EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Compassionate Use of Delamanid in Adults and Children for Drug-resistant TB: 5-year Update

Sambuddha Ghosh, Lusine Breitscheidel, Natasa Lazarevic, Alexandra Martin, Jeffrey Hafkin, Norbert Hittel

Please cite this article as: Ghosh S, Breitscheidel L, Lazarevic N, *et al*. Compassionate Use of Delamanid in Adults and Children for Drug-resistant TB: 5-year Update. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.02483-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©ERS 2020

Compassionate Use of Delamanid in Adults and Children for Drug-resistant TB: 5-year Update

Sambuddha Ghosh[1]

Lusine Breitscheidel[1]

Natasa Lazarevic[1]

Alexandra Martin[1]

Jeffrey Hafkin[2]

Norbert Hittel[1]

[1] Otsuka Novel Products GmbH, Munich, Germany

[2] Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA

Correspondence: Lusine Breitscheidel, Otsuka Novel Products GmbH, Erika-Mann-Strasse 21, 80636 Munich, Germany. E-mail: lbreitscheidel@otsuka-onpg.com

Take Home Message:

This Compassionate Use programme constitutes one of the largest cohorts of patients treated with delamanid in a resource-limited, non-clinical trial setting.

Abstract

Background: Although delamanid has been approved for the treatment of multidrug-resistant tuberculosis (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 (CU) programme. Here we present the analysis of interim treatment outcomes by 24 weeks of more than 200 multidrug-resistant tuberculosis (MDR-TB) patients globally who received delamanid under the Otsuka CU programme.

Methods: We evaluated the treatment efficacy, with respect to culture negativity at 24 weeks, and safety profile of delamanid in a MDR-TB cohort of patients treated under CU between 2014 and 2019.

Results: Among patients who received delamanid as part of a multidrug regimen, 123/202 (61%) had extensively drug-resistant tuberculosis (XDR-TB), 66/202 (33%) had HIV co-infection, and 34/202 (17%) were children ages between 6 and 17 years. Of those patients who were culture positive at delamanid treatment initiation and completed 24 weeks of delamanid treatment in combination with other anti-TB drugs, culture negativity was achieved in 116/147 (79%). The corresponding rates of culture negativity for patients with XDR-TB, HIV co-infection, and the paediatric subgroup were 69/90 (77%), 44/48 (92%), and 20/25 (80%), respectively. QT interval prolongation was the most frequently observed serious adverse event (reported in 8% of patients receiving delamanid). 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 tuberculosis cases, with a favourable safety profile.

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 having extensively drug-resistant TB (XDR-TB) (defined as MDR-TB with additional resistance to a fluoroquinolone and an injectable agent). [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 use of drugs with frequent adverse events 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 in 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 204/208/116), and one Phase 3 clinical trial (Trial 213). [13-16] Additionally, early data from children with MDR-TB from a Phase 1 pharmacokinetics (PK) and safety study (Trial 232) and a Phase 2, six-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 ages 3 to 18 years. [19]

The Otsuka Compassionate Use (CU) 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), providing delamanid access to patients with very limited treatment options. [20] An update on the safety and efficacy outcomes

of patients enrolled since the start of the CU programme (February 2014) until November 2019 are presented here. [20, 21]

Methods:

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

Decisions to include patients in the CU programme were made by Otsuka's CU Committee in consultation with an independent panel of experts based on baseline data including sputum culture status, ECG, demographics, extent of TB disease, presence of lung cavities, drug resistance, prior treatment, comorbidities, serum electrolytes and albumin levels. Drug-susceptibility testing (DST) results to all first- and second-line anti-TB drugs within 60 days prior to enrolment were also assessed. Requests for DLM CU were reviewed by Otuska, the ERS/WHO TB Consilium or MSF/PIH provided patient-specific recommendations about regimen and appropriateness of inclusion in the delamanid CU programme. Final decision on enrollment of patients in the CU 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 parent/legal guardian for minors) and signed application form by the 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 hospitalization 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 treatment of MDR-TB; 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/dL, or taking medicinal products that are strong inducers of CYP3A); previous treatment with delamanid; QTcF at baseline > 500 ms or > 450 ms in case of bedaquiline co-administration; serum potassium, magnesium, or calcium outside normal range at baseline; <2

active or likely to be active drugs (not counting delamanid) to be included in the proposed optimised background regimen based on recent DST and/or treatment history.

