Compassionate use of delamanid in adults and children for drug-resistant tuberculosis: 5-year update

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This compassionate use programme constitutes one of the largest cohorts of TB patients treated with delamanid in a resource-limited, non-clinical trial setting https://bit.ly/3nDSw52

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ABSTRACT

Background: Although delamanid has been approved for the treatment of multidrug-resistant TB (MDR-TB) in numerous regions, in areas where it is not yet registered it can be accessed as part of salvage therapy (in particular for those patients with limited treatment options) *via* the Otsuka compassionate use programme. Here we present the analysis of interim treatment outcomes by 24 weeks of more than 200 MDR-TB patients globally who received delamanid under this programme.

Methods: We evaluated treatment efficacy with respect to culture negativity at 24 weeks, as well as the safety profile of delamanid, in an MDR-TB patient cohort treated under compassionate use between 2014 and 2019.

Results: Among patients who received delamanid as part of a multidrug regimen, 123 (61%) out of 202 had extensively drug-resistant TB (XDR-TB), 66 (33%) out of 202 had HIV co-infection and 34 (17%) out of 202 were children aged between 6 and 17 years. Of those patients who were culture positive at delamanid treatment initiation and who completed 24 weeks of delamanid treatment in combination with other anti-tuberculosis (TB) drugs, culture negativity was achieved in 116 (79%) out of 147 cases. The corresponding rates of culture negativity for patients with XDR-TB and HIV co-infection, as well as the paediatric subgroup were 69 (77%) out of 90, 44 (92%) out of 48 and 20 (80%) out of 25, respectively. QT interval prolongation was the most frequently observed serious adverse event (5%). Overall, treatment safety outcomes did not reveal any new or unidentified risks.

Conclusions: The use of delamanid combined with other active drugs has the potential to achieve high rates of culture negativity in difficult-to-treat drug-resistant TB cases, with a favourable safety profile.

Data availability: To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit https://clinical-trials.otsuka.com/. For all approved IPD access requests, Otsuka will share anonymised IPD on a remotely accessible data sharing platform.

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Introduction

In 2018, about 10 million people contracted tuberculosis (TB) globally resulting in over 1.5 million deaths [1]. Half a million new cases of rifampicin-resistant TB were reported globally, of whom 78% had multidrug-resistant TB (MDR-TB) (defined as resistance to isoniazid and rifampicin) [1]. Moreover, 6.2% of MDR-TB cases were additionally identified as being extensively drug-resistant TB (XDR-TB) (defined as MDR-TB with additional resistance to a fluoroquinolone (FQ) and an injectable anti-TB drug (INJ)) [1].

Patients with MDR-TB and especially those with XDR-TB are difficult to treat and require prolonged regimens compared to those used for the treatment of drug-susceptible TB [2, 3]. Current challenges in the management of drug-resistant cases include the use of drugs with frequent adverse events (AEs) and poor tolerability, as well as worse long-term outcomes (*i.e.* higher rates of relapse and treatment failure) [4–10]. Treatment among the paediatric population is further complicated by a lack of paediatric formulations and adequate data on safety and dosing [11]. Therefore, appropriate combination regimens with newer, more potent and less toxic drugs are needed to cope with the challenges of managing both adult and paediatric MDR-TB patients [12].

Delamanid, a nitroimidazole bactericidal agent, has been in use since 2014 for the treatment of pulmonary MDR-TB in adult patients (where it has been difficult to construct a regimen due to tolerability and/or resistance issues). It has exhibited anti-TB activity and a favourable safety profile in multiple Otsuka-sponsored clinical trials, including two phase 2 studies, an open-label registry (trials 204, 208 and 116) and one phase 3 clinical trial (trial 213) [13–16]. Additionally, early data from children with MDR-TB in a phase 1 pharmacokinetics (PK) and safety study (trial 232) and a phase 2, 6-month safety, efficacy and PK trial (trial 233; ongoing) have also demonstrated a favourable safety profile [17, 18]. Furthermore, the World Health Organization (WHO) has endorsed the use of delamanid for children with MDR-TB from the age of 3 years to 18 years old [19].

