 did not indicate the presence of a structural alert suggestive of carcinogenicity. In addition, in the 39-week repeated oral dose toxicity study in dogs (4.2.3.2-04) in which animals were exposed to a high level of DM-6718, $AUC_{0\text{-}24h}$ of DM-6718 in animals receiving the maximum dose of 30 mg/kg/day was 11,379.6 ng·h/mL in males and 10,784.5 ng·h/mL in females at Week 39 of administration, which was 3.6 (male) and 3.8 (female) times higher than $AUC_{0\text{-}24h}$ at the recommended clinical dosage,[57)] but a histopathological examination of these animals showed neither necrotic lesions nor proliferative lesions. Based on the above, the applicant considers that DM-6718 is unlikely to pose any carcinogenic risk in clinical use.

PMDA considers as follows:
Because carcinogenicity studies in mice and rats (4.2.3.4.1-02, 4.2.3.4.1-03) demonstrated low exposure to DM-6718, the carcinogenicity of DM-6718 has not been evaluated sufficiently. However, taking account of the fact that there were no events suggestive of carcinogenic risk of DM-6718 in genotoxicity studies on metabolites (4.2.3.3.1-04, 4.2.3.3.2-03), in the 39-week repeat-dose toxicity study in dogs (4.2.3.2-04), and in the *in silico* evaluation, and considering the seriousness of the indicated disease, there should be no significant problem in the clinical use of delamanid.

3.(iii).B.(3) Fetal toxicity
The proposed package insert (draft) contains, in the "Use during Pregnancy, Delivery or Lactation" section, the description "the drug should be used in pregnant women or in women who may

possibly be pregnant only if the expected therapeutic benefit outweighs the possible risks associated with treatment."

PMDA considers that delamanid should be contraindicated in pregnant women or in women who may possibly be pregnant for the following reasons, and instructed the applicant to contraindicate delamanid in these patients and to elaborate the findings in embryo-fetal development studies in the "Use during Pregnancy, Delivery or Lactation" section in the package insert. The applicant agreed and took appropriate measures.

- The embryo-fetal toxicity study of delamanid in rabbits was conducted only at an exposure level of approximately 1 times that in humans because of the toxicity of delamanid in parent animals. However, increased frequency of early resorption of embryos was observed at the exposure level of 1.0 times that in humans, indicating the effect on embryonic development.

- External anomaly, visceral variation, and skeletal variation (safety margin, 3.8 fold) were observed in the study on the effect of metabolite DM-6702 on embryofetal development, and effects on fetuses such as external anomaly (safety margin, 0.9 fold) were observed in the study on the effect of metabolite DM-6718 on embryofetal development.

4. Clinical data

4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods

4.(i).A Summary of the submitted data

[redacted]. In phase I studies conducted during the early stage of the development of the product, tablets manufactured using the drug substance produced by the old manufacturing process (Tablet A) were used. In order to improve the bioavailability (BA) of delamanid and thereby to reduce the variation in plasma delamanid concentration, delamanid tablets were developed using the drug substance produced by the new manufacturing process.[62)] In this application, data of 2 studies on food effect using Tablet A were submitted. In this section, data of studies using Tablet A are omitted. Data of the following pharmacokinetic studies on delamanid were submitted: 2 Japanese phase I studies (food effect was investigated in both studies), 8 foreign phase I studies (food effect was investigated in 2 studies. 3 drug interaction studies are included), 4 phase II studies, and data of population pharmacokinetic (PPK) analysis based on the results of phase I and phase II studies.

62) Pharmacokinetic parameters in Study 242-[redacted]-101 using delamanid and in the clinical pharmacology study using delamanid Tablet A, both following a single oral administration under identical conditions, were as follows. BA of delamanid was higher following the administration of delamanid than following the administration of Tablet A.
- 100 mg under fasted conditions: delamanid, C_{max} 49.10 ng/mL, $AUC_{0-\infty}$ 715.4 ng·h/mL; Tablet A, C_{max} 20.92 ng/mL, $AUC_{0-\infty}$ 213.1 ng·h/mL
- 200 mg under fasted conditions: delamanid, C_{max} 60.05 ng/mL, $AUC_{0-\infty}$ 1100 ng·h/mL; Tablet A, C_{max} 33.29 ng/mL, $AUC_{0-\infty}$ 495.3 ng·h/mL
- 200 mg after standard diet: delamanid, C_{max} 205.4 ng/mL, $AUC_{0-\infty}$ 3153 ng·h/mL; Tablet A, C_{max} 169.5 ng/mL, $AUC_{0-\infty}$ 2742 ng·h/mL
- 400 mg after standard diet: delamanid, C_{max} 250.6 ng/mL, $AUC_{0-\infty}$ 4304 ng·h/mL; Tablet A, C_{max} 172.4 ng/mL, $AUC_{0-\infty}$ 2814 ng·h/mL
- 400 mg after high fat diet: delamanid, C_{max} 384.5 ng/mL, $AUC_{0-\infty}$ 7250 ng·h/mL; Tablet A, C_{max} 263.2 ng/mL, $AUC_{0-\infty}$ 4610 ng·h/mL

LC/MS/MS was used to measure plasma and urinary delamanid concentrations.[63] Accelerator mass spectrometry was used to measure radioactivity concentration in the plasma and blood in Study 242-[redacted]-102, and a liquid scintillation counter was used to measure radioactivity in urine and feces.

Pharmacokinetic parameters are expressed in geometrical means unless specified otherwise.

4.(i).A.(1) *In vitro* studies in human samples

The following *in vitro* studies were conducted using human biomaterials: a study on human serum protein binding, *in vitro* metabolism studies using human liver microsomes, liver S9 fraction, human CYP-expressing cells, and human plasma, and *in vitro* CYP inhibition and induction studies using human liver microsomes or primary cultured hepatocytes [for the summary of study results, see "3.(ii).A.(2) Distribution," and "3.(ii).A.(3) Metabolism"].

4.(i).A.(2) Studies in healthy adult subjects

4.(i).A.(2).1) Phase I single dose study in Japanese healthy adult subjects (5.3.3.1-01, Study 242-[redacted]-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A pharmacokinetic study was conducted involving Japanese healthy male adults (42 subjects included in pharmacokinetic assessment, 6 subjects per group) in which delamanid was orally administered in a single dose at 50, 100, 200, or 400 mg under fasted conditions, at 200 mg or 400 mg after intake of the standard diet,[64] or at 400 mg after intake of a high fat diet.[65] The results were as shown in Table 14. C_{max} and $AUC_{0-\infty}$ of delamanid in plasma were non-linear under fasted conditions. C_{max} and $AUC_{0-\infty}$ after fed administration were higher than those after fasted administration, and C_{max} and $AUC_{0-\infty}$ after the high fat diet were higher than those after the intake of standard diet.

[63] The lower limit of quantitation in the assay method used in each biopharmaceutic study and clinical pharmacology study is as follows.
- Studies 242-[redacted]-001, 242-[redacted]-101, 242-[redacted]-001, 242-[redacted]-801-01, 242-[redacted]-802-02, and 242-[redacted]-211: 1.00 ng/mL or 1.000 ng/mL (plasma), 5.000 ng/mL (urine)
- Study 242-[redacted]-101: 0.250 ng/mL (delamanid), or 0.105 to 0.209 ng/mL (metabolites)
- Study 242-[redacted]-102: 1.000 ng/mL (delamanid), or 1.000 ng/mL (metabolites)
- Studies 242-[redacted]-204, 242-[redacted]-208, 242-[redacted]-202, 242-[redacted]-209, and 242-[redacted]-212: 1.00 ng/mL

[64] Total calories, 555.3 kcal; fat, 15.6 g

[65] Total calories, 913.4 kcal; fat, 54.4 g

Table 14. Pharmacokinetic parameters of delamanid following a single oral dose of delamanid (50-400 mg) in Japanese healthy adults

Dose	Treatment group [a)]	N	C_{max} (ng/mL)	t_{max} [b)] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Geometric mean ratio [90% CI]	
							C_{max}	$AUC_{0-\infty}$
50 mg	Male, fasted	6	70.3 (45.6)	3.0 [2.0, 5.0]	991.3 (43.2)	21.4 (14.8)	NA	NA
100 mg	Male, fasted	6	72.3 (41.8)	3.0 [2.0, 4.0]	1101.9 (39.1)	18.5 (34.9)	NA	NA
200 mg	Male, fasted	6	109.7 (31.3)	3.5 [2.0, 4.0]	1871.8 (41.1)	27.7 (27.5)	Standard diet/ fasted 1.89 [1.37, 2.61]	Standard diet/ fasted 1.79 [1.26, 2.53]
	Male, standard diet	6	208.0 (33.1)	4.5 [3.0, 5.0]	3243.2 (27.1)	20.6 (22.7)		
400 mg	Male, fasted	6	165.07 (22.2)	3.5 [2.0, 4.0]	2820.0 (13.0)	20.9 (26.5)	Standard diet/ fasted 1.42 [1.10, 1.84]	Standard diet/ fasted 1.30 [1.08, 1.58]
	Male, standard diet	6	238.2 (29.4)	4.0 [3.0, 4.0]	3740.2 (26.4)	26.1 (52.8)	High fat diet/ fasted 3.15 [2.51, 3.95]	High fat diet/ fasted 2.68 [2.30, 3.13]
	Male, high fat diet	6	520.6 (22.6)	4.5 [3.0, 5.0]	7592.7 (16.6)	27.9 (14.8)	High fat diet/ standard diet 2.21 [1.70, 2.87]	High fat diet/ standard diet 2.06 [1.67, 2.53]

Mean (coefficient of variation [CV%])
t_{max}: Time to maximum plasma concentration, $t_{1/2}$; Elimination half-life in blood in the terminal phase
NA: Not assessable, ND: Not determined
a) Delamanid was administered with 200 mL of water under fasted conditions or within 30 minutes after intake of breakfast (standard diet or high fat diet)
b) Median [range]

After a single oral dose of delamanid (100 mg) under fasted conditions, C_{max} and $AUC_{0-\infty}$ values of metabolites were 2.28 ng/mL and 381.4 ng·h/mL, respectively, for DM-6704;[66)] 0.0394 ng/mL and 766.5 ng·h/mL, respectively, for DM-6705; and 0.840 ng/mL and 544.6 ng·h/mL, respectively, for DM-6706.

4.(i).A.(2).2) Phase I single and multiple dose study in Japanese healthy adult subjects (5.3.3.1-03, Study 242-[redacted]-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid (100, 200, or 400 mg) was orally administered after the intake of the standard diet[64)] in a single dose or QD for 10 days to Japanese healthy male adults (18 subjects included in pharmacokinetic assessment, 6 subjects per group) to assess pharmacokinetics. Pharmacokinetic parameters after the single-dose or multiple-dose administration of delamanid were as shown in Table 15. C_{max} and AUC_{0-24h} values of delamanid in plasma were non-linear. At all doses tested, plasma delamanid concentrations almost reached a steady state on Day 10, with the ratios of accumulation (R_{ac}) after 10-day administration being 1.45 to 1.98 (C_{max}) and 1.82 to 2.70 (AUC_{0-24h}).

66) Regarding the delamanid metabolites DM-6704, DM-6705, and DM-6706, their *R*-optical isomers were initially measured using their racemates DM-6701, DM-6702, and DM-6703 as the standards. In "3.(ii) Summary of pharmacokinetic studies," *R*-optical isomers of DM-6704, DM-6705, and DM-6706 were measured using (*R*)-DM-6701, (*R*)-DM-6702, and (*R*)-DM-6703 as the standards.

Table 15. Pharmacokinetic parameters of delamanid in Japanese healthy adults receiving single or multiple oral doses of delamanid (100-400 mg)

Dose		N	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-24h} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
Single dose	100 mg	6	201.13 (17.5)	4.00 [4.0, 5.0]	1898.2 (22.1)	25.62 (35.2)	511.5 (14.4)
	200 mg	6	212.37 (26.9)	4.50 [2.0, 5.0]	1908.8 (15.6)	29.40 (18.7)	963.3 (19.4)
	400 mg	6	267.75 (12.0)	4.00 [4.0, 4.0]	2754.3 (17.6)	25.80 (14.3)	1346.8 (22.4)
Multiple dose[b)]	100 mg	6	327.73 (16.5)	4.50 [4.0, 5.0]	4207.5 (20.9)	26.38 (32.3)	385.5 (10.1)
	200 mg	6	421.96 (20.1)	4.00 [3.0, 5.0]	5230.0 (16.2)	33.00 (10.4)	578.4 (12.5)
	400 mg	6	384.57 (19.9)	4.00 [3.0, 4.0]	5015.7 (19.3)	31.95 (31.7)	1286.2 (11.9)

Mean (CV%)
CL/F: Apparent clearance
a) Median [range]
b) Value on Day 10

When delamanid (100 mg) was orally administered after the intake of the standard diet QD for 10 days, the exposure level (C_{max}, AUC_{0-24h}) of each metabolite was as shown in Table 16.

Table 16. Pharmacokinetic parameters of metabolites in plasma in Japanese healthy adults receiving multiple oral doses of delamanid (100 mg)

Metabolite	N	Day of administration	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)
DM-6704	6	Day 1	1.49 ± 1.49	9.22 ± 9.49
		Day 10	17.60 ± 11.96	375.93 ± 246.17
DM-6705	6	Day 1	2.32 ± 0.42	43.48 ± 10.50
		Day 10	28.20 ± 7.42	621.18 ± 171.53
DM-6706	6	Day 1	0.77 ± 0.96	1.12 ± 2.74
		Day 10	13.51 ± 4.72	293.30 ± 101.18
DM-6717	6	Day 1	0	0
		Day 10	1.75 ± 1.16	11.98 ± 18.56
DM-6718	6	Day 1	0	0
		Day 10	7.99 ± 3.17	85.56 ± 30.14
DM-6720	6	Day 1	0	0
		Day 10	8.45 ± 2.18	116.91 ± 30.55
DM-6721	6	Day 1	0	0
		Day 10	0.84 ± 0.96	12.19 ± 16.82
DM-6722	6	Day 1	0	0
		Day 10	6.44 ± 3.81	137.96 ± 78.69

Mean ± SD

4.(i).A.(2).3) Phase I single- and multiple-dose study in foreign healthy adult subjects conducted in the UK (5.3.1.1-02, Study 242-[redacted]-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid was orally administered in a single dose at 100, 200, or 400 mg under fasted conditions, at 200 or 400 mg after intake of the standard diet,[67)] or at 400 mg after the intake of a high fat diet[68)] to foreign healthy male and female adults (42 subjects included in pharmacokinetic assessment, 6 subjects per group) to evaluate pharmacokinetics. The results were as shown in Table 17. C_{max} and $AUC_{0-\infty}$ of delamanid in plasma under fasted conditions were non-linear. C_{max} and $AUC_{0-\infty}$under fed conditions were higher than those under fasted conditions, and C_{max} and $AUC_{0-\infty}$ after the intake of the high fat diet were higher than those after the intake of the standard diet.

67) Total calories, 552.0 kcal; fat, 16.6 g
68) Total calories, 725.0 kcal; fat, 55.6 g

Table 17. Pharmacokinetic parameters of delamanid following single oral dose of delamanid (100-400 mg) to foreign healthy adults

Dose	Treatment group [a)]	N	C_{max} (ng/mL)	t_{max} [b)] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Geometric mean ratio [90% CI]	
							C_{max}	$AUC_{0-\infty}$
100 mg	Male, fasted	6	49.1 (35.1)	2.0 [1.0, 4.0]	715.4 (35.9)	23.3 (19.8)	NA	NA
200 mg	Female, fasted	6	80.0 (27.0)	3.0 [2.0, 4.0]	1567 (31.9)	37.4 (21.3)	NA	NA
	Male, fasted	6	60.1 (32.9)	2.5 [1.0, 4.0]	1100 (35.4)	26.6 (17.4)	Standard diet/ fasted 3.49 [2.56, 4.78]	Standard diet/ fasted 2.91 [2.02, 4.21]
	Male, standard diet	6	205.4 (25.6)	4.0 [3.0, 5.0]	3153 (33.5)	31.6 (36.5)		
400 mg	Male, fasted	6	117.5 (28.7)	2.50 [1.0, 4.0]	2086 (38.5)	25.5 (26.2)	Standard diet/ fasted 2.20 [1.76, 2.74]	Standard diet/ fasted 2.17 [1.65, 2.84]
	Male, standard diet	6	250.6 (14.2)	3.0 [2.0, 5.0]	4304 (9.5)	21.5 (12.8)	High fat diet/ fasted 3.37 [2.70, 4.20]	High fat diet/ fasted 3.53 [2.69, 4.62]
	Male, high fat diet	6	384.5 (14.7)	3.5 [1.0, 5.0]	7250 (31.3)	33.7 (13.8)	High fat diet/ standard diet 1.53 [1.23, 1.91]	High fat diet/ standard diet 1.63 [1.24, 2.13]

Mean (CV%)
NA: Non-assessable
a) Delamanid was administered together with 240 mL of water under fasted conditions or within 5 minutes after intake of breakfast (standard diet or high fat diet)
b) Median [range]

In a separate study, delamanid (100, 200, or 400 mg) was orally administered after the intake of the standard diet[67)] QD for 10 days to foreign healthy adult male and female subjects (36 subjects included in the pharmacokinetic analysis, 6 subjects per group) to assess pharmacokinetics. The results of multiple doses of delamanid were as shown in Table 18. C_{max} and AUC_{0-24h} of delamanid in plasma were non-linear. Following the multiple administration, R_{ac} (C_{max}) values were 1.5 to 2.3 and R_{ac} (AUC_{0-24h}) values were 1.8 to 3.2.

Table 18. Pharmacokinetic parameters of delamanid in foreign healthy adults receiving multiple oral doses of delamanid (100-400 mg)

Dose	Treatment group	N	Day of administration	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-24h} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
100 mg	Male, standard diet	6	Day 1	146.5 (33.5)	4.52 [3.00, 5.00]	1542 (33.4)	29.10 (15.6)	556.7 (49.4)
		6	Day 10	212.7 (14.5)	3.50 [2.00, 4.00]	2621 (18.7)	34.62 (16.6)	515.6 (11.0)
	Female, standard diet	6	Day 1	133.7 (10.5)	4.00 [3.03, 4.00]	1130 (21.8)	38.40 (14.9)	700.3 (28.1)
		6	Day 10	194.7 (17.1)	4.00 [2.00, 4.00]	2373 (5.2)	42.79 (17.4)	656.2 (13.1)
200 mg	Male, standard diet	6	Day 1	181.1 (26.7)	3.00 [2.00, 4.00]	1851 (22.9)	27.07 (20.2)	812.1 (7.7)
		6	Day 10	255.0 (18.3)	3.50 [3.00, 5.00]	3259 (20.3)	31.24 (17.7)	776.3 (18.6)
	Female, standard diet	6	Day 1	182.1 (18.1)	4.00 [3.00, 5.02]	1934 (20.8)	39.23 (20.5)	850.9 (31.3)
		6	Day 10	292.8 (25.9)	4.50 [4.00, 5.00]	4075 (19.5)	44.85 (23.5)	801.7 (23.6)
400 mg	Male, standard diet	6	Day 1	275.7 (28.3)	3.50 [1.00, 4.00]	2806 (31.8)	24.91 (27.2)	1399 (29.8)
		5	Day 10	421.8 (26.0)	4.00 [3.00, 5.00]	5851 (41.8)	27.56 (17.1)	1098 (34.1)
	Female, standard diet	6	Day 1	215.6 (32.0)	3.00 [1.02, 4.00]	1888 (29.1)	46.02 (25.1)	1555 (20.2)
		6	Day 10	450.9 (18.6)	4.00 [3.00, 4.00]	5525 (21.4)	45.47 (19.0)	1117 (25.1)

Mean (CV%)
a) Median [range]

4.(i).A.(2).4) Mass balance study in foreign healthy adult subjects conducted in the UK (5.3.4.1-01, Study 242-[redacted]-102 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A capsule containing ^{14}C-labeled delamanid (100 mg) was orally administered in a single dose to 6 foreign healthy male adults after the intake of the standard diet[67)] and absorption, metabolism, and excretion of the administered delamanid were investigated. C_{max} of delamanid in plasma was 49.14 (35.2) ng/mL, accounting for 45.6% of the total radioactivity in plasma. The profiles of metabolites in plasma showed that delamanid was metabolized mainly to DM-6705, and that DM-6705 and delamanid accounted for 18.29% and 11.72%, respectively, of the total radioactivity in plasma 8 hours after administration, and 3.3% and 2.8%, respectively, 72 hours after administration. The half-life ($t_{1/2}$) of delamanid in plasma was 31.9 hours while $t_{1/2}$ of the total radioactivity was 180.0 hours, suggesting that the metabolites are present for a longer time period in plasma as compared with delamanid. Within 196 hours after administration, 92.4% of the total radioactivity was recovered, 89.3% in feces and 3.1% in urine. The main component detected in feces was the unchanged delamanid (52.9%-74.8% of the dose), and DM-6704 (0.4%-11.0%) and DM-6705 (1.0%-3.8%) were detected in 5 of 6 subjects. In urine, delamanid was not detected while DM-6705 was detected at an amount corresponding to 0.14% to 0.22% of the dose.

4.(i).A.(2).5) Phase I single dose study in Chinese healthy adult subjects (5.3.1.1-03, Study 242-[redacted]-801-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid was orally administered in a single dose at 100, 200, or 400 mg under fasted conditions, or at 400 mg after the intake of a high fat diet,[69)] to Chinese healthy male adults (36 subjects included in pharmacokinetic assessment, 9 subjects per group), and pharmacokinetics was evaluated. The results were as shown in Table 19. C_{max} and $AUC_{0-\infty}$ of delamanid in plasma were non-linear. C_{max} and $AUC_{0-\infty}$ of delamanid following the single dose of 400 mg of delamanid after

69) Total calories, 800 to 1000 kcal; fat, 66.4 g

the intake of the high fat diet[69] were higher than those observed following administration under fasted conditions.

Table 19. Pharmacokinetic parameters of delamanid following a single oral dose of delamanid (100-400 mg) to Chinese healthy adults

Dose	Treatment group [a]	N	C_{max} (ng/mL)	t_{max} [b] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)	Geometric mean [90% CI]	
							C_{max}	$AUC_{0-\infty}$
100 mg	Male, fasted	9	80.7 (19.3)	3.0 [2.0, 4.0]	1130 (19.5)	16.6 (28.8)	NA	NA
200 mg	Male, fasted	9	108 (19.2)	2.0 [2.0, 4.0]	1630 (24.2)	22.4 (28.4)	NA	NA
400 mg	Male, fasted	9	126 (26.7)	3.0 [1.0, 6.0]	2010 (26.0)	24.3 (28.8)	High fat diet/ fasted	High fat diet/ fasted
	Male, high fat diet	9	592 (29.7)	4.0 [2.0, 5.0]	9210 (30.4)	25.6 (22.6)	4.68 [3.69, 5.93]	4.51 [3.54, 5.73]

Mean (CV%)
NA: Non-assessable
a) Delamanid was administered together with 200 mL of water under fasted conditions or within 30 minutes after intake of breakfast (high fat diet).
b) Median [range]

4.(i).A.(2).6) Phase I multiple-dose study in Chinese healthy adults (5.3.1.1-04, Study 242-[redacted]-802-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid (100, 200 mg) was orally administered for 10 days to Chinese healthy male and female adults (24 subjects included in the pharmacokinetic analysis, 12 subjects per group) after the intake of the standard diet,[70] and pharmacokinetics was evaluated. The results were as shown in Table 20. After 10-day administration by BID, R_{ac} values were 2.41 to 2.83 (C_{max}) and 3.30 to 3.40 (AUC_{0-12h}).

Table 20. Pharmacokinetic parameters of delamanid following a single dose or multiple BID oral dose of delamanid (100-200 mg) to Chinese healthy adults

Dose		N	C_{max} (ng/mL)	t_{max} [a] (h)	AUC_{0-24h} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
Single dose [b]	100 mg	12	238 (18.2)	3.50 [2.00, 6.00]	3470 (23.3)	ND	ND
	200 mg	12	301 (23.4)	3.50 [2.00, 5.00]	4350 (16.5)	ND	ND
Multiple dose [c]	100 mg BID	12	672 (20.7)	4.00 [3.00, 5.00]	10,100 (18.7)	37.11 (30.3)	344 (14.1)
	200 mg BID	12	709 (27.1)	4.00 [2.00, 8.00]	12,200 (17.7)	37.87 (19.1)	549 (23.1)

Mean (CV%)
ND: Not determined
a) Median [range]
b) Value after the first dose on Day 1 of administration
c) Value after the second dose on Day 10 of administration

4.(i).A.(2).7) Phase I multiple dose study in foreign healthy adults conducted in the US (5.3.3.1-04, Study 242-[redacted]-211 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid (300 mg/day) was orally administered QD, BID, or 3 times daily (TID) to foreign healthy male and female adults (28 subjects included in the pharmacokinetic analysis) after the intake of the standard diet[70] for 10 days, and pharmacokinetics was evaluated. The results were as shown in Table 21. Plasma delamanid concentrations reached a steady state at 10 days of treatment, and steady-state AUC_{0-24h} values were high in the 100 mg TID and 150 mg BID groups, which were 2.02 times and 1.75 times, respectively, as compared with the 300 mg QD group.