At the start of the CU programme, concomitant use of delamanid and bedaquiline was not permitted, however, following publication of additional safety data on both compounds, patients were enrolled in the programme using the combination of the two drugs starting in 2016 under specific conditions (including hospitalization and frequent monitoring of QTc interval). [21]

In accordance with national and WHO recommendations for the management of MDR-TB, patients accepted for CU were administered delamanid as part of an optimised background regimen (OBR) for 24 weeks – 100 mg twice daily with body weight ≥ 35kg or 50 mg twice daily for patients weighing more than 20kg and less than 35kg. [17] Following the 24-week delamanid treatment course, the OBR was then 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 adverse events (AEs) were collected throughout the entire treatment period, until the end of the treatment with 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. Culture status of patients at the end of delamanid treatment (i.e. 24 weeks) was collected from treating physicians as available. Culture-negativity was defined as having one or more negative cultures within 24 weeks since 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 CU requests for delamanid, 238 of which were approvedsee **Figure 1**. Of those approved, 202 patients received delamanid as part of a multidrug regimen within the CU programme. The first CU patient started treatment in March 2014 and last CU patient started delamanid treatment on March 2019.

The mean time to initiate delamanid therapy following the receipt of an initial CU request was 61 days (median 45 days, range 3–449). 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.

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

A significant proportion of patients had co-infections: 33% (66/202) with HIV, 5% (11/202) with HCV of which 3 (1%, 3/202) patients had HIV and HCV co-infection, and 1% (3/202) with HBV of which 2 (1%, 2/202) patients had HBV and HCV co-infection. All patients with HIV co-infection received anti-retroviral therapy concomitantly during their MDR/XDR-TB treatment. Diabetes mellitus was present in 5% (11/202) of patients.

The majority of patients (54%, 106/202) received delamanid in combination with bedaquiline, 40% (42/106) of whom started bedaquiline prior to initiating delamanid (mean of 204 days before start of delamanid; range: 6 – 1113 days), and 59% (63/106) 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%) patients either permanently

discontinued treatment or were lost to follow-up. Nineteen (9%) patients died prior to the completion of 24 weeks of treatment, and an additional 4 patients died after the 24-week period. Among those who completed the 24-week delamanid plus OBR treatment, 85% (147/172) 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, 79% (116/147) achieved sputum culture negativity at 24 weeks, and 15% (22/147) of patients remained culture positive, while results for 6% (9/147) of patients were unavailable. Among the paediatric subgroup who were culture positive at enrolment and completed delamanid plus OBR treatment, 80% (20/25) achieved negative 24-week culture status. Results for 2 paediatric patients were unavailable. Of the 123 XDR-TB patients enrolled and who completed their delamanid therapy, 73% (90/123) were culture positive prior to delamanid start, and 77% (69/90) achieved culture negativity. Furthermore, 73% (48/66) patients with HIV co-infection who completed delamanid were culture positive at enrolment, and 92% (44/48) achieved culture negativity. One patient, a 38-y.o. patient from Switzerland, developed resistance to delamanid. [22]

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 (SAEs). Abnormal QT interval or prolongation was the most commonly observed SAE (8/173). In 3/202 (1%) patients who received delamanid, a corrected QT prolongation (QTc) interval > 500 ms was observed (note: for most cases, the QT correction method was unknown or not reported). All three of these patients received clofazimine, two of whom additionally received moxifloxacin, and one patient received bedaquiline in addition to clofazimine and moxifloxacin. In the first patient, delamanid was permanently withdrawn after 2 weeks while the patient continued to use clofazimine and moxifloxacin. In the second case, all anti-TB medications, including delamanid and clofazimine, were interrupted and reintroduced two weeks later. In the third case, thepatient continued to received delamanid while actions were taken withmedications bedaquiline and clofazimine. QT prolongation subsequently resolved for all patients with no further cardiac manifestations observed in any of them.

Among the SAEs reported that were assessed as being causally related to delamanid, there were 4/202 (2%) events classified within liver disorders : hepatitis, hepatic encephalopathy, drug-induced liver injury (DILI) and hepatotoxicity, respectively. Of note, the number of concomitant anti-TB medications used by these patients developing liver toxicity ranged from 5 to 9, and all four patients had one to three of the following conditions in their medical history: hepatitis C (3/4), HIV (2/4), drug abuse (1/4), drug reaction with eosinophilia and systemic symptoms (DRESS) (1/4). Event outcomes for the episodes of hepatitis and hepatotoxicity were reported as "recovered / resolved", the outcome for the DILI event was unknown, while the event outcome for the patient with hepatic encephalopathy was fatal.

