# The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents

Interim policy guidance

THE END TB STRATEGY

World Health Organization

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# Contents

# Abbreviations

| | |
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| ART | antiretroviral therapy |
| AUC | area under the curve |
| BID | bis in die (Latin for "twice a day") |
| BMI | body mass index |
| Cl/F | apparent oral clearance |
| Cmax | maximum plasma concentration |
| CU | compassionate use |
| DOI | declaration of interest |
| DST | drug-susceptibility testing |
| EBA | early bactericidal activity |
| ECG | electrocardiogram |
| EMA | European Medicines Agency |
| ERP | External Review Panel |
| GDG | Guideline Development Group |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| GRC | Guidelines Review Committee |
| HIV | human immunodeficiency virus |
| MDR-TB | multidrug-resistant tuberculosis |
| OBR | optimized background regimen |
| PD | pharmacodynamics |
| PICO | population, intervention, comparator, outcome |
| PK | pharmacokinetics |
| PMDT | programmatic management of drug-resistant tuberculosis |
| RCT | randomized controlled trial |
| RR-TB | rifampicin-resistant tuberculosis |
| TB | tuberculosis |
| US | United States |
| WHO | World Health Organization |
| XDR-TB | extensively drug-resistant tuberculosis |

# Acknowledgements

# Declarations of interest

Declaration of interest forms were completed by all non-WHO members of the Guideline Development Group (GDG) and the External Review Group, and by the members of the academic centres who were involved in the reviews. One member of the GDG (Daniela Cirillo) declared interests that were judged to be non-significant, and five experts disclosed interests that were deemed to be significant, as outlined below:

- Grania Brigden indicated that her employer (Médecins Sans Frontières) received a donation of 400 treatments of delamanid (programmatic use) from Otsuka pharmaceuticals (manufacturer of delamanid) in February 2016. This was a one-off donation and is not expected to be repeated because MSF now procures delamanid directly from the Global Drug Facility.

- At the time of the guidance revision, Anneke Hesseling was the principal investigator in two Phase II, open-label, multiple-dose trials funded by Otsuka pharmaceuticals (Study 242-12-232 and Study 242-12-233). She has also received research support to fund a multisite Phase I/II trial of bedaquiline in HIV-infected and HIV-uninfected children with multidrug-resistant tuberculosis (MDR-TB), through the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network (P1108). Anneke Hesseling joined the meeting remotely via web conferencing.

- Erica Lessem disclosed that her employer (Treatment Action Campaign) received a total of $108 000 as means of general support from Janssen Pharmaceutical / Tibotec Therapeutics from 2010 to 2015. These funds were allocated to the Hepatitis C/HIV Programme and not to her work or the TB/HIV Project.

- Alena Skrahina contributed to the development of the document "Rapid clinical advice – the use of delamanid and bedaquiline for children with drug-resistant tuberculosis", which was made publically available on 20 May 2016 via the TB Online portal. The document provides clinical statements related to the subject of the meeting.

- Fraser Wares's employer, KNCV, manages the United States Agency for International Development (USAID)–Johnson & Johnson bedaquiline donation programme through its Challenge TB project.

In consultation with the WHO departments *Compliance, Risk Management and Ethics* and *Legal*, and the Chairman of the GDG meeting, the WHO Guideline Steering Committee at the Global TB Programme decided to assign these experts the status of "technical resource persons", allowing them to contribute in the technical discussions but not to take part in final decision-making and in any vote deemed necessary.

All of the aforementioned, as well as the independent expert who performed the review of evidence (Susan Abdel-Rahman) and observers, did not participate in the final decision-making and formulation of recommendations.

# Executive summary

## Background

In October 2014, the World Health Organization (WHO) issued an interim policy guidance on the use of delamanid in the treatment of patients with multidrug-resistant tuberculosis (MDR-TB), [a] recommending that delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (*conditional recommendation; very low confidence in estimates of effect*), under five conditions: proper patient inclusion, adherence to the principles of designing a WHO-recommended MDR-TB regimen, close treatment monitoring, active pharmacovigilance and proper management of adverse drug reactions, and informed patient consent. This interim policy did not include children, because of the absence of data in this population. However, data describing safety, tolerability and pharmacokinetics (PK) of delamanid in children with MDR-TB aged 6–17 years recently became available;[b, c] hence, WHO convened a Guideline Development Group (GDG) meeting on 29 June 2016 to review this evidence.

## Evidence assessment

In response to a request from WHO, Otsuka, the drug manufacturer, provided WHO with the source files containing PK and safety data collected in children and adolescents aged 6–17 years under a confidential disclosure agreement. These data came from an ongoing Phase I, open-label, age de-escalation trial designed to assess PK, safety and tolerability of delamanid administered twice daily (BID) for 10 days in children with MDR-TB on therapy with an optimized background regimen (OBR) (Protocol 242-12-232),[d] and its subsequent open-label Phase II extension study, which aimed to assess the safety, tolerability, PK and efficacy of long-term (6-month) treatment with delamanid plus an OBR in paediatric patients (Protocol 242-12-233).[e] Six children aged 6–11 years were administered a 50 mg BID dosing regimen, and seven adolescents aged 12–17 years were administered a 100 mg BID dosing regimen. The PK data provided were restricted to delamanid and its DM-6705 metabolite. Physiologic data available for review were restricted to serum chemistries and electrocardiograms (ECG). Both of these studies were ongoing at the time the GDG meeting was convened. Additional safety data were available through a report detailing information derived from the compassionate use (CU) of delamanid in children. The case series describes 19 paediatric patients (aged 8–17 years) with bacteriologically confirmed pulmonary MDR-TB or extensively drug-resistant TB (XDR-TB) enrolled in a delamanid CU programme.[f]

Owing to the nature of the paediatric drug development studies (i.e. observational and lacking in comparator data), adult reference data were used for comparison. These reference data were derived primarily from the data that served as the basis for the initial interim guidance issued in 2014.

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[a] World Health Organization (WHO). The use of delamanid in the treatment of multidrug-resistant tuberculosis: Interim Policy Guidance. 2014.

[b] Otsuka Pharmaceutical. Pharmacokinetic and safety trial to determine the appropriate dose for pediatric patients with multidrug resistant tuberculosis (Protocol 242-12-232).2013.

[c] Otsuka Pharmaceutical. A 6-month safety, efficacy and pharmacokinetic trial of delamanid in pediatric patients with multidrug resistant tuberculosis (Protocol 242-12-233). clinicaltrials. gov [NCT01859923]. 2013.

[d] Pharmacokinetic and safety trial to determine the appropriate dose for pediatric patients with multidrug resistant tuberculosis [Internet]. [cited 18 July 2016]. Available from:
 https://clinicaltrials.gov/ct2/show/NCT01856634?term=Delamanid+in+Pediatric+Patients&rank=2

[e] A 6-month safety, efficacy and pharmacokinetic trial of delamanid in pediatric patients with multidrug resistant tuberculosis [Internet]. [cited 18 July 2016]. Available from: https://clinicaltrials.gov/ct2/show/NCT01859923.