The Otsuka compassionate use programme began in 2014 as part of a global access initiative in coordination with the European Respiratory Society (ERS)/WHO TB Consilium and Médecins sans Frontières (MSF)/Partners in Health (PIH), and provides access to delamanid for patients with very limited treatment options [20]. An update on the safety and efficacy outcomes of patients enrolled since the start of the compassionate use programme (February 2014) until November 2019 are presented here [20, 21].

Methods

Requests for participation in the compassionate use programme were submitted to Otsuka by treating physicians. Assessment of eligibility was provided by an ERS/WHO TB Consilium or MSF/PIH Medical Committee. Patient access forms along with expert summaries and recommendations from the Consilium were then evaluated by the Otsuka compassionate use committee for inclusion in the programme, in agreement with the compassionate use protocol.

Decisions to include patients in the compassionate use programme were made by Otsuka's compassionate use committee, in consultation with an independent panel of experts, based on baseline data including sputum culture status, ECG results, demographics, extent of TB disease, presence of lung cavities, drug resistance, prior treatment, comorbidities, serum electrolytes and albumin levels. Drug-susceptibility testing (DST) results for all first-line and second-line anti-TB drugs were also assessed within 60 days prior to enrolment. Requests for delamanid compassionate use providing patient-specific recommendations about regimen and appropriateness of inclusion in the programme were reviewed by Otuska, the ERS/WHO TB Consilium or MSF/PIH. The final decision on enrolment of patients in the compassionate use programme was made by Otsuka.

To determine eligibility for the programme, patients were required to meet the following inclusion criteria: signed informed consent by the patient (or by their parent/legal guardian for minors) and a signed application form by their treating physician; MDR-TB with limited therapeutic options; inability to participate in a delamanid clinical trial; age 6 years and above with body weight >20 kg; receiving treatment at a centre experienced in MDR-TB management; and an agreement to hospitalisation for the initial 4 months of combination therapy for patients receiving delamanid along with other potentially QT-prolonging drugs. Exclusion criteria included: any previous (during the last 6 months) or concomitant use of experimental MDR-TB treatments; contraindications to delamanid as per the summary of product characteristics (SmPC) (*i.e.* hypersensitivity to the active substance or to any of the excipients listed in the SmPC, serum albumin <2.8 $g \cdot dL^{-1}$, or use of medicinal products that are strong inducers of CYP3A); previous treatment with delamanid; QTcF at baseline >500 ms or >450 ms in the case of bedaquiline co-administration; serum potassium, magnesium, or calcium outside of normal range at baseline; less than two active or likely to be active drugs (not counting delamanid) to be included in the proposed optimised background regimen (OBR) based on recent DST and/or treatment history.

At the start of the compassionate use programme, concomitant use of delamanid and bedaquiline was not permitted; however, following the publication of additional safety data on both compounds, patients were enrolled in the programme using this combination starting in 2016, albeit under specific conditions including hospitalisation and frequent monitoring of the QTc interval [21].

In accordance with national and WHO recommendations for the management of MDR-TB, patients accepted for compassionate use were administered delamanid as part of an OBR for 24 weeks (100 mg twice daily with body weight ⩾35 kg or 50 mg twice daily for patients weighing >20 kg and <35 kg) [17]. Following the 24-week delamanid course, the OBR was continued for the remaining treatment period as determined by the treating physician.

All decisions regarding general patient management, *i.e.* not related to delamanid therapy, including dose and duration of other anti-TB drugs, changes to the regimen and duration of follow-up, were made by the treating physicians. Patients receiving delamanid in combination with other potentially QT-prolonging drugs were recommended to have weekly ECGs for the entire duration of the co-administration. Pharmacovigilance (PV) training of treating physicians was performed prior to treatment initiation and AEs were collected throughout the entire treatment period until the end of treatment with the OBR (and thereafter if an AE was considered to be related to delamanid). All AEs reported to Otsuka were assessed for seriousness, severity and causality. The culture status of patients at the end of delamanid treatment (*i.e.* at 24 weeks) was collected from treating physicians as available. Culture-negativity was defined as having one or more negative cultures within 24 weeks of the start of delamanid therapy, without any subsequent positive cultures within that period.