Deaths were reported for 23/202 (11%) patients. For 16/23 (70%) of fatal cases worsening of MDR-/XDR-TB was reported as the cause or suspected cause of death. Death in 5/23 (22%) patients 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 (history of SIADH and pancreatitis), and persistent electrolyte imbalance (HIV co-infected patient with QTc interval of 487 ms, 455 ms and 443 ms reported 30, 11 and 5 days before death outcome and no ECG recordings thereafter). Overall, for all but one of the patients with fatal outcome, 1-6 pre-existing medical conditions were reported, among which the most frequent one was HIV [11/23 (48%)). In one case of a 29-year-old male patient, AEs of shortness of breath, chest pain and vomiting subsequently led to fatal outcome. Although a myocardial infarction was suspected, an autopsy was not performed to confirm the diagnosis. Finally, a single paediatric fatal outcome was reported in an 8-year-old child who died due to viral meningitis 4 months after the treatment with delamanid was completed.

In the subgroup of 34 paediatric patients treated within the CU programme 102 AEs were reported in 31 (91%) patients, of which 21 were SAEs reported in 5/34 (15%) patients. Twelve SAEs (e.g. suicidal ideation, decubitus ulcer, pneumonia necrotising, respiratory distress, varicella, joint effusion, vulval cellulitis, hypoalbuminemia, hepatotoxicity, pain in extremity, depression and DRESS) were reported in a 16 years old patient who experienced worsening of pre-existing DRESS while being on delamanid. The event of DRESS was assessed as not related to delamanid. Five SAEs (hypomagnesemia, hypoalbuminemia, hypocalcaemia, hypokalaemia, and ECG QT prolonged) were reported in a 17 years old patient with renal failure attributed to

concomitant use of injectable anti-TB agents. Polycythaemia was reported in a 13 years old patient, however, it was assessed as no related to delamanid. The outcome of all those 19 SAEs was “recovered / resolved”. Viral meningitis and seizure were reported in an 8 years old patient with a fatal outcome, while treatment noncompliance with the unknown event outcome was reported in a 17 years old patient.

Discussion:

This CU programme constitutes one of the largest cohorts of patients treated with delamanid in a resource-limited, non-clinical trial setting. The majority (116/147, 79%) of all patients who completed a 24-week of delamanid treatment 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 experienced sputum culture conversion (SCC) within 6 months, respectively. [16, 23] Outcomes of this programme are also similar to some of the recent studies among drug-resistant patients receiving delamanid or bedaquiline or both in combination in an injectable-free regimen, where SCC at 6 months was noted in 79% and 74% of patients in delamanid cohorts, 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, 27, 28, 29] The results are encouraging, especially as many patients had XDR-TB, and/or HIV co-infection and cavitary disease; such populations are often difficult to treat and tend to have poor outcomes. [5]

As the CU programme was not conducted in a randomised clinical trial setting and included a considerable number of extremely ill patients with extensive drug resistance or 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 and thereby further establishing its acceptable safety and tolerability profile. [30, 31] QTc prolongation of > 500 ms was reported for only 3 (1%) patients, all of whom who received clofazimine in combination with delamanid, two of whom also received moxifloxacin, while one received bedaquiline additionally. This is in

line with the interim analysis report of the ongoing endTB prospective observational cohort study (ClinicalTrials.gov Identifier: NCT03259269). In this among a large cohort of 1,244 rifampicin-resistant disease which included patients on delamanid, bedaquiline, or both, QTcF interval prolongation >500ms, was reported in only 2.7% of patients. [32] These findings further support the therapeutic potential for a favourable and safe combination regimen of delamanid and bedaquiline to manage MDR-TB patients with limited treatment options. [33]

The current report is aimed to evaluate delamanid efficacy through analysis of interim treatment outcomes by 24 weeks. Final treatment outcomes data were not routinely collected in CU DLM framework as patients were not followed further after they completed DLM CU (lack of such data on final outcomes represents a study limitation). Furthermore, the absence of a control group, lack of clinical trial settings, no long-term clinical outcomes, lack of information on QT interval correction formula used, assessing AEs in an already potentially toxic combination regimen, and unavailability of culture conversion data or monthly culture status to determine the time to culture conversion are important limitations of this analysis. Nevertheless, these results are noteworthy despite the co-morbidities 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.

Correspondence: Lusine Breitscheidel, Otsuka Novel Products GmbH, Erika-Mann-Strasse 21, 80636 Munich, Germany. E-mail: lbreitscheidel@otsuka-onpg.com

Conflict of interests: All co-authors are an employee of either Otsuka Novel Products GmbH, Munich, Germany or Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA.

Acknowledgements: We would like to thank Marion Lozano, Ingeborg Knebel and Denis Punin (Otsuka Novel Products GmbH, Munich, Germany), Allison Stogdale and Alisha Thomas (Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA) for their assistance with data collection and review of the manuscript.