[70] Total calories, 550 kcal; fat ≥15.3 g

Table 21. Pharmacokinetic parameters of delamanid in foreign healthy adults receiving 10-day multiple oral doses of delamanid (300 mg)

Dosage regimen	Treatment group	N	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-24h} (ng·h/mL)	CL/F (mL/h/kg)
300 mg QD	Males and females, standard diet	9	412 (12.3)	5.00 [2.03, 6.00]	5840 (17.0)	729 (16.6)
150 mg BID	Male and females, standard diet	10	512 (15.8)	5.00 [1.00, 6.00]	10,200 (15.4)	396 (19.0)
100 mg TID	Males and females, standard diet	9	606 (27.8)	11.92 [10.00, 12.00]	11,800 (17.70)	ND

Mean (CV%)
ND: Not determined
a) Median [range]

4.(i).A.(3) Studies in patients with tuberculosis

4.(i).A.(3).1) Phase II study in foreign patients with sputum smear-positive pulmonary tuberculosis without complications (5.3.3.2-02, Study 242-[redacted]-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid (100, 200, 300, or 400 mg) was administered QD for 14 days to foreign patients with sputum smear-positive pulmonary tuberculosis without complications (43 patients included in the pharmacokinetic analysis) after food intake, and pharmacokinetics was evaluated. The results were as shown in Table 22. R_{ac}s (C_{max}) were 1.41 to 2.00 and R_{ac}s (AUC_{0-24h}) were 1.96 to 2.75.

Table 22. Pharmacokinetic parameters of delamanid in patients with sputum smear-positive pulmonary tuberculosis without complications who received doses of delamanid (100-400 mg)

Dose	N	Day of treatment	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{0-24h} (ng·h/mL)
100 mg	11	Day 1	123.80 (23.4)	4.00 [2.08, 7.97]	1273.79 (33.6)
	11	Day 14	174.55 (46.8)	3.97 [3.90, 6.08]	2500.22 (58.2)
200 mg	11	Day 1	146.71 (37.7)	5.97 [1.93, 7.97]	1763.78 (36.5)
	10	Day 14	227.81 (37.0)	4.03 [2.08, 11.98]	3550.60 (43.7)
300 mg	10	Day 1	176.28 (33.5)	4.08 [3.97, 6.08]	1998.18 (46.6)
	10	Day 14	351.74 (25.6)	4.96 [2.08, 7.93]	5488.70 (27.0)
400 mg	11	Day 1	181.22 (32.7)	5.88 [2.08, 8]	2162.75 (39.2)
	11	Day 14	285.86 (32.3)	4.08 [2.25, 12]	4877.25 (43.1)

Mean (CV%)
a) Median [range]

4.(i).A.(3).2) Phase II studies in patients with multidrug-resistant pulmonary tuberculosis (5.3.5.1-01, Study 242-[redacted]-204 [[redacted] 20[redacted] to [redacted] 20[redacted]]; 5.3.5.2-01, Study 242-[redacted]-208 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid (100 mg BID or 200 mg BID) was administered in combination with an optimized background treatment regimen (OBR) for 56 days to 321 patients with multidrug-resistant pulmonary tuberculosis, and pharmacokinetics of delamanid and its metabolites in plasma was evaluated. Pharmacokinetic parameters of delamanid in plasma in this study were as shown in Table 23. The plasma delamanid concentration reached a steady state within 14 days of treatment. At the steady state, R_{ac}s (C_{max1}) were 3.37 to 5.90, R_{ac}s (C_{max2}) were 2.81 to 2.92, and R_{ac}s (AUC_{0-24h}) were 3.41 to 3.52.

Table 23. Pharmacokinetic parameters of delamanid in plasma in patients with multidrug-resistant pulmonary tuberculosis who were treated with delamanid (100, 200 mg) and OBR for 56 days

Dose [a]	Day of treatment	N	C_{max1} [a] (ng/mL)	C_{max2} [a] (ng/mL)	t_{max1} [a),b] (h)	t_{max2} [a),b] (h)	AUC_{0-24h} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (mL/h/kg)
100 mg	Day 1	159	135 (40.7)	151 (40.1)	4.00 [1.85, 10.0]	4.00 [1.7, 14.0]	2441 (36.1)	ND	ND
	Day 14	149-150	369 (37.1)	361 (35.3)	3.02 [0.00, 10.0]	4.00 [1.9, 14.0]	7234 (32.4)	ND	602 (47.8)
	Day 28	144-145	404 (35.7)	381 (33.5)	3.02 [0.00, 10.0]	4.00 [2.0, 14.0]	7700 (30.2)	ND	546 (36.5)
	Day 56	66-144	414 (39.9)	400 (40.5)	3.02 [0.00, 9.97]	4.00 [2.0, 14.0]	7925 (37.5)	37.8 (34.3)	597 (73.6)
200 mg	Day 1	159	187 (39.7)	228 (40.2)	4.00 [2.00, 10.0]	4.00 [1.9, 14.0]	3598 (36.5)	ND	ND
	Day 14	153	547 (36.5)	513 (34.7)	3.00 [0.00, 10.0]	4.00 [2.0, 14.0]	10,490 (32.2)	ND	825 (45.1)
	Day 28	150	599 (37.0)	560 (35.0)	3.00 [0.00, 10.0]	4.00 [2.0, 14.0]	11,251 (32.2)	ND	764 (40.8)
	Day 56	59-145	611 (35.6)	588 (36.2)	3.02 [0.00, 10.0]	4.00 [2.0, 14.0]	11,837 (33.6)	38.3 (37.5)	801 (93.6)

Mean (CV%)
ND: Not determined
a) C_{max1}: C_{max} after the first dose on Day 1, C_{max2}: C_{max} after the second dose on Day 1, t_{max1}: t_{max} after the first dose on Day 1, t_{max2}, t_{max} after the second dose on Day 1
b) Median [range]

In all the treatment groups, the metabolites[71)] of delamanid were eliminated only gradually ($t_{1/2}$ on Day 56, 134-424 hours), with the plasma metabolite concentrations increasing up to Day 56. On Day 56 of treatment with delamanid (100 mg) + OBR or delamanid (200 mg) + OBR, C_{max} values of the main metabolite DM-6705 were 151 ng/mL and 233 ng/mL, respectively, and AUC_{0-24h} values were 3125 ng·h/mL and 4907 ng·h/mL, respectively. Plasma metabolite concentrations were measured on Day 84 (28 days after the end of administration). The results showed that DM-6705 had almost been eliminated.

Delamanid + OBR were administered for a maximum of 6 months (26 weeks) to 213 patients with multidrug-resistant pulmonary tuberculosis who had completed Study 242-[redacted]-204 and the pharmacokinetics of delamanid and of its metabolites was evaluated. At time points post-dose (1.6-13.9 hours post-dose; median, 2.0 hours) from Week 6 through Week 26, the median plasma delamanid concentrations were 365 to 408 ng/mL in the delamanid 100 mg BID + OBR group and 378 to 540 ng/mL in the delamanid 200 mg BID + OBR group. Plasma concentrations of DM-6704, DM-6705, and DM-6706 reached a steady state by Weeks 6 to 10, and DM-6717, DM-6718, DM-6720, DM-6721, and DM-6722 reached a steady state by Week 14.

4.(i).A.(3).3) Phase II study in patients with multidrug-resistant pulmonary tuberculosis refractory to conventional treatment (5.3.5.2-02, Study 242-[redacted]-210 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Delamanid (250 mg BID) + OBR or delamanid (300 mg BID) + OBR was administered for a maximum of 6.5 months to 10 patients with multidrug-resistant pulmonary tuberculosis refractory to conventional treatment, and the pharmacokinetics of delamanid and of its metabolites in plasma was evaluated. Plasma delamanid concentration reached a steady state by Day 14 and, at the steady state, R_{ac} (C_{max}) values of delamanid were 1.42 to 2.10 and R_{ac} (AUC_{0-24h}) values were 1.93 to 2.98. Plasma concentrations of DM-6704, DM-6705, and DM-6706 reached a steady state by Day 56. AUC_{0-24h} of DM-6705 56 days after the start of administration was 3100 ng·h/mL in the delamanid 250 mg + OBR group and 3150 ng·h/mL in the delamanid 300 mg + OBR group.

71) DM-6704 [(*R*)-DM-6701], DM-6705 [(*R*)-DM-6702], DM-6706 [(*R*)-DM-6703], DM-6717, DM-6718, DM-6720, DM-6721, and DM-6722

4.(i).A.(4) Studies on drug interactions

4.(i).A.(4).1) Study of drug interactions with anti-tuberculosis drugs (5.3.3.4-01, Study 242-[redacted]-202 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Drug interactions of delamanid with anti-tuberculosis drugs INH/RFP/PZA and EB were investigated in foreign healthy adults (30 subjects were included in pharmacokinetic assessment). The results were as shown in Table 24. C_{max} and $AUC_{0\text{-}24h}$ values of delamanid and the metabolites were decreased by approximately 15% to 45% by concomitant use with anti-tuberculosis drugs.
The decreased C_{max} and $AUC_{0\text{-}24h}$ of delamanid and the metabolites were explained as follows: the concomitant use of delamanid with INH/RFP/PZA and EB led to RFP-mediated induction of CYP isozymes and also to a decrease in the absorption of delamanid caused by its reduced solubility that was attributed to the simultaneous use of as many as 15 tablets of anti-tuberculosis drugs, thereby resulting in decreased BA of delamanid.
The exposure to EB was increased by approximately 25% by concomitant use with delamanid, but no particularly significant safety problems were observed in the INH/RFP/PZA and EB co-administration group as compared with the placebo co-administration group. Based on the results, the applicant explained that the concomitant use would not pose any clinical problems.

Table 24. Drug interactions between delamanid and anti-tuberculosis drugs

Analyte	Dosage regimen [a)]	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Ratio of pharmacokinetic parameter [b)] [90% CI]	
				C_{max}	$AUC_{0\text{-}24h}$
Delamanid	Delamanid + placebo	476 (24.9)	5950 (24.2)	0.577 [0.49, 0.68]	0.525 [0.439, 0.628]
	Delamanid/(INH/RFP/PZA + EB)	270 (14.4)	3110 (22.7)		
RFP	Placebo/(INH/RFP/PZA + EB)	11,200 (34.7)	48,200 (37.8)	1.141 [0.78, 1.68]	1.071 [0.687, 1.670]
	Delamanid/(INH/RFP/PZA + EB)	13,200 (40.9)	55,900 (51.1)		
INH	Placebo/(INH/RFP/PZA + EB)	5540 (30.5)	20,000 (39.7)	0.854 [0.68, 1.08]	0.588 [0.40, 0.87]
	Delamanid/(INH/RFP/PZA + EB)	4620 (21.2)	12,100 (56.9)		
PZA	Placebo/(INH/RFP/PZA + EB)	49,700 (21.0)	488,000 (18.5)	1.043 [0.88 1.24]	1.074 [0.89, 1.30]
	Delamanid/(INH/RFP/PZA + EB)	51,400 (17.6)	533,000 (26.4)		
EB	Placebo/(INH/RFP/PZA + EB)	35,600 (26.1)	18,200 (17.6)	1.268 [1.05, 1.54]	1.226 [1.04, 1.44]
	Delamanid/(INH/RFP/PZA + EB)	4450 (18.5)	22,400 (21.3)		

Pharmacokinetic parameter values are given as a mean (CV%).

a) Delamanid: Delamanid 200 mg QD for 15 days (13 subjects), Delamanid/(INH/RFP/PZA + EB): Delamanid 200 mg QD for 15 days, INH/RFP/PZA 720/300/1800 mg QD and EB 1100 mg QD for 19 days (8 subjects), Placebo/(INH/RFP/PZA + EB): INH/RFP/PZA 720/300/1800 mg QD + EB 1100 mg QD for 19 days (8 subjects)
Delamanid was administered together with 240 mL of water within 30 minutes after the start of intake of the standard breakfast. INH/RFP/PZA and EB were administered at 1 hour before the start of breakfast. Pyridoxine 25 mg was administered QD to all subjects.

b) The ratio of each pharmacokinetic parameter was calculated as [delamanid and (INH/RFP/PZA + EB)]/[delamanid and placebo] or [delamanid and (INH/RFP/PZA + EB)]/[placebo and (INH/RFP/PZA + EB)]

4.(i).A.(4).2) Study on drug interactions with anti-HIV drugs (5.3.3.4-02, Study 242-[redacted]-209 [[redacted] 20[redacted] to [redacted] 20[redacted]]; 5.3.3.4-03, Study 242-[redacted]-212 [[redacted] 20[redacted] to [redacted] 20[redacted]]

Drug interactions of delamanid with efavirenz (EFV), tenofovir (TFV), or lopinavir (LPV)/ritonavir (RTV) were investigated in foreign healthy adults (59 subjects were included in the pharmacokinetic analysis)[72)] (Study 242-[redacted]-209). In a separate study (Study 242-[redacted]-212),

72) After the study initiation, nervous system- and psychiatric disorder-related adverse events were observed in all subjects in the delamanid/EFV group, which resulted in the discontinuation of EFV administration. Therefore, pharmacokinetics of EFV was not evaluated.

interactions of delamanid with EFV were investigated in foreign healthy adults (28 subjects were included in the pharmacokinetic analysis). The results were as shown in Table 25. EFV, TFV, and LPV/RTV did not significantly affect C_{max} or $AUC_{0\text{-}24h}$ of delamanid. In contrast, concomitant use with LPV/RTV increased C_{max} and $AUC_{0\text{-}24h}$ of the metabolite DM-6704 by 74.7% and 72.9%, respectively. (C_{max}, 68.2 [48.8] ng/mL in the delamanid monotherapy group, 120 [53.3] ng/mL in the delamanid + LPV/RTV group; $AUC_{0\text{-}24h}$, 1470 [47.1] ng·h/mL in the delamanid monotherapy group, 2570 [53.8] ng·h/mL in the delamanid + LPV/RTV group). The concomitant use of delamanid did not affect C_{max} or $AUC_{0\text{-}24h}$ of each anti-HIV drug.

Table 25. Drug interactions between delamanid and anti-HIV drugs

Concomitant drug	Analyte	Dosage regimen[a)]	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	Ratio of pharmacokinetic parameter[b)] [90% CI]	
					C_{max}	$AUC_{0\text{-}24h}$
EFV	Delamanid	Delamanid	391 (16.9)	4382 (17.2)[c)]	0.995 [0.926, 1.069]	0.968 [0.910, 1.030]
		Delamanid + EFV	394 (18.5)	4239 (18.3)[c)]		
	EFV	EFV	5952 (28.0)	84,678 (44.6)[c)]	0.937 [0.754, 1.165]	0.937 [0.715, 1.228]
		Delamanid + EFV	5809 (52.1)	83,056 (69.6)[c)]		
TFV	Delamanid	Delamanid	617 (21.8)	9610 (21.3)	0.844 [0.714, 0.989]	0.958 [0.835, 1.099]
		Delamanid + TFV	518 (22.0)	8860 (17.5)		
	TFV	TFV	326 (21.1)	3130 (23.3)	0.894 [0.768, 1.040]	0.914 [0.781, 1.068]
		Delamanid + TFV	294 (26.0)	2850 (22.6)		
LPV/RTV	Delamanid	Delamanid	617 (21.8)	9610 (21.3)	1.177 [0.997, 1.390]	1.216 [1.057, 1.399]
		Delamanid + LPV/RTV	734 (26.6)	11,800 (32.6)		
	LPV	LPV	12,900 (24.6)	211,000 (21.5)	1.050 [0.880, 1.254]	1.036 [0.864, 1.244]
		Delamanid + LPV/RTV	13,600 (24.9)	226,000 (31.4)		
	RTV	RTV	1300 (52.7)	10,500 (31.5)	0.959 [0.657, 1.399]	1.031 [0.773, 1.373]
		Delamanid + LPV/RTV	1270 (63.1)	11,800 (52.3)		

Pharmacokinetic parameter values are given as a mean (CV%).

a) Concomitant use with EFV:
Delamanid: Delamanid 100 mg BID for 7 days (14 subjects), Delamanid + EFV: Delamanid 100 mg BID for 18 days and EFV 600 mg QD for 10 days (12 subjects), EFV: EFV 600 mg QD for 10 days (14 subjects)
Delamanid was administered with 240 mL of water within 30 minutes after the start of the standard diet in the morning and in the evening. The evening dose was to be administered at 10 hours after the morning dose. EFV was administered QD at 2 hours after the standard diet in the evening.
Concomitant use with TFV:
Delamanid: Delamanid 100 mg BID for 14 days (11 subjects), Delamanid + TFV: Delamanid 100 mg BID for 14 days and TFV 300 mg QD for 14 days (13 subjects), TFV: TFV 300 mg QD for 14 days (12 subjects). TFV was administered in the form of tenofovir disoproxil fumarate (TDF).
Delamanid was administered with 240 mL of water within 30 minutes after the start of the standard diet in the morning and in the evening. The evening dose was to be administered at 12 hours after the morning dose. TFV was co-administered with delamanid in the morning.
Concomitant use with LPV/RTV:
Delamanid: Delamanid 100 mg BID for 14 days (11 subjects), Delamanid + LPV/RTV: Delamanid 100 mg BID and LPV/RTV 400/100 mg BID for 14 days (12 subjects), LPV/RTV: LPV/RTV 400/100 mg BID for 14 days (11 subjects)
Delamanid was administered with 240 mL of water within 30 minutes after the start of the standard diet in the morning and in the evening. The evening dose was to be administered at 12 hours after the morning dose. LPV/RTV was co-administered with delamanid.

b) The ratio of each pharmacokinetic parameter was calculated as (delamanid + concomitant drug(s))/delamanid or as (delamanid + concomitant drug(s))/(concomitant drugs).

c) As AUC of delamanid in concomitant use with EFV, the area under the concentration-time curve until the dosing interval (AUC_{τ}) was calculated.

4.(i).A.(5) Study on QT prolongation by delamanid (5.3.5.1-01, 5.3.3.5-04)

In the global phase II study (Study 242-[redacted]-204), the effect of delamanid on QT interval was investigated.[73] Table 26 shows the change in QTcF adjusted for baseline and time (ΔQTcF) in the placebo/OBR, the delamanid 100 mg/OBR, and the delamanid 200 mg/OBR groups, and the changes in QTcF from baseline corrected for placebo (ΔΔQTcF) in the delamanid 100 mg/OBR and the delamanid 200 mg/OBR groups.

Table 26. ΔQTcF and ΔΔQTcF following the administration of delamanid + OBR or placebo + OBR (population for ECG analysis)

Day of administration	Hours post-dose	ΔQTcF after delamanid 100 mg BID + OBR [a]	ΔQTcF after delamanid 200 mg BID + OBR [a]	ΔQTcF after placebo + OBR [a]	ΔΔQTcF after delamanid 100 mg BID + OBR [b]	ΔΔQTcF after delamanid 200 mg BID + OBR [b]
		N = 161	N = 160	N = 160		
Day 1	2	-3.6 (10.8)	-2.3 (9.9)	-3.6 (9.6)	0.0 [-1.90, 1.87]	1.2 [-0.56, 3.05]
	3	-0.1 (11.7)	-1.2 (10.5)	-3.2 (10.4)	3.1 [1.05, 5.14]	1.9 [0.01, 3.86]
	4	1.6 (11.9)	0.1 (11.2)	-1.1 (11.3)	2.6 [0.49, 4.76]	1.2 [-0.89, 3.27]
	10	1.3 (12.6)	2.1 (11.8)	-0.9 (12.9)	2.1 [-0.22, 4.49]	2.9 [0.63, 5.20]
	12	0.5 (11.9)	-1.2 (11.4)	-2.2 (13.2)	2.7 [0.40, 5.03]	1.0 [-1.29, 3.28]
	24	0.3 (14.0)	1.1 (14.3)	-0.8 (18.2)	1.1 [-1.85, 4.15]	2.0 [-1.07, 4.99]
Day 14	2	4.9 (12.8)	6.2 (14.1)	-2.3 (14.6)	7.2 [4.57, 9.75]	8.5 [5.81, 11.19]
	3	6.7 (13.2)	6.8 (13.1)	-1.2 (14.6)	7.9 [5.22, 10.48]	8.0 [5.38, 10.59]
	4	9.5 (13.6)	10.0 (14.2)	2.6 (14.5)	6.9 [4.24, 9.54]	7.3 [4.63, 10.01]
	10	10.1 (17.0)	11.2 (16.6)	2.6 (15.5)	7.6 [4.51, 10.63]	8.6 [5.58, 11.60]
	12	7.3 (15.4)	8.5 (14.0)	0.9 (13.2)	6.4 [3.74, 9.14]	7.7 [5.12, 10.23]
	24	7.5 (15.7)	12.4 (15.3)	1.6 (15.3)	5.8 [2.92, 8.74]	10.7 [7.86, 13.60]
Day 28	2	6.7 (16.1)	10.5 (17.0)	0.5 (14.9)	6.2 [3.21, 9.12]	10.0 [6.97, 13.04]
	3	6.1 (17.7)	11.4 (15.1)	0.1 (15.1)	6.0 [2.87, 9.12]	11.3 [8.40, 14.13]
	4	11.7 (14.9)	14.5 (15.1)	3.3 (14.5)	8.4 [5.56, 11.16]	11.2 [8.36, 13.98]
	10	12.6 (15.4)	16.5 (16.5)	3.6 (13.2)	9.0 [6.26, 11.73]	12.9 [10.04, 15.72]
	12	10.6 (15.3)	13.3 (16.7)	1.9 (14.3)	8.7 [5.85, 11.48]	11.4 [8.41, 14.32]
	24	11.5 (16.6)	17.8 (17.0)	3.9 (14.0)	7.6 [4.68, 10.51]	13.9 [10.99, 16.89]
Day 56	2	11.8 (16.3)	14.6 (18.8)	-0.5 (14.3)	12.3 [9.34, 15.25]	15.1 [11.87, 18.29]
	3	12.8 (16.6)	14.7 (16.0)	-0.4 (14.5)	13.1 [10.14, 16.14]	15.1 [12.13, 18.00]
	4	16.8 (16.3)	19.4 (17.3)	5.0 (15.8)	11.9 [8.76, 14.96]	14.4 [11.20, 17.57]
	10	16.5 (17.4)	20.8 (17.3)	5.2 (15.5)	11.3 [8.09, 14.45]	15.6 [12.45, 18.76]
	12	15.6 (17.4)	16.7 (17.0)	2.6 (15.6)	13.0 [9.80, 16.19]	14.1 [10.99, 17.28]
	24	15.5 (18.9)	18.3 (18.5)	3.4 (15.0)	12.0 [8.75, 15.32]	14.9 [11.64, 18.10]

Unit: msec
a) Mean (SD)
b) Mean [90% CI]

The study results were analyzed using a linear model and a maximum pharmacological effect (E_{max}) model.

Using the linear model, the mean ΔΔQTcF and the upper limit of 95% confidence interval were calculated at the time point of mean C_{max} of delamanid, DM-6704, DM-6705, and DM-6720 in the 56-day administration of delamanid 100 mg + OBR or delamanid 200 mg + OBR. The predicted value of ΔΔQTcF peaked at the time point of C_{max} of plasma delamanid and DM-6705 on Day 56, and the QT prolongation associated with delamanid + OBR resolved after the completion of administration. Based on the exposure to DM-6705 in the global phase II study (Study 242-[redacted]-204), C_{max} of DM-6705 (151 ng/mL) on Day 56 in the delamanid 100 mg + OBR

[73] The applicant explained the reason for QT interval in the global phase II study (Study 242-[redacted]-204) as follows: Prolonged QT interval was observed after the long-term administration of delamanid, and the result of the safety pharmacology study [see "3.(i).A.(3) Safety pharmacology"] suggested that the prolonged QT interval was possibly due to plasma DM-6705 concentration. However, it takes 6 weeks before plasma DM-6705 level reaches the steady state [see "4.(i).A.(3).2) Phase II studies in patients with multidrug-resistant pulmonary tuberculosis"], suggesting the difficulty of conducting a Thorough QT/QTc study in healthy adult subjects. Therefore, QT evaluation (primary endpoints in a Thorough QT/QTc study according to ICH E14 guideline, except the establishment of a positive control) was planned and conducted in this study involving patients with multidrug-resistant pulmonary tuberculosis.

group or the delamanid 200 mg + OBR group was predicted using the linear model and E_{max} model of ΔQTcF. At this time point, ΔΔQTcF (upper limit of 95% CI) was 14.24 msec (15.39 msec) and 13.72 msec (14.90 msec), respectively.