Confirmation of the regimen given at baseline and changes to the use of delamanid, including temporary interruptions, permanent withdrawals from therapy and completion of a treatment course, were also collected. Descriptive statistical analyses were performed for all patients who initiated treatment with delamanid.

Results

Otsuka received 284 compassionate use requests for delamanid, 238 of which were approved (figure 1). Of those patients approved, 202 received delamanid as part of a multidrug regimen within the compassionate use programme. The first compassionate use patient started treatment in March 2014 and the last started delamanid treatment in March 2019.

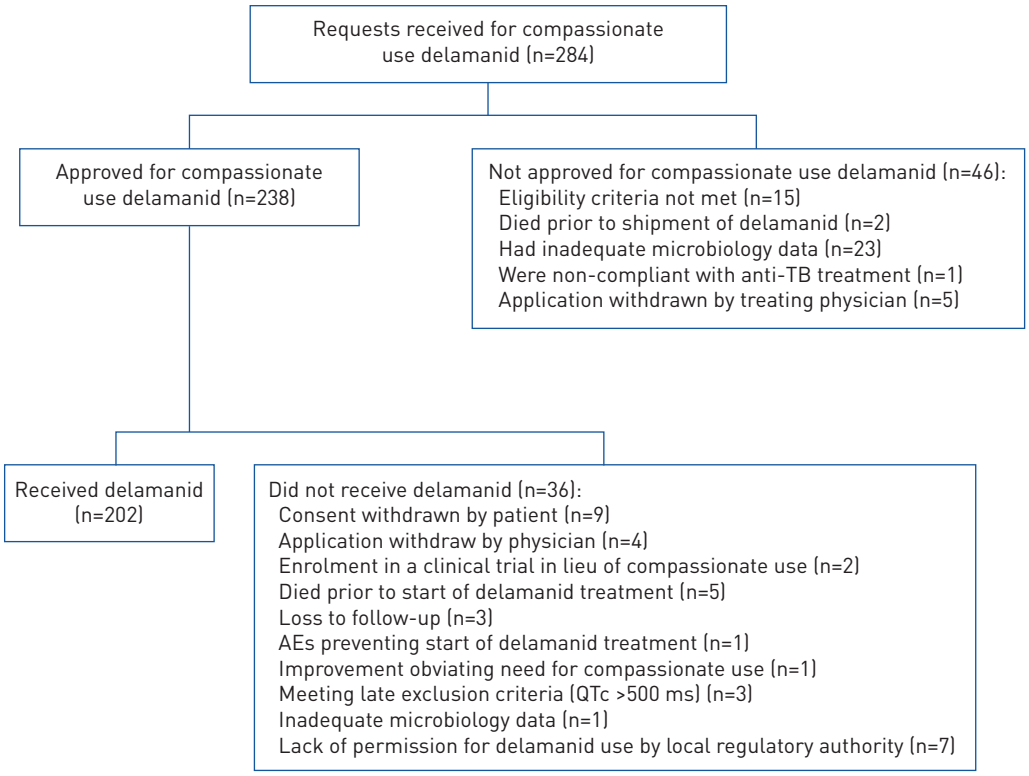

FIGURE 1 Flowchart for delamanid compassionate use. TB: tuberculosis; AE: adverse event.

The mean time to initiate delamanid therapy following the receipt of an initial compassionate use request was 61 days (median 45 days, range 3–449 days). The time to treatment initiation depended upon multiple factors, including delays in obtaining an import permit, shipping time, customs delays, availability of concomitant medications and pending culture/DST results.

Geographic distribution, demographics and the clinical characteristics of those receiving delamanid-containing treatment are summarised in table 1. The majority of patients, 105 out of 202 (52%), originated from South Africa, followed by the Russian Federation/CIS countries (44 out of 202, 22%) and India (30 out of 202, 15%). The mean age of patients was 35 years (range 6–76 years), with the majority (124 out of 202, 61%) being male. Patients' mean weight was 53±14.9 kg. Of the 202 patients receiving delamanid, 34 out of 202 (17%) were children aged from 6 years to 17 years. The majority of paediatric patients, 24 out of 34 (71%), received the adult delamanid dosage (*i.e.* 100 mg twice daily); however, 10 out of 34 (29%) received 50 mg of delamanid twice daily due to having a body weight of between 20 kg and 35 kg.