Funding Statement: Funding for the Otsuka Compassionate Use programme was provided by Otsuka Novel Products GmbH, Munich, Germany.

References:

1. World Health Organization. Global tuberculosis report 2019. Geneva, Switzerland: World Health Organization; 2019.
2. Diel R, Vandeputte J, de Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J. 2014;43(2):554-565..
3. Diel R, Rutz S, Castell S, Schaberg T. Tuberculosis: cost of illness in Germany. Eur Respir J. 2012;40(1):143-151..
4. Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis. 2010;51(1):6-14..
5. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, DeRiemer K, Centis R, Hollm-Delgado MG, Palmero D, Pérez-Guzmán C, Vargas MH, D'Ambrosio L, Spanevello A, Bauer M, Chan ED, Schaaf HS, Keshavjee S, Holtz TH, Menzies D; "The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB". Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J. 2013 Jul;42(1):169-179.
6. Rendon A, Tiberi S, Scardigli A, D'Ambrosio L, Centis R, Caminero JA, Migliori GB. Classification of drugs to treat multidrug-resistant tuberculosis (MDR-TB): evidence and perspectives. J Thorac Dis. 2016 Oct;8(10):2666-2671..
7. Caminero JA, Scardigli A. Classification of antituberculosis drugs: a new proposal based on the most recent evidence. Eur Respir J. 2015;46(4):887-893.
8. Caminero JA, García-Basteiro AL, Rendon A, Piubello A, Pontali E, Migliori GB. The future of drug-resistant tuberculosis treatment: learning from the past and the 2019 World Health Organization consolidated guidelines. Eur Respir J. 2019 Oct 10;54(4):1901272.
9. Pontali E, Raviglione MC, Migliori GB; and the writing group members of the Global TB Network Clinical Trials Committee. Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives. Eur Respir Rev. 2019 May 29;28(152):190035.

10. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Alffenaar JW, Caminero JA, Abdo Arbex M, Alarcon Guizado V, Aleksa A, Dore S, Gaga M, Gualano G, Kunst H, Payen MC, Roby Arias AJ, Skrahina A, Solovic I, Sulis G, Tadolini M, Zumla A, Migliori GB; International Carbapenem Study Group. Faster for less: the new "shorter" regimen for multidrug-resistant tuberculosis. Eur Respir J. 2016 Nov;48(5):1503-1507.
11. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, Pagano M, Becerra MC, Cohen T. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014 May 3;383(9928):1572-9.
12. Lienhardt C, Raviglione M, Spigelman M, Hafner R, Jaramillo E, Hoelscher M, Zumla A, Gheuens J. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. J Infect Dis. 2012 May 15;205 Suppl 2:S241-9.
13. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, Gao M, Awad M, Park SK, Shim TS, Suh GY, Danilovits M, Ogata H, Kurve A, Chang J, Suzuki K, Tupasi T, Koh WJ, Seaworth B, Geiter LJ, Wells CD. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012 Jun 7;366(23):2151-60.
14. Wells CD, Gupta R, Hittel N, Geiter LJ. Long-term mortality assessment of multidrug-resistant tuberculosis patients treated with delamanid. Eur Respir J. 2015 May;45(5):1498-501.
15. Blair HA, Scott LJ. Delamanid: a review of its use in patients with multidrug-resistant tuberculosis. Drugs. 2015;75(1):91-100.
16. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V Jr, Ticona E, Segura P, Cadena E, Yu C, Cirule A, Lizarbe V, Davidaviciene E, Domente L, Variava E, Caoili J, Danilovits M, Bielskiene V, Staples S, Hittel N, Petersen C, Wells C, Hafkin J, Geiter LJ, Gupta R. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med. 2019 Mar;7(3):249-259.
17. Hafkin J, et al. Long-term safety, tolerability, and pharmacokinetics of delamanid in children ages 12–17. EP-115-04. Presentation at 46th Union World Conference on Lung

Health, Cape Town, South Africa, 2–6 December 2015. Int J Tuberc Lung Dis 2015: 19 (12 Suppl 2): S91. [EP-115-04].