Table 27 shows ΔQTcF during the 26-week continuous treatment in Study 242-[redacted]-208 after Study 242-[redacted]-204. The changes from baseline (at 24 hours pre-dose, i.e., the day before the start of administration) in Study 242-[redacted]-204 were estimated. Similarly to plasma DM-6705 concentration, no change was observed from Week 10 onward.

Table 27. ΔQTcF in delamanid + OBR administration

Week	Delamanid 100 mg BID + OBR		Delamanid 200 mg BID + OBR	
	N	ΔQTcF (msec)	N	ΔQTcF (msec)
2	115	10.4 (194.2)	68	11.2 (192.2)
6	110	13.5 (140.8)	65	9.60 (195.2)
10	74	16.5 (133.8)	39	10.4 (249.0)
14	104	13.7 (141.7)	60	10.0 (217.5)
18	86	13.0 (167.9)	43	12.3 (188.5)
22	94	14.4 (147.0)	49	9.73 (223.7)
26	98	14.6 (140.7)	55	13.7 (154.3)

Mean (CV%)

4.(i).A.(6) PPK analysis of delamanid in healthy adults and patients with tuberculosis (5.3.3.5-01, 5.3.3.5-02)

A phase I PPK analysis was conducted[74] using the data of plasma delamanid concentrations obtained from 9 phase I studies[75] and from the phase II study (Study 242-[redacted]-101) in patients with sputum smear-positive pulmonary tuberculosis without complications (6715 data points in 357 subjects [314 healthy adults, 43 patients with sputum smear-positive pulmonary tuberculosis without complications]) to evaluate the effects of the dosage and administration (including the food effect), demographic characteristics (race, body weight, sex), drug interactions (anti-tuberculosis drugs, anti-HIV drugs), and disease conditions on the pharmacokinetics of orally administered delamanid. The dose, food intake, administration method, and body weight were found to affect the pharmacokinetics of delamanid. The relative bioavailability (F_1) was shown to decrease with the increase in dose. In contrast, F_1 increased with food intake, being 36% under fasted condition and 165% after the intake of high fat diet, as compared with the value after the intake of the standard diet. Apparent clearance was estimated to decrease by 15% by multiple QD administration and by 35% by multiple BID/TID administration as compared with single-dose administration. The parameters of apparent clearance (CL/F, intercompartmental clearance [Q/F]) increased with body weight, and the apparent distribution volume (central compartment [V_2/F], peripheral compartment [V_3/F]) exceeded the body weight ratio. The applicant explained that age (18-58 years), sex, and race did not affect the pharmacokinetics of delamanid.

A phase II PPK analysis was conducted[76] using the data of plasma concentrations (12,503 data points in 405 patients) obtained from 3 phase II studies (Studies 242-[redacted]-204, 242-[redacted]-208, and 242-[redacted]-210) in patients with multidrug-resistant pulmonary tuberculosis, and the effects of the dose, demographic characteristics, renal impairment, hepatic impairment,[77] laboratory test values, and concomitant drugs (including OBR) on the pharmacokinetics of orally administered

[74] Plasma delamanid concentrations were analyzed using the first-order 2-compartment model with lag time (NONMEM ver. 7.1.2).

[75] Studies 242-[redacted]-101, 242-[redacted]-001, 242-[redacted]-001, 242-[redacted]-801-01, 242-[redacted]-802-01, 242-[redacted]-211, 242-[redacted]-202, 242-[redacted]-209, and 242-[redacted]-212. Data of plasma delamanid concentrations in the mass balance study (Study 242-[redacted]-102) were not included in the phase I PPK analysis.

[76] Plasma delamanid concentrations were analyzed using the first-order 2-compartment model with lag time, with the effect of dose-dependent F_1 decrease included (NONMEM ver. 7.2).

[77] Patients with hepatic impairment were not registered in 3 phase II studies in patients with multidrug-resistant pulmonary tuberculosis.

delamanid were evaluated. In a typical patient with multidrug-resistant pulmonary tuberculosis (a male subject weighing 55 kg, serum albumin >3.4 mg/dL), the values [95% CI] of the pharmacokinetic parameters of delamanid were estimated as follows: CL/F = 39.3 [37.5, 41.1] L/h, Q/F = 106 [92.3, 120] L/h, V_2/F = 624 [573, 675] L, and V_3/F = 930 [843, 1020] L. The exposure level of delamanid increased less than in proportion to dose, and F_1 values after the administration of delamanid 200 mg and higher doses (250 mg, 300 mg) were estimated to decrease by 28.6% and 42.3%, respectively, as compared with delamanid 100 mg. F_1 was 45% higher after the evening dose than after the morning dose and was 19% higher in outpatients than in hospitalized patients. The applicant explained that contributory factors of these differences were the type of diet and amount of food taken. F_1 values in patients (or in study sites) in Northeast and Southeast Asia were estimated to be 50% and 39% higher than that in patients (or study sites) in non-Asian regions. However, no regional difference was observed in the safety or efficacy of delamanid in phase II studies in patients with multidrug-resistant pulmonary tuberculosis. Therefore the applicant considered that the mentioned difference in F_1 values was of no clinical significance. The applicant also explained that age (18-63 years), sex, body weight, resistance of extensively drug-resistant *M. tuberculosis* at baseline, concomitant drugs including OBRs,[78)] and mild renal impairment[79)] did not affect the pharmacokinetics of delamanid.

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Food effect on pharmacokinetics of delamanid

Given that the administration of delamanid under fed conditions has been specified in the proposed dosage and administration, PMDA asked the applicant to explain the effect of food on the pharmacokinetics of delamanid, in particular, the cause of increased C_{max} and $AUC_{0-\infty}$ of delamanid administered under fed conditions relative to fasted conditions and the reasons why no significant differences in C_{max} or $AUC_{0-\infty}$ were shown between delamanid 200 mg and delamanid 400 mg administered after the intake of the standard diet.

The applicant explained as follows:
The low solubility of delamanid leads to a less than dose-proportional increase in the exposure to delamanid in plasma. At the same time, delamanid is highly lipophilic and is thought to be dissolved more easily under fed conditions than under fasted conditions, with the help of the effects of fats in the meal and of bile acid secreted in response to food intake, and is consequently absorbed at high rate. In the study of food effect in British healthy adults (Study 242-[redacted]-101) and the study of food effect in Japanese healthy adults (Study 242-[redacted]-001), the administration of delamanid after a high fat diet resulted in increased C_{max} and $AUC_{0-\infty}$ as compared with after the standard diet. However, since the saturation solubility of delamanid was eventually reached with increasing doses even under fed conditions, the differences in C_{max} and $AUC_{0-\infty}$were not significant between delamanid 200 mg and delamanid 400 mg.

PMDA accepted the applicant's explanation that the increased C_{max} and $AUC_{0-\infty}$ of delamanid administered under fed conditions were attributable to the effects of fat in the meal and bile acid secreted following food intake, both resulting from the high lipophilicity of delamanid, and that the absorption rate of delamanid was assumed to decrease with increasing doses because of its low solubility, leading to a trend toward non-linear increases that was more significant under fed conditions than under fasted conditions, which in turn resulted in no significant differences in C_{max} and $AUC_{0-\infty}$ between delamanid 200 mg and delamanid 400 mg after the intake of the standard diet.

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78) An OBR includes AMK, PAS, amoxicillin/clavulanic acid, capreomycin, CS, EB, TH, gatifloxacin, INH, KM, LVFX, ofloxacin, prothionamide, and PZA. Other concomitant drugs include pyridoxine, CYP inhibitors, CYP inducers, and gastrointestinal drugs for gastric acid-related diseases.

79) 50 mL/min < estimated creatinine clearance (CrCLN) <80 mL/min

Taking account that delamanid is highly lipophilic, that its saturation solubility is reached under fasted conditions, and that the BA of delamanid increased under fed conditions, PMDA considers that there is no particular problem in requiring the administration of delamanid in the postprandial state.

4.(i).B.(2) Drug interactions with other drugs

4.(i).B.(2).1) Interactions with other anti-tuberculosis drugs

Since delamanid is required to be co-administered with at least 3 existing anti-tuberculosis drugs, PMDA asked the applicant to explain drug interactions between delamanid and anti-tuberculosis drugs co-administered in clinical practice.

The applicant explained as follows:

According to a Japanese literature survey on anti-tuberculosis drugs (antibacterial agents) used against multidrug-resistant pulmonary tuberculosis, anti-tuberculosis drugs (antibacterial agents) that are possibly co-administered with delamanid in clinical practice in Japan are LVFX, PZA, CS, TH, PAS, KM, SM, linezolid, clarithromycin (CAM), EB, rifabutin (RBT), enviomycin, sitafloxacin, garenoxacin, and MFX.

The applicant considers the effects of these concomitant drugs on the pharmacokinetics of delamanid as follows:

CAM potently inhibits CYP3A4, and RBT induces CYP3A and CYP1A isozymes.

In the study on drug interactions between delamanid and 3 anti-HIV drugs (Study 242-[redacted]-209) [see "4.(i).A.(4).2) Study on drug interactions with anti-HIV drugs"], concomitant use with LPV/RTV (a combination containing RTV which is a potent inhibitor of CYP3A4 as with CAM) did not significantly change C_{max} or $AUC_{0\text{-}24h}$ of delamanid in plasma but increased C_{max} and $AUC_{0\text{-}24h}$ of DM-6705 in plasma by 28.1% and 27.5%, respectively, and therefore the concentrations of metabolites of delamanid are expected to be increased by concomitant CAM as with concomitant LPV/RTV. However, the increase in the exposure to DM-6705 in plasma in concomitant use with LPV/RTV was smaller than the increase in the exposure observed when the dose was increased from delamanid100 mg BID (the proposed dosage) to 200 mg BID (C_{max}, 54.3%; $AUC_{0\text{-}24h}$, 57.0%), and no clinically significant adverse events were observed in subjects receiving delamanid 200 mg BID. IC_{50} of CAM against CYP3A4 is 99 μmol/L, indicating that CAM is less potent in inhibiting CYP3A4 as compared with RTV (IC_{50}, 0.0042 μmol/L).[80)] Based on these findings, the applicant considers that concomitant use of delamanid with CAM is unlikely to cause drug interactions that warrant special precautions.

Antipyrine, a substrate for CYP3A4, was coadministered with RFP or RBT. CL of antipyrine was reduced 90% by concomitant RFP but only 29% by concomitant RBT.[81)] This finding indicates that both RBT and RFP induce CYP3A4 but the induction effect of RBT is weaker than that of RFP, and that the effect of concomitant RBT on the exposure to delamanid is therefore weaker than that of concomitant RFP.

The applicant considers the effect of delamanid and its metabolites on the pharmacokinetics of concomitant drugs as follows:

Delamanid has little or no inhibitory effect on CYP isozymes even at 100 μmol/L, a concentration far exceeding exposure levels achieved by the clinical dosage. On the other hand, results of nonclinical studies showed that the metabolites inhibit CYP isozymes. However, the IC_{50} of each metabolite (≥10.9 to 25 μmol/L) far exceeds the maximum plasma concentrations of the metabolites predicted in patients on treatment with delamanid and OBR in clinical practice.

80) Obach RS et al, *JPET*. 2006;316:336-348.

81) Published document of Mycobutin Capsules 150 mg (rifabutin) CTD 2.5.3.3.2

According to the package inserts of the above-mentioned anti-tuberculosis drugs (antibacterial agents) that are possibly co-administered with delamanid, most of these drugs do not, or only partly, undergo CYP isozymes-catalyzed metabolism.

Based on the above discussions, the applicant considers that the concomitant use of delamanid with anti-tuberculosis drugs (antibacterial agents) that are possibly co-administered with delamanid is unlikely to significantly affect the pharmacokinetics of delamanid, the metabolites, or the concomitant drugs.

4.(i).B.(2).2) Interactions with drugs (other than anti-tuberculosis drugs and anti-HIV drugs) possibly co-administered with delamanid

Studies on the interactions between delamanid and anti-tuberculosis drugs or anti-HIV drugs were conducted. PMDA asked the applicant to explain interactions of delamanid with other drugs that are possibly co-administered.

The applicant explained as follows:
Using the Claims Database of Japan Medical Data Center (JMDC Claims Database), the use of concomitant drugs in patients with tuberculosis as of December 2012 (estimated number of patients, 17,106) were studied. Among concomitant drugs except anti-tuberculosis drugs, anti-HIV drugs, and fluid replacements, 21 drugs were used in ≥10% of patients.[82)] Of these drugs, solifenacin succinate is known to prolong QT, atorvastatin calcium and amlodipine besilate to inhibit CYP3A4, and metoclopramide hydrochloride to inhibit CYP2D6.

In light of the result of the study on the drug interactions between delamanid and LPV/RTV, potent inhibitors of CYP3A4, atorvastatin calcium and amlodipine besilate only weakly inhibit CYP3A4 as compared with LPV/RTV and are therefore unlikely to markedly increase the exposures to delamanid and its metabolites when co-administered with delamanid. CYP2D6, an enzyme inhibited by metoclopramide hydrochloride, contributes only minimally to the metabolism of delamanid [see "3.(ii).A.(3).1) Possible metabolic pathway"]. Therefore, the applicant considers that concomitant use with these drugs will not affect the pharmacokinetics of delamanid or its metabolites.

On the other hand, solifenacin succinate is known to prolong QT and so is delamanid. Therefore, solifenacin succinate will be listed in the "Precautions for Concomitant Use" section in the package insert.

PMDA's views on the applicant's claimes presented in 4.(i).B.(2).1) and 4.(i).B.(2).2) above are as follows:
Taking account of the results of the nonclinical and clinical studies on delamanid and anti-tuberculosis drugs (antibacterial agents) that are possibly co-administered with delamanid, PMDA accepted the explanation of the applicant that among the drugs that are likely to be co-administered with delamanid (except possible concomitant anti-tuberculosis and anti-HIV drugs), drugs other than those with QT-prolongation effect do not necessarily require precautions for concomitant use currently from the aspect of drug interactions. However, delamanid is intended for use in combination with other anti-tuberculosis drugs, and patients with multidrug-resistant tuberculosis need to be on long-term drug treatment. Therefore, delamanid is therefore assumed to be co-administered with a variety of drugs in clinical practice. After the market launch, the applicant should continue collecting information on the safety and pharmacokinetics of delamanid co-administered with other drugs and provide any new findings to medical practice in an

[82)] Rebamipide, ursodeoxycholic acid, thiamine chloride hydrochloride/pyridoxine hydrochloride/cyanocobalamin, pyridoxal phosphate, lansoprazole, magnesium oxide, allopurinol, sitagliptin phosphate, ketoprofen, glimepiride, atorvastatin calcium, solifenacin succinate, povidone iodine, valsartan/amlodipine besilate, metoclopramide hydrochloride, alprostadil, trafermin, prednisolone, loxoprofen sodium, folic acid, and methotrexate

appropriate manner whenever available.

4.(i).B.(3) Pharmacokinetics of delamanid in patients with hepatic impairment

No pharmacokinetic studies of delamanid were conducted in patients with hepatic impairment. Therefore, PMDA asked the applicant to explain the effect of delamanid and its metabolites on the pharmacokinetics in patients with hepatic impairment and the necessity of dose adjustment in this patient population.

The applicant explained as follows:

Although the pharmacokinetics of delamanid in patients with hepatic impairment was not investigated, decreased hepatic function may be accompanied by a decrease in the activity of drug-metabolizing enzymes in the liver. Delamanid is metabolized mainly by albumin but partially metabolized by primarily hepatic CYP3A4. It is reported that the metabolic clearance by CYP3A4 decreases by 36% in patients with chronic hepatitis and by 50% in patients with hepatic cirrhosis as compared with healthy adults.[83)] In the study on the drug interaction between delamanid and CYP3A4 inhibitors LPV/RTV, AUC values of delamanid and the metabolite DM-6705 were increased by 22% and 28%, respectively, by concomitant use with CYP3A4 inhibitors [Study 242-[redacted]-209, see "4.(i).A.(4).2) Study on drug interactions with anti-HIV drugs"]. These results suggest that the administration of delamanid to patients with hepatic impairment may cause increases in the exposures to delamanid and DM-6705, as observed in the above study. Moreover, DM-6705 is partly metabolized by CYP3A4 but is also metabolized via metabolic routes (CYP1A1, CYP2D6, CYP2E1) other than CYP3A4 [see "3.(ii).A.(3).1) Possible metabolic pathway"]. Therefore, when delamanid is administered to patients with hepatic impairment, the exposure to DM-6705 may further increase due to decreases in other CYP isozymes in addition to the increase in exposure resulting from CYP3A4 inhibition.

Therefore, in patients with hepatic impairment, although an increase in the exposure to delamanid is considered insignificant, it is unknown how metabolic pathways other than CYP3A4 affect the exposure to DM-6705 that has a risk of QT-prolongation. Thus, a possible effect of the exposure level on safety cannot be excluded.

Based on the discussion, the "Careful Administration" section of the package insert will include a precautionary statement that the administration of delamanid in patients with hepatic impairment may result in increases in plasma concentrations of delamanid and its metabolite (DM-6705). Dose adjustment is unnecessary in these patients, because the extent of the increase in the exposure level caused by the decreased hepatic function is unknown and because dose reduction may result in the lack of efficacy and the emergence of drug-resistant strains.

PMDA considers as follows:

Since the pharmacokinetics of delamanid in patients with hepatic impairment was not investigated, the effect of hepatic impairment on the pharmacokinetics of delamanid and DM-6705 following the administration of delamanid is unknown. It cannot be ruled out that the exposure levels of delamanid and DM-6705 may increase. Taking account of these facts and the possible occurrence of DM-6705-induced QT-prolongation, delamanid should be carefully administered to patients with hepatic impairment, and information should be provided on potential increases in the concentrations of delamanid and its metabolite. In addition, when delamanid is administered to patients with hepatic impairment after the market launch, safety information should be collected from these patients, and new findings should be provided to clinical practice in an appropriate manner whenever available. PMDA accepts the applicant's view that the pharmacokinetics of delamanid in patients with hepatic impairment is currently unknown and it is unnecessary to consider dose adjustment from the aspect of possible emergence of drug-resistant strains.

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83) Ohnishi A, *Jikeikai Medical Journal*. 2011;126:71-78.

4.(ii) Summary of clinical efficacy and safety

4.(ii).A Summary of the submitted data

The results from 2 global phase II studies including Japanese patients and 1 foreign phase II study, which were all conducted in patients with multidrug-resistant pulmonary tuberculosis, were submitted in this application as evaluation data for efficacy and safety, and the result from 1 observational study intended to confirm the final outcome of the treatment were submitted as reference data. In addition, 2 clinical pharmacology studies in Japanese healthy adults, 3 biopharmaceutical studies, 5 clinical pharmacology studies, and 1 clinical pharmacodynamic study, which were all conducted in foreign subjects, were submitted as evaluation data for safety. One biopharmaceutics study and 2 clinical pharmacology studies were submitted as reference data for safety.

Table 28 shows the clinical data package for this application.

Table 28. Clinical data package

Japanese/ foreign	Study number	Subjects	Dosage and administration	Number of subjects [a)]	Study objectives
Evaluation data					
Japanese	242-[redacted]-001	Healthy adult male subjects	Delamanid 50, 100, 200, 400 mg, or placebo in a single dose	42 subjects in the delamanid group 14 subjects in the placebo group	Pharmacokinetics, safety
Japanese	242-[redacted]-001	Healthy adult male subjects	Delamanid 100, 200, or 400 mg, or placebo in a single dose and QD for 10 days	18 subjects in the delamanid group 6 subjects in the placebo group	Pharmacokinetics, safety
Foreign	242-[redacted]-101	Healthy adult male subjects	Delamanid 100, 200, or 400 mg, or placebo in a single dose, and delamanid 100, 200, or 400 mg, or placebo QD for 10 days	78 subjects in the delamanid group 26 subjects in the placebo group	Pharmacokinetics, safety
Foreign	242-[redacted]-801-01	Healthy adult male subjects	Delamanid 100, 200, or 400 mg in a single dose	36 subjects in the delamanid group 12 subjects in the placebo group	Pharmacokinetics, safety
Foreign	242-[redacted]-802-01	Healthy adult subjects	Delamanid 100, 200 mg BID for 10 days	24 subjects in the delamanid group 8 subjects in placebo group	Pharmacokinetics, safety
Foreign	242-[redacted]-211	Healthy adult subjects	Delamanid 300 mg QD, 150 mg BID, 100 mg TID for 10 days	12 subjects in each delamanid group	Pharmacokinetics, safety
Foreign	242-[redacted]-202	Healthy adult subjects	Delamanid 200 mg + placebo (delamanid group), delamanid 200 mg/EB 1100 mg/Rifater tablet[84)] (delamanid/EB/Rifater group), or placebo/EB 1100 mg/Rifater tablet (EB/Rifater group) QD for 19 days (delamanid from Day 1 to Day 15)	14 subjects in the delamanid group 22 subjects in the delamanid/EB/Rifater group 19 subjects in the EB/Rifater group	Drug interactions, safety

84) Combination tablet containing RFP 120 mg, INH 50 mg, and PZA 300 mg. Six tablets were given daily.

Japanese/ foreign	Study number	Subjects	Dosage and administration	Number of subjects [a)]	Study objectives
Foreign	242-[redacted]-209	Healthy adult subjects	Delamanid 100 mg BID (delamanid group), EFV 600 mg QD (EFV group), delamanid 100 mg BID + EFV 600 mg QD (delamanid/EFV group), tenofovir disoproxil fumarate (TDF) 300 mg QD (TDF group), delamanid 100 mg BID + DF 300 mg QD (delamanid/TDF group), LPV/RTV 400/100 mg BID (LPV/RTV group), or delamanid 100 mg BID + LPV/RTV 400/100 mg BID (delamanid/LPV/RTV group) for 14 days	15 subjects in the delamanid group 5 subjects in EFV group 4 subjects in the delamanid/EFV group 17 subjects in the TDF group 18 subjects in the delamanid/TDF group 14 subjects in the LPV/RTV group 16 subjects in the delamanid/LPV/RTV group	Drug interactions, safety
Foreign	242-[redacted]-212	Healthy adult subjects	Delamanid 100 mg BID for 7 days, followed by delamanid 100 mg BID + EFV 600 mg QD for 10 days (delamanid/EFV group) or EFV 600 mg QD for 10 days (EFV group)	15 subjects in the delamanid/EFV group 15 subjects in the EFV group	Drug interactions, safety
Foreign	242-[redacted]-102	Healthy adult male subjects	^{14}C-labeled delamanid (capsule) 100 mg in a single dose	6 subjects	Pharmacokinetics, safety
Foreign	242-[redacted]-101	Patients with pulmonary tuberculosis	Delamanid 100, 200, 300, 400 mg QD for 14 days or Rifafour tablet[85)]QD for 10 days	12 subjects in each delamanid dose group 6 subjects in the Rifafour tablet group	Safety, efficacy, pharmacokinetics
Foreign	242-[redacted]-210	Patients with multidrug-resistant pulmonary tuberculosis	Delamanid 250-400 mg BID + OBR	10 subjects	Efficacy, safety, pharmacokinetics
Global	242-[redacted]-204	Patients with multidrug-resistant pulmonary tuberculosis	Delamanid 100 mg, 200 mg, or placebo BID + OBR	161 subjects in the delamanid 100 mg group 160 subjects in the delamanid 200 mg group 160 subjects in the placebo group	Efficacy, safety, pharmacokinetics
Global	242-[redacted]-208	Patients with multidrug-resistant pulmonary tuberculosis	Delamanid 100 or 200 mg BID + OBR	137 subjects in the delamanid 100 mg group 76 subjects in the delamanid 200 mg group	Efficacy, safety
Reference data					
Foreign	242-[redacted]-101	Healthy adult subjects	Delamanid 5, 15, 50, 100, 200, 300 mg in a single dose (fasted) 200 mg in a single dose (high fat diet)	42 subjects in the delamanid group 14 subjects in the placebo group	Pharmacokinetics, safety
Foreign	242-[redacted]-101	Healthy adult subjects	Delamanid (tablets produced by old manufacturing process) 100, 400 mg in a single dose and multiple dose for 10 days	36 subjects in the delamanid group 16 subjects in the placebo group	Pharmacokinetics, safety
Foreign	242-[redacted]-102	Patients with pulmonary tuberculosis	Delamanid 400 mg (tablets produced by old manufacturing process) QD + INH 300 mg QD	24 subjects	Drug interactions, safety
Japanese and foreign	242-[redacted]-116	Patients with multidrug-resistant pulmonary tuberculosis	None [b)]	425 subjects	Final outcome

[85)] Combination tablet containing RFP 150 mg, INH 75 mg, PZA 400 mg, and EB 275 mg. Refafour were administered at the following dosage according to body weight: 30-37 kg, 2 tablets per day; 38-54 kg, 3 tablets per day, 55-70 kg, 4 tablets per day, ≥71 kg, 5 tablets per day

a) Safety analysis set
b) Study to evaluate the final outcome of patients who participated in Study 242-[redacted]-204 or 242-[redacted]-210

4.(ii).A.(1) Clinical pharmacokinetic studies

4.(ii).A.(1).1) Phase I single dose study in Japanese healthy adults (5.3.3.1-01, Study 242-[redacted]-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at a single center in Japan to investigate the safety and pharmacokinetics of delamanid in Japanese healthy adult males (target sample size, 56 [6 subjects in the delamanid group and 2 subjects in the placebo group in each step, 7 steps in total]) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Delamanid (50, 100, 200, 400 mg) or placebo was to be administered orally in a single dose under fasted condition or after a meal (standard diet[64)] or high fat diet[65)]).[86)]

All of the 56 subjects (42 subjects in the delamanid group, 14 subjects in the placebo group) who received the study drug were included in the safety analysis set.