A significant proportion of patients had co-infections: 66 out of 202 (33%) with HIV; 11 out of 202 (5%) with hepatitis C virus (HCV) (of which three out of 202 (1%) had both HIV and HCV co-infection); and three out of 202 (1%) with hepatitis B virus (HBV) (of which two out of 202 (1%) had both HBV and HCV co-infection). All patients with HIV co-infection received anti-retroviral therapy concomitantly during their MDR-TB/XDR-TB treatment. Diabetes mellitus was present in 11 out of 202 patients (5%). The majority of patients (106 out of 202, 52%) received delamanid in combination with bedaquiline, 42 out of 106 of whom (40%) started bedaquiline prior to initiating delamanid (mean of 204 days before start of delamanid; range: 6 days–1113 days) and 63 out of 106 of whom (59%) were treatment naïve to both drugs at baseline. Patient demographics and clinical characteristics are presented in table 1.

Of the 202 patients who were initiated with a delamanid-containing regimen, 172 (85%) completed 24 weeks of treatment with delamanid, while 11 (5%) either permanently discontinued treatment or were lost to follow-up. Nineteen patients (9%) died prior to the completion of 24 weeks of treatment and an additional four patients died after the 24-week period. Among those who completed the 24-week delamanid plus OBR treatment, 147 out of 172 (85%) were culture positive prior to delamanid start and were subsequently assessed for culture negativity. All 202 patients enrolled were also assessed for treatment safety.

Sputum culture status for all patient subgroups at 24 weeks are shown in figures 2 and 3. Of the patients who were culture positive at enrolment and who completed the 24-week delamanid treatment, 116 out of 147 (79%) achieved sputum culture negativity at 24 weeks, while 22 out of 147 (15%) remained culture positive (results for nine out of 147 patients (6%) were unavailable). Of those patients among the paediatric subgroup who were culture positive at enrolment and completed the delamanid plus OBR treatment, 20 out of 25 (80%) achieved a negative 24-week culture status (results for two paediatric patients were unavailable). Of the 123 XDR-TB patients who were enrolled, 104 completed their delamanid therapy; 90 out of 104 (87%) patients completing therapy were culture positive prior to delamanid start and 69 out of 90 (77%) achieved culture negativity. Furthermore, 56 out of 66 patients (85%) with HIV co-infection completed delamanid treatment; among 48 (73%) HIV co-infected patients with positive sputum culture at enrolment, 44 (92%) achieved culture negativity.

A summary of safety findings is presented in tables 2 and 3. The most commonly reported AEs were nausea, vomiting and ECG QT interval prolongation. Out of 431 reported AEs, 173 (40%) were assessed as serious adverse events (SAEs). Abnormal QT interval or prolongation was the most commonly observed SAE (eight out of 173). A corrected QT prolongation (QTc) interval of ˃500 ms was observed in three out of 202 patients (1%) who received delamanid; however, for most cases the QT correction method was unknown or not reported. All three of these patients received clofazimine and two additionally received moxifloxacin. Of these two patients one also received bedaquiline. In one case, delamanid was permanently withdrawn after 2 weeks and the patient continued to use clofazimine and moxifloxacin. In a second case, all anti-TB medications, including delamanid and clofazimine, were interrupted and reintroduced 2 weeks later. In the third case, the patient continued to receive delamanid while bedaquiline and clofazimine were interrupted for several days, one after the other, then bedaquiline was restarted. QT prolongation subsequently resolved for all patients with no further cardiac manifestations observed in any of them.