18. Hafkin J, et al. Updates on delamanid pharmacokinetic and safety data in children with MDR-TB. Presentation at 48th Union World Conference on Lung Health, Guadalajara, Mexico, 11-14 October 2017. Int J Tuberc Lung Dis 2017: 21 (11 Suppl 2): S27.
19. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland: World Health Organization; 2019
20. Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. Eur Respir J. 2017 Jul 27;50(1):1700311.
21. Hafkin J, Hittel N, Martin A, Gupta R. Compassionate use of delamanid in combination with bedaquiline for the treatment of multidrug-resistant tuberculosis. Eur Respir J. 2019 Jan 10;53(1):1801154.
22. Hoffmann H, Kohl TA, Hofmann-Thiel S, Merker M, Beckert P, Jaton K, Nedialkova L, Sahalchyk E, Rothe T, Keller PM, Niemann S. Delamanid and Bedaquiline Resistance in Mycobacterium tuberculosis Ancestral Beijing Genotype Causing Extensively Drug-Resistant Tuberculosis in a Tibetan Refugee. Am J Respir Crit Care Med. 2016;193 (3):337-40.
23. Seung KJ, Khan P, Franke MF, Ahmed S, Aiylchiev S, Alam M, Putri FA, Bastard M, Docteur W, Gottlieb G, Hewison C, Islam S, Khachatryan N, Kotrikadze T, Khan U, Kumsa A, Lecca L, Tassew YM, Melikyan N, Naing YY, Oyewusi L, Rich M, Wanjala S, Yedilbayev A, Huerga H, Mitnick CD. Culture Conversion at 6 Months in Patients Receiving Delamanid-containing Regimens for the Treatment of Multidrug-resistant Tuberculosis. Clin Infect Dis. 2020 Jul 11;71(2):415-418
24. Mohr-Holland E, Reuter A, Furin J, Garcia-Prats A, De Azevedo V, Mudaly V, Kock Y, Trivino-Duran L, Isaakidis P, Hughes J. Injectable-free regimens containing bedaquiline, delamanid, or both for adolescents with rifampicin-resistant tuberculosis in Khayelitsha, South Africa. EClinicalMedicine. 2020 Mar 3;20:100290
25. Kempker RR, Mikiashvili L, Zhao Y, Benkeser D, Barbakadze K, Bablishvili N, Avaliani Z, Peloquin CA, Blumberg HM, Kipiani M. Clinical Outcomes among Patients

with Drug-resistant Tuberculosis receiving Bedaquiline or Delamanid Containing Regimens. Clin Infect Dis. 2019 Nov 12:ciz1107

26. Kurbatova EV, Cegielski JP, Lienhardt C, Akksilp R, Bayona J, Becerra MC, Caoili J, Contreras C, Dalton T, Danilovits M, Demikhova OV, Ershova J, Gammino VM, Gelmanova I, Heilig CM, Jou R, Kazennyy B, Keshavjee S, Kim HJ, Kliiman K, Kvasnovsky C, Leimane V, Mitnick CD, Quelapio I, Riekstina V, Smith SE, Tupasi T, van der Walt M, Vasilyeva IA, Via LE, Viiklepp P, Volchenkov G, Walker AT, Wolfgang M, Yagui M, Zignol M. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. Lancet Respir Med. 2015 Mar;3(3):201-9.
27. Wallis RS, Pai M, Menzies D, Doherty TM, Walzl G, Perkins MD, Zumla A. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. Lancet. 2010 May 29;375(9729):1920-37.
28. Rodriguez M, Monedero I, Caminero JA, Encarnación M, Dominguez Y, Acosta I, Muñoz E, Camilo E, Martinez-Selmo S, de los Santos S, del Granado M, Casals M, Cayla J, Marcelino B. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Int J Tuberc Lung Dis. 2013 Apr;17(4):520-5
29. Tadolini M, Lingtsang RD, Tiberi S, Enwerem M, D'Ambrosio L, Sadutshang TD, Centis R, Migliori GB. First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline. Eur Respir J. 2016 Sep;48(3):935-8
30. Gupta R, Geiter LJ, Wells CD, Gao M, Cirule A, Xiao H. Delamanid for Extensively Drug-Resistant Tuberculosis. N Engl J Med. 2015 Jul 16;373(3):291-2.
31. Gupta R, Wells CD, Hittel N, Hafkin J, Geiter LJ. Delamanid in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2016 Dec 1;20(12):33-37.
32. Bedaquiline- and delamanid-containing regimens achieve excellent interim treatment response without safety concerns: endTB interim analysis. endTB. Boston, USA. 2018. [http://www.endtb.org/resources/endtb-interim-analysis-july2018].
33. Maryandyshev A, Pontali E, Tiberi S, Akkerman O, Ganatra S, Sadutshang TD, Alffenaar JW, Amale R, Mullerpattan J, Topgyal S, Udwadia ZF, Centis R, D'Ambrosio

L, Sotgiu G, Migliori GB. Bedaquiline and Delamanid Combination Treatment of 5 Patients with Pulmonary Extensively Drug-Resistant Tuberculosis. Emerg Infect Dis. 2017 Oct;23(10):1718–21.

.

.

.

.

.