Adverse events were observed in 21.4% (9 of 42 subjects) in the delamanid group and in 35.7% (5 of 14 subjects) in the placebo group. Adverse events observed in the delamanid group were ALT increased and blood cortisol increased in 2 subjects each, AST increased, blood triglycerides increased, diarrhoea, faeces hard, white blood cells urine positive, protein urine present, headache, and mental impairment in 1 subject each. Adverse events observed in the placebo group were diarrhoea in 2 subjects, and headache, somnolence, blood bilirubin increased, blood corticotrophin increased, and white blood cell count increased in 1 subject each. Except blood triglycerides increased in 1 subject in the delamanid group, a causal relationship to the study drug could not be ruled out for all observed adverse events. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).2) Phase I multiple dose study in Japanese healthy adults (5.3.3.1-03, Study 242-[redacted]-001 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at a single center in Japan to investigate the safety and pharmacokinetics of delamanid in Japanese healthy male adults (target sample size, 24 [6 subjects in the delamanid group and 2 subjects in the placebo group in each step; 3 steps in total]) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

The study drug was administered orally in a single dose after a meal (standard diet[64)]) according to the following dosage regimen: step 1, delamanid 100 mg or placebo; step 2, delamanid 200 mg or placebo; step 3, delamanid 400 mg or placebo. From 7 days after single dose administration, the study drug was administered orally QD for 10 days.

All of the 24 subjects who received the study drug (18 subjects in the delamanid group, 6 subjects in the placebo group) were included in the safety analysis set.

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86) Step 1, delamanid 50 mg or placebo under fasted conditions; Step 2, delamanid 100 mg or placebo under fasted conditions; Step 3, delamanid 200 mg or placebo under fasted conditions; Step 4, delamanid 200 mg or placebo under fed conditions (standard diet); Step 5, delamanid 400 mg or placebo under fasted conditions; Step 6, delamanid 400 mg or placebo under fed conditions (standard diet); and Step 7, delamanid 400 mg or placebo under fed conditions (high fat diet)

Adverse events were observed in 66.7% (12 of 18 subjects) in the delamanid group and 50.0% (3 of 6 subjects) in the placebo group. Adverse events observed in the delamanid group were INR increased in 4 subjects, ALT increased, blood corticotrophin increased, blood glucose increased, blood triglycerides increased, and headache in 2 subjects each, faeces hard, APTT shortened, blood bilirubin increased, blood cholesterol increased, blood cortisol increased, back pain, rash, and glucose urine present in 1 subject each. Adverse events observed in the placebo group were diarrhoea in 2 subjects, stomach discomfort, abdominal pain, faeces hard, nausea, stomatitis, asthenia, nasopharyngitis, APTT shortened, ALT increased, and PT prolonged in 1 subject each. Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions[87]) occurred in 44.4% of subjects in the delamanid group (8 of 18 subjects [INR increased in 4 subjects, headache in 2 subjects, APTT shortened and blood bilirubin increased in 1 subject each]) and 50.0% of subjects in the placebo group (3 of 6 subjects [diarrhoea in 2 subjects, abdominal pain, faeces hard, stomatitis, and asthenia in 1 subject each]) (including duplicate counting). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).3) Single and multiple dose study in foreign healthy adults (5.3.1.1-02, Study 242-[redacted]-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at a single center in the UK to investigate the safety and pharmacokinetics of delamanid, as well as the effect of sex difference in foreign healthy adults (target sample size; 56 subjects in the single dose period [6 subjects each in the delamanid group, 2 subjects each in the placebo group], 48 subjects in the multiple dose period [6 subjects each in the delamanid group, 2 subjects each in the placebo group]). [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

In the single dose stage, delamanid (100, 200, 400 mg) or placebo was administered orally in a single dose under fasted conditions or after a meal (standard diet[67] or high fat diet[68]). In the multiple dose period, delamanid (100, 200, 400 mg) or placebo was administered orally QD under fed conditions (standard diet[67]) for 10 days.

All of the 104 subjects (56 subjects in the single dose stage, 48 subjects in the multiple dose period) who received the study drugs were included in the safety analysis set.

The incidences of adverse events observed during the single dose stage were 33.3% (2 of 6 subjects) in the delamanid 100 mg group, 50.0% (9 of 18 subjects) in the delamanid 200 mg group, 55.6% (10 of 18 subjects) in the delamanid 400 mg group, and 64.3% (9 of 14 subjects) in the placebo group. Adverse events reported by ≥2 subjects in any group were pharyngolaryngeal pain in 2 subjects in the delamanid 100 group; abdominal pain in 2 subjects in the delamanid 200 mg group; headache in 4 subjects, post-procedural local reaction in 3 subjects, and pharyngolaryngeal pain in 2 subjects in the delamanid 400 mg group; and pharyngolaryngeal pain in 4 subjects, post-procedural local reaction in 3 subjects, and nasopharyngitis in 2 subjects in the placebo group. In the multiple dose period, adverse events were observed in 75.0% (9 of 12 subjects) in the delamanid 100 mg group, 75.0% (9 of 12 subjects) in the delamanid 200 mg group, 58.3% (7 of 12 subjects) in the delamanid 400 mg group, and 75.0% (9 of 12 subjects) in the placebo group. Adverse events reported by ≥2 subjects in any group were headache in 6 subjects, pharyngolaryngeal pain in 4 subjects, dizziness and rash in 3 subjects each, conjunctivitis, abdominal pain lower, neck pain, and alopecia in 2 subjects each in the delamanid 100 mg group; nasopharyngitis and headache in 4 subjects each, constipation, post-procedural local reaction, back pain, and alopecia in 2 subjects each in the delamanid 200 mg group; headache in 5 subjects,

[87] Adverse events were classified as "not related," "possibly related," or "related" to the study drug, and those rated as "possibly related" or "related" were regarded as adverse drug reactions.

nasopharyngitis, arthralgia, dizziness, and pharyngolaryngeal pain in 2 subjects each in the delamanid 400 mg group; and epistaxis in 4 subjects, headache and pharyngolaryngeal pain in 3 subjects, and dysmenorrhoea in 2 subjects in the placebo group.

The incidences of adverse drug reactions[88)] in the single dose stage were 0% (0 of 6 subjects) in the delamanid 100 mg group, 16.7% (3 of 18 subjects, abdominal pain upper, nausea, and ALT increased in 1 subject each) in the delamanid 200 mg group, 11.1% (2 of 18 subjects, headache and flushing in 1 subject each) in the delamanid 400 mg group, and 7.1% (1 of 14 subjects, leukocyturia in 1 subject) in the placebo group. In the multiple dose period, adverse drug reactions occurred in 58.3% (7 of 12 subjects) in the delamanid 100 mg group, 50.0% (6 of 12 subjects) in the delamanid 200 mg group, 33.3% (4 of 12 subjects) in the delamanid 400 mg group, and 25.0% (3 of 12 subjects) in the placebo group. Adverse events reported by ≥2 subjects in any group were headache in 3 subjects, rash and alopecia in 2 subjects each in the delamanid 100 mg group; headache and alopecia in 2 subjects each in the delamanid 200 mg group; headache in 3 subjects in the delamanid 400 mg group; and headache in 2 subjects in the placebo group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).4 Phase I single dose study in foreign healthy made adults (5.3.1.1-03, Study 242-[redacted]-801-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel group comparative study was conducted in a single center in China to investigate the safety and pharmacokinetics of delamanid in foreign healthy adult male subjects (target sample size, 48 [9 subjects each in the delamanid group, 3 subjects each in the placebo group]). [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Delamanid (100, 200, 400 mg) or placebo was to be administered orally under fasted conditions, and delamanid (400 mg) or placebo was to be administered orally under fed conditions (high fat diet[69)]).

All of the 48 subjects who received the study drug were included in the safety analysis set.

Adverse events were observed in 66.7% (6 of 9 subjects) in the delamanid 100 mg group, 33.3% (3 of 9 subjects) in the delamanid 200 mg group, 33.3% (3 of 9 subjects) in the delamanid 400 mg group (fasted), 11.1% (1 of 9 subjects) in the delamanid 400 mg group (fed), and 16.7% (2 of 12 subjects) in the placebo group. Adverse drug reactions[89)] occurred in 55.6% (5 of 9 subjects) in the delamanid 100 mg group, 33.3% (3 of 9 subjects) in the delamanid 200 mg group, 33.3% (3 of 9 subjects) in the delamanid 400 mg group (fasted), 11.1% (1 of 9 subjects) in the delamanid 400 mg group (fed), and 16.7% (2 of 12 subjects) in the placebo group. Adverse events and adverse drug reactions reported by ≥2 subjects were pruritus in 2 subjects in the delamanid 100 mg group and rash in 2 subjects in the placebo group.

There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).5 Multiple dose study in foreign healthy adults (5.3.1.1-04, Study 242-[redacted]-802-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at a single center in China to investigate the safety and pharmacokinetics of delamanid in foreign healthy adults (target sample size, 32; 12 subjects each in the delamanid group, 4

88) Adverse events were classified as "related" or "not related" to the study drug, and those rated as "related" were regarded as adverse drug reactions.

89) Adverse events were classified as "related," "possibly related," "unlikely to be related," or "not related" to the study drug, and those rated as "related" or "possibly related" were regarded as adverse drug reactions.

subjects each in the placebo group) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Delamanid (100, 200 mg) or placebo was to be administered orally BID after meal for 10 days.

All of the 32 subjects who received the study drugs were included in the safety analysis set.

Adverse events and adverse drug reactions[89)] were observed in 41.7% (5 of 12 subjects) in the delamanid 100 mg group, 25.0% (3 of 12 subjects) in the delamanid 200 mg group, and 12.5% (1 of 8 subjects) in the placebo group. Adverse events and adverse drug reactions reported by ≥2 subjects were rash in 3 subjects, and dizziness and headache in 2 subjects each in the delamanid 100 mg group; and ALT increased in 2 subjects in the delamanid 200 mg group. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(1).6) Study on administration method in foreign healthy adults (5.3.3.1-04, Study 242-[redacted]-211 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, parallel group, comparative study was conducted at a single center in the US to investigate the safety and pharmacokinetics of delamanid in foreign healthy adults (target sample size, 36; 12 subjects in each dosage group) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Subjects received delamanid 300 mg QD, delamanid 150 mg BID, or delamanid 100 mg TID orally for 10 days.

All of the 36 subjects who received the study drug were included in the safety analysis set.

Adverse events were observed in 91.7% (11 of 12 subjects) in the delamanid 300 mg QD group, 66.7% (8 of 12 subjects) in the delamanid 150 mg BID group, and 83.3% (10 of 12 subjects) in the delamanid 100 mg TID group. Adverse events reported by ≥2 subjects were headache in 8 subjects, nausea in 7 subjects, dizziness in 4 subjects, diarrhoea, constipation, dysgeusia, insomnia, and epistaxis in 2 subjects each in the delamanid 300 mg QD group; headache in 4 subjects, vertigo, abdominal pain, and nausea in 2 subjects each in the delamanid 150 mg BID group; and nausea in 7 subjects, headache in 6 subjects, back pain and insomnia in 4 subjects each, diarrhoea in 3 subjects, abdominal pain, haematochezia, and vomiting in 2 subjects each in the delamanid 100 mg TID group. Adverse drug reactions[89)] were observed in 83.3% (10 of 12 subjects) in the delamanid 300 mg QD group, 58.3% (7 of 12 subjects) in the delamanid 150 mg BID group, and 83.3% (10 of 12 subjects) in the delamanid 100 mg TID group. Adverse drug reactions reported by ≥2 subjects were headache in 8 subjects, nausea in 7 subjects, dizziness in 4 subjects, diarrhoea, constipation, dysgeusia, and insomnia in 2 subjects each in the delamanid 300 mg QD group; headache in 4 subjects, vertigo, abdominal pain, and nausea in 2 subjects each in the delamanid 150 mg BID group; and nausea in 7 subjects, headache in 6 subjects, insomnia and diarrhoea in 3 subjects each, abdominal pain, haematochezia, and vomiting in 2 subjects each in the delamanid 100 mg TID group.

Neither death nor serious adverse events were reported. Adverse events leading to treatment discontinuation occurred in 3 subjects in the delamanid 300 mg QD group (haematochezia, haematemesis, and headache in 1 subjects each), 2 subjects in the delamanid 150 mg BID group (headache in 2 subjects), and 3 subjects in the delamanid 100 mg TID group (haematochezia in 2 subjects, diarrhoea in 1 subject), all of which resolved eventually.

4.(ii).A.(1).7) Study on interactions in concomitant use with anti-tuberculosis drugs in foreign healthy adults (5.3.3.4-01, Study 242-[redacted]-202 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at a single center in the US to investigate the safety and drug interactions of delamanid in healthy adults (target sample size, 39 [≥12 subjects were to be assigned to each group]) [for drug interactions, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Subjects received orally delamanid 200 mg and placebo (delamanid group), delamanid 200 mg, EB 1100 mg, and Rifater tablet[84)] (delamanid/EB/Rifater group), or placebo, EB 1100 mg, and Rifater tablet (EB/Rifater group) QD for 19 days (delamanid or placebo from Day 1 to Day 15) (delamanid after breakfast, EB and Rifater tablet before breakfast).

All of the 55 subjects who received the study drug (14 subjects in the delamanid group, 22 subjects in the delamanid/EB/Rifater group, 19 subjects in the EB/Rifater group) were included in the safety analysis set.

Adverse events were observed in 85.7% (12 of 14 subjects) in the delamanid group, 90.9% (20 of 22 subjects) in the delamanid/EB/Rifater group, and 94.7% (18 of 19 subjects) in the EB/Rifater group. Adverse events reported by ≥2 subjects were abdominal pain and headache in 3 subjects each and toothache in 2 subjects in the delamanid group; rash generalised in 12 subjects, headache in 7 subjects, abdominal pain and chromaturia in 4 subjects each, nausea, chills, gamma-glutamyltransferase (γ-GTP) increased, and parosmia in 3 subjects each, abdominal distension, meteorism, pyrexia, ALT increased, AST increased, decreased appetite, arthralgia, dizziness, acne, pruritus, pruritus generalised, and flushing in 2 subjects each in the delamanid/EB/Rifater group; and rash generalised in 9 subjects, chromaturia in 6 subjects, pruritus generalised and headache in 4 subjects each, diarrhoea and somnolence in 2 subjects each in the EB/Rifater group (including duplicate counting). Adverse drug reactions[89)] were observed in 50.0% (7 of 14 subjects) in the delamanid group, 45.5% (10 of 22 subjects) in the delamanid/EB/Rifater group, and 31.6% (6 of 19 subjects) in the EB/Rifater group. Adverse drug reactions reported by ≥2 subjects in any group were abdominal pain and headache in 3 subjects each in the delamanid group; headache in 6 subjects, abdominal pain in 4 subjects, γ-GTP increased in 3 subjects, abdominal distension, meteorism, nausea, ALT increased, AST increased, dizziness, pruritus, and rash generalised in 2 subjects each in the delamanid/EB/Rifater group; and headache in 4 subjects, diarrhoea and pruritus generalised in 2 subjects each in the EB/Rifater group (including duplicate counting).
There were neither deaths nor serious adverse events. Adverse events leading to treatment discontinuation occurred in 21 subjects (1 subject in the delamanid group, 12 subjects in the delamanid/EB/Rifater group, 8 subjects in the EB/Rifater group). In 19 of the 21 subjects, rash generalised developed before the administration of delamanid or placebo after the first dose of EB/Rifater tablet (active drug or placebo), and the treatment was discontinued. Rash generalised and pyrexia developed in 2 subjects in the delamanid/EB/Rifater group, and the treatment was discontinued. The outcomes of events in all 21 subjects were "recovered" or "resolved".

4.(ii).A.(1).8) Study on interactions in concomitant use with anti-HIV drugs in foreign healthy adults (5.3.3.4-02, Study 242-[redacted]-209 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, parallel group, comparative study was conducted at a single center in the US to investigate the safety and drug interactions of delamanid in foreign healthy adults (target sample size, 84 [12 subjects per group]) [for drug interactions, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Subjects orally received the following drug(s) under fed conditions for 14 days: (a) delamanid 100 mg BID (delamanid group), (b) EFV 600 mg QD (EFV group), (c) delamanid 100 mg BID

and EFV 600 mg QD (delamanid/EFV group), (d) TDF 300 mg QD (TDF group), (e) delamanid 100 mg BID and TDF 300 mg QD (delamanid/TDF group), (f) LPV/RTV 400/100 mg BID (LPV/RTV group), or (g) delamanid 100 mg BID and LPV/RTV 400/100 mg BID (delamanid/LPV/RTV group).

All of the 89 subjects who received the study drug (15 subjects in the delamanid group, 5 subjects in the EFV group, 4 subjects in the delamanid/EFV group, 17 subjects in the TDF group, 18 subjects in the delamanid/TDF group, 14 subjects in the LPV/RTV group, 16 subjects in the delamanid/LPV/RTV group) were included in the safety analysis set.

Adverse events were observed in 26.7% (4 of 15 subjects) in the delamanid group, 60.0% (3 of 5 subjects) in the EFV group, 100.0% (4 of 4 subjects) in the delamanid/EFV group, 52.9% (9 of 17 subjects) in the TDF group, 55.6% (10 of 18 subjects) in the delamanid/TDF group, 71.4% (10 of 14 subjects) in the LPV/RTV group, and 68.8% (11 of 16 subjects) in the delamanid/LPV/RTV group. Adverse events reported by ≥2 subjects were nausea, dizziness, and headache in 2 subjects each in the delamanid group; feeling drunk in 2 subjects in the EFV group; feeling drunk and headache in 3 subjects each, dry mouth, fatigue, and abnormal dreams in 2 subjects each in the delamanid/EFV group; viral infection and dermatitis contact in 2 subjects each in the TDF group; nausea in 5 subjects, dizziness and headache in 4 subjects each, back pain in 3 subjects, abdominal pain, vomiting, abnormal dreams, insomnia, and early menarche in 2 subjects each in the delamanid/TDF group; headache in 4 subjects, dysgeusia in 3 subjects, and abnormal dreams in 2 subjects in the LPV/RTV group; and diarrhoea in 4 subjects, oropharyngeal pain in 3 subjects, eye irritation, vision blurred, abdominal pain, nausea, vomiting, musculoskeletal chest pain, dizziness, headache, rhinorrhoea, and dermatitis contact in 2 subjects each in the delamanid/LPV/RTV group.

Adverse drug reactions[89)] were observed in 13.3% (2 of 15 subjects) in the delamanid group, 60.0% (3 of 5 subjects) in the EFV group, 100.0% (4 of 4 subjects) in the delamanid/EFV group, 11.8% (2 of 17 subjects) in the TDF group, 33.3% (6 of 18 subjects) in the delamanid/TDF group, 35.7% (5 of 14 subjects) in the LPV/RTV group, and 43.8% (7 of 16 subjects) in the delamanid/LPV/RTV group. Adverse drug reactions reported by ≥2 subjects were headache in 2 subjects in the delamanid group; feeling drunk in 2 subjects in the EFV group; feeling drunk in 3 subjects, dry mouth, headache, and abnormal dreams in 2 subjects each in the delamanid/EFV group; nausea in 4 subjects, abdominal pain, vomiting, and headache in 2 subjects each in the delamanid/TDF group; dysgeusia in 3 subjects in the LPV/RTV group; and diarrhoea in 4 subjects, nausea and vomiting in 2 subjects each in the delamanid/LPV/RTV group.

No death occurred. Serious adverse events were observed in 1 subject in the delamanid/EFV group (delirium) and in 1 subject in the delamanid/LPV/RTV group (colitis ischaemic); the outcomes of the both events were either "recovered" or "resolved". Adverse events leading to treatment discontinuation occurred in 1 subject in the delamanid/EFV group (anxiety) and in 1 subject in the delamanid/TDF group (vomiting); the outcomes of the both events were either "recovered" or "resolved".

4.(ii).A.(1).9) Study on interactions in concomitant use with efavirenz in foreign healthy adults (5.3.3.4-03, Study 242-[redacted]-212 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, parallel group, comparative study was conducted at a single center in the US to investigate the safety and drug interactions of delamanid in foreign healthy adults (target sample size, 36 [18 subjects per group]) [for drug interactions, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Delamanid 100 mg was orally administered BID for 7 days, followed by oral dose of delamanid 100 mg BID and EFV 600 mg QD for 10 days (delamanid/EFV group) or EFV 600 mg QD for 10 days (EFV group).

All of the 30 subjects who received the study drugs were included in the safety analysis set.

Adverse events were observed in 93.3% (14 of 15 subjects) in the delamanid/EFV group and 73.3% (11 of 15 subjects) in the EFV group. Adverse drug reactions[89)] were observed in 93.3% (14 of 15 subjects) in the delamanid/EFV group and 66.7% (10 of 15 subjects) in the EFV group. Adverse events and adverse drug reactions reported by ≥5 subjects were nausea and headache in 9 subjects each, dizziness and euphoric mood in 5 subjects each in the delamanid/EFV group; and euphoric mood in 5 subjects in the EFV group. There were neither deaths nor serious adverse events. Adverse events leading to treatment discontinuation were observed in 1 subject in the delamanid/EFV group (liver function test abnormal [ALP, AST, ALT, γ-GTP]), but the outcome of the event was "resolved".

4.(ii).A.(1).10) Single-dose mass balance study in foreign healthy adults (5.3.4.1-01, Study 242-[redacted]-102 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at a single center in the UK to investigate the pharmacokinetics and safety of ^{14}C-labeled delamanid in foreign healthy adult male subjects (target sample size, 6) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

^{14}C-labeled delamanid (100 mg) was orally administered in a single dose.

All of the 6 subjects who received the study drug were included in the safety analysis set.

Adverse events were observed in 66.7% (4 of 6 subjects). Atrial fibrillation, nasopharyngitis, ALT increased, γ-GTP increased, and urethral haemorrhage were observed in 1 subject each (including duplicate counting). A causal relationship of ALT increased and γ-GTP increased to the study drug could not be ruled out. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(2) Phase II studies

4.(ii).A.(2).1) Study on early bactericidal effect in foreign patients with pulmonary tuberculosis (5.3.3.2-02, Study 242-[redacted]-101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, open-label, parallel group, comparative study was conducted at 3 centers in the Republic of South Africa to investigate the efficacy, safety, and pharmacokinetics of delamanid in foreign patients with sputum culture-positive pulmonary tuberculosis without complications (target sample size, 54 [12 subjects each in the delamanid group, 6 subjects in the standard treatment group]) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

Delamanid (100, 200, 300, 400 mg) was orally administered QD after breakfast for 14 days or Rifafour tablet[85)] was orally administered QD before breakfast for 10 days (Rifafour was administered using the regimen of 5 days on/2 days off).

All of the 54 subjects who were randomized and received the study drugs were included in the safety analysis set. Of these, 45 subjects (10 subjects in each delamanid group, 5 subjects in the Rifafour group) were included in the per protocol set (PPS) for efficacy analysis, except 9 subjects (lack of efficacy endpoint data, resistance to RFP detected, insufficient treatment duration, use of prohibited drugs before the administration of the study drug, no written informed consent, GCP violation).