Among the reported SAEs that were assessed as being causally related to delamanid, there were four out of 202 events (2%) classified within the category of liver disorders (hepatitis, hepatic encephalopathy, drug-induced liver injury (DILI) and hepatotoxicity, respectively). Notably, the number of concomitant anti-TB medications used by the patients developing liver toxicity ranged from five to nine and all four patients had one to three of the following conditions in their medical history: hepatitis C (three out of four), HIV (two out of four), drug abuse (one out of four), drug reaction with eosinophilia and systemic

TABLE 1 Demographic and clinical characteristics of patients treated with delamanid under compassionate use

Characteristics	Result
Patients n	202
Age years	35 (6–76)
Sex	
Female	78 (39)
Male	124 (61)
Paediatric patients	34 (17)
Weight kg	53 (17–110)
Region	
Europe	46 (23)
Asia	35 (17)
Africa	108 (53)
Americas (including the USA)	13 (6)
Disease type	
Pulmonary disease alone	189 (94)
Extrapulmonary involvement	13 (6)
Pulmonary and extrapulmonary disease	7 (3)
Extrapulmonary disease alone	6 (3)
Cavitary disease	
None	40 (20)
Yes	139 (69)
Unknown	23 (11)
Resistance type	
Rifampicin	1 (0)
MDR-TB	21 (10)
Pre-XDR-TB[#]	54 (27)
MDR-TB+FQ resistance	35 (17)
MDR-TB+INJ resistance	15 (7)
Functionally pre-XDR-TB (rifampicin resistance+INJ resistance+unknown FQ resistance)	4 (2)
XDR-TB	123 (61)
Comorbidities	
HIV co-infection	66 (33)
HCV co-infection	11 (5)
HBV co-infection	3 (1)
Diabetes mellitus	11 (5)
Patients previously receiving an anti-TB regimen	169 (84)
Patients with a prior failing regimen	151 (75)
Co-administration of delamanid and bedaquiline[¶]	
Yes	106 (52)
No	96 (48)
Baseline culture status	
Negative	30 (15)
Positive	171 (85)
Unknown	1 (0)
Number of drugs to which resistant[+]	6.3±3.2
Number of drugs to which susceptible	2.9±2.1
Completed 24-week delamanid treatment	
Yes	172 (85)
No	30 (15)
Culture status at delamanid start[§]	
Negative	25 (15)
Positive	147 (85)
Culture status at 24 weeks[f]	
Negative	116 (79)
Positive	22 (15)
Unknown	9 (6)
Delamanid discontinued/patients lost-to-follow up	11 (5)

Data are presented as n (%), mean (range) or mean±SD, unless otherwise stated. TB: tuberculosis; MDR-TB: multidrug-resistant TB; XDR-TB: extensively drug-resistant TB; FQ: fluoroquinolone; INJ: injectable anti-TB drug; HBV: hepatitis B virus; HCV: hepatitis C virus. [#]: MDR-TB plus resistance to an FQ or INJ; [¶]: other anti-TB drugs administered concomitantly with delamanid: rifabutin (n=20, 10%), moxifloxacin (n=36, 18%), levofloxacin (n=92, 46%), ofloxacin (n=1, 0%), amikacin (n=16, 8%), kanamycin (n=9, 4%), capreomycin (n=27, 13%), linezolid (n=165, 82%), pyrazinamide (n=111, 55%), para-aminosalicylic acid (n=108, 53%), ethambutol (n=24, 12%), meropenem (n=24, 12%), amoxicillin with clavulanic acid (n=75, 37%), cycloserin (n=44, 22%), clofazimine (n=148, 73%), ethionamide (n=39, 19%), proteonamide (n=5, 2%), clarithromycin (n=2, 1%), imipenem (n=35, 17%), imipenem/cilastatin (n=11, 5%), ertapenem (n=5, 2%) and high-dose isoniazid (n=24, 12%); [+]: drugs to which patients were resistant: amikacin (n=77, 38%), kanamycin (n=85, 42%), capreomycin (n=91, 45%), INJ (n=2, 1%), ofloxacin (n=131, 65%), levofloxacin (n=53, 26%), moxifloxacin (n=76, 38%), proteonamide (n=26, 13%), ethionamide (n=38, 19%), cycloserin (n=16, 8%), para-aminosalicylic acid (n=28, 14%), linezolid (n=6, 3%) and clofazimine (n=4, 2%); [§]: for those patients who completed their 24-week delamanid treatment; [f]: for those patients who were culture positive at the start of delamanid treatment.