[f] Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively-drug resistant tuberculosis: early experiences and challenges (unpublished work). Eur Respir J. 2016.

## Summary of results

Children enrolled in these studies were diagnosed with either presumed or confirmed MDR-TB. Children with MDR-TB with comorbidities such as HIV, hepatitis B or C, severe malnutrition, underlying heart disease or any pathologic condition that could alter the disposition of delamanid were excluded from these studies.

### Evaluation of paediatric pharmacokinetics data

Delamanid doses administered to paediatric participants in these studies ranged from 1.5 to 3.8 mg/kg, comparable to the range of doses administered to adults. Analysis of the PK data demonstrated a nonlinear dose–exposure relationship. In both paediatric dosing cohorts, delamanid concentrations fell within the range of exposures seen in the adult population; however, on average, paediatric exposures were at the middle or high end of the adult range.

### Evidence for the safety of delamanid use in treatment of MDR-TB

In the 10-day 232 trial, no discernible time-dependent trend in baseline-corrected QTcF (where the "F" denotes Fridericia corrected QTc) was observed over the 10 days. However, a significant temporal trend was observed in the 233 trial, with QTcF increasing over the first month of exposure, plateauing at 4 weeks and then returning to baseline over the course of 27 weeks. Thorough QTc evaluations in early phase adult trials revealed the same time-dependent increase in baseline-corrected QTcF, with a larger effect in adults receiving 200 mg BID than in those receiving 100 mg BID. In both the adult and paediatric populations, the increase in QTcF was correlated with the expected accumulation of DM-6705.

There was a significant association between delamanid plasma concentration and QTcF, although this relationship was much more pronounced for the DM-6705 metabolite. Serum electrolytes were also examined for their association with QTcF changes in paediatric participants. DM-6705 concentrations and albumin levels were significantly correlated with QTcF. There was no difference in rates of ΔQTcF between 30 and 60 msec elevation between children and adults.

## Guideline Development Group findings

The GDG evaluated the quality of the evidence to determine whether, based on the available data, delamanid should be added to a WHO-recommended longer MDR-TB regimen for children aged 6–11 years and adolescents aged 12–17 years. In general, provided that efficacy data from adults are considered relevant and drug exposures associated with favourable outcomes in adults are known, PK/pharmacodynamics (PK/PD) data from adults coupled with PK data from children can be used to find drug doses in children that achieve adult PK targets; safety and efficacy can then be extrapolated from adults to the paediatric population. The GDG agreed that [partial] extrapolation of efficacy and safety data for delamanid for treatment of MDR-TB from the adult groups (on which the WHO interim policy recommendation issued in October 2014 was based) to children was reasonable, although with some limitation due to the imprecision of the data (based on small sample sizes).[a,b]

However, the GDG expressed concerns about the extrapolation of safety data and the unknown probability of unstudied potential toxicities. One of the major analytic limitations was that the only

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[a] Mulugeta Y, Barrett JS, Nelson R, Eshete AT, Mushtaq A, Yao L, et al. Exposure Matching for Extrapolation of Efficacy in Pediatric Drug Development. J Clin Pharmacol. 2016.

[b] United States, Food and Drug Administration. Draft Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products. Access at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm425885.pdf Last accessed. 2016/08/16

safety data available for analysis were raw ECG data provided by the drug manufacturer; there were no full safety data, which could provide a better understanding of other toxicities in children and adolescents exposed to delamanid. Also, given that HIV-coinfected children were not included in these cohorts, drug–drug interactions with antiretroviral therapy (ART) could not be assessed. The panel agreed that special considerations must be taken regarding drug–drug interaction data extrapolated from adults, especially in younger children in whom the presence and magnitude of interactions may be difficult to predict. Members of the GDG panel noted that the certainty in the evidence for safety end-points was very limited, because the principal focus of study was cardiac safety, and other potential toxicities were not investigated or reported.

The GDG questioned the dose selection approach by the drug manufacturer for these paediatric studies, particularly in the absence of knowledge on whether PK/PD modelling was carried out to estimate optimal dosing for paediatric populations. The GDG also noted that, at the doses under investigation in the ongoing paediatric studies, paediatric exposure profiles appeared to be more consistent with the profiles seen in adults receiving a regimen of 200 mg BID as opposed to the labelled dose of 100 mg BID. In these paediatric studies as well as the reference adult studies, bioavailability of the drug was optimized with administration of a 25% fat meal at the time of dosing.

The GDG rated the quality of the evidence for the efficacy and safety of the use delamanid in children aged 6–11 years and adolescents aged 12–17 years as "very low". The GDG made a series of recommendations that served as a basis for WHO to develop its interim policy recommendation.

## WHO interim policy recommendations for the use of delamanid in children and adolescents

**Based on GDG recommendations, WHO recommends that delamanid may be added to the WHO-recommended longer regimen in children and adolescents (6 – 17 years) with multidrug- or rifampicin-resistant TB (MDR/RR-TB) who are not eligible for the shorter MDR-TB regimen, [a] under specific conditions (*conditional recommendation; very low confidence in estimates of effect*):**

### Condition 1. Proper patient inclusion

The population to whom this recommendation applies is children and adolescents with MDR-TB or RR-TB aged 6–17 years who are not eligible for the WHO-recommended shorter MDR-TB regimen[b]. The population includes those patients who have previously received treatment with second-line anti-TB medicines, or who have isolates with additional resistance to fluoroquinolones or second-line injectable agents (including XDR-TB), or in whom components of the shorter MDR-TB regimen are contraindicated. The shorter MDR-TB regimen is also not recommended in pregnancy and extrapulmonary TB. Delamanid is thus only indicated as a component of longer regimens that have been individualized to increase a patient's likelihood of success.

The recommended dose of delamanid in children (aged 6–11 years) is 50 mg BID for 6 months, and in adolescents (aged 12–17 years) it is 100 mg BID for 6 months. Because bioavailability was found to be higher when given after a standard meal, delamanid should preferably be delivered after a meal. Given that TB regimens are generally administered once a day, any observation of treatment needs to be adapted to ensure supervision of the BID intake of delamanid in patients on this medication.

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[a] For the purpose of this Interim Policy Guidance, a WHO-recommended longer regimen is understood to be a 20- month or longer duration treatment regimen (formerly known as "conventional regimen"). The shorter MDR-TB regimen refers to a standardised 9-12 month regimen as recommended by WHO since 2016 (see citation below)

[b] WHO treatment guidelines for drug-resistant tuberculosis 2016 update. Geneva, World Health Organization. 2016

Because delamanid is shown to cause prolongation of the QT interval, children with a QTcF > 500 msec should not receive the drug.

Children and adolescent MDR-TB/RR-TB in whom delamanid may have a particular role include those with the following:

- higher risk for poor outcomes (e.g. drug intolerance or contraindication, extensive or advanced disease);
- additional resistance to fluoroquinolones or injectable drugs; or
- XDR-TB (see **Condition 2.d** below for additional measures to apply when the drug is used in XDR-TB patients).