Table 29 shows the primary endpoint of viable counts of *M. tuberculosis* that were calculated from the sputum culture.[90)]

Table 29. Viable counts of *M. tuberculosis* calculated from sputum culture (CFU × 10^3/mL)

	100 mg	200 mg	300 mg	400 mg
Number of subjects	10	10	10	10
Viable bacterial count before the treatment with the study drug [a)]	16,871 (12,495.04)	16,997 (31,272.9)	8405.7 (8158.42)	21,844 (47,544.6)
Final viable bacterial count [b)]	14,397.8 (20,177.16)	1579 (1816.4)	7824.25 (15,671.34)	5805.4 (7651)
Change in viable bacterial count [c)]	-2473.2 (19,561.23)	-15,418 (29,877.5)	-581.44 (8653.4)	-16,038.6 (43,033.7)

Mean (SD)

a) Mean of viable bacterial count 2 days and 1 day before the start of treatment

b) Viable bacterial count calculated from the last sputum culture obtained after the treatment with the study drug

c) Difference in the viable bacterial count between the final bacterial count and the baseline viable bacterial count

Adverse events were observed in 58.3% (7 of 12 subjects) in the delamanid 100 mg group, 50.0% (6 of 12 subjects) in the delamanid 200 mg group, 41.7% (5 of 12 subjects) in the delamanid 300 mg group, 33.3% (4 of 12 subjects) in the delamanid 400 mg group, and 83.3% (5 of 6 subjects) in the Rifafour group. Adverse events reported by ≥2 subjects were pleuritic pain in 2 subjects in the delamanid 100 mg group, application site pruritus and pruritus generalised in 2 subjects in the delamanid 300 mg group, and haemoptysis in 2 subjects in the Rifafour group. Adverse drug reactions[91)] were observed in 0% (0 of 12 subjects) in the delamanid 100 mg group, 25.0% (3 of 12 subjects) in the delamanid 200 mg group, 8.3% (1 of 12 subjects) in the delamanid 300 mg group, 8.3% (1 of 12 subjects) in the delamanid 400 mg group, and 50.0% (3 of 6 subjects) in the Rifafour group. There were no adverse drug reactions reported by ≥2 subjects. No death occurred, but serious adverse events were observed in 4 subjects (1 subject in the delamanid 100 mg group [electrocardiogram QT prolonged], 1 subject in the delamanid 200 mg group [electrocardiogram QT prolonged], 1 subject in the delamanid 300 mg group [electrocardiogram QT prolonged, transaminases increased], 1 subject in the delamanid 400 mg group [transaminases increased]). For electrocardiogram QT prolonged in 1 subject in the delamanid 200 mg group, a causal relationship to delamanid could not be ruled out. There were no adverse events leading to treatment discontinuation.

4.(ii).A.(2).2) Phase II study in foreign patients with multidrug-resistant pulmonary tuberculosis refractory to conventional treatment (5.3.5.2-02, Study 242-[redacted]-210 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A dose titration, open-label study was conducted at 3 centers in 2 foreign countries (1 center in Latvia, 2 centers in Lithuania) to investigate the safety, efficacy, and pharmacokinetics in concomitant use of delamanid with OBRs in foreign patients with multidrug-resistant pulmonary tuberculosis refractory to conventional treatment[92)] (target sample size, 30 [5 subjects per group]) [for pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies, clinical pharmacology studies, and associated analytical methods"].

In combination with an OBR selected for each subject, delamanid (250 mg) was administered BID and was allowed to be titrated by 100 mg/day (50 mg/dose) up to 400 mg BID. The treatment duration was 196 days. According to the WHO guidelines[3)], each OBR was required to include at

90) Each subject was to pool 16-hour sputum at 2 days and 1 day before the start oftreatment, on the next day of starting the treatment, then every 2 days up to Day 15.

91) Adverse events were classified as "definitely related," "probably related," "possibly related," "unlikely to be related," or "not related" to the study drug, and those rated as "definitely related," "probably related," or "possibly related" were regarded as adverse drug reactions.

92) Patients who are resistant to INH and RFP treatment (as assessed by *in vitro* test) and who remain sputum culture-positive for ≥3 times (should be positive at least once within 60 days before the scheduled date of enrollment) over 270 days (9 months) despite treatment with the first-line or the second-line anti-tuberculosis drugs.

least 4 drugs that were known or expected to be effective against the strain of *M. tuberculosis* detected each patient and the drugs were to be selected according to the steps stipulated in Table 30.

Table 30. Step-wise approach for selecting drugs against multidrug-resistant pulmonary tuberculosis (from WHO guidelines)

Step 1	Group 1: any available first-line oral agents: PZA, EB, RBT	Use any Group 1 drugs that is the most potent and the most tolerable drugs when the patient's laboratory findings and the history of clinical treatment suggest that Group 1 drugs are effective.
Step 2	Group 2:at least one of these injectable agents: KM (or AMK), capreomycin, SM	Make sure to add an injectable agent in this group when susceptibility to the drug is recorded or expected. As a rule, taking account of the high rate of emergence of resistance to SM in this patient population (when SM was used as the first-line drug), use KM or AMK as the first-choice.
Step 3	Group 3: at least one of these fluoroquinolones: LVFX, MFX, ofloxacin	Add a fluoroquinolone based on a drug sensitivity test (DST) and treatment history. In cases where resistance to ofloxacin or extensively drug-resistant tuberculosis is suspected, use a higher-generation fluoroquinolone.
Step 4	Group 4: at least one of these second-line oral bacteriostatic agents: PAS, CS (or terizidone), TH (or prothionamide)	Add Group 4 drugs until the regimen has at least four drugs likely to be effective. The patient's treatment history, adverse effect profile, and costs should be taken into consideration to best select drugs. DST is not standardized for the drugs in this group.
Step 5	Group 5: agents of unclear role in DR-TB treatment: lofazimine, linezolid, amoxicillin/clavulanic acid, thioacetazone, imipenem/cilastatin, high-dose INH, CAM	The efficacy of drugs in this group has not been established in multi-drug therapies. Consider adding Group 5 drugs in consultation with an MDR-TB expert if there are not four drugs that are likely to be effective from Group 1 to 4. If drugs are needed from this group, it is recommended to add at least two. DST is not standardized for the drugs in this group.

All of the 10 subjects (5 subjects in the delamanid 250 mg group, 5 subjects in the delamanid 300 mg group) who received the study drug were included in the intention-to-treat population (ITT population) and were evaluable for both safety and efficacy.

Sputum culture conversion (SCC)[93] in mycobacterium growth indicator tubes (MGIT) or on the solid medium on Day 168, the efficacy endpoint, was achieved in 0 of 5 subjects in the delamanid 250 mg group and in 1 of 5 subjects in the delamanid 300 mg group.[94]

Adverse events (including laboratory changes)[95] were observed in 5 of 5 subjects in the delamanid 250 mg group and in 5 of 5 subjects in the delamanid 300 mg group. Adverse events reported by ≥2 subjects in either group were as shown in Table 31. Adverse drug reactions[89] were observed in 1 subject in the delamanid 300 mg group (acute myocardial infarction, atrial fibrillation, atrioventricular block first degree, coronary artery disease, sinus tachycardia, electrocardiogram QT prolonged, electrocardiogram ST-T change).

93) SCC was defined as the condition where a negative culture was observed, sampled at least once at intervals of at least 28 days and confirmed to be negative throughout the rest of the study period.

94) This study failed to demonstrate the efficacy. Plasma delamanid concentration was non-linear and, as a result of the data review by the data monitoring committee, no additional subjects were enrolled after the first 2 groups.

95) Adverse events were defined as (i) harmful events that occurred after the start of the study drug or (ii) those persisting from before the start of the administration that were serious, study-drug related, fatal, or resulted in discontinuation or interruption of administration or dose reduction.

Table 31. Adverse events reported by ≥2 subjects in either group

Dosage and administration	Delamanid 250 mg BID	Delamanid 300 mg BID
Number of subjects	5	5
No. of subjects with events (incidence %)	5 (100)	5 (100)
Anaemia	2 (40.0)	0 (0.0)
Abdominal distension	2 (40.0)	0 (0.0)
Abdominal pain upper	2 (40.0)	0 (0.0)
Diarrhoea	2 (40.0)	0 (0.0)
Nausea	3 (60.0)	1 (20.0)
Vomiting	3 (60.0)	0 (0.0)
Chest pain	2 (40.0)	0 (0.0)
Hepatomegaly	3 (60.0)	0 (0.0)
Tuberculosis	1 (20.0)	4 (80.0)
Viral upper respiratory tract infection	1 (20.0)	3 (60.0)
Weight decreased	2 (40.0)	0 (0.0)
Decreased appetite	3 (60.0)	0 (0.0)
Hyperglycaemia	4 (80.0)	2 (40.0)
Hyperkalaemia	2 (40.0)	0 (0.0)
Insomnia	2 (40.0)	0 (0.0)
Asthma	0 (0.0)	2 (40.0)
Cough	3 (60.0)	0 (0.0)
Lung lobectomy	2 (40.0)	0 (0.0)

Number of subjects (%)

Death occurred in 1 subject in the delamanid 300 mg group (tuberculosis, alcohol abuse, acute myocardial infarction, coronary artery disease). A causal relationship of acute myocardial infarction and coronary artery disease to the study drug could not be ruled out. Other serious adverse events occurred in 2 subjects in the 250 mg group (lung lobectomy in 2 subjects, post procedural haemorrhage and anaemia in 1 subject each [including duplicate counting]) and in 2 subjects in the 300 mg group (tuberculosis, pneumonectomy, atrial fibrillation, electrocardiogram QT prolonged in 1 subject each [including duplicate counting]), but all symptoms improved or resolved. Adverse events leading to treatment discontinuation were observed in 2 subjects in the delamanid 300 mg group (atrial fibrillation and tuberculosis in 1 subject each), and both symptoms resolved or improved after treatment discontinuation.

4.(ii).A.(2).3) Global phase II study in patients with multidrug-resistant pulmonary tuberculosis (5.3.5.1-01, Study 242-[redacted]-204 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A placebo-controlled, randomized, double-blind, parallel group, comparative study was conducted at 17 centers in 9 countries (4 centers in Korea, 3 centers in Peru, 2 centers in Estonia, 2 centers in China, 2 centers in Japan, 1 center in the US, 1 center in Latvia, 1 center in Egypt, 1 center in the Philippines) to investigate the efficacy, safety, and pharmacokinetics in concomitant use of delamanid with OBRs in patients with multidrug-resistant, sputum culture-positive pulmonary tuberculosis[96)] (target sample size, 430 [approximately 140 subjects per group]).

Delamanid (100 mg, 200 mg) or placebo was orally administered BID for 56 days in combination with an OBR selected for each patient.

A total of 481 subjects who were randomized to receive the study drugs (161 subjects in the delamanid 100 mg group, 160 subjects in the delamanid 200 mg group, 160 subjects in the placebo group) were included in the ITT population and the safety analysis set. A total of 402 subjects (141 subjects in the delamanid 100 mg group, 136 subjects in the delamanid 200 mg group, 125 subjects in the placebo group) were included in the modified ITT (mITT) population for efficacy

96) Patients with tuberculosis caused by *Mycobacteria* strains (i) resistant to treatment with INH and RFP,(ii) positive for rapid test for RFP resistance and positive for sputum smear test for acid-fast bacilli, or (iii) positive for *M. tuberculosis* culture, as assessed by a sputum test.

analysis, excluding 79 subjects who were not confirmed to have multidrug-resistant pulmonary tuberculosis by sputum culture using MGIT before the start of administration (1 day before the start of treatment and/or Day 1 of treatment).

The percentages of subjects who achieved the primary efficacy endpoint of MGIT-assessed SCC by Day 57 of treatment,[97)] (the achievement rate of 2-month SCC) were 45.4% (64 of 141 subjects) in the delamanid 100 mg group, 41.9% (57 of 136 subjects) in the delamanid 200 mg group, and 29.6% (37 of 125 subjects) in the placebo group, with the risk ratios [95% CI] of delamanid 100 mg and delamanid 200 mg relative to placebo being 1.53 [1.11, 2.12] and 1.42 [1.01, 1.98], and these results demonstrated the superiority of the delamanid 100 mg group and the delamanid 200 mg group to the placebo group. ($P = 0.0083$ and $P = 0.0393$, respectively, by Cochran-Mantel Haenszel test stratified by the presence/absence of cavitation. Adjusted for multiplicity of test by Hochberg method).

A total of 12 Japanese subjects were enrolled in the study, of whom 8 subjects were included in the primary efficacy endpoint assessment. As a result, 3 subjects (1 subject each in the delamanid 100 mg group, delamanid 200 mg group, and placebo group) achieved 2-month SCC.

Adverse events[98)] were observed in 90.1% (145 of 161 subjects) in the delamanid 100 mg group, 93.1% (149 of 160 subjects) in the delamanid 200 mg group, and 93.1% (149 of 160 subjects) in the placebo group. Adverse drug reactions[89)] were observed in 38.5% (62 of 161 subjects) in the delamanid 100 mg group, 40.6% (65 of 160 subjects) in the delamanid 200 mg group, and 35.6% (57 of 160 subjects) in the placebo group. Adverse events and adverse drug reactions reported by ≥10% of subjects in any group were as shown in Table 32.

97) Subjects who achieved SCC by MGIT within 57 days of treatment, maintained SCC at 27 days after the first SCC achievement, and did not show positive sputum culture at any time points during the remaining treatment period after SCC (up to Day 84).

98) Adverse events were defined as (i) harmful events that occurred after the start of the study drug or (ii) those persisting from before the start of the administration that were serious, study-drug related, fatal, or resulted in discontinuation or interruption of administration or dose reduction.

Table 32. Adverse events reported by ≥10% of subjects in any group (ITT population)

	Delamanid 100 mg group (N = 161)		Delamanid 200 mg group (N = 160)		Placebo group (N = 160)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Number of subjects with events	145 (90.1)	62 (38.5)	149 (93.1)	65 (40.6)	149 (93.1)	57 (35.6)
Anaemia	18 (11.2)	2 (1.2)	10 (6.3)	2 (1.3)	14 (8.8)	1 (0.6)
Reticulocytosis	19 (11.8)	2 (1.2)	20 (12.5)	2 (1.3)	17 (10.6)	3 (1.9)
Palpitations	13 (8.1)	2 (1.2)	20 (12.5)	8 (5.0)	10 (6.3)	4 (2.5)
Tinnitus	16 (9.9)	2 (1.2)	22 (13.8)	2 (1.3)	12 (7.5)	1 (0.6)
Abdominal pain upper	41 (25.5)	1 (0.6)	36 (22.5)	4 (2.5)	38 (23.8)	3 (1.9)
Diarrhoea	20 (12.4)	1 (0.6)	12 (7.5)	4 (2.5)	22 (13.8)	2 (1.3)
Gastritis	8 (5.0)	1 (0.6)	14 (8.8)	1 (0.6)	16 (10.0)	1 (0.6)
Nausea	58 (36.0)	6 (3.7)	65 (40.6)	7 (4.4)	53 (33.1)	6 (3.8)
Vomiting	48 (29.8)	10 (6.2)	58 (36.3)	5 (3.1)	44 (27.5)	2 (1.3)
Asthenia	20 (12.4)	4 (2.5)	27 (16.9)	2 (1.3)	20 (12.5)	1 (0.6)
Injection site pain	13 (8.1)	0 (0)	12 (7.5)	0 (0)	23 (14.4)	0 (0)
Malaise	12 (7.5)	0 (0)	16 (10.0)	2 (1.3)	12 (7.5)	0 (0)
Pyrexia	9 (5.6)	0 (0)	18 (11.3)	1 (0.6)	18 (11.3)	0 (0)
Electrocardiogram QT prolonged	16 (9.9)	10 (6.2)	21 (13.1)	13 (8.1)	6 (3.8)	2 (1.3)
Anorexia	23 (14.3)	1 (0.6)	34 (21.3)	3 (1.9)	24 (15.0)	5 (3.1)
Hyperuricaemia	31 (19.3)	0 (0)	38 (23.8)	1 (0.6)	35 (21.9)	1 (0.6)
Hypokalaemia	20 (12.4)	6 (3.7)	31 (19.4)	2 (1.3)	24 (15.0)	3 (1.9)
Arthralgia	32 (19.9)	4 (2.5)	43 (26.9)	1 (0.6)	46 (28.8)	3 (1.9)
Back pain	12 (7.5)	0 (0)	16 (10.0)	0 (0)	19 (11.9)	1 (0.6)
Myalgia	15 (9.3)	3 (1.9)	21 (13.1)	1 (0.6)	26 (16.3)	1 (0.6)
Dizziness	48 (29.8)	4 (2.5)	49 (30.6)	7 (4.4)	49 (30.6)	6 (3.8)
Headache	36 (22.4)	3 (1.9)	41 (25.6)	5 (3.1)	30 (18.8)	5 (3.1)
Paraesthesia	17 (10.6)	1 (0.6)	20 (12.5)	0 (0)	12 (7.5)	1 (0.6)
Tremor	19 (11.8)	4 (2.5)	16 (10.0)	2 (1.3)	13 (8.1)	1 (0.6)
Insomnia	42 (26.1)	13 (8.1)	52 (32.5)	19 (11.9)	42 (26.3)	9 (5.6)
Haemoptysis	19 (11.8)	1 (0.6)	15 (9.4)	0 (0)	17 (10.6)	0 (0)
Rales	12 (7.5)	0 (0)	11 (6.9)	0 (0)	16 (10.0)	0 (0)
Pruritus	15 (9.3)	2 (1.2)	15 (9.4)	1 (0.6)	20 (12.5)	4 (2.5)

Number of affected subjects (%)

Death occurred in 1 subject in the delamanid 200 mg group (respiratory failure). A causal relationship of the death to the study drug was ruled out. Other serious adverse events were observed in 9.9% (16 of 161 subjects) in the delamanid 100 mg group (electrocardiogram QT prolonged in 7 subjects, anaemia and haemoptysis in 3 subjects each, psychotic disorder in 2 subjects, and thrombocytopenia, hepatitis, fall, agitation, hallucination auditory, ideas of reference, pneumothorax, haematoma, and hypotension in 1 subject each [including duplicate counting]), in 12.5% (20 of 160 subjects) in the delamanid 200 mg group (electrocardiogram QT prolonged in 9 subjects, anaemia, hypokalaemia, and psychotic disorder in 2 subjects each, leukopenia, thrombocytopenia, sinus tachycardia, deafness, chest discomfort, hepatitis, liver disorder, lower respiratory tract infection, oropharyngeal candidiasis, electrocardiogram T wave abnormal, syncope, agitation, anxiety, delusional disorder persecutory type, mental disorder, suicidal ideation, renal failure, haemoptysis, and respiratory failure in 1 subject each [including duplicate counting]), and in 8.8% (14 of 160 subjects) in the placebo group (electrocardiogram QT prolonged and psychotic disorder in 3 subjects each, haemoptysis in 2 subjects, and anaemia, hepatitis, pneumonia, hypoglycaemia, syncope, hallucination, schizophrenia paranoid type, hydropneumothorax, pneumothorax, and dermatitis allergic in 1 subject each [including duplicate counting]). Adverse events leading to treatment discontinuation occurred in 4 subjects in the delamanid 100 mg group (thrombocytopenia, aggression, dysphoria, and erythema nodosum in 1 subject each), 6 subjects in the delamanid 200 mg group (psychotic disorder in 2 subjects, leukopenia, mental disorder, respiratory failure, and rash generalised in 1 subject each), and 4 subjects in the placebo group (hepatitis, syncope, psychotic disorder, and dermatitis allergic in 1 each). A causal relationship to the study drug was ruled out for respiratory failure and rash generalised in 2 subjects in the delamanid 200 mg group. All the events except respiratory failure

in 1 subject in the delamanid 100 mg group resolved or improved.

Among 12 Japanese subjects, adverse events were observed in 4 of 4 subjects in the delamanid 100 mg group (induration in 4 subjects, anaemia, gastritis, malaise, headache, hypoaesthesia, skin haemorrhage, eczema, and dry skin in 1 subject each [including duplicate counting]), in 5 of 6 subjects in the delamanid 200 mg group (rash and eosinophil count increased in 2 subjects each, nausea, gastritis, dyspepsia, hepatic function abnormal, haemoglobin decreased, depression, upper respiratory tract inflammation, eczema, psoriasis, rash generalised, and alopecia in 1 subject each [including duplicate counting]), and in 2 of 2 subjects in the placebo group (gastritis in 2 subjects, anaemia, folate deficiency, osteoporosis, paraesthesia, somnolence, insomnia, depression, rash, and eczema in 1 subject each [including duplicate counting]). Adverse drug reaction observed was dyspepsia in 1 of 6 subjects in the delamanid 200 mg group. Neither death nor serious adverse event occurred. An adverse event leading to treatment discontinuation was observed in 1 subject in the delamanid 200 mg group (rash generalised), for which a causal relationship to the study drug could not be ruled out.

4.(ii).A.(2).4) Global long-term study in patients with multidrug-resistant pulmonary tuberculosis (5.3.5.2-01, Study 242-[redacted]-208 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 14 centers in 7 countries (3 centers each in Peru and Korea, 2 centers each in Japan, Estonia, and China, 1 center each in Latvia and the Philippines) to investigate the safety and efficacy in concomitant use of delamanid with OBRs in patients with multidrug-resistant pulmonary tuberculosis who completed the global phase II study (Study 242-[redacted]-204) (target sample size, 250).

Delamanid 100 mg was orally administered BID for 26 weeks in combination with an OBR selected for each subject. The dose of delamanid was allowed to be increased to 200 mg BID after 2 weeks of treatment at the discretion of the investigator.

A total of 213 subjects who received the study drug (137 subjects in the delamanid 100 mg group[99)], 76 subjects in the delamanid 200 mg group[100)]) were included in the safety analysis set, and 205 subjects were included in the efficacy analysis set, excluding 8 subjects (5 subjects in the delamanid 100 mg group, 3 subjects in the delamanid 200 mg group) in whom efficacy was not evaluated before and after administration.

The percentages of subjects achieved the efficacy endpoint of sustained negative or sputum culture conversion to negative by MGIT or by solid medium[101)] were 79.5% (105 of 132 subjects) in the delamanid 100 mg group and 75.3% (55 of 73 subjects) in the delamanid 200 mg group according to the results of culture by MGIT, and 81.8% (108 of 132 subjects) in the delamanid 100 mg group and 82.2% (60 of 73 subjects) in the delamanid 200 mg group according to the assessment of the culture in solid medium.

A total of 7 Japanese subjects were enrolled in the study. Results of the sputum culture tests were sustained negative or sputum culture conversion to negative in 4 of 4 subjects in the delamanid

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99) The population consisting of subjects who were treated with delamanid 100 mg BID for a longer period than with delamanid 200 mg BID

100) The population consisting of subjects who were treated with delamanid 200 mg BID for a longer period than with delamanid 100 mg BID

101) (a) "Sustained negative": SCC was achieved on the visit day before treatment and the culture test did not become positive during the subsequent 26-week treatment period. (b) "Sputum culture conversion": Sputum culture was positive on the visit day before treatment but SCC was achieved after treatment start. (c) "Without sputum culture conversion": Sputum culture was positive on the visit day before treatment and the culture did not become negative during the subsequent 26-week treatment period. (d) "Positive reconversion": SCC was achieved on the visit day before treatment, but the culture test was positive at least once during the subsequent 26-week treatment period. Of classification (a) to (d), "sustained negative" cases and "sputum culture conversion" cases were regarded as effective cases, and cases of "without sputum culture conversion" and of "positive reconversion" were regarded as ineffective cases.

100 mg group and in 2 of 3 subjects in the delamanid 200 mg group, according to the assessment by MGIT culture and by solid medium culture.

Adverse events[102)] were observed in 92.0% (126 of 137 subjects) in the delamanid 100 mg group and 97.4% (74 of 76 subjects) in the delamanid 200 mg group. Adverse drug reactions[89)] were observed in 64.2% (88 of 137 subjects) in the delamanid 100 mg group and 34.2% (26 of 76 subjects) in the delamanid 200 mg group. Adverse events and adverse drug reactions reported by ≥10% of subjects in either group were as shown in Table 33.