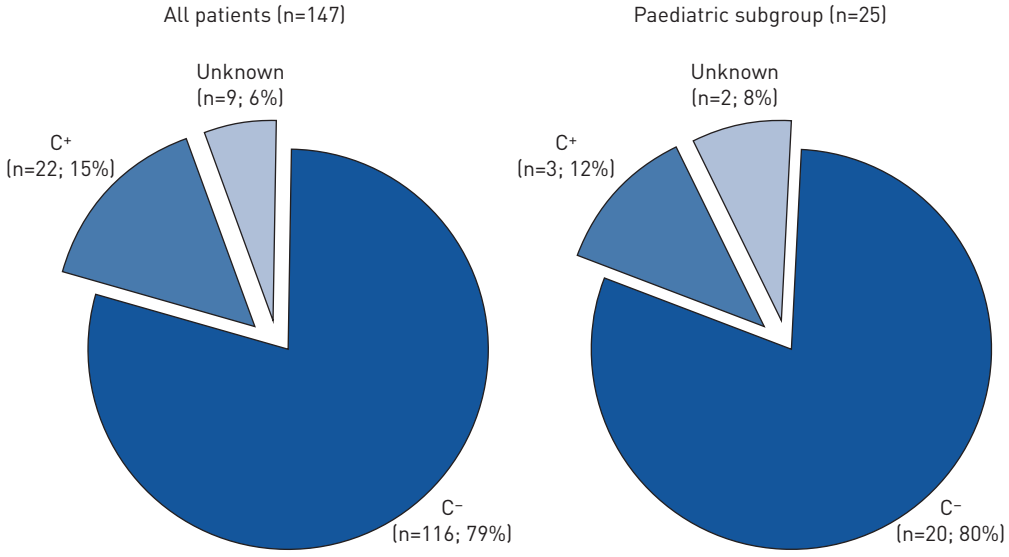

FIGURE 2 Culture status at 24 weeks for all patients and paediatric patients. C+: culture positive; C−: culture negative.

symptoms (DRESS) (one out of four). Event outcomes for the episodes of hepatitis and hepatotoxicity were reported as "recovered/resolved", the outcome for the DILI event was unknown and the event outcome for the patient with hepatic encephalopathy was fatal.

Deaths were reported for 23 out of 202 patients (11%). For 16 out of 23 fatal cases (70%), worsening of MDR-TB/XDR-TB was reported as the cause or suspected cause of death. Death in five out of 23 patients (22%) was attributed to pre-existing conditions (hepatic encephalopathy (history of HCV/HIV), cirrhosis (history of alcohol abuse), left foot gangrene (history of peripheral vascular disease and HIV), syndrome of inappropriate antidiuretic hormone secretion (SIADH) (history of SIADH and pancreatitis) and persistent electrolyte imbalance (HIV co-infected patient with a QTc interval of 487 ms, 455 ms and 443 ms reported 30 days, 11 days and 5 days before death, with no ECG recordings thereafter)). Overall, one to six pre-existing medical conditions were reported for all but one of the patients with a fatal outcome. Amongst these the most frequent was HIV (11 out of 23, 48%). In one case, a 29-year old male patient, the AEs shortness of breath, chest pain and vomiting subsequently led to a fatal outcome. Although a myocardial infarction was suspected, an autopsy was not performed to confirm this diagnosis. Finally,