While patients with exclusively extrapulmonary disease were not included in the delamanid trials, there is no absolute contraindication for its use in such patients, and inclusion may be considered where any potential harms that delamanid may cause are offset by the benefits expected. However, the effectiveness of delamanid in the treatment of TB of the central nervous system is as yet unestablished. Of note, there are no data on the safety of delamanid in pregnancy; hence, this medication is not currently indicated in pregnant females.

## Condition 2. Adherence to the principles of designing a WHO-recommended longer MDR-TB regimen

Delamanid is indicated as an add-on agent to a longer MDR-TB regimen designed using a minimum of core second-line anti-TB drugs, as per the updated WHO treatment guidelines[a]. The cardinal rules governing the inclusion of delamanid in a MDR-TB regimen are as follows:

a. The WHO-recommended longer MDR-TB treatment regimen is composed of at least pyrazinamide and four core second-line drugs considered to be effective (based on DST and/or previous use and/or drug resistance surveillance data): if the minimum number of five effective TB medicines cannot be composed as indicated, delamanid *may be added to bring the total to at least five*. The regimen may be further strengthened with high-dose isoniazid or ethambutol (or both).

b. The WHO-recommended longer MDR-TB treatment regimens usually last 20 months or more.[b] Delamanid is, however, only to be used for a maximum of 6 months, preferably at the start of the initial (intensive) phase.

c. *In view of the absence of evidence on its effectiveness and safety as part of, or in addition to, a shorter regimen for the treatment of MDR-TB, no recommendation on the use of delamanid in addition to or as part of the WHO-recommended 9–12 month shorter regimen can be made.*

d. MDR-TB patients with confirmed resistance or intolerance to either fluoroquinolones or the second-line injectable agents represent a particular treatment challenge. In such cases, delamanid may have a crucial role to play in strengthening a regimen, bringing the number of drugs likely to be effective to a minimum of five, and reducing the risk of acquisition of additional resistance and progression towards XDR-TB.

e. Although experience in the use of delamanid in the management of XDR-TB is limited, there may be a benefit given the limitations in designing an effective regimen. In such patients, delamanid may lower the need to include other drugs belonging to group D3,[c]

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[a] WHO treatment guidelines for drug-resistant tuberculosis 2016 update. Geneva, World Health Organization. 2016
[b] Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update. Geneva, World Health Organization. 2011.
[c] Drug classification: Group A = levofloxacin, moxifloxacin, gatifloxacin; Group B = amikacin, capreomycin, kanamycin (streptomycin); Group C = ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine; Group D2 = pyrazinamide, ethambutol, high-dose isoniazid; Group D2 = bedaquiline, delamanid; Group D3 = *p*-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate (thioacetazone)

which either have an unclear role in MDR-TB regimens or a higher harm-to-benefit potential. However, special caution is necessary when delamanid is used with a fluoroquinolone or other medicines with the potential for synergistic drug–drug interactions effects, particularly on QT prolongation.[a]

**f.** *There are currently no data on the simultaneous use of bedaquiline and delamanid in the same patient. Until such data become available, no recommendation on the joint administration of these two medicines is possible within the scope of this interim guidance. Moreover, bedaquiline is only recommended for use in adults.*

**g.** There is as yet no standardized drug-susceptibility testing (DST) method for delamanid, nor a commercially available test. DSTs for second-line drugs other than fluoroquinolones and injectable agents (kanamycin, amikacin and capreomycin) are not accurate or reproducible. Moreover, and MDR-TB patients may respond poorly to treatment for reasons other than drug resistance. A change in medication may, therefore, have to be based on persistence of positive sputum culture, or reversion to positive following initial culture conversion, rather than DST.

**h.** In line with general principles of TB therapeutics, delamanid should not be introduced into a regimen in which the other companion drugs are known or believed to be ineffective, or are failing to show effectiveness. This means that delamanid should not be added alone to a failing regimen. Given the risk of emergence of resistance to delamanid, all possible measures should be taken to protect the efficacy of the drug through rational use.

**i.** *Although studies are under way, there are so far no data on the use of delamanid in children aged under 6 years, so no recommendation can be made on the use of delamanid in that age group.*

## Condition 3. Close monitoring of patients

Adherence to best practices when administering treatment is imperative to ensure optimal drug effectiveness and patient safety. It is therefore recommended that the following measures be in place:

**a.** Sound treatment and management protocols, including clear patient eligibility criteria, locally appropriate procedures for informed consent (see **Condition 5** below), and defined roles and responsibilities of all professionals involved. Measures to safeguard patients from avoidable harms are best addressed by observing the principles of active TB drug safety monitoring and management.[b]

**b.** National guidance on the implementation of MDR/RR-TB treatment should allow for the prospective capture of key variables for both the effectiveness and safety of delamanid-containing regimens, ensuring that the good practices equivalent to those applied in the conduct of observational studies, are adhered to.[c]

**c.** Treatment guidelines are preferably submitted to and approved by the relevant national ethics authority in the country before patient enrolment on treatment.

**d.** Preferably, oversight of treatment programmes is provided by an independent group of experts in clinical management and public health (e.g. a national MDR-TB advisory group).

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[a] A QTcF value of > 440 msec is considered prolonged. A value of > 480 msec (or an increase of > 60 msec from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTcF interval of > 500 msec is considered dangerous and an indication to stop QT-prolonging agents.
[b] Active tuberculosis drug-safety monitoring and management (aDSM): framework for implementation. Geneva, World Health Organization. 2015.
[c] Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization. 2014.

**e.** The potential for emergence of delamanid resistance during the course of therapy requires that all measures to enable the patient's adherence are in place before starting treatment.

## Condition 4. Active TB drug safety monitoring and management

Alongside the measures in **Condition 3** above, in order to monitor treatment adherence and effectiveness, special vigilance is needed for adverse events, including potential reactions to delamanid that are as yet undescribed.

**a.** Given that the results of Phase III trials are not yet available, it is particularly important that the introduction of delamanid be accompanied by enhanced monitoring for adverse events. For this purpose, spontaneous reporting is insufficient; instead, active TB drug safety monitoring and management is needed to improve the early detection of adverse drug events.

**b.** Any adverse drug reaction attributed to delamanid should be reported to the national pharmacovigilance centre. As with any other drug in an MDR-TB regimen, the patient should be encouraged to report to the attending health worker any adverse event that occurs during the time the drug is being taken. Such occurrence should also trigger a rapid response to manage these untoward effects in the patient.