Table 33. Adverse events and adverse drug reactions reported by ≥10% of subjects in either group

	Delamanid 100 mg group (N = 137)		Delamanid 200 mg group (N = 76)		Total (N = 213)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
No. of subjects with events	126 (92.0)	88 (64.2)	74 (97.4)	26 (34.2)	200 (93.9)	53.5 (114)
Palpitations	18 (13.1)	9 (6.6)	0 (0)	0 (0)	18 (8.5)	9 (4.2)
Tinnitus	16 (11.7)	1 (0.7)	5 (6.6)	0 (0)	21 (9.9)	1 (0.5)
Abdominal pain upper	19 (13.9)	10 (7.3)	6 (7.9)	1 (1.3)	25 (11.7)	11 (5.2)
Diarrhoea	14 (10.2)	1 (0.7)	7 (9.2)	1 (1.3)	21 (9.9)	2 (0.9)
Gastritis	10 (7.3)	7 (5.1)	8 (10.5)	4 (5.3)	18 (8.5)	11 (5.2)
Nausea	20 (14.6)	6 (4.4)	15 (19.7)	1 (1.3)	35 (16.4)	7 (3.3)
Vomiting	24 (17.5)	5 (3.6)	5 (6.6)	0 (0)	29 (13.6)	5 (2.3)
Nasopharyngitis	12 (8.8)	0 (0)	12 (15.8)	0 (0)	24 (11.3)	0 (0)
Arthralgia	21 (15.3)	2 (1.5)	8 (10.5)	0 (0)	29 (13.6)	2 (0.9)
Myalgia	15 (10.9)	5 (3.6)	2 (2.6)	0 (0)	17 (8.0)	5 (2.3)
Dizziness	19 (13.9)	6 (4.4)	3 (3.9)	0 (0)	22 (10.3)	6 (2.8)
Headache	42 (30.7)	25 (18.2)	12 (15.8)	8 (10.5)	54 (25.4)	33 (15.5)
Somnolence	14 (10.2)	11 (8.0)	4 (5.3)	3 (3.9)	18 (8.5)	14 (6.6)
Tremor	9 (6.6)	2 (1.5)	0 (0)	0 (0)	9 (4.2)	2 (0.9)
Insomnia	30 (21.9)	10 (7.3)	20 (26.3)	6 (7.9)	50 (23.5)	16 (7.5)
Pruritus	14 (10.2)	6 (4.4)	4 (5.3)	1 (1.3)	18 (8.5)	7 (3.3)

Number of affected subjects (%)

Death occurred in 1 subject in the delamanid 100 mg group (right heart failure). Serious adverse events were observed in 13.9% (19 of 137 subjects) in the delamanid 100 mg group (hyperbilirubinaemia, tuberculosis, and haemoptysis in 2 subjects each, right ventricular failure, appendicitis, lung infection, pulmonary tuberculoma, gun shot wound, blood pressure increased, electrocardiogram QT prolonged, hypokalaemia, headache, polyneuropathy, abortion incomplete, completed suicide, dyspnoea, hydropneumothorax, respiratory failure, and transaminases increased in 1 subject each [including duplicate counting]), and 7.9% (6 of 76 subjects) in the delamanid 200 mg group (electrocardiogram QT prolonged, hepatitis acute, hyperbilirubinaemia, tuberculosis, intentional overdose, lip and/or oral cavity cancer, and suicide attempt in 1 subject each [including duplicate counting]). A causal relationship to the study drug could not be ruled out for adverse events in 4 subjects in the delamanid 100 mg group (headache, electrocardiogram QT prolonged, transaminases increased, and abortion incomplete in 1 subject each) and in 1 subject in the delamanid 200 mg group (electrocardiogram QT prolonged), but all these events resolved or improved. Adverse events leading to treatment discontinuation were observed in 3 subjects in the delamanid 100 mg group (right heart failure, electrocardiogram QT prolonged, and abortion incomplete in 1 subject each [including 1 fatal case]) and in 4 subjects in the delamanid 200 mg group (hepatitis acute, electrocardiogram QT prolonged, suicide attempt, and lip and/or oral cavity cancer in 1 subject each). A causal relationship to the study drug could not be ruled out for the adverse events except those in 3 subjects in the delamanid 200 mg group (hepatitis acute, suicide attempt, lip and/or oral cavity cancer), but these events resolved or improved except

[102)] Adverse events were defined as (i) harmful events that occurred after the start of the study drug or (ii) those persisting from before the start of the administration that were serious, study-drug related, fatal, or resulted in discontinuation or interruption of administration or dose reduction.

in 1 subject (right heart failure) who died.

In the 7 Japanese subjects, adverse events were observed in 3 of 4 subjects in the delamanid 100 mg group (pruritus and alopecia in 2 subjects each, palpitations, hypothyroidism, dry eye, vomiting, diarrhoea, abdominal pain, cheilitis, stomatitis, chest pain, platelet count increased, nicotinic acid deficiency, muscular weakness, headache, depression, throat irritation, blister, and hyperkeratosis in 1 subject each [including duplicate counting]), and in 3 of 3 subjects in the delamanid 200 mg group (gastritis, anal fistula, stomatitis, contusion, heat illness, nasopharyngitis, tinea infection, arthralgia, depression, and skin ulcer in 1 subject each [including duplicate counting]). An adverse drug reaction was observed in 1 subject in the delamanid 100 mg group (pruritus). There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

4.(ii).A.(2).5) Registration study to evaluate treatment outcome (Reference data 5.3.5.4-01, Study 242-[redacted]-116 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An observational study was conducted at 18 centers in 9 countries (4 centers in Korea, 3 centers in Peru, 2 centers each in China, Estonia, Japan, and Latvia, 1 center each in Egypt, the Philippines, and the US) to collect the data of final outcome in patients with multidrug-resistant pulmonary tuberculosis who participated in study 242-[redacted]-204 or 242-[redacted]-210 (target sample size, 491 subjects at the maximum).

A total of 425 subjects enrolled in the study (421 participants in Study 242-[redacted]-204, 4 participants in Study 242-[redacted]-210) were included in the efficacy analysis set.

The primary efficacy endpoint of the final treatment outcomes assessed by the investigator[103)] were "cured" in 52.2% (222 of 425 subjects), "treatment completed" in 11.3% (48 of 425 subjects), "defaulted" in 17.2% (73 of 425 subjects), "failed" in 14.1% (60 of 425 subjects), and "died" in 5.2% (22 of 425 subjects).

Safety was not evaluated in this study.

A total of 11 Japanese subjects were enrolled in the study. The primary efficacy endpoint of the final treatment outcomes assessed by the investigator were "cured" in 3 subjects and "failed" in 8 subjects (when the final outcomes were assessed based on sputum culture conversion at the time point of 24 months according to the WHO criteria[3)] , the final outcomes were "cured" in 6 subjects, "treatment completed" in 3 subjects and "failed" in 2 subjects).

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Design of global phase II study (Study 242-[redacted]-204)

4.(ii).B.(1).1) Appropriateness of mainly evaluating the data of global phase II study (Study 242-[redacted]-204)

In Japan, there are only approximately 100 patients with multidrug-resistant pulmonary tuberculosis each year.[5)] PMDA asked the applicant to explain the appropriateness of creating the

[103)] The final outcome of each subject was assessed at the end of the extended treatment period according to the following definitions described in "Guidelines for the Programmatic Management of Drug-resistant Tuberculosis (2008)." "Cured": Patient who has completed treatment according to the treatment protocol and has at least 5 consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. (If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart). "Treatment completed": Patient who has completed treatment according to treatment protocol but does not meet the definition for cure because of a lack of bacteriological results (i.e. fewer than 5 cultures were performed in the final 12 months of treatment). "Died": Patient who dies for any reason during the course of multi-drug resistant tuberculosis treatment. "Failed": If 2 or more of the 5 cultures recorded in the final 12 months of therapy are positive, or if any one of the final 3 cultures is positive. "Defaulted": Patient whose treatment was interrupted for 2 or more consecutive months for any reason without medical approval.

clinical data package for the application with a focus on the data from the global phase II study (Study 242-[redacted]-204) in which Japanese patients participated from the following 3 aspects.

(a) Similarities or differences in patient characteristics and pharmacokinetics between Japanese and foreign patients
(b) Effect of regional similarities/differences in OBRs on the evaluation of the efficacy and safety of delamanid
(c) Effect of similarities/differences between Japan and other countries in the sensitivity of multidrug-resistant *M. tuberculosis* on the efficacy of delamanid

The applicant explained as follows:

(a) Similarities or differences in patient characteristics and pharmacokinetics between Japanese and foreign patients

When a human body is exposed to *M. tuberculosis,* the natural immune system of the body responds nonspecifically to and kills the bacteria. Then the alveolar macrophages that have phagocytosed the bacteria present antigenic substances to T lymphocytes, which results in a specific, cell-mediated immune reaction, thereby leading to the inactivation of bacteria. However, it is known that *M. tuberculosis* cells are latent in foci and that the dormant cells become reactivated when the resistance of the host is decreased. Latent infection develops into an active disease in approximately 10% of patients with *M .tuberculosis* infection. Factors that trigger the activation of bacteria include immune dysfunction (HIV infection in particular), some immune depressants (e.g., corticosteroids, infliximab and other tumor necrosis factor inhibitors), gastrectomy, jejunoileal bypass, silicosis, renal failure, stress, diabetes mellitus, head and neck cancer, adolescence, and advanced age (>70 years of age, in particular). Since these factors depend on the conditions of individual patients rather than on ethnic differences, there is no significant difference in patient characteristics between Japanese and foreign patients.

The global phase II study (Study 242-[redacted]-204) also showed that C_{max} and $AUC_{0\text{-}24h}$ of delamanid and C_{max} of DM-6705 in Japanese patients were within the range of variations of these parameters in foreign patients [see "4.(i).A.(3).2) Phase II studies in patients with multidrug-resistant pulmonary tuberculosis"]. Based on this finding, the applicant considers that there is no significant difference in the pharmacokinetics of delamanid between Japanese and foreign patients.

(b) Effect of regional similarities/differences in OBRs on the efficacy and safety assessments of delamanid

The guidelines[3)] for the treatment of multidrug-resistant tuberculosis prepared by WHO is used worldwide for the treatment of the disease. The guidelines classify anti-tuberculosis drugs into 5 groups (Table 30) and require the use of at least 4 supposedly effective drugs during the intensive treatment phase (a 6-month intensive care from the start of treatment including the use of an injectable drug) and at least 3 drugs during the maintenance phase (a 20-month treatment period with oral drugs alone following the intensive treatment phase), and recommend to follow the rules 1) to 5) below for the selection of the anti-tuberculosis drugs.

1) Use any agents in Group 1 that are likely to be effective.
2) Add 1 injectable agents in Group 2 that is likely to be effective.
3) Select 1 fluoroquinolone in Group 3 that is likely to be effective.
4) Select Group 4 drugs until you have at least 4 drugs that are likely to be effective (during the intensive treatment phase).
5) If there are not 4 drugs from Groups 1 to 4, consider adding Group 5 drugs (at least 2 drugs) in consultation with an expert on drug-resistant tuberculosis.

In Japan, the Treatment Committee of the Japanese Society for Tuberculosis has proposed a guideline on the classification of anti-tuberculosis drugs including fluoroquinolones in addition to those commercially available in Japan and a method for selecting the drugs.[44)] The guideline requires physicians to select drugs according to the procedure stipulated in Table 34 and to administer at least 3 (4 or 5, if feasible) effective drugs during an early phase of the treatment and continue the treatment until 24 months after the culture test has become negative.

Table 34. Classification of anti-tuberculosis drugs and rules for use in Japan

	Characteristics	Drugs
First-line drugs (a)	Drugs that exhibit the most potent antibacterial activity and are essential for eradicating the bacteria	INH, RFP [RBT][a)], PZA
First-line drugs (b)	Drugs that are expected to exhibit efficacy when co-administered with the first-line drugs (a)	SM, EB
Second-line drugs	Drugs that are less effective than the first line drugs but are expected to be effective when used in combination with multiple drugs	KM, TH, enviomycin, PAS, CS, LVFX[b)]

Drugs in the table are listed in the order of priority.
SM, KM, and enviomycin cannot be used simultaneously. Drugs are selected in the order of SM→KM→enviomycin with consideration given to antibacterial activity and cross resistance.
a) If RFP cannot be used because of drug interactions or adverse drug reactions, the use of RBT is considered.
b) LVFX may be replaced by other fluoroquinolone drugs. Drug are selected one from MFX, gatifloxacin, ciprofloxacin, and sparfloxacin with consideration given to antibacterial activity, adverse drug reactions, etc.

A difference between the WHO guidelines and the treatment guidelines of Japan is the priority in the selection of drugs, which is due to the fact that fluoroquinolones are not indicated for tuberculosis in Japan. However, both guidelines recommend the use of a total of 4 drugs (or 3 drugs if PZA cannot be used) including at least 1 available first-line oral drug, 1 injectable aminoglycoside, and 1 fluoroquinolone. Thus, there are no significant differences in the treatment policies for multidrug-resistant tuberculosis between Japan and other countries.

(c) Effect of similarities/differences between Japan and other countries in the sensitivity of multidrug-resistant *M. tuberculosis* on the efficacy of delamanid

Table 35 shows the sensitivity to the drugs in Groups 1 to 4 of multidrug-resistant *M. tuberculosis* isolated in 9 countries where the global phase II study (Study 242-[redacted]-204) was conducted (the Philippines, Latvia, Estonia, Korea, China, Japan, Peru, the US, Egypt), based on the WHO's report on the resistance to anti-tuberculosis drugs and literature published in Japan and other countries.

Table 35. Rate of emergence of resistance to existing anti-tuberculosis drugs

	Group 1	Group 2				Group 3	Group 4	
	EB	SM	AMK	KM	Capreomycin	Fluoroquinolone	TH	PAS
Philippines	54.5%[1)]	60.6%[1)]	1.8%[2)]	1.8%[2)]	0.3%[2)]	50.9%[1)]	30.5%[2)]	2.0%[2)]
	77.6%[2)]	60.4%[2)]				7.1%[2)]		
Latvia	88.1%[1)]	98.8%[1)]	35.0%[2)]	42.0%[2)]	15.0%[2)]	0%[1)]	23.0%[2)]	24.0%[2)]
	65.0%[2)]	96.0%[2)]				14.0%[2)]		
Estonia	93.7%[1)]	98.7%[1)]	23.9%[2)]	28.3%[2)]	4.4%[2)]	0%[1)]	10.9%[2)]	4.4%[2)]
	89.1%[2)]	100.0%[2)]				26.1%[2)]		
Korea	58.2%[1)]	20.9%[1)]	18.2%[2)]	23.2%[2)]	14.1%[2)]	11.8%[1)]	11.1%[2)]	34.3%[2)]
	57.6%[2)]	46.5%[2)]				32.3%[2)]		
China	51.0%[1)]	52.2%[1)]	16.3%[3)]	18.6%[3)]	14.0%[3)]	30.2%[3)]		
			11.9%[4)]	16.1%[4)]	17.5%[4)]	34.3%[4)]		
Japan	65.0%[1)]	71.7%[1)]	56.1% (extensively drug-resistant tuberculosis)[5)]			38.2%[1)]		
Peru	35.0%[1)]	75.0%[1)]	17.5%[2)]	17.0%[2)]	17.0%[2)]	9.0%[2)]	7.3%[2)]	13.0%[2)]
	52.0%[2)]	55.9%[2)]						
US	54.8%[1)]	66.9%[1)]				9.2%[1)]		
Egypt	68.0%[1)]	92.8%[1)]						

1) WHO: Anti-tuberculosis drug resistance in the world Forth Global Report. 2008
2) Dalton et al, *Lancet*. 2012;380(9851):1406-1417.
3) Hu Y et al, *Antimicrob Agents Chemother*. 2013;57(8):3587-3863.
4) Shi D et al, *Emerg Infect Dis*. 2012;18(11):1904-1905.
5) Kazumi Y et al, *Kekkaku*. 2007;82(12):891-896.

Oral and injectable drugs in Groups 1 to 3 are critical for the treatment of multidrug-resistant tuberculosis, and there are no significant differences in the rates of emergence of resistance to EB, SM, and fluoroquinolones in Japan from those observed in other countries where the global phase II study was conducted. The rates of emergence of resistance to AMK and KM in Group 2 were as high as 56.1% in Japan. However, given that the high drug-resistance rates were based on sensitivity data in Japan that were obtained from extensively drug-resistant *M. tuberculosis* and that resistance to KM was high also in other regions including Latvia, the applicant considers that the sensitivity of multidrug-resistant *M. tuberculosis* in Japan is not significantly different from that in other countries. Thus, it is presumed that there is no significant difference in the sensitivity of multidrug-resistant *M. tuberculosis* between Japan and other countries.

Since patients with multidrug-resistant pulmonary tuberculosis have a poor prognosis, the development of novel therapeutic drugs is awaited. However, because of the limited number of patients in Japan, the feasibility of clinical studies is low in Japanese patients alone. Therefore, PMDA considers it justifiable to evaluate the efficacy and safety of delamanid based on the data from global studies involving Japanese patients.

PMDA accepts the applicant's explanation that the pathology of pulmonary tuberculosis is significantly affected by the characteristics of individual patients and that there are no significant differences in the pathology of the disease between Japan and other countries. PMDA also considers that there are no significant differences in the pharmacokinetics between Japanese and foreign patients.

Furthermore, given that the OBRs used in the global phase II study (Study 242-[redacted]-204) were selected according to the criteria stipulated in the WHO guidelines, PMDA considers that the treatment for multidrug-resistant tuberculosis is similar between Japan and other countries.

On the other hand, sensitivities to Group-2 anti-tuberculosis drugs are shown to be different from region to region. Therefore, the frequency of emergence of particularly intractable extensively drug-resistant pulmonary tuberculosis which is resistant to Group-2 anti-tuberculosis drugs and fluoroquinolones may vary by region and affect the efficacy assessment. The pathology of

patients with extensively drug-resistant pulmonary tuberculosis is also assumed to be affected significantly by the characteristics of individual patients, which is similar between Japan and other countries. Therefore, it is possible to evaluate the efficacy of delamanid in treating Japanese patients with extensively drug-resistant pulmonary tuberculosis, based on the efficacy of delamanid in treating patients with extensively drug-resistant pulmonary tuberculosis in the global phase II study (Study 242-[redacted]-204). Given that no significant differences in the sensitivity of multidrug-resistant *M .tuberculosis* to other anti-tuberculosis drugs or no significant differences in the sensitivity of multidrug-resistant *M. tuberculosis* to delamanid were found between Japan and other countries [see "3.(i).B.(1). Anti-*M. tuberculosis* activity of delamanid and the sensitivity to delamanid of multidrug-resistant *M. tuberculosis* in Japan and other countries"], PMDA concluded that it is appropriate to evaluate the efficacy and safety of delamanid in Japanese patients mainly based on the result of the global phase II study (Study 242-[redacted]-204).

4.(ii).B.(1).2) Primary efficacy endpoint in global phase II study (Study 242-[redacted]-204)

The applicant explained the reason why the primary efficacy endpoint in the global phase II study (Study 242-[redacted]-204) was defined as the percentages of patients achieving SCC 2 months after the start of treatment as follows:

According to the WHO guidelines,[104)] bacteriological testing is the most reliable way to evaluate the sustained efficacy of treatment against both drug-susceptible and multidrug-resistant tuberculosis. Based on the results of investigations in patients with drug-susceptible tuberculosis, sputum culture conversion (SCC) from positive to negative for the growth of *M. tuberculosis* is known to be the only available predictor of the cure of tuberculosis without relapse.[105)] Also, the results of many comparative studies conducted for the optimization of treatment for tuberculosis showed that patients with drug-susceptible tuberculosis who achieved SCC within 2 months after the start of treatment had a favorable outcome without relapse after the completion of treatment.[106)]

At the same time, an observational study[107)] on multidrug-resistant pulmonary tuberculosis conducted in Latvia to investigate a relationship between time to SCC and treatment outcome[108)] found a trend toward favorable treatment outcomes (cure, treatment completion) when SCC was achieved within the first 2 months also in the treatment of multidrug-resistant pulmonary tuberculosis. Among 1146 patients with multidrug-resistant pulmonary tuberculosis, 82.6% (328 of 397 patients) of those who achieved SCC within 2 months after the start of treatment showed favorable treatment outcomes,[109)] whereas favorable treatment outcomes were observed in 75.7% (364 of 481 patients) of those who achieved SCC 3 to 6 months after the start of treatment and in 64.6% (173 of 268 patients) of those who achieved SCC at 7 to 24 months after the start of treatment. Based on these findings, the report notes that SCC 2 months after the start of treatment is an indicator that most accurately predicts outcomes in the treatment of tuberculosis.[106)] These findings suggest that the achievement of SCC in the early stage of treatment for multidrug-resistant tuberculosis may reduce the burden of treatment on the patient and may help contain the spread of the disease. Therefore, the applicant considers it appropriate to have defined the primary efficacy endpoint as the percentage of patients who achieved SCC 2 months after the start of

104) World Health Organization (WHO). Treatment of tuberculosis. 4th ed. Geneva: WHO; 2009
105) Wallis RS et al, *Lancet Infect Dis*. 2010;10:68-69.
106) Gammino VM et al, *Int J Tuberc Lung Dis*. 2011;15:1315-1322.
107) Holtz TH et al, *Ann Intern Med*. 2006;144:650-659.
108) The final treatment outcome was assessed according to the following criteria: "Cured": 5 or more negative cultures during the 12 months in the latter half of the treatment period); "Treatment completed": Patients who completed administration except "cured" and "treatment failure"; "Died": All-cause deaths during the course of treatment; "Treatment interrupted": Treatment interruption during treatment process for any reason; "Treatment failure": Positive in 2 or more cultures out of 5 or more cultures, or positive in 1 or more cultures out of the last 3 cultures, during 12 months in the latter half of the treatment period.
109) Patients assessed as "cured" or "treatment completed" in the last treatment outcome were regarded as those with "favorable treatment outcome."

treatment in the global phase II study (Study 242-[redacted]-204).

PMDA asked the applicant to explain the relationship between SCC 2 months after the start of treatment and tuberculosis-related deaths in patients with multidrug-resistant tuberculosis.

The applicant explained as follows:
According to a report on the relationship between SCC 2 months from the start of treatment and deaths in the treatment of multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis, among 2942 patients with multidrug-resistant tuberculosis who were sputum culture positive before treatment, in those who achieved SCC 2 months after the start of treatment, the mortality within 4 years after the start of treatment was 3.9% (42 of 1090 patients), whereas it was 16.7% (309 of 1852 patients) in those who did not achieve SCC 2 months after the start of treatment.[110)] In another analysis of data from 1768 patients with multidrug-resistant tuberculosis who were treated with the second-line drugs in Estonia, Latvia, the Philippines, Russia, and Peru, failure to achieve SCC within 3 months was one of independent predictors of death that included ≥45 years of age, HIV infection, extrapulmonary tuberculosis, BMI <18.5, past use of quinolones, resistance to thioamide, and positive smear culture before treatment.[111)] Other studies on 289 patients in Dominica,[112)] 167 patients in Latvia,[113)] and 114 patients in South Africa[114)] also reported that the achievement of SCC within 2 months after the start of treatment is correlated with survival in patients with multidrug-resistant pulmonary tuberculosis. Based on these facts, the applicant considers that the achievement of SCC 2 months after the start of treatment is a good predictor of the outcomes of long-term treatment including a decrease in the mortality of patients with multidrug-resistant tuberculosis.

PMDA asked the applicant to explain the relationship between SCC 2 months after the start of treatment and resistance acquisition during treatment or at relapse in patients with multidrug-resistant pulmonary tuberculosis.

The applicant explained as follows:
There is a report[115)] that fluoroquinolone resistance and extensively drug-resistant tuberculosis emerged even during treatment given under well-controlled conditions in compliance with the WHO guidelines.[104)] A large scale study in the US revealed that resistance to injectable drugs and fluoroquinolones emerged at the rates of 2.2% and 2.8%, respectively.[116)] In several observational studies of multidrug-resistant tuberculosis, a delay in SCC of more than 2 to 3 months after the start of treatment was reported to be a risk factor for treatment failure and the emergence of extensively drug-resistant *M. tuberculosis*.[117,118,119)]

PMDA considers the achievement of SCC 2 months after the start of treatment (the primary efficacy end point) in the global phase II study (Study 242-[redacted]-204) as follows:
The results from multiple clinical studies of drug-susceptible tuberculosis demonstrated the relationship between SCC 2 months after the start of treatment and the final treatment outcome. On the other hand, there are no reports of prospective clinical studies of multidrug-resistant pulmonary tuberculosis on the relationship between SCC 2 months after the start of treatment and the final treatment outcomes. However, multiple observational studies provided data that

110) Ahuja SD et al, *PLoS Med*. 2012;9(8):e1001300.
111) Kurbatova EV et al, *Tuberculosis*. 2012;92(5):397-403.
112) Rodriguez M et al, *Int J Tuberc Lung Dis*. 2013;17(4):520-555.
113) Holtz TH et al, *Ann Intern Med*. 2006;144(9):650-659.
114) O'Donnell MR et al, *Emerg Infect Dis*. 2013;19(3):416-424.
115) Cox HS et al, *N Engl J Med*. 2008;359:2398-2400.
116) Ershova JV et al, *Clin Infect Dis*. 2012;55(12):1600-1607.
117) Ekaterina V et al, *Tuberculosis*. 2012;92(5):397-403.
118) Sonya S et al, *Am J Respir Crit Care Med*. 2010;182:426-432.
119) Beth Temple et al, *Clin Infect Dis*. 2008;47(9):1126-1134.

suggested a relationship between SCC 2 months after the start of treatment and important final treatment outcomes such as cure and death. SCC achieved later than 2 to 3 months after the start of treatment was shown to be a risk factor for the emergence of extensively drug-resistant *M. tuberculosis*. A clinical study with the efficacy endpoint of the final treatment outcomes of multidrug-resistant pulmonary tuberculosis would require an extremely long study period. Given these facts and the urgent need of a novel anti-tuberculosis drug in the context of the current shortage of effective drugs, there is no particular problem in assessing the efficacy of delamanid based on the primary efficacy endpoint of the achievement of 2-month SCC in the global phase II study (Study 242-[redacted]-204) in patients with multidrug-resistant pulmonary tuberculosis.

The above conclusion of PMDA will be finalized, taking account of comments raised in the Expert Discussion.

4. (ii).B.(2) Efficacy

Based on the following review, PMDA considers that the efficacy of delamanid against multidrug-resistant tuberculosis has been demonstrated.