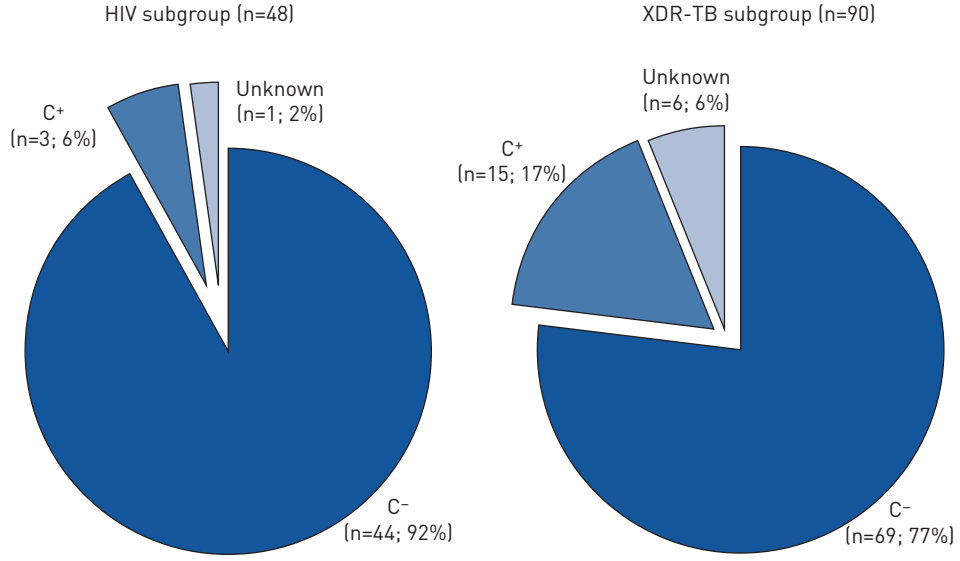

FIGURE 3 Culture status at 24 weeks amongst HIV co-infected patients and extensively drug-resistant tuberculosis (XDR-TB) patients. C+: culture positive; C−: culture negative.

TABLE 2 Safety summary for all 202 patients

Event	Result
Total AEs reported	431
Patients with AEs	139 (69)
Most commonly reported AEs (n=431)	
Nausea	19 (4)
Vomiting	17 (4)
ECG QT prolonged/abnormal	13 (3)
Total SAEs reported	173
Patients with SAEs	73 (36)
Most commonly reported SAEs (n=173)	
ECG QT prolonged/abnormal	8 (5)
Vomiting	5 (3)
Nausea, anaemia, hypokalaemia	4 (2)
Death	23 (11)
Cause of death (n=23)	
Worsening of MDR-TB/XDR-TB	16 (70)
Pre-existing condition[#]	5 (22)
Shortness of breath/chest pain/vomiting	1 (4)
Viral meningitis	1 (4)
Most commonly reported pre-existing conditions (n=23)	
HIV	11 (48)
Chronic liver disease due to HCV or alcohol abuse	5 (22)
Diabetes mellitus	3 (13)
Hyponatraemia/hypoalbuminaemia	3 (13)

Data are presented as n or n (%). Serious adverse events (SAEs) were defined as any adverse events (AEs) that led to death, were life threatening, were a persistent or significant disability/incapacity, required hospitalisation/prolongation of hospitalisation, were congenital anomalies, or were any other event deemed clinically significant by the treating physician. MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; HCV: hepatitis C virus. [#]: pre-existing conditions were: hepatic encephalopathy (n=1), cirrhosis (n=1), left foot gangrene/sepsis (n=1), syndrome of inappropriate antidiuretic hormone secretion (SIADH) (n=1) and persistent electrolyte imbalance (n=1).

a single paediatric fatal outcome was reported in an 8-year old child who died due to viral meningitis 4 months after treatment with delamanid was completed.

In the subgroup of paediatric patients treated within the compassionate use programme, 102 AEs were reported in 31 out of 34 patients (91%), of which 21 were SAEs reported in five out of 34 patients (15%). Twelve SAEs (*e.g.* suicidal ideation, decubitus ulcer, necrotising pneumonia, respiratory distress, varicella,

TABLE 3 Safety summary for the paediatric subgroup (n=34)

Event	Result
Total AEs reported	102
Patients with AEs	31/34 (91)
Most commonly reported AEs	
ECG QT prolonged/abnormal	4/102 (4)
Vomiting	4/102 (4)
Hypoalbuminaemia	3/102 (3)
Total SAEs reported	21
Patients with SAEs	5/34 (15)
Most commonly reported SAEs	
Hypoalbuminaemia[#]	2/102 (2)
Death	1/102 (1)

Data are presented as n or n/n (%). Serious adverse events (SAEs) were defined as any adverse events (AEs) that led to death, were life threatening, were a persistent or significant disability/incapacity, required hospitalisation/prolongation of hospitalisation, were a congenital anomaly, or were any other event deemed clinically significant by the treating physician. [#]: all other SAEs were single reported events.

joint effusion, vulval cellulitis, hypoalbuminemia, hepatotoxicity, extremity pain, depression and DRESS) were reported in a 16-year old patient, who experienced worsening of pre-existing DRESS whilst being on delamanid. The event of DRESS was assessed as being "not related" to delamanid. Five SAEs (hypomagnesemia, hypoalbuminemia, hypocalcaemia, hypokalaemia and ECG QT prolongation) were reported in a 17-year old patient with renal failure attributed to concomitant use of injectable anti-TB agents. Polycythaemia was reported in a 13-year old patient; however, it was assessed as being "not related" to delamanid. The outcome of all these 19 SAEs was assessed as "recovered/resolved". Viral meningitis and seizure were reported in an 8-year old patient with a fatal outcome, while treatment noncompliance with the event outcome "unknown" was reported in a 17-year old patient.