**c.** Delamanid may interact with other medications administered concurrently, with synergistic or antagonistic action resulting in additive or lowered effects. Other second-line drugs that are likely to be administered with delamanid, notably fluoroquinolones or clofazimine, may increase the risk of cardiotoxicity. Although there are data showing QT prolongation when delamanid is administered simultaneously with levofloxacin, no data are available on concomitant use with moxifloxacin or clofazimine (or both). Also, some antiretroviral medications can cause modest QT prolongation, especially ritonavir-containing regimens. Therefore, it is imperative to monitor patients for cardiac dysrhythmias or QT prolongation (using ECG), and for electrolyte imbalances (especially serum potassium) that can predispose to cardiotoxicity.[a]

**d.** Drug–drug interaction studies of delamanid with tenofovir, efavirenz and lopinavir/ritonavir, conducted among healthy individuals who did not have HIV or TB, suggested that no dose adjustments were needed when delamanid was used with any of these antiretroviral agents. However, there is no published evidence so far on the use of delamanid in HIV-infected MDR-TB children on ART. Therefore, people living with HIV who will be receiving delamanid as part of MDR-TB treatment should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

**e.** Lastly, caution is advised in patients with pre-existing health conditions that may be exacerbated or worsened by delamanid. Currently, there are no data on the efficacy and safety of delamanid in patients with comorbid conditions such as diabetes, liver or renal dysfunction, malignancies, and alcohol and substance use; therefore, careful screening for these conditions before treatment initiation is advised. Hypersensitivity reactions to delamanid have not yet been described, but vigilance is nevertheless required.

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[a] It is imperative that ECG is used to monitor the QT interval regularly during delamanid use. QT interval monitoring should preferably be done using ECG machines that directly report the QTc interval. A value of > 440 msec is considered prolonged. A value of > 480 msec (or an increase of > 60 msec from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTc interval of > 500 msec is considered dangerous and should lead to stopping of the intake of the responsible QT prolonging drug(s).

## Condition 5. Informed decision-making process ensured

Health-care workers should follow due process for informed consent by ensuring that the parent or legal guardian is aware of the novel nature of delamanid; appreciates why is it proposed that the drug be included in their treatment regimen; and recognizes the possible benefits and potential harms, including the uncertainties that surround outcomes. This informed consent process applies to all situations where delamanid is employed, including under CU programmes, and follows the rules and conditions for MDR-TB treatment as stipulated.

Parental or legal guardian permission as well as child or adolescent assent to receive the delamanid should be at the discretion of national TB control programmes. National authorities must ensure adequate protection for minors, including parental permission and assent of able children, assurance of direct benefit for the child and minimization of any risks.

# Implementation considerations

- Key stakeholders, especially end-users and policy-makers, must consider that the design of the paediatric studies was highly optimized as a means to maximize drug exposure in the selected sample of patients, as well as to enhance drug absorption. Data seen in adults have provided information on the effect of meals with a high fat content, which is more pronounced than the effect of standard low-fat meals on delamanid bioavailability. Therefore, dietary fat intake can alter bioavailability of delamanid. The implications for health-care settings in terms of drug introduction and service delivery relate to requirements to evaluate nutritional status in all children, especially those at risk, and to provide sustainable food support for children who have a low body weight and those with limited access to food.

- With regard to special populations, such as people living with HIV, implementers are to exercise caution. Although drug–drug interactions between ART and delamanid have been studied in healthy volunteers, studies suggest that the CYP3A4 inhibitor lopinavir/ritonavir increases delamanid total body exposure by, on average, 22% (geometric mean ratio: 1.22 [90% confidence interval: 1.06–1.40])[a]. In the currently reviewed studies, children infected with HIV were excluded. Thus, special attention must be given to this subgroup. Potential drug–drug interaction with specific antiretroviral drugs in paediatric populations is to be further investigated.

- Requirements for ECG may reduce feasibility although cost effectiveness is present and given that resource estimates in the CEA included this requirement for ECG monitoring. Availability of ECG machines is not given in all settings - may require referral to specialist or extension of ECG access and mobilizing resources to monitor ECG.

- The risk of emergence of resistance to delamanid should be a key consideration when the drug is being used, and appropriate DST should be conducted, when available.

*This WHO interim policy recommendation is valid for a maximum of 2 years, unless additional PK/PD and safety data become available sooner – particularly data relating to children aged under 6 years – that would prompt a revision of the guidance.*

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[a] Paccaly A, Petersen C, Patil S, Bricmont P, Kim J, Harlin M et al. Absence of clinically relevant drug interaction between delamanid, a new drug for multidrug-resistant tuberculosis (MDR-TB) and tenofovir or lopinavir/ritonavir in healthy subjects, in Book Absence of clinically relevant drug interaction between delamanid, a new drug for multidrug-resistant tuberculosis (MDR-TB) and tenofovir or lopinavir/ritonavir in healthy subjects. City, 2012:22-27

**THE USE OF DELAMANID IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS IN CHILDREN AND ADOLESCENTS**

## 1. Background

The emergence of drug-resistant tuberculosis (TB) is a major threat to global TB care and control. In 2015, the World Health Organization (WHO) estimated that 580 000 people developed multidrug-resistant TB (MDR-TB), and more than 40% (250 000) of them died *(1)*. The development of public health policies for the introduction and implementation of new drugs, as it is the case of delamanid, has offered a treatment alternative for patients in need. *(2)* Despite of this, current treatment regimens for MDR-TB patients continue to be far from satisfactory, and current options are limited, to an extent, to a subset of patients *(3)*. Although significant progress has been made with the new recommendations for the use of shorter regimens for patients with MDR-TB or rifampicin-resistant TB (RR-TB), the standardized 9–12 months shorter regimen will not be applicable in all settings *(4)*; in particular, it may not be applicable in patients with a high prevalence of resistance to fluoroquinolones or second-line injectable drugs. For adults and children who are not eligible for short regimens, the WHO-recommended longer treatment regimen is appropriate *(4)*. This usually requires at least 20 months of treatment with a combination of second-line drugs, which are unfortunately more toxic and less effective than the drugs used to treat drug-susceptible TB. In the 2012 global cohort of detected MDR-TB cases, only 50% were successfully treated, mainly because of a high frequency of death (16%), treatment failure (10%) and loss to follow-up (16%) *(1)*. Furthermore, 105 countries have reported at least one case of extensively drug-resistant TB (XDR-TB), a form of MDR-TB with additional resistance to fluoroquinolones and second-line injectable drugs (amikacin, kanamycin or capreomycin). On average, about 10 *per cent* % of MDR-TB cases develop XDR-TB. Treatment options for XDR-TB patients are even more limited, with low cure rates compared to the rate for MDR-TB. In a subset of 200 XDR-TB patients in 14 countries, treatment was successful in only 33% of the cases, and 26% of the patients died *(5)*.