Given that there are only 110 to 120 patients with multidrug-resistant pulmonary tuberculosis each year in Japan, it is understandable that only a limited number of Japanese subjects (12 of 481 subjects) were enrolled in the global phase II study (Study 242-[redacted]-204). SCC 2 months after the start of treatment was evaluated in only 8 of 12 subjects, precluding the assessment of the consistency in the efficacy of delamanid between Japan and other countries. However, there was no significant difference in treatment outcomes based on the negative culture 24 months after the start of treatment between Japanese and foreign subjects who received delamanid, thus high efficacy of delamanid is expected in Japanese patients with multidrug-resistant pulmonary tuberculosis. Nevertheless, because of the extremely limited experiences in the use of delamanid in Japanese patients with multidrug-resistant tuberculosis, information should be further collected after the market launch.

4. (ii).B.(2).1) Efficacy of delamanid in global phase II study (Study 242-[redacted]-204)

In the global phase II study (Study 242-[redacted]-204), the percentages of subjects who achieved SCC 2 months after the start of treatment, the primary efficacy endpoint, were 45.4% (64 of 141 subjects) in the delamanid 100 mg twice daily + OBR group (delamanid 100 mg group), 41.9% (57 of 136 subjects) in the delamanid 200 mg twice daily + OBR group (delamanid 200 mg group), and 29.6% (37 of 125 subjects) in the placebo group, with the risk ratios [95% CI] of delamanid 100 mg and delamanid 200 mg relative to placebo being 1.53 [1.11, 2.12] and 1.42 [1.01, 1.98]. The result demonstrated the superiority of the delamanid 100 mg and the delamanid 200 mg to placebo ($P = 0.0083$ and $P = 0.0393$, respectively, by Cochran-Mantel Haenszel test stratified by the presence/absence of cavitation. Adjusted for multiplicity of test by Hochberg method).

The applicant explained the types and distribution of OBRs used in each treatment group in the global phase II study (Study 242-[redacted]-204) as follows:

Although the types of anti-tuberculosis drugs used as OBRs in this study varied from subject to subject, no significant difference was observed in the types of the drugs classified by group among treatment groups (Table 36).

Table 36. Anti-tuberculosis drugs used as OBR by ≥10% of subjects in any group

Drug	Delamanid 100 mg group (N = 161)	Delamanid 200 mg group (N = 160)	Placebo group (N = 160)
Group 1	**131 (81.4)**	**131 (81.9)**	**132 (82.5)**
EB	100 (62.1)	101 (63.1)	95 (59.4)
INH	17 (10.6)	13 (8.1)	10 (6.3)
PZA	118 (73.3)	119 (74.4)	120 (75.0)
Group 2	**158 (98.1)**	**156 (97.5)**	**157 (98.1)**
AMK	12 (7.5)	12 (7.5)	11 (9.4)
KM	97 (60.2)	88 (55.0)	97 (60.6)
Capreomycin	42 (26.1)	41 (25.6)	39 (24.4)
SM	18 (11.2)	24 (15.0)	24 (15.0)
Group 3	**155 (96.3)**	**157 (98.1)**	**156 (97.5)**
Gatifloxacin	7 (4.3)	10 (6.3)	12 (7.5)
LVFX	94 (58.4)	103 (64.4)	97 (60.6)
Ofloxacin	56 (34.8)	48 (30.0)	50 (31.3)
Group 4	**160 (99.4)**	**158 (98.8)**	**159 (99.4)**
PAS	79 (49.1)	84 (52.5)	88 (55.0)
CS	135 (83.9)	137 (85.6)	136 (85.0)
TH	49 (30.4)	51 (31.9)	49 (30.6)
Prothionamide	101 (62.7)	97 (60.6)	101 (63.1)
Group 5	**26 (16.1)**	**23 (14.4)**	**30 (18.8)**
Amoxicillin/potassium clavulanate	5 (3.1)	7 (4.4)	8 (5.0)

Number of subjects (%)

PMDA asked the applicant to explain whether or not the difference in the sensitivity of the causative bacteria to OBRs at enrollment affected the evaluation of the efficacy of delamanid in the global phase II study (Study 242-[redacted]-204).

The applicant explained as follows:
Table 37 shows the percentages of strains susceptible to major anti-tuberculosis drugs among those clinically isolated one day before the start of treatment. The sensitivities to RBT and to prothionamide were difficult to accurately evaluate because of the limited number of strains tested. The sensitivity to CS tended to be high in the delamanid 100 mg group, whereas there was no significant difference among the treatment groups in the sensitivities of clinical isolates to main OBR drugs recommended by WHO, i.e., those in Group 1 (INH, RFP, PZA, EB), Group 2 (injectable anti-tuberculosis drugs), or those in Group 3 (fluoroquinolones). The applicant therefore considers that the difference in the sensitivities of the clinically isolated strains to the OBRs had little effect on the evaluation of the efficacy of delamanid.

Table 37. Percentage of strains susceptible to existing anti-tuberculosis drugs among strains clinically isolated one day before the start of treatment (global phase II study [Study 242-[redacted]-204], MITT population)

Anti-tuberculosis drug	Delamanid 100 mg group	Delamanid 200 mg group	Placebo group
Group 1			
INH	0.8% (1/133)	0.0% (0/120)	0.0% (0/114)
RFP	0.8% (1/133)	0.0% (0/120)	1.8% (2/114)
PZA	40.5% (53/131)	37.8% (45/119)	37.7% (43/114)
EB	47.4% (63/133)	53.3% (64/120)	47.4% (54/114)
RBT	0.0% (0/7)	10.0% (1/10)	33.3% (2/6)
Group 2			
KM	79.5% (97/122)	83.3% (95/114)	79.0% (83/105)
AMK	73.3% (63/86)	77.5% (55/71)	72.9% (51/70)
Capreomycin	68.6% (59/86)	75.0% (54/72)	74.6% (53/71)
SM	24.8% (33/133)	32.8% (39/119)	28.9% (33/114)
Group 3			
Ofloxacin	68.3% (43/63)	73.2% (41/56)	61.5% (32/52)
LVFX	88.7% (86/97)	92.6% (88/95)	87.9% (80/91)
Group 4			
CS	93.8% (30/32)	85.2% (23/27)	82.4% (14/17)
TH	74.6% (50/67)	70.4% (38/54)	70.0% (35/50)
Prothionamide	56.3% (9/16)	53.3% (8/15)	50.0% (7/14)
PAS	82.7% (67/81)	82.1% (55/67)	75.8% (47/62)

(Drug-susceptible strains/[drug-susceptible strains + drug-resistant strains]) × 100

PMDA asked the applicant to explain the effect of anti-tuberculosis drugs used before the administration of the study drug on the evaluation of the efficacy of delamanid in the global phase II study (Study 242-[redacted]-204).

The applicant explained as follows:
Table 38 shows the achievement rates of SCC (assessed by MGIT) 2 months after the start of treatment in patients classified by the duration of treatment with other anti-tuberculosis drugs before the administration of the study drug (limited, ≤90 days before the start of the study drug; moderate, 90 to 180 days before the start of the study drug; extensive, ≥180 days before the start of the study drug). In all treatment groups, the achievement rate of SCC was highest in subjects who had previous treatment with other anti-tuberculosis drugs for 90 to 180 days (moderate treatment). This finding may be explained by the assumption that the number of patients who had previous treatment with other anti-tuberculosis drugs for 90 to 180 days (moderate treatment) and were in partial remission at the time of enrollment in the global phase II study (Study 242-[redacted]-204) was greater than those who had limited or extensive previous treatment. However, the achievement rates of SCC 2 months after the start of treatment in the delamanid 100 mg group and the delamanid 200 mg group were high as compared with the placebo group regardless of the duration of previous treatment with other anti-tuberculosis drugs. The applicant therefore considers that the duration of treatment with other anti-tuberculosis drugs before the administration of the study drug had only a minimal effect on the efficacy evaluation of delamanid.

Table 38. Achievement rates of 2-month SCC (MGIT) classified by OBR treatment duration before the administration of the study drug

History of treatment with anti-tuberculosis drugs before the start of the administration of the study drug	Delamanid 100 mg group	Delamanid 200 mg group	Placebo group
≤90 days (Limited)	41.7% (15/36)	54.3% (19/35)	24.0% (6/25)
90-180 days (Moderate)	60.0% (9/15)	75.0% (12/16)	50.0% (2/4)
≥180 days (Extensive)	44.4% (40/90)	30.6% (26/85)	30.2% (29/96)
Total	45.4% (64/141)	41.9% (57/136)	29.6% (37/125)

PMDA considers the effects of OBRs co-administered in the global phase II study (Study 242-[redacted]-204) on the efficacy evaluation of delamanid as follows:
Given that OBRs used in the treatment of multidrug-resistant tuberculosis have a variety of combinations of anti-tuberculosis drugs and that the characteristics of patients with multidrug-resistant pulmonary tuberculosis vary in clinical practice, it is understandable that no particular OBR was specified. The use statuses of OBRs were similar among the treatment groups in the global phase II study. The superiority of delamanid 100 mg and 200 mg to placebo was demonstrated by the achievement rates of SCC 2 months after the start of treatment classified by the duration of treatment with other anti-tuberculosis drugs before the start of the study drug. Thus, the variety in concomitant OBRs among the treatment groups was not significant enough to affect the efficacy evaluation of delamanid.

4.(ii).B.(2).2) Efficacy in subpopulations

(a) Efficacy in extensively drug-resistant pulmonary tuberculosis

The applicant explained the efficacy of delamanid against extensively drug-resistant pulmonary tuberculosis as follows:
Table 39 shows the achievement rates of SCC 2 months after the start of treatment in patients with multidrug-resistant pulmonary tuberculosis and in patients with extensively drug-resistant pulmonary tuberculosis in the global phase II study (Study 242-[redacted]-204). The achievement rates of 2-month SCC were low in patients with extensively drug-resistant pulmonary tuberculosis as compared with patients with multidrug-resistant pulmonary tuberculosis and were higher in the delamanid groups than in the placebo group.

Table 39. Achievement rates of 2-month SCC (MGIT) in patients with multidrug-resistant pulmonary tuberculosis and in patients with extensively drug-resistant pulmonary tuberculosis

	Delamanid 100 mg group	Delamanid 200 mg group	Placebo group
Multidrug-resistant pulmonary tuberculosis	51.3% (60/117)	44.1% (52/118)	35.7% (35/98)
Extensively drug-resistant pulmonary tuberculosis	16.7% (4/24)	27.8% (5/18)	7.4% (2/27)
Total	45.4% (64/141)	41.9% (57/136)	29.6% (37/125)

(b) Efficacy of delamanid by presence or absence of cavitation before the start of treatment

The applicant explained the efficacy of delamanid by presence or absence of cavitation at the screening test as follows:
Table 40 shows the achievement rates of 2-month SCC by presence or absence of cavitation in the global phase II study (Study 242-[redacted]-204). The achievement rates of 2-month SCC of the delamanid groups were high as compared with the placebo group, regardless of the presence or absence of cavitation.

Table 40. Achievement rates of 2-month SCC by presence/absence of cavitation (MGIT, MITT population)

	Delamanid 100 mg group (N = 141)	Delamanid 200 mg group (N = 136)	Placebo group (N = 125)
With cavitation	46.0% (46/100)	44.2% (42/95)	28.7% (25/87)
Without cavitation	43.9% (18/41)	36.6% (15/41)	31.6% (12/38)
Total	45.4% (64/141)	41.9% (57/136)	29.6% (37/125)

The achievement rates of 2-month SCC tended to be high in the delamanid groups as compared

with the placebo group, regardless of the resistance of *M. tuberculosis* and of the presence or absence of cavitation at the start of treatment, which are background factors that could possibly affect the efficacy. Therefore, PMDA considers that these factors do not pose any significant problems of the efficacy of delamanid.

4.(ii).B.(2).3) Opinion of European regulatory agency

The Committee for Medicinal Products for Human Use (CHMP) expressed a negative opinion on the approval of delamanid as of July 26, 2013.[120] However, after the subsequent re-examination, the committee presented a favorable opinion on the approval of delamanid as of November 21, 2013.[121),122]

A major concern in CHMP's initial negative opinion was the duration of the global phase II study (Study 242-[redacted]-204). The study was designed to evaluate the achievement of SCC after the concomitant use of delamanid with OBRs for a period of 2 months, which was considered not long enough to evaluate the efficacy of delamanid because the drug is intended to be administered for 6 months. In response to the request of the applicant for re-examination, CHMP reviewed the data and, as a result, presented the favorable opinion that the efficacy of 6-month treatment can be predicted from the result of 2-month treatment in the global phase II study (Study 242-[redacted]-204).

PMDA concluded that the opinion of the European regulatory agency is consistent with the discussion made in "4.(ii).B.(1) Design of global phase II study (Study 242-[redacted]-204)," and does not affect the conclusion on the efficacy of delamanid reached in "4.(ii).B.(2) Efficacy."

4.(ii).B.(3) Safety

In the global phase II study (Study 242-[redacted]-204), the incidences of adverse events were similar among the delamanid 100 mg group, the delamanid 200 mg group, and the placebo group, being 90.1% (145 of 161 patients), 93.1% (149 of 160 patients), and 93.1% (149 of 160 patients), respectively, and did not show a tendency toward an increase by the concomitant use of delamanid with OBRs. In addition, the severity or timing of the occurrence of adverse events did not differ between the delamanid groups and the placebo group. Based on these findings, PMDA considers that the safety of delamanid in concurrent use with an appropriate OBR is acceptable. However, since delamanid has been used in only an extremely limited number of Japanese patients and since delamanid-associated electrocardiogram QT prolongation has been reported, the collection of safety information should be further continued after the market launch.

The above conclusion of PMDA will be finalized, taking account of comments raised in the Expert Discussion.

4.(ii).B.(3).1) Risk of electrocardiogram QT prolongation

The applicant explained the risk of electrocardiogram QT prolongation as follows:
Although no thorough QT/QTc study was conducted for this application,[73] QT/QTc was evaluated in the global phase II study (Study 242-[redacted]-204). The placebo-corrected change in QTcF from baseline increased with treatment duration, being prolongation of 11.3 to 13.1 msec in the delamanid 100 mg group and 14.1 to 15.6 msec in the delamanid 200 mg group at all measuring

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120) Questions and answers (EMA/CHMP/446276/2013, July 26, 2013)
http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002552/WC500146651.pdf#search='%EF%BC%89Questions+and+answers+%28EMA%2FCHMP%2F446276%2F2013%2C+26+July+2013%29' (URL confirmed in March 2014)

121) Summary of opinion (EMA/CHMP/713909/2013, November 21, 2013)
https://www.ghdonline.org/uploads/EMA_conditional_authorization_on_Delamanid.pdf#search='Summary+of+opinion+%28EMA%2FCHMP%2F713909%2F2013%2C+21+November+2013%29' (URL confirmed in March 2014)

122) Questions and answers (EMA/CHMP/713953/2013, November 22, 2013)
http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/human/002552/WC500155462.pdf#search='Questions+and+answers+%28EMA%2FCHMP%2F713953%2F2013%2C+22+November+2013%29' (URL confirmed in March 2014)

time points on Day 56, and showing a dose-dependency in QT prolongation. The incidence of QT/QTc prolongation as adverse events[123)] in the global phase II study (Study 242-[redacted]-204) was 3.8% (6 of 160 subjects) in the placebo group, 9.9% (16 of 161 subjects) in the delamanid 100 mg group, and 13.1% (21 of 160 subjects) in the delamanid 200 mg group.

In the global long-term administration study (Study 242-[redacted]-208), the mean QTcF intervals from Week 6 onward were stabilized (mean absolute value, 415.5-417.5 msec; mean change from baseline, 6.48-8.52 msec). QTcF intervals exceeded 500 msec in 2 patients but decreased to ≤500 msec after the discontinuation of delamanid. The adverse event of QT/QTc prolongation[123)] was observed in 2.8% (6 of 213 patients). Of these, electrocardiogram QT prolonged in 2 patients was regarded as serious adverse events, but the event resolved after the discontinuation of the study drug.

Patients with the absolute QTcF exceeding 500 msec and those with QTcF change from baseline exceeding 60 msec had known risk factors such as being female, cardiovascular disease, and hypokalemia, but no torsade de pointes was observed in the global phase II study (Study 242-[redacted]-204) or the global long-term administration study (Study 242-[redacted]-208).

PMDA asked the applicant to explain whether or not there were racial differences in the risk of QT prolongation in the global phase II study (Study 242-[redacted]-204).

The applicant explained as follows:
Table 41 shows the comparisons of the ranges of QTcF change (mean change at Day 56 from baseline) observed in the safety data of the global phase II study (Study 242-[redacted]-204) by race. The ranges of QT prolongation tended to be larger in Asian subjects.

Table 41. Comparison of QT interval prolongation (ms) from baseline among treatment groups (Study 242-[redacted]-204, by race)

Race	Delamanid 100 mg group		Delamanid 200 mg group		Placebo group	
	N	Mean [90% CI]	N	Mean [90% CI]	N	Mean [90% CI]
Caucasians	36	11.3 [8.0, 14.6]	28	16.4 [13.1, 19.7]	23	0.2 [-3.6, 3.9]
Blacks	0	-	1	10.7	0	-
Asians	75	18.8 [15.8, 21.8]	79	20.5 [17.8, 23.2]	83	3.1 [0.6, 5.6]
Other	33	9.6 [6.1, 13.0]	38	11.9 [8.2, 15.5]	42	2.9 [0.2, 5.6]
Total	144	14.8 [12.8, 16.8]	146	17.4 [15.5, 19.3]	148	2.6 [0.9, 4.3]

The total number of patients in each group indicates the number of patients in whom QTcF interval was measured on day 56.

Since Asian subjects tended to have larger QT intervals, QTcF intervals were investigated by region. The largest QTcF interval was observed in patients in Southeast Asia, whereas the extent of interval prolongation in patients in Northeast Asia (Japan, Korea, China) was similar to that in patients in Europe/Mediterranean area and Americas (Table 42). Factors of larger QTcF intervals in Southeast Asia were studied but remained unclear.

[123)] Among events reported as adverse events according to the assessment of the investigator, those judged as "electrocardiogram QT prolonged" in PT of MedDRA (Version 13.1).

Table 42. Comparison of changes in QT intervals (ms) from baseline among treatment groups (Study 242-[redacted]-204, by region)

Region	Delamanid 100 mg group		Delamanid 200 mg group		Placebo group	
	N	Mean [90% CI]	N	Mean [90% CI]	N	Mean [90% CI]
Southeast Asia	43	23.6 [19.7, 27.4]	45	26.2 [22.7, 29.7]	50	5.2 [1.9, 8.6]
Europe/Mediterranean area	36	11.3 [8.0, 14.6]	26	15.8 [12.3, 19.3]	22	0.2 [-3.7, 4.1]
Northeast Asia	31	12.4 [8.2, 16.7]	34	13.3 [10.0, 16.7]	33	-0.1 [-3.7, 3.6]
North and South America	34	9.6 [6.2, 12.9]	41	12.1 [8.6, 15.6]	43	2.8 [0.2, 5.5]
Total	144	14.8 [12.8, 16.8]	146	17.4 [15.5, 19.3]	148	2.6 [0.9, 4.3]

The total number of patients in each group indicates the number of patients in whom QTcF interval was measured on Day 56.

PMDA asked the applicant to explain the risk of QT prolongation in the long-term treatment with delamanid.

The applicant explained as follows:
In the global phase II study (Study 242-[redacted]-204) and in the global long-term treatment study (Study 242-[redacted]-208), the timing of onset and the severity[124)] of electrocardiogram QT prolonged as adverse event (16 patients in the delamanid 100 mg, 21 patients in the delamanid 200 mg group, 6 patients in the placebo group) were investigated. In the global phase II study (Study 242-[redacted]-204), electrocardiogram QT prolonged occurred 22.4 days after the start of treatment in the delamanid 100 mg group, 31.5 to 32.9 days in the delamanid 200 mg group, and 30.7 days in the placebo group, showing no trend toward late onset in the delamanid groups as compared with the placebo group. The QT prolongation was moderate in severity in 2 patients in the delamanid 200 mg group and mild in other patients.

In the global long-term treatment study (Study 242-[redacted]-208), in which delamanid 200 mg was eventually administered to approximately two thirds of the participants, electrocardiogram QT prolonged was observed in only 2.8% (6 of 213 patients) as compared with that in the global phase II study (Study 242-[redacted]-204). The event occurred between 7 and 126 days after the start of treatment and was moderate in severity in 1 patient and mild in other patients.

Based on these findings, the applicant considers that the long-term treatment with delamanid is unlikely to increase the risk of QT prolongation.

PMDA considers the risk of delamanid-induced QT prolongation as follows:
In the global phase II study (Study 242-[redacted]-204), the changes in the placebo-corrected QTcF from baseline to Day 56 of treatment were prolongation of 11.3 to 13.1 msec in the delamanid 100 mg group and 14.1 to 15.6 msec in the delamanid 200 mg group, showing a dose-response relationship, and QTcF intervals tended to increase with the duration of treatment with delamanid. Therefore, QT prolongation is considered an important safety concern with delamanid.

However, electrocardiogram QT prolonged observed in the global phase II study (Study 242-[redacted]-204) seldom affected the patient's daily living, and no serious cardiovascular events such as torsade de pointes were observed. Given that multidrug-resistant pulmonary tuberculosis is an intractable disease with poor prognosis and has limited treatment options, treatment with delamanid is feasible for multidrug-resistant pulmonary tuberculosis as long as the patient's condition is carefully monitored by electrocardiogram on a regular basis.

[124)] The investigator classified the severity of adverse events as mild, moderate, or severe according to the following criteria.
Mild: Adverse events that are only slightly uncomfortable, not interfering with the activities of daily living, and easily tolerated.
Moderate: Adverse events that are uncomfortable and interfere with the activities of daily living.
Severe: Adverse events that cause dysfunction and disable the activities of daily living.

After the market launch, the risk of delamanid-induced QT prolongation should be explained to physicians and patients, and a survey should be conducted on the occurrences of events related to QT prolongation.

4.(ii).B.(4) Clinical positioning

PMDA asked the applicant to explain the clinical positioning of the treatment regimen including delamanid.

The applicant explained as follows:

Multidrug-resistant tuberculosis is resistant to INH and RFP that are defined as first-line drugs by the WHO guidelines and is therefore treated with "second-line" drugs, which are considered to be less potent and more harmful than the "first-line" drugs used in the treatment of drug-susceptible tuberculosis.[3)] The WHO guidelines[3)] recommend including either one of injectable drugs in the treatment regimen whenever possible because they are the most potent among the second-line drugs. The guidelines also strongly recommend the concomitant use of fluoroquinolones. The revised WHO guidelines[125)] published in 2011 also emphasize the importance of a treatment regimen including injectable anti-tuberculosis drugs and fluoroquinolones. By the same token, the treatment regimen for multidrug-resistant tuberculosis recommended by the Treatment Committee of the Japanese Society for Tuberculosis requires the use of at least 3 effective drugs selected from options including fluoroquinolones and injectable anti-tuberculosis drugs.[4)]

According to several reports, while ≥90% of patients with drug-susceptible tuberculosis achieve a cure after 6-month treatment with the first-line drugs, a favorable treatment outcome was achieved by only 60% to 70% of patients with multidrug-resistant pulmonary tuberculosis even if they are treated for ≥24 months with treatment regimens including injectable anti-tuberculosis drugs and fluoroquinolone,[126),127)] and a favorable outcome was achieved by as low as 35% to 55% of patients with extensively drug-resistant tuberculosis.[128),129)] Thus, the limited options of effective treatment is a critical problem in the treatment of multidrug-resistant pulmonary tuberculosis.

The global phase II study (Study 242-[redacted]-204) confirmed that the concomitant use of delamanid with an OBR including fluoroquinolones and injectable anti-tuberculosis drugs significantly improved the achievement rate of 2-month SCC as compared with the concomitant use of placebo with an OBR.

As of now, no major safety concerns have been observed with delamanid except QT prolongation. In concomitant use with injectable anti-tuberculosis drugs, fluoroquinolones, and CS, delamanid has not shown a trend toward increases in the frequency or severity of adverse events that was observed with each concomitant drug. Because of the possible occurrence of QT prolongation associated with the use of delamanid, the checking of patient characteristics before starting treatment and the performance of electrocardiography on a regular basis during treatment are essential so that the safe use of delamanid is ensured.

Based on these discussions, the applicant considers that delamanid can be a new treatment option for multidrug-resistant tuberculosis because the concurrent use of delamanid with at least 3

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125) World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis–2011 update. WHO/HTM/TB/2011.6. Geneva: WHO; 2011.
126) Orenstein EW et al, *Lancet Infect Dis*. 2009;9(3):153-161.
127) Johnston J et al, *PLoS ONE*. 2009;4:e-6914.
128) Jacobson KR et al, *Clin Infect Dis*. 2010;51(1):6-14.
129) Jeon DS et al., *Int J Tuberc Lung Dis*. 2009;13(5):594-600.

effective anti-tuberculosis drugs will lead to early sputum culture conversion of multidrug-resistant tuberculosis, while attention is paid to possible cardiovascular adverse events.