.

Tables and Figures

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

Characteristics	N (%)
Patients [n]	202
Mean age (range)	35 (6 - 76)
Sex [n (%)]	
Female	78 (39)
Male	124 (61)
Pediatric patients [n (%)]	34 (17)
Mean weight (range)	53 (17-110)
Region [n (%)]	
Europe	46
Asia	35
Africa	108
Americas (including patients from the USA)	13
Disease type [n (%)]	

Pulmonary disease alone	189 (94)
Extrapulmonary involvement	13 (6)
Pulmonary and extrapulmonary disease	7
Extrapulmonary disease alone	6
Cavitary disease [n (%)]	
None	40 (20)
Yes	139 (69)
Unknown	23 (11)
Resistance type [n (%)]	
Rifampicin-resistant	1 (0)
MDR-TB	21 (10)
Pre-XDR-TB[α]	54 (27)
MDR-TB + FQ resistance	35 (17)
MDR-TB + Inj-resistance	15 (7)
Pre-XDR-TB with unknown information on FQ and Inj resistance	4 (2)
XDR-TB	123 (61)
Comorbidities [n (%)]	
HIV co-infection	66 (33)
HCV co-infection	11 (5)
HBV co-infection	3 (1)
Diabetes mellitus	11 (5)
Patients previously receiving anti-TB regimen [n (%)]	169 (84)
Patients with prior failing regimen [n (%)]	151 (75%)
Co-administration [β] of delamanid and bedaquiline [n (%)]	
Yes	106 (52)
No	96 (48)
Baseline culture status [n (%)]	
Negative	30 (15)
Positive	171 (85)
Unknown	1 (0)

Number of resistant drugs[γ], mean (SD)	6.3 (±3.2)
Number of susceptible drugs, mean (SD)	2.9 (±2.1)
Patients completing 24-week delamanid treatment [n (%)]	
Yes	172 (85)
No	30 (15)
Culture status at start of delamanid treatment [n (%)][*]	
Negative	25 (15)
Positive	147 (85)
Culture status at 24 weeks [n (%)][#]	
Negative	116 (79)
Positive	22 (15)
Unknown	9 (6)
Delamanid discontinued/patients lost-to-follow up	11 (5)

Data are presented as mean (range) or n (%), unless otherwise stated.

α MDR-TB plus resistance to a fluoroquinolone or an injectable anti-TB drug.

β Other anti-TB drugs administered concomitantly with Dlm n (%) were: Rifabutin 20 (10%), Mfx 36 (18%), Lfx 92 (46%), Ofx 1 (0%), Am 16 (8%), Km 9 (4%), Cm 27 (13%), Lzd 165 (82%), Z 111 (55%), PAS 108 (53%), E 24 (12%), Mpn 24 (12%), Amx/Clv 75 (37%), Cs 44 (22%), Cfz 148 (73%), Eto 39 (19%), Pto 5 (2%), Clr 2 (1%), Imi 35 (17%), Imi/Cln 11 (5%), Ertapenem 5 (2%), HD-H 24 (12%)

γ Resistant to n (%): Am 77 (38%), Km 85 (42%), Cm 91 (45%), Injectables 2 (1%), Ofx 131 (65%), Lfx 53 (26%), Mfx 76 (38%), Pto 26 (13%), Eto 38 (19%), Cs 16 (8%), PAS 28 (14%), Lzd 6 (3%), Cfz 4 (2%).

* Refers to those patients who completed their 24-week delamanid treatment.

\# Refers to those patients who were culture positive at start of delamanid treatment.

Am: amikacin; Amx/Clv: amoxicillin with clavulanic acid; Cln: cilastatin; Clr: clarithromycin; Cm: capreomycin; Cfz: clofazimine; Cs: cycloserin; E: ethambutol; Eto: ethionamide; HBV: hepatitis B virus; HCV: hepatitis C virus; HD-H: high-dose izoniasid; Imi: imipenem; Km: kanamycin; Lfx: levofloxacin; Lzd: linezolid; MDR-TB: multidrug-resistant tuberculosis; Mfx: moxifloxacin; Mpn: meropenem; N = number of patients; n = number of observations; Ofx: ofloxacin; PAS: para-aminosalycilic acid; Pto: proteonamide; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; Z: pyrazinamide.