The burden of MDR-TB disease in children is difficult to determine, but researchers estimate that over 30 000 children develop MDR-TB each year *(6)*. In addition, case detection and treatment options for paediatric MDR-TB patients are limited. Current recommendations for regimen design in paediatric TB follow the same principles as in adults. Treatment is tailored based on the child's drug-susceptibility testing (DST) results (*if specimen collection is possible*); otherwise, a treatment regimen is designed based on the source case DST results or on prevailing resistance patterns in the area *(7, 8)*. A systematic review and meta-analysis to determine treatment outcomes for children with MDR-TB suggested that administering appropriate MDR-TB regimens could lead to successful treatment in about 80% of paediatric cases, but there is wide uncertainty around this estimate *(9)*. Studies suggest that – when diagnosed and treated appropriately – children have good treatment outcomes and also tolerate treatment better than adults; nevertheless, adverse events are often not actively monitored or systematically recorded *(10)*. Whereas treatment regimens for drug-susceptible TB in children are well established, including dosages (e.g. fixed-dosed combinations), an additional consideration for paediatric MDR-TB treatment is that of dosing and paediatric formulations, few of which are available *(11)*.

The landscape of drug development for treatment of TB has evolved dramatically over the past 10 years, and six new compounds are in the final stages of clinical development. One of those, delamanid, a nitroimidazole, was granted a conditional marketing authorization by the European Medicines Agency (EMA) in April 2014; this authorization is valid throughout the European Union *(12)*. Only limited data are available, and the drug has not been tested in a full Phase III randomized controlled trial (RCT) in humans (only in a limited Phase II b trial). However, in view of the importance of this progress, the likelihood that this drug will contribute effectively to the treatment of a life-threatening

disease, and the request by Member States to obtain guidance on how to use the drug, coupled with the recommendations of the WHO Guidelines Review Committee (GRC), in May 2014 WHO organized a Guideline Development Group (GDG) meeting to review all available data. Based on the careful assessment of data on the safety and efficacy of the product, the evaluation of the balance of potential harms and expected benefits, the target population(s) and the likely conditions of use in association with the MDR-TB treatment currently recommended by WHO, the GDG advised WHO that the drug may be used under five strict conditions (see **Box 1**). This led to the issuance of an *Interim guidance for the use of delamanid in the treatment of MDR-TB* in October 2014 *(2)*.

**Box 1.** **Brief summary of the main recommendations of the 2014 interim policy guidance on the use of delamanid for treatment of MDR-TB**

> *WHO recommends that delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation; very low confidence in estimates of effect)*
>
> In view of the insufficient experience with the use of delamanid and the uncertainty about its overall added value in the treatment of MDR-TB patients, WHO recommends that the use of delamanid in the treatment regimen of MDR-TB be made subject to the following five conditions:
>
> **Condition 1. Proper patient inclusion**
> The current recommendation for the use of delamanid applies to adults (aged ≥ 18 years) with pulmonary MDR-TB disease, including people living with HIV. Use of the drug in children, and in pregnant and breastfeeding women, is not currently advised due to a lack of evidence on safety, efficacy and proper dosing in these groups.
>
> **Condition 2. Adherence to the principles of designing a WHO-recommended MDR-TB regimen**
> Delamanid is intended to be introduced alongside other anti-TB drugs in composing an effective second-line regimen based on WHO guidelines and in accordance with the cardinal rules governing the general composition and duration of MDR-TB regimens. In MDR-TB patients with confirmed resistance or intolerance to either fluoroquinolones or the second-line injectable drugs, delamanid may have a crucial role to play in strengthening a regimen, and in reducing the risk of acquisition of additional resistance and progression towards XDR-TB. In patients with XDR-TB, delamanid may reduce the need to include other drugs belonging to Group 5, which have unproven anti-TB activity or a lower safety profile.
>
> **Condition 3. Treatment is closely monitored**
> Adherence to best practices of treatment administration is imperative to ensure optimal drug effectiveness and safety. Best practices include sound treatment and management protocols (preferably submitted to and approved by the relevant national ethics authority in the country), including clear patient eligibility criteria; locally appropriate procedures for informed consent; defined roles and responsibilities for all professionals involved; and review of treatment and management programmes by an independent group of experts in clinical management and public health, such as the national MDR-TB advisory group (recommended).
>
> **Condition 4. Active pharmacovigilance and proper management of adverse drug reactions**
> Alongside the measures to monitor treatment adherence and effectiveness, special vigilance is needed for adverse events, including potential reactions to delamanid that are as yet undescribed. Active pharmacovigilance techniques are needed to improve the early detection of adverse drug reactions.
>
> **Condition 5. Informed patient consent**
> Health-care workers should follow due process for informed consent by ensuring that the patient is aware of the novel nature of delamanid; appreciates why the drug is being proposed to be included in their treatment regimen; and recognizes the possible benefits and potential harms, including the uncertainties that surround outcomes.
>
> *Notes:*
> - Special caution is necessary when delamanid is used with a fluoroquinolone or a Group 5 drug, given the potential for synergistic drug–drug interaction effects, particularly on QT prolongation.
> - There are currently no data on the simultaneous use of bedaquiline and delamanid in the same patient. Until such data become available, no recommendation on the joint administration of these two medicines is possible within the scope of this interim guidance.

According to the manufacturer, by 2015, the drug had been introduced and used at least once in 39 countries worldwide for the treatment of MDR-TB/XDR-TB, as part of expanded access, for compassionate use (CU) or for normal programmatic use, whether in the public or private sector (excluding situations where the drug was used solely as part of a trial). Additionally, through a public–private partnership between the Global Drug Facility and the drug manufacturer, countries eligible for financing through the Global Fund to Fight AIDS, TB and Malaria can now procure delamanid through the Global Drug Facility.

In the 2014 interim guidance, the use of delamanid in children was not advised because of a lack of evidence on safety, efficacy and proper dosing in these groups (see **Box 1**, *"Proper patient inclusion"*). However, in view of the increased access to the drug and paediatric pharmacokinetics (PK) and safety data reported at conferences by the manufacturer in late 2015, WHO convened a group of experts to assess whether delamanid – in addition to a WHO-recommended regimen – should be used in newly diagnosed MDR-TB paediatric patients.

## 2. Guideline purpose and target audience

### Purpose

The first edition of the interim policy guidance for the use of delamanid was published in 2014 *(2)*. The interim recommendation contained in this guidance document was developed as a collaborative effort among many partners and stakeholders in response to the global MDR-TB crisis and its limited therapeutic options. This recommendation was conditional and applied only to adults with MDR-TB, given the absence of evidence for affected people aged under 18 years. The availability of new data on PK/pharmacodynamics (PK/PD), and the tolerability of delamanid in paediatric populations led the WHO Global TB Programme to review these data to examine the potential for updating of the initial interim recommendation and expanding it to children aged 6 years and over.

Of note, since May 2016, WHO (conditionally) recommends a *shorter* MDR-TB treatment regimen of 9-12 months duration that has been shown to have rates of relapse-free cure topping 85% in different Asian and African countries under observational study conditions *(4)*. WHO recommends the use of this regimen conditionally among selected MDR/RR-TB patients with pulmonary TB and no previous exposure or known resistance to fluoroquinolones or injectable drugs (pregnancy excluded). It is a standardized treatment in content and duration. The regimen has an initial, intensive phase of four months (extended up to a maximum of six months in case of lack of sputum smear conversion), with gatifloxacin (or moxifloxacin), kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide and ethambutol. This is followed by a continuation phase of five months with gatifloxacin (or moxifloxacin), clofazimine, pyrazinamide, and ethambutol.