PMDA considers as follows:
Current standard therapies for multidrug-resistant pulmonary tuberculosis common to Japan and other countries include the combination use of injectable anti-tuberculosis drugs and fluoroquinolones. However, due to the insufficient efficacy of these therapies, there is a need for the development of new drugs that improve treatment outcomes. In the global phase II study (Study 242-[redacted]-204), the use of delamanid in combination with a standard therapy for multidrug-resistant tuberculosis was shown to lead to early sputum culture conversion. Therefore, delamanid can be a new treatment option for multidrug-resistant tuberculosis.

4.(ii).B.(5) Indication
Based on the above discussions, PMDA considers that the efficacy of delamanid against pulmonary tuberculosis caused by multidrug-resistant *M. tuberculosis* has been demonstrated. The proposed indication is "multidrug-resistant pulmonary tuberculosis." However, taking account of the facts that the term "pulmonary tuberculosis" is adopted as the disease classification in "International Statistical Classification of Diseases and Related Health Problems (ICD-10)" and that approved anti-tuberculosis drugs are indicated for "pulmonary tuberculosis," PMDA considers that the indication of delamanid should be "multidrug-resistant pulmonary tuberculosis."

4.(ii).B.(6) Dosage and administration
The applicant explained the justification for the dosage and administration of delamanid as follows:
In the global phase II study (Study 242-[redacted]-204), the MGIT-assessed the achievement rates of SCC 2 months after the start of treatment(the primary efficacy endpoint) were 45.4% (64 of 141 patients) in the delamanid 100 mg BID group and 41.9% (57 of 136 patients) in the delamanid 200 mg BID group, showing no difference between the dose groups. $AUC_{0\text{-}24h}$ values of delamanid in plasma were 7925 ng·h/mL in the delamanid 100 mg BID group and 11,837 ng·h/mL in the delamanid 200 mg BID group. Thus, although increasing the delamanid dose from 100 mg BID to 200 mg BID increased $AUC_{0\text{-}24h}$ of delamanid in plasma, the achievement rates of 2-month SCC were similar between the 2 dose groups, based on which the applicant considered that delamanid 100 mg BID is adequate from the aspect of efficacy.

The incidences of adverse events in the global phase II study (Study 242-[redacted]-204) were similar between the delamanid groups and the placebo group except electrocardiogram QT prolonged [see "4.(ii).A.(2).3) Global phase II study in patients with multidrug-resistant pulmonary tuberculosis"]. A dose-response relationship was observed in the incidence of electrocardiogram QT prolonged [see "4.(ii).B.(3).1) Risk of electrocardiogram QT prolongation"].

Based on these findings, the applicant considered that "100 mg BID" is the most appropriate dose for the treatment of multidrug-resistant tuberculosis and has the most favorable risk-benefit balance.

PMDA asked the applicant to explain the persistence of efficacy in the long-term treatment with delamanid.

The applicant explained as follows:
Table 43 shows the mortality rate, sustained SCC, and "favorable treatment outcomes" in subjects enrolled in the global phase II study (Study 242-[redacted]-204) classified by participation (delamanid 100 or 200 mg BID co-administered with an OBR for 6 months)/non-participation (no administration of delamanid) in the global long-term treatment study (Study 242-[redacted]-208).

Subjects who participated in the global long-term treatment study (Study 242-[redacted]-208) showed low mortality rates and high achievement of sustained SCC as compared with those who did not, whereas no significant difference was observed in the mortality rates between the dose groups.

Table 43. Mortality rates, sustained SCC achievement rate, and rate of "favorable treatment outcomes" in subjects enrolled in global phase II study (Study 242-[redacted]-204), classified by participation/non-participation in global long-term treatment study (Study 242-[redacted]-208)

Treatment group in Study 242-[redacted]-204	Study 242-[redacted]-208	Mortality rate		Sustained SCC achievement rate		Rate of "favorable treatment outcome"	
Delamanid 100 mg BID group (n = 155)	Delamanid 100 mg BID	42	2.4% (1)	25	96.0% (24)	25	64.0% (16)
	Delamanid 200 mg BID	22	4.5% (1)	17	88.2% (15)	17	82.4% (14)
	Non-participation	91	13.2% (12)	58	60.3% (35)	58	41.4% (24)
Delamanid 200 mg BID group (n = 157)	Delamanid 100 mg BID	47	2.1% (1)	34	100% (34)	34	88.2% (30)
	Delamanid 200 mg BID	25	0	19	89.5% (17)	19	78.9% (15)
	Non-participation	85	8.2% (7)	52	80.8% (42)	52	61.5% (32)
Placebo group (n = 152)	Delamanid 100 mg BID	41	2.4% (1)	29	89.7% (26)	29	79.3% (23)
	Delamanid 200 mg BID	28	7.1% (2)	19	84.2% (16)	19	78.9% (15)
	Non-participation	83	14.5% (12)	48	81.3% (39)	48	60.4% (29)
Total (n = 464)		464	8.0% (37)	301	82.4% (248)	301	65.4% (197)

PMDA asked the applicant to explain the expected duration of treatment with delamanid.

The applicant explained as follows:
The WHO guidelines for the treatment of multidrug-resistant pulmonary tuberculosis[3), 130)] recommend the use of second-line drugs (including 1 injectable anti-tuberculosis drug) during the intensive treatment phase of at least 6 months and the continuation of the drug therapy for 18 to 24 months after sputum culture conversion using other than injectable anti-tuberculosis drugs. In contrast, the standards for tuberculosis therapy in Japan do not define an intensive treatment phase as stipulated in the WHO guidelines but require continued treatment for 24 months after sputum culture conversion.

Given the current practice for the treatment of tuberculosis in Japan, limiting the treatment duration would be an unrealistic approach. However, delamanid has never been used for >6 consecutive months in clinical studies, and this fact will be included in the package insert. After the market launch of delamanid, a responsible access program [see "4.(ii).B.(8).2) Responsible Access Program (RAP)"] will be implemented and an post-marketing surveillance involving all patients treated with delamanid will be conducted aiming to collect safety information throughout the treatment period.

For the treatment of tuberculosis, directly observed treatment, short-course (DOTS) is recommended, in which the patient takes drugs under direct observation by a healthcare professional, to ensure high compliance for a long-term period.[104),131)] High compliance is critical particularly in the treatment of intractable multidrug-resistant pulmonary tuberculosis. Therefore, PMDA asked the applicant to explain whether or not the dosing frequency of delamanid may be reduced to once daily for ease of DOTS.

The applicant explained as follows:
At present, there are no clinical data on the efficacy or safety of delamanid QD. Meanwhile, a phase III comparative study (Study 242-[redacted]-213) is underway in patients with sputum culture-

130) The revised WHO guideline published in 2011 (WHO/HTM/TB/2011.6) recommends the intensive treatment phase of 8 months for most of the patients with multidrug-resistant pulmonary tuberculosis and the entire treatment period of 20 months for most of the patients with newly diagnosed multidrug-resistant pulmonary tuberculosis, but states that the treatment period may be changed depending on the response of individual patients to the treatment.
131) The guidelines for the prevention of specific infectious diseases: tuberculosis (MHLW Ministerial Announcement No. 72 of 2007)

positive multidrug-resistant tuberculosis in 7 countries including the Philippines and Latvia, and in this study, delamanid 100 mg or placebo is administered BID in combination with an OBR for the first 2 months, after which delamanid 200 mg or placebo will be administered QD in concomitant use with an OBR for 4 months for the comparison of the safety and efficacy.

Also, in response to a request from the European regulatory agency to confirm the efficacy of delamanid at higher doses than the proposed 100 mg BID, the applicant is considering the investigation of the efficacy and safety of delamanid 400 mg QD in this study.

When results of these studies become available, the dosage and administration in Japan will be reviewed.

PMDA considers the dosage and administration of delamanid as follows:
In the global phase II study (Study 242-[redacted]-204), both delamanid 100 mg BID and delamanid 200 mg BID were shown to be superior to placebo in the achievement of 2-month SCC (the primary efficacy endpoint), but no dose-response relationship was observed. On the other hand, delamanid is known to prolong QT intervals in a dose-dependent manner, which is of a safety concern with high doses. Therefore, the applicant's justification for the recommended clinical dosage for delamanid (100 mg BID) is acceptable.

In the global long-term treatment study (Study 242-[redacted]-208), there was no tendency of occurrence of new adverse events resulting from the prolonged treatment duration. Also, the subjects who participated in the global long-term treatment study (Study 242-[redacted]-208) did not show a higher mortality rate than those who participated only in the global phase II study (Study 242-[redacted]-204). In the treatment of multidrug-resistant tuberculosis, anti-tuberculosis drugs other than injectable drugs are generally intended to be given for ≥18 months to control the growth of *M. tuberculosis*[3)] sufficiently, and delamanid may also need to be administered for >6 months. Taking account of these findings, PMDA considers it difficult to define a specific treatment duration for delamanid. However, the lack of experiences in the continuous administration of delamanid for >6 months in both Japan and other countries should be included in the package insert to raise caution.

For the treatment of tuberculosis, a once-daily regimen will improve compliance and thus improve prognoses and prevent the spread of infection. Once the results of the ongoing and planned clinical studies on the once-daily administration of delamanid (including the doses of ≥100 mg BID) become available, the applicant should consider developing a once-daily regimen for delamanid in Japan.

The above conclusion of PMDA will be finalized, taking account of comments raised in the Expert Discussion.

4.(ii).B.(7) Pediatric patients
PMDA asked the applicant to explain a development plan of delamanid for pediatric patients with multidrug-resistant pulmonary tuberculosis.

The applicant explained as follows:
In recent years, the number of pediatric patients with tuberculosis has been decreasing in Japan, and the number of pediatric patients with multidrug-resistant tuberculosis is presumed extremely limited. Therefore, there is no development plan of delamanid for pediatric use at present. In Europe, on the other hand, there was a discussion on the development of delamanid for pediatric use with the European regulatory agency when the application was submitted for the treatment of adult patients with multidrug-resistant pulmonary tuberculosis, and a development plan for pediatric use was drawn up. The plan includes a clinical pharmacology study in pediatric patients with multidrug-resistant pulmonary tuberculosis to determine the appropriate dosage and

administration for this population. In the study, with consideration given to the convenience of dosing in pediatric patients, the current available tablets (used in the clinical studies in adults) will be used in children ≥6 years of age, and dispersible tablets, currently under development for children, will be used in children ≤5 years of age. Pediatric patients who have completed this study will be enrolled in a succeeding long-term treatment study for the investigation of the long-term safety and the final treatment outcomes.

PMDA considers as follows:
Due to only a small number of pediatric patients with multidrug-resistant pulmonary tuberculosis in Japan, it is understandable that the development of delamanid for pediatric use is not planned in Japan currently. However, the potential risks of infection of children with multidrug-resistant *M. tuberculosis* cannot be ruled out, and treatment options are limited when it occurs. Therefore, the development of delamanid for pediatric patients in Japan should be further considered.

4.(ii).B.(8) Post-marketing investigations
4.(ii).B.(8).1) Post-marketing surveillance
The applicant plans to conduct the following use-result survey after the market launch.

- Objective of the surveillance: to confirm the safety and efficacy in all patients treated with delamanid in routine clinical practice.
- Planned number of subjects to be surveyed: all patients enrolled within the 5-year enrollment period
- Survey method: all-case-surveillance (ECG test is to be performed during the surveillance period, and test for drug resistance acquisition is to be performed before and after administration)
- Priority items: QT prolongation, drug resistance

PMDA considers that the following should also be investigated in the post-marketing surveillance.

- Effect of co-administered OBRs on the efficacy and safety of delamanid
- Occurrences of cardiovascular events associated with delamanid-induced QT prolongation
- Safety and efficacy of delamanid in patients with hepatic impairment

The above conclusion of PMDA will be finalized, taking account of comments raised in the Expert Discussion.

4.(ii).B.(8).2) Responsible Access Program (RAP)
It is important to prevent the emergence of drug-resistant strains caused by the inappropriate use of anti-tuberculosis drugs and to ensure the safety of delamanid. The applicant therefore plans to implement a responsible access program (RAP) that includes limited distribution to facilitate the proper use of delamanid after the market launch.

The applicant explained the details of the program as follows:
The RAP consists of the following procedures: (a) the determination of the appropriateness of drug distribution using an eligibility checking system, (b) reliable collection of safety information through all-case surveillance, (c) the provision of information to healthcare professionals and patients, (d) precautionary statements included in the package insert. Of these, to (a) determine the appropriateness of drug distribution using an eligibility checking system, the following procedures will be employed.

1) After obtaining consent from a patient, the physician enters necessary information for the determination of the appropriateness of treatment with delamanid (e.g., the name of medical institution, the disease to be treated) in the patient registration server.

2) Based on the information entered in the patient registration server, any efficacy and safety concerns in the use of delamanid are submitted to the independent committee[132)] for consultation (and the independent committee evaluates the concerns according to the internal rules of the committee established based on both the guidelines for anti-tuberculosis drug use prepared by the Treatment Committee of the Japanese Society for Tuberculosis and the package insert). After obtaining a decision and advice from the independent committee on the appropriateness of the use of delamanid, the applicant determines the appropriateness of distribution of delamanid.[133)]

3) When the distribution of delamanid to the medical institution is judged appropriate, the applicant requests the medical institution to conduct all-case surveillance and provides the institution with information on the proper use of delamanid before distributing delamanid.

4) The applicant obtains progress reports from the physician on the use of delamanid (results of sputum smear cultures and drug sensitivity tests, information on concomitant drugs) every 90 days and submits the data to the independent committee for the determination of whether treatment with delamanid should be continued. The independent committee advises the discontinuation of treatment with delamanid in patients who have not achieved sputum culture conversion and are thus at high risk for the acquisition of drug resistance.

During the prolonged treatment of multidrug-resistant tuberculosis, patients are assumed to be transferred from the highly specialized center to a local hospital when they are medically stable. PMDA asked the applicant to explain measures to be taken to ensure that information is collected seamlessly even on patients who have been transferred from one medical institution to another.

The applicant explained as follows:
In order to facilitate the proper use of delamanid, when a patient who was initially registered as an inpatient at a highly specialized center is transferred to a local hospital to continue receiving treatment, the patient is re-registered in the local hospital so that delamanid can be distributed to the hospital. Treatment in the local hospital is also subject to all-case surveillance. The hospital is asked to use delamanid properly, and information is collected from the hospital on a regular basis. Decision on whether or not treatment with delamanid should be continued is made by the independent committee based on the data obtained.

The RAP requires the physician who initiated treatment at the highly specialized center, a qualified board-certified instructor for the treatment of tuberculosis and *Mycobacterium* infection, to continue offering advice on the efficacy and safety of the delamanid treatment to a physician at the local hospital.

PMDA's view on the measures for the proper use of delamanid is as follows:
In the context of extremely limited therapeutic agents available for multidrug-resistant tuberculosis, delamanid is one of the few drugs that are expected to be effective against the disease. Therefore, in order to minimize risks of the emergence and spread of drug-resistant strains that may be caused by the indiscriminate use of delamanid, it is important that delamanid be administered by physicians with vast experiences in the treatment of multidrug-resistant tuberculosis at a well-established medical institution in the same therapeutic area. Also, since

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[132)] The independent committee will consist of outside experts (experts of tuberculosis such as members of Treatment Committee of the Japanese Society for Tuberculosis, experts of cardiovascular medicine)

[133)] Appropriateness of the distribution of delamanid is to be evaluated according to the following criteria:
- Delamanid is used for the indicated disease.
- Delamanid is not contraindicated in the patient.
- The independent committee approves the use of delamanid.

delamanid is expected to be used for a long period of time, a cooperative relationship should be established between a highly specialized center and local hospitals for appropriate sharing of patient information. The proper use of delamanid will be ensured by the appropriate implementation of a controlled distribution system for delamanid according to the RAP that is currently being planned by the applicant. Therefore, the appropriate implementation of RAP is essential after the market launch.

The above conclusion of PMDA will be finalized, taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-01, 5.3.5.2-01). Protocol deviations (enrollment of subjects who met the exclusion criteria, failure to perform part of blood sampling and testing for pharmacokinetics study) were found in some medical institutions. Also, the sponsor failed to identify some of these protocol deviations through monitoring. Improvements were needed in these matters but the cases were handled appropriately, and PMDA therefore concluded that the clinical studies as a whole had been conducted in compliance with GCP and that there should be no problem in proceeding with a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, PMDA has concluded that the efficacy of delamanid in multidrug-resistant pulmonary tuberculosis has been demonstrated and the safety of delamanid is acceptable in view of its benefits observed. The data suggested that the concomitant use of delamanid with a standard therapy for tuberculosis leads to early sputum culture conversion. Delamanid is a new option for the treatment of multidrug-resistant tuberculosis and thus is of clinical significance. At the same time, there are only extremely limited use experiences of delamanid in Japanese patients. Delamanid causes QT prolongation, and the efficacy and safety of delamanid have not been investigated in long-term use. These remaining issues require further investigations. Also, since delamanid is expected to be one of the few therapeutic agents available for multidrug-resistant pulmonary tuberculosis, the careful selection of eligible patients is critical for the prevention of the emergence of strains resistant to delamanid, and thus the appropriate implementation of RAP is important.

PMDA considers that delamanid may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

April 18, 2014

I. Product Submitted for Registration

[Brand name]	Deltyba Tablets 50 mg
[Non-proprietary name]	Delamanid
[Applicant]	Otsuka Pharmaceutical Co., Ltd.
[Date of application]	March 27, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

The conclusion of PMDA described in Review Report (1) was supported by the Expert Discussion. PMDA conducted an additional review of the following points and took necessary actions.

(1) Safety

1) QT prolongation

Since there are only extremely limited experiences with delamanid in Japanese patients, and QT prolongation was associated with the administration of delamanid, PMDA concluded that precautionary statements for QT prolongation should be included in the package insert and that safety information should be collected after the market launch to be provided appropriately to clinical practice.

PMDA's above conclusion was supported by the expert advisors while the following additional comments were made:

- In clinical studies, QT prolongation was observed in patients with acute myocardial infarction and those with coronary artery disease. Therefore, it is necessary to caution that the use of delamanid should be considered carefully in patients with coronary artery disease.
- In Japan, many patients to be treated with delamanid are elderly, who are at high risk of QT prolongation, warranting due caution.
- In particular, QT prolongation should be checked before and during the treatment. Information on the risk should be provided at least in the "Warning" section of the package insert to raise an alert.

Based on the comments of the expert advisors and the fact that some drugs co-administered with delamanid for the treatment of multidrug-resistant pulmonary tuberculosis such as fluoroquinolone antibacterials are likely to cause QT-prolongation, PMDA considers that QT prolongation is an important safety concern posed by treatment regimens which include delamanid. Therefore, PMDA instructed the applicant to provide the following precautions in the "Warnings" and "Precautions for Indications" sections of the package insert, and to require careful administration to patients with cardiac disease because of their high risk for QT prolongation. The applicant agreed to the instruction.

[Warnings]
QT prolongation may occur after the administration of delamanid. ECG should be monitored before the start of treatment and on a regular basis during the treatment. The administration of delamanid should be carefully considered by weighing benefits versus risks.

[Precautions for indications]
QT prolongation may occur after the administration of delamanid. In patients who have or are prone to QT prolongation, the administration of delamanid should be carefully considered by weighing benefits versus risks.

(2) Dosage and administration

1) Treatment duration

The global long-term treatment study (Study 242-[redacted]-208) did not show any trend of the occurrence of new adverse events with the prolongation of the treatment duration. The mortality rate in the subjects who participated in the study did not exceed that in the patients who participated only in the global phase II study (Study 242-[redacted]-204). In the treatment of multidrug-resistant pulmonary tuberculosis, drugs other than injectable anti-tuberculosis drugs are generally intended to be used for at least 18 months after sputum culture conversion for the purpose of controlling the growth of *M. tuberculosis*3) sufficiently. Therefore, delamanid may also need to be administered for a period exceeding 6 months. Taking account of these facts, PMDA considered it difficult to define a specific duration of treatment with delamanid. However, scanty experiences in treatment withf delamanid for >6 months either in Japan or in other countries should be highlighted in the package insert to raise an alert.

PMDA's above conclusion was supported by the expert advisors while the following additional comments were made:

- The expression "there are scanty experiences in the administration of delamanid for >6 months" might be taken as discouragement of the use of delamanid for a period exceeding 6 months. A supplementary explanation is needed to avoid such misunderstanding.

In response to the comment of the expert advisors, PMDA instructed the applicant to include the following description in the package insert to raise an alert: "In the prolonged use of delamanid, whether to continue the treatment should be carefully considered by weighing benefits versus risks (there is no experience of continuous treatment for >6 months)." The applicant agreed.

(3) Risk management plan (draft)

Taking account of the discussion in "Review Report (1), II. 4.(ii).B.(8).1) Post-marketing surveillance" and the comments from the expert advisors at the Expert Discussion, PMDA instructed the applicant to add the following investigations in the post-marketing surveillance. The applicant agreed to the instruction.

- Effects of co-administered OBRs on the efficacy and safety of delamanid
- Occurrences of delamanid-induced QT prolongation and other cardiovascular events
- Safety and efficacy of delamanid in patients with hepatic impairment
- Treatment courses and outcomes in patients who have failed to achieve 2-month SCC

Also, the following comments were offered by the expert advisors on the resistance to delamanid.

- According to the submitted data, the breakpoint of delamanid is MIC 0.2 μg/mL. However, a more accurate breakpoint should be established by accumulating information from patients treated with delamanid after the market launch.

- A testing method for the sensitivity of bacteria to delamanid should be established through continuous discussion.

Taking account of these comments of the expert advisors, PMDA instructed the applicant to continue to improve testing methods for the sensitivity of bacteria to delamanid, determine a more accurate breakpoint, and provide information in an appropriate manner. The applicant agreed.

Based on the above discussions, PMDA has concluded that safety- and efficacy-related issues listed in Table 44 should be included in the current risk management plan for delamanid and that additional pharmacovigilance activities and risk minimization actions listed in Table 45 should be conducted, and that there are no particular problems in the outline of the use result survey plan (draft) as listed in Table 46.

Table 44. Safety and efficacy specifications in risk management plan

Safety specification		
Important identified risk	Important potential risk	Important missing information
- QT prolongation	- Drug resistance	- Long-term use
Efficacy follow-up		
- Efficacy of delamanid in routine clinical use (sputum culture conversion of multidrug-resistant *M. tuberculosis*)		

Table 45. Outline of additional pharmacovigilance and risk minimization activities in risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
- Early post-marketing phase vigilance - Use-results survey (all-case surveillance)	- Provision of information obtained from early post-marketing phase vigilance - Reference materials for healthcare professionals - Reference materials for patients - Limited distribution medication program for proper use of new drug (Responsible Access Program)

Table 46. Outline of use results survey plan (draft)

Objective	The investigation of the safety and efficacy of delamanid in all patients treated with delamanid in routine clinical practice
Method for investigation	All-case surveillance (ECG will be monitored during the survey. Drug resistance will be tested before and after treatment.)
Patients population	All patients who have a diagnosis of "multidrug-resistant pulmonary tuberculosis" and newly started treatment with delamanid
Observation period	2 years after the end of the treatment period in patients who have completed the delamanid treatment
Planned number of subjects	All patients registered within a 5-year registration period
Main investigation items	Study site information, patient information, patient characteristics, history of the administration of delamanid, history of adverse drug reactions, status of use of delamanid and compliance, clinical symptoms, imaging tests, sputum test, drug sensitivity test, sputum culture conversion (SCC), bacteriological relapse, the discontinuation of treatment, final outcome, change of hospital, status of use of anti-tuberculosis drugs other than delamanid, status of use of drugs other than anti-tuberculosis drugs, pulmonary tuberculosis treatment other than chemotherapy, ECG, laboratory test values, adverse events after starting the treatment with delamanid.

III. Overall Evaluation

As a result of the review, PMDA has concluded that the product may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions for approval. Since the product is an orphan drug, the re-examination period is 10 years. Both the drug substance and the drug product are classified as powerful drugs. The product is not classified as a biological product or a specified biological product.

[Indication] Bacterial microorganisms:

	Delamanid-susceptible strains of *Mycobacterium tuberculosis* Disease: Multidrug-resistant pulmonary tuberculosis
[Dosage and administration]	The usual adult dosage of delamanid is 100 mg administered orally twice daily in the morning and in the evening after meals.
[Conditions for approval]	Because of the extremely limited clinical experience with the product in Japanese patients, the applicant is required to conduct a drug use results survey, which covers all patients treated with the product, for a certain period of time after the market launch in order to understand the characteristics of patients treated with the product and collect safety and efficacy data on the product during the early post-marketing period, thereby taking necessary measures to facilitate the proper use of the product.