Figure Titles:

Figure 1: Flowchart on delamanid compassionate use

Figure 2: Culture status at 24 weeks for all patients (N=147) and for paediatric patients (N=25)

Figure 3: Culture status at 24 weeks among HIV co-infected patients (N=48) and among XDR-TB patients (N=90)

Table 2: Safety summary for all patients (N=202)

All patients	**N = 202**
Total number of AEs reported	431
Number of patients with AEs (%)	139 (69%)
Most commonly reported AEs (%)	
Nausea	19/431 (4%)
Vomiting	17/431 (4%)
ECG QT prolonged/abnormal	13/431 (3%)
Total number of SAEs reported	173
Number of patients with SAEs (%)	73 (36%)
Most commonly reported SAEs (%)	
Deaths (%)	23 (11%)
Causes of death (%)	
Worsening of MDR/XDR-TB	16/23 (70%)
Causes attributed to pre-existing conditions*	5/23 (22%)
Shortness of breath/chest pain/vomiting	1/23 (4%)
Viral meningitis	1/23 (4%)
Most frequently reported pre-existing medical conditions (%)	
HIV	11/23 (48%)
Chronic liver disease due to HCV or alcohol abuse	5/23 (22%)
Diabetes mellitus	3/23 (13%)

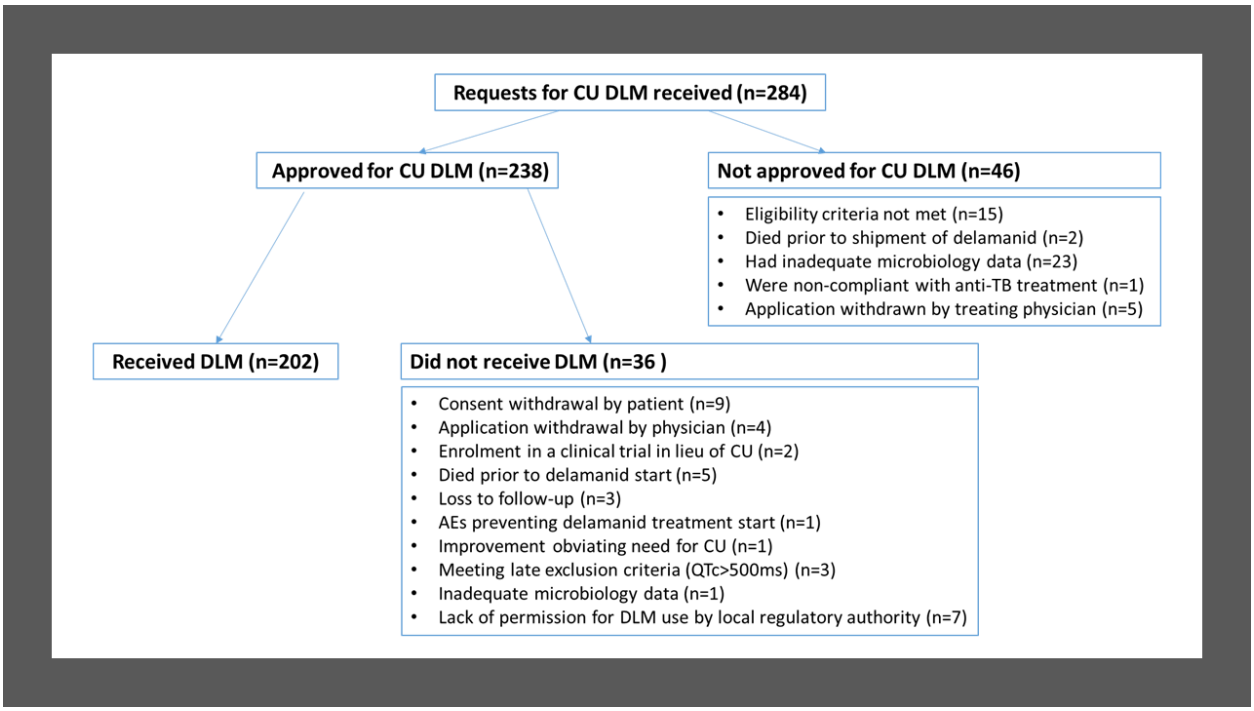
Hyponatraemia / Hypoalbuminaemia	3/23 (13%)

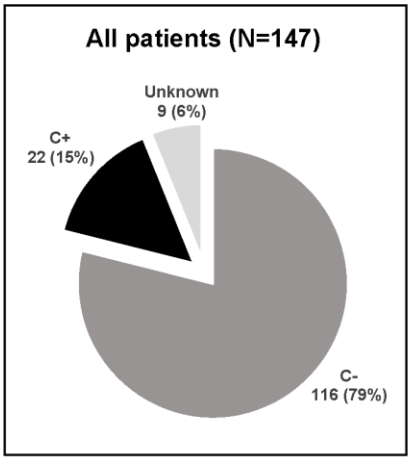
AE = adverse event; ECG = electrocardiogram; N = number of patients; SAE = serious adverse event; defined as any AE that led to death, was life threatening, a persistent or significant disability/incapacity, required hospitalization/prolongation of hospitalization, congenital anomaly or any other event deemed by the treating physician as clinically significant.
*A case each of: hepatic encephalopathy, cirrhosis, left foot gangrene/sepsis, syndrome of inappropriate antidiuretic hormone secretion (SIDAH), persistent electrolyte imbalance