MDR/RR-TB patients who are not eligible to the shorter MDR-TB regimen and XDR-TB patients are to be treated with a *longer* regimen which is designed to increase the chances of success, with at least four core second line drugs likely to be effective plus pyrazinamide. Longer regimens usually last at least 20 months in previously untreated patients, with an initial phase of about 8 months.

Further details on the design of these regimens can be accessed in the 2016 update of the WHO treatment guidelines for drug-resistant tuberculosis *(4)* and the revised version of the WHO companion handbook for PMDT *(13)*.

This interim policy is intended as an addendum to the initial interim policy guidance issued in 2014 and is to be considered within the context of the above updated guidelines for the treatment of MDR-TB.

## Target audience

The intended audience for this revised guideline is policy-makers in ministries of health and national TB control programme managers responsible for developing country-specific TB treatment guidelines. In addition, this guideline will reach health-care workers (end-users), including doctors, nurses and educators in both, the government and nongovernmental sectors as well as academics, donors and technical partners, including civil society organizations.

# 3. Guideline development process

The process developed by the GRC was strictly followed. A WHO Guideline Steering Group was formed (see **Annex 1**), which, together with the Chairman of the GDG, identified the areas requiring evidence synthesis.

The GDG comprised researchers, epidemiologists, end-users (clinicians and national TB control programme officers), community representatives and experts in evidence synthesis. In compliance with the procedures and practices established by the GRC, declarations of interest (DOI) were managed according to the WHO Conflict of Interest Policy, including review of curriculum vitae and critical evaluation of DOI. Additionally, the full list of GDG members and their biographies were published on the WHO website on 3 May 2016. This was followed by a public notice and comment period, during which the WHO Global TB Programme allowed members of the public to provide comments pertinent to any competing interests that may have gone unnoticed or not reported during earlier assessments. No additional information on any competing interest was provided to WHO.

## Guideline Development Group meeting

A GDG meeting was convened by the WHO Global TB Programme on 29 June 2016 in Geneva, Switzerland. The *overall objective* of the meeting was to develop an addendum to the WHO interim guidance on delamanid issued in October 2014, in view of recent data on the use of delamanid in children aged 6 years and over affected with MDR-TB, a life-threatening form of TB.

The *specific objectives* were as follows:

1.1. To evaluate the harms to benefits ratio of delamanid in combination with the currently recommended MDR-TB treatment regimen in children according to the following criteria:

    i. evaluation of the PK characteristics of delamanid in children aged 6–17 years;

    ii. evaluation of the type, frequency and severity of adverse events related to the use of delamanid in this cohort of children; and

    iii. extrapolation from adults to children of efficacy data collected in RCTs and observational cohort conditions.

1.2. Based on this evaluation, to develop recommendations on the use of delamanid as part of WHO-recommended longer MDR-TB treatment regimens, as appropriate, keeping in mind the attention to concerns relevant to the use of a new medicine for which Phase III clinical trial data are not yet available.

## Management of conflicts of interest

All experts participating in the process to develop recommendations on the use of delamanid for paediatric patients submitted a completed DOI form (see participants in **Annex 1** to **Annex 3**). These were reviewed by the WHO Guideline Steering Committee. In cases where potential conflicts were unclear, the WHO departments *Compliance, Risk Management and Ethics* and *Legal* were consulted for further clarification and advice on how to manage competing interests. A summary of DOI

statements is given in **Annex 4**. Technical resource consultants participated in the meeting to provide specific information on technical issues, but were not involved in the preparation of the actual recommendations. For experts attending the meeting as members of the GDG but for whom significant competing interests were identified, their status was changed to "technical resource persons" for this meeting (i.e. they provided technical expertise during discussions of the data, but did not take part in the discussion and deliberations on the development of recommendations). All participants signed a confidentiality agreement and were reminded of the need for confidentiality until the conclusion of the full WHO process.

## Review of evidence

The process for retrieving and assessing the evidence was initiated and supported by a systematic review in order to ensure quality throughout the data review process. This approach is in line with the recommendations of the GRC for development of standard guidelines.

The data reviewer assessed the evidence through a systematic literature search following an approved methodology. The search aimed to identify studies conducted in children diagnosed with MDR-TB and in whom delamanid was added to an anti-TB regimen for at least 6 months. The following exclusion criteria were applied: case reports not providing safety or outcome information, and case reports or other observational studies with sample size smaller than five individuals. The search was performed on PubMed (five hits), the Cochrane Central Register of Controlled Trials (CENTRAL) (one hit), LILACS (zero hits) and EMBASE (seven hits). The search was not limited by study type or time period. Titles, abstracts and full text of potentially relevant literature were screened using key subject and text words. Only 13 studies were identified on the use of delamanid in paediatric populations, of which 12 were then excluded. The main reasons for exclusion were the reporting of studies in adult TB patients, adult PK/PD studies, and comment papers. The one remaining publication was a case study that described the use of delamanid in a 12-year-old patient diagnosed with laryngeal and pulmonary TB under a CU programme *(14)*. Although case reports and case series can sometimes be useful for identifying uncommon or unstudied adverse events, this particular report was insufficient to make an objective assessment of the added value of delamanid in children. First and foremost, the authors failed to report objectively any patient outcomes (e.g. culture conversion at 2 months or time to culture conversion) or to describe any adverse events. Second, given that only one case was being reported, it was unfeasible to calculate and compare the frequency or comparative risk of adverse events because there were no other patients receiving delamanid under the same circumstances as those reported in this single case. Consequently, this case report was not considered (**Fig. 1**).

Further to this search, and on WHO's request, the drug manufacturer provided access to data from two ongoing paediatric studies: "Pharmacokinetics and safety of delamanid in paediatric MDR-TB patients, ages 6–17 years" and "Long-term safety, tolerability and pharmacokinetics of delamanid in paediatric MDR-TB patients, ages 12–17 years" (**Fig. 1**). Data from children enrolled in the two oldest cohorts were provided via a confidential disclosure agreement.

An independent paediatric PK specialist was appointed as a consultant by the WHO Guideline Steering Committee to critically review the above data and prepare a concise synthesis report of the available evidence, to be circulated to the GDG for scrutiny before the meeting. This report was based on the analysis of raw paediatric data derived from the following trials:

- ▪ "Pharmacokinetic and safety trial to determine the appropriate dose for paediatric patients with multidrug resistant tuberculosis" – this is an ongoing Phase I, open-label, age de-escalation trial designed to determine the paediatric dose of delamanid that is equivalent to the adult dose already shown to be effective against MDR-TB (Protocol 242-12-232) *(15)*; and
- ▪ "A 6-month safety, efficacy, and PK trial of delamanid in paediatric patients with multidrug resistant tuberculosis" – this is an open-label extension Phase II study designed to assess the

safety, tolerability, PK and efficacy of long-term (6-month) treatment with delamanid plus an optimized background regimen (OBR) of other anti-TB drugs in paediatric patients (Protocol 242-12-233) *(16)*.