Discussion

This compassionate use programme constitutes one of the largest cohorts of patients treated with delamanid in a resource-limited, nonclinical trial setting. The majority of all patients who completed a 24-week delamanid treatment (116 out of 147, 79%) revealed a short-term favourable outcome (culture negativity at 24 weeks). This is consistent with previously observed large cohorts of patients receiving delamanid as part of a multidrug regimen in a clinical trial setting, such as the endTB observational study and the Otsuka phase 3 study, where 80% and 88% of patients, respectively, experienced sputum culture conversion (SCC) within 6 months [16, 23]. Outcomes in this programme are also similar to those in recent studies, where drug-resistant patients received delamanid, bedaquiline or both delamanid and bedaquiline in combination, in an injectable-free regimen. Here, SCC at 6 months was noted in the delamanid cohorts in 79% and 74% of patients, respectively [24, 25]. Past studies have demonstrated that early culture conversion is a clinically relevant predictor of positive long-term treatment outcome, suggesting that patients with a negative 24-week culture status would have favourable long-term outcomes and lower mortality [14, 26–29]. The results are encouraging, especially as many patients had XDR-TB and/or HIV co-infection and cavitary disease, with such populations often being difficult to treat and tending to have poor outcomes [5]. As the compassionate use programme was not conducted in a randomised clinical trial setting and included a considerable number of extremely ill patients with extensive drug resistance and/or intolerance to other drugs, HIV co-infection and bilateral cavitation, the lower success rate is therefore not unexpected.

Safety outcomes among all patients treated with delamanid, including the paediatric subgroup, exhibited no unidentified patterns or unexpected concerns, thereby further establishing the acceptable safety and tolerability profile of this compound [30, 31]. QTc prolongation of ˃500 ms was reported for only three patients (1%), all of whom received clofazimine in combination with delamanid, while two also received moxifloxacin (one of whom also received bedaquiline). This is in line with the interim analysis report of the ongoing endTB prospective, observational cohort study (ClinicalTrials.gov, identifier: NCT03259269). In this study of a large cohort of 1244 rifampicin-resistant cases, which included patients on delamanid, bedaquiline, or both delamanid and bedaquiline, QT interval corrected using Fridericia's formula (QTcF) prolongation of >500 ms was reported in only 2.7% of patients [32]. These findings further support the therapeutic potential of a favourable and safe combination regimen of delamanid and bedaquiline to manage MDR-TB patients with limited treatment options [33].

The current report aims to evaluate delamanid efficacy through analysis of interim treatment outcomes by 24 weeks. Final treatment outcomes data were not routinely collected in the compassionate use delamanid framework, as patients were not followed further after they completed delamanid compassionate use treatment (lack of such data on final outcomes represents a study limitation). Furthermore, the absence of a control group, the lack of a clinical trial setting and the lack of long-term clinical outcomes, as well as a lack of information on the QT interval correction formula used, are important limitations of this analysis. Assessing AEs in an already potentially toxic combination regimen, together with the lack of culture conversion data or monthly culture status data (such as might be used to determine the time to culture conversion) are also limiting. Nevertheless, these results are noteworthy despite the comorbidities of the patients enrolled in the programme, as they represent a diverse and difficult to treat population who generally would not have been included in a clinical trial due to the severe nature of their disease.

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is an employee of Otsuka Novel Products GmbH. A. Martin is an employee of Otsuka Novel Products GmbH. J. Hafkin is an employee of Otsuka Pharmaceutical Development & Commercialisation, Inc. N. Hittel is an employee of Otsuka Novel Products GmbH.

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