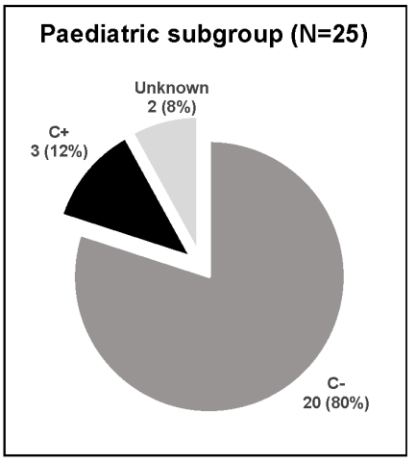
Table 3: Safety summary of paediatric subgroup (N=34)

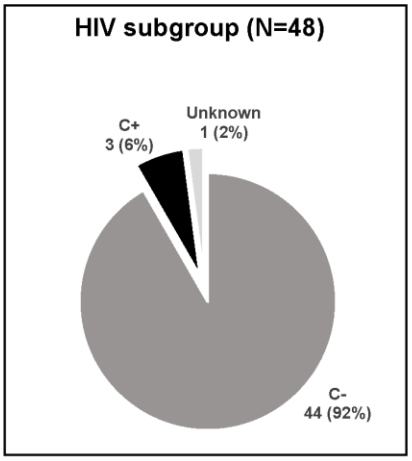
Paediatric subgroup	**N = 34**
Total number of AEs reported	102
Number of patients with AEs (%)	31 (91%)
Most commonly reported AEs (%)	
ECG QT prolonged/abnormal	4/102 (4%)
Vomiting	4/102 (4%)
Hypoalbuminaemia	3/102 (3%)
Total number of SAEs reported	21
Number of patients with SAEs (%)	5 (15%)
Most commonly reported SAEs (%)	
Hypoalbuminaemia*	2/102 (2%)
Deaths (%)	1 (3%)

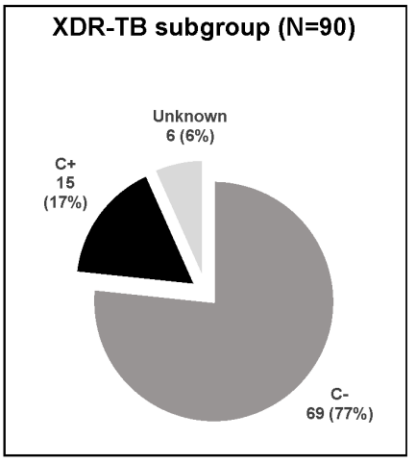
AE = adverse event; N = number of patients; SAE = serious adverse event; defined as any AE that led to death, was life threatening, a persistent or significant disability/incapacity, required hospitalization/prolongation of hospitalization, congenital anomaly or any other event deemed by the treating physician as clinically significant.
*All other SAEs were single reported events


Requests for CU DLM received (n=284)
Approved for CU DLM (n=238)
Not approved for CU DLM (n=46)
Eligibility criteria not met (n=15)
Died prior to shipment of delamanid (n=2)
Had inadequate microbiology data (n=23)
Were non-compliant with anti-TB treatment (n=1)
Application withdrawn by treating physician (n=5)
Received DLM (n=202)
Did not receive DLM (n=36)
Consent withdrawal by patient (n=9)
Application withdrawal by physician (n=4)
Enrolment in a clinical trial in lieu of CU (n=2)
Died prior to delamanid start (n=5)
Loss to follow-up (n=3)
AEs preventing delamanid treatment start (n=1)
Improvement obviating need for CU (n=1)
Meeting late exclusion criteria (QTc>500ms) (n=3)
Inadequate microbiology data (n=1)
Lack of permission for DLM use by local regulatory authority (n=7)


All patients (N=147)
Unknown
9 (6%)
C+
22 (15%)
C-
116 (79%)


Paediatric subgroup (N=25)
Unknown
2 (8%)
C+
3 (12%)
C-
20 (80%)


HIV subgroup (N=48)
C+
3 (6%)
Unknown
1 (2%)
C-
44 (92%)


XDR-TB subgroup (N=90)
Unknown
6 (6%)
C+
15
(17%)
C-
69 (77%)