The analysis of safety data was complemented by a report that described the initial experience of CU of delamanid in children and adolescents in various countries *(17)*.

Data from the following adult trials – which served as the basis for the interim guidance issued in 2014 – were used for comparison on efficacy for the current update for children and adolescents (**Fig. 1**):

- "A placebo-controlled, phase II trial to evaluate OPC 67683 in patients with pulmonary sputum culture-positive, multidrug-resistant tuberculosis (TB)" – this is a clinical trial to evaluate the safety and efficacy of OPC-67683 in the treatment of MDR-TB for 56 days, in addition to an OBR *(18)*;
- "A phase II, multicentre, uncontrolled, open-label trial to evaluate safety, tolerability, and efficacy of orally administered OPC-67683" – this is a Phase II, multicentre, uncontrolled, open-label trial in patients with MDR-TB *(19)*;
- an observational study (Protocol 242-10-116) aimed at capturing data from the microbiological assessments and clinical monitoring of these adult patients after full treatment with delamanid in addition to OBR *(20)*; and
- unpublished adult data from EMA's public assessment report *(12)*.

**Fig. 1. Flow diagram for study search and selection of data**
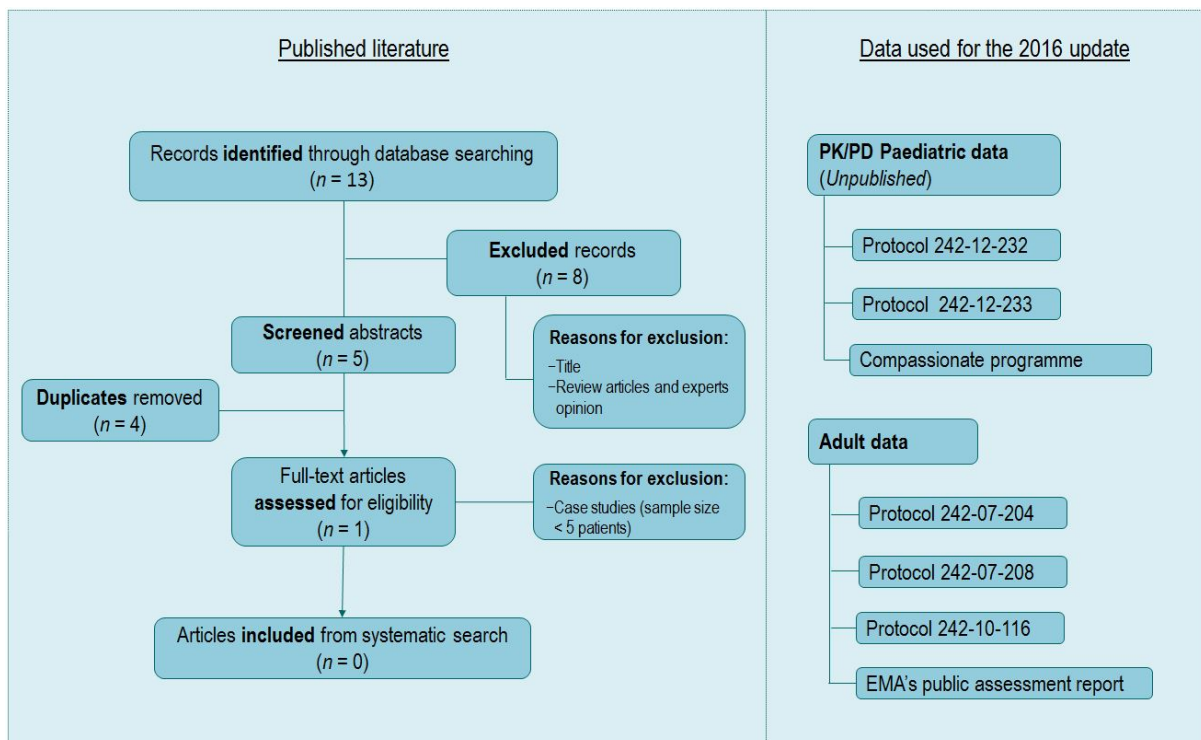


EMA, European Medicines Agency; PD, pharmacodynamic; PK, pharmacokinetic

Members of the GDG were asked to evaluate the available evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for grading quality of evidence and assessing strength of recommendations, based on the formulation of an a priori agreed-upon question, worded in the population, intervention, comparator, outcome (PICO) format:

*In children with MDR-TB aged 6 years and above, does the addition of delamanid to a WHO-recommended second-line drug therapy improve efficacy of treatment without increasing safety concerns?*

*Determination of relative importance of patient outcomes*

To preserve consistency within successive iterations of the policy guidance documents, it was proposed to the GDG that the same patient outcomes be used for the GRADE evaluation as were used for the evaluation of delamanid data in adult patients in 2014. Additionally, considering that a partial extrapolation approach using adult reference data derived from the drug manufacturer's earlier studies in adults was to be used, no modifications or additions to the below outcomes were necessary (see **Table 6**: *GRADE evidence to decision framework*). Subsequently, the following outcomes were evaluated for the evidence profile:

1. Sputum culture conversion at 2 months.
2. Time to sputum culture conversion over 2 months.
3. Sustained sputum culture conversion at 24 months.
4. Cure at 24 months.
5. Mortality at 24 months.
6. Serious adverse events in pivotal RCT.
7. Acquired resistance to delamanid.

These outcomes were scored by the GDG members on a scale from 1 to 9, based on their relative importance; all were considered "*Critical*" (score 7, 8 or 9).

For each of these outcomes, the *quality of evidence* was evaluated according to the following criteria:

- *overall study design:* RCTs or observational studies (RCTs start as high-quality evidence, observational studies as low-quality evidence);
- *risk of bias or limitations in study design and execution*;
- *inconsistency:* unexplained heterogeneity between studies' end-points or treatment outcome estimates;
- *indirectness:* interventions, population and outcomes on which the evidence is based differs from the interventions, populations and outcomes of interest;
- *imprecision:* wide confidence intervals around treatment outcome estimates; and
- *other considerations:* possibility of publication bias; upgrading factors (applicable to observational studies).

GRADE categorizes the quality of evidence as high, moderate, low or very low to reflect the overall confidence in the effect under evaluation, as shown in **Table 1**.

**Table 1. Significance of the four levels of evidence**

| Quality | Definition | Implications |
|---|---|---|
| **High** ⊕⊕⊕⊕ | The GDG is very confident that the true effect lies close to that of the estimate of effect | Further research is very unlikely to change confidence in the estimate of effect |
| **Moderate** ⊕⊕⊕○ | The GDG is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different | Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate |
| **Low** ⊕⊕○○ | Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect | Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate |
| **Very low** ⊕○○○ | The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect | Any estimate of effect is very uncertain |

GDG, Guideline Development Group

## Decision-making during the Guideline Development Group meeting

The GDG meeting was chaired by a recognized expert in methodology and evidence synthesis. Decision-making was based on unanimous agreement between all GDG members or consensus (preferred option). Concerns and opinions by GDG members during the meeting were noted and included in the final meeting report. In all instances, consensus was reached among members, and it was therefore unnecessary to proceed to a vote. The detailed meeting report was prepared by the WHO Guideline Steering Committee and was revised based on input and sign-off by all GDG members. The list of GDG members is at **Annex 1**.

## External peer review

An External Review Panel (ERP) independently reviewed the draft interim guidance prepared by the WHO Guideline Steering Group on the basis of the recommendations made by the GDG. The ERP included content experts and end-users from high TB and HIV burden countries. There were no areas of disagreement among ERP members, all of whom supported the proposed recommendation. The list of ERP members is at **Annex 2**.

## 4. Evidence for policy formulation

This section presents a summary of the data analysis results. The findings presented here were derived from an ongoing Phase I, open-label, age de-escalation trial designed to assess the PK, safety and tolerability of delamanid in two subgroups of children, and the related Phase II extension study. Adult reference data, used here for comparison, were derived from Protocol 242-07-204, a Phase II study of delamanid administered twice daily (BID) for 8 weeks in addition to OBR in subjects with MDR-TB and from two add-on studies: the corresponding voluntary, open-label, add-on Study 242-07-208, and a multicentre, observational study describing microbiological assessments and clinical monitoring in recruited patients, Study 242-10-116. In addition, data from EMA's public assessment report were consulted. Standard descriptive statistics were applied to describe the continuous demographic, PK and electrocardiogram (ECG) data (e.g. mean, standard deviation, confidence interval and range).

Discrete variables were summarized by counts and percentages. Associations were explored using both linear and nonlinear regression techniques.

In total, data were obtained from six children aged 6–11 years and seven children aged 12–17 years. Children enrolled in Study 242-12-232 were stratified by age into either a 50 mg BID (children aged 6–11 years) or 100 mg BID (children aged 12–17 years) dosing cohort. Children were required to have confirmed or presumptive MDR-TB with exclusions for HIV, hepatitis B or C, severe malnutrition, underlying heart disease and pathologic conditions that could alter the disposition of delamanid. Use of rifampicin and moxifloxacin was prohibited within 1 week of enrolment. These same children carried forward into the long-term open-label Study 242-12-233. Children enrolled in the 100 mg cohort were significantly older, taller and heavier than children enrolled in the 50 mg cohort. The 100 mg cohort was balanced for sex, but the 50 mg cohort favoured males. In both cohorts, Asian ethnicity predominated. The lack of difference in absolute body mass index (BMI) values between the 50 mg and 100 mg dosing groups corresponded to a lower overall body mass for age in the 100 mg cohort, as evidenced by significantly lower BMI z-scores ($P < 0.05$).

The baseline demographic characteristics for both children and adults are detailed in **Table 2**. Although the labelled dosing for delamanid is 100 mg BID, data from the adult 200 mg BID cohort are reviewed in this report for the purpose of comparison with the paediatric data.

**Table 2.** **Baseline characteristics of paediatric and adult participants**

| Characteristic | Paediatric 50 mg BID | Paediatric 100 mg BID | Adult 100 mg BID | Adult 200 mg BID |
|---|---|---|---|---|
| **Count** | 6 | 7 | 161 | 160 |
| **Dose (mg/kg)** | $2.15 \pm 0.64$ | $2.71 \pm 0.54$ | 1.75 | 3.7 |
| **Age (years)** | $9.2 \pm 1.5$ | $14.7 \pm 1.5$ | $37.4 \pm 12.1$ | $35.4 \pm 12.0$ |
| **Sex (male:female)** | 2:4 | 4:3 | 105:56 | 108:52 |
| **Height (cm)** | $122.3 \pm 11.3$ | $150.9 \pm 10.8$ | $168.3 \pm 9.4$ | $164.5 \pm 10.2$ |
| **Weight (kg)** | $24.9 \pm 6.8$ | $38.0 \pm 6.4$ | $57.1 \pm 10.6$ | $54.0 \pm 11.8$ |
| **BMI (kg/m$^2$)** | $16.3 \pm 2.4$ | $16.7 \pm 2.2$ | $19.8 \pm 3.5$ | $19.9 \pm 3.8$ |
| **BMI z-score** | $-0.25 \pm 0.9$ | $-1.6 \pm 1.2$ | | |

BID, twice a day; BMI, body mass index

## 4.1 Evaluation of paediatric pharmacokinetics data

### Dose exposure

Delamanid doses administered to paediatric participants in these studies ranged from 1.5 to 3.8 mg/kg, which was comparable to the range of doses administered to adults. Systemic exposure between parent and metabolite DM-6705 were highly correlated. Analysis of the PK data demonstrated a nonlinear dose–exposure relationship. This finding is consistent with data from the healthy adult cohorts enrolled in ascending dose studies, in which no differences were observed in exposures between the 50 mg and the 100 mg dosing groups, and a less than dose-proportional increase in exposure was seen with increases in dose from 100 to 400 mg. The absence of a clear dose–exposure relationship may also be confounded by age effects or by the limited sample size.

### Dose–exposure and age–exposure relations

Exploration of the dose–exposure relationship showed a weak but insignificant relationship between weight-adjusted dose and maximum plasma concentrations (Cmax) for delamanid and the metabolite DM-6705 after the first dose, with dose accounting for just over 20% of the variability observed in exposure. However, no relationship was observed between dose 1 and total body exposure of delamanid or DM-6705, as reflected by the area under the curve (AUC). Similarly, only weak and

insignificant relationships between the weight-adjusted dose of delamanid and DM-6705 exposure were observed on day 10. Although these results may be imprecise because of the limited sample size, this finding is consistent with data from the healthy adult cohort enrolled in an ascending dose study, in which no differences in exposure between the 50 mg and 100 mg dosing groups were noted, and less than proportional increases in exposure were observed through 400 mg. The absence of a dose–exposure relationship may also be confounded by age effects, which are described in greater detail below.

**Fig. 2** shows the effect of age on exposure. As indicated earlier, older children enrolled in the 100 mg cohort received a weight-adjusted delamanid dose that was about 25% higher than that of the younger children enrolled in the 50 mg dosing group. Despite this dosing difference, estimates of exposure to delamanid, and to a lesser extent DM-6705, were slightly lower in the older 100 mg cohort.

**Fig. 2. Age-exposure and plasma concentrations.** (left) Median (interquartile range) of weight-adjusted doses received by children in the 50 mg and 100 mg cohorts of Study 242-12-232. (centre and right) Mean (90% confidence interval) 24-hour plasma concentration versus time profiles for delamanid and DM-6705 by dosing cohort on days 1 and 10 ($n = 13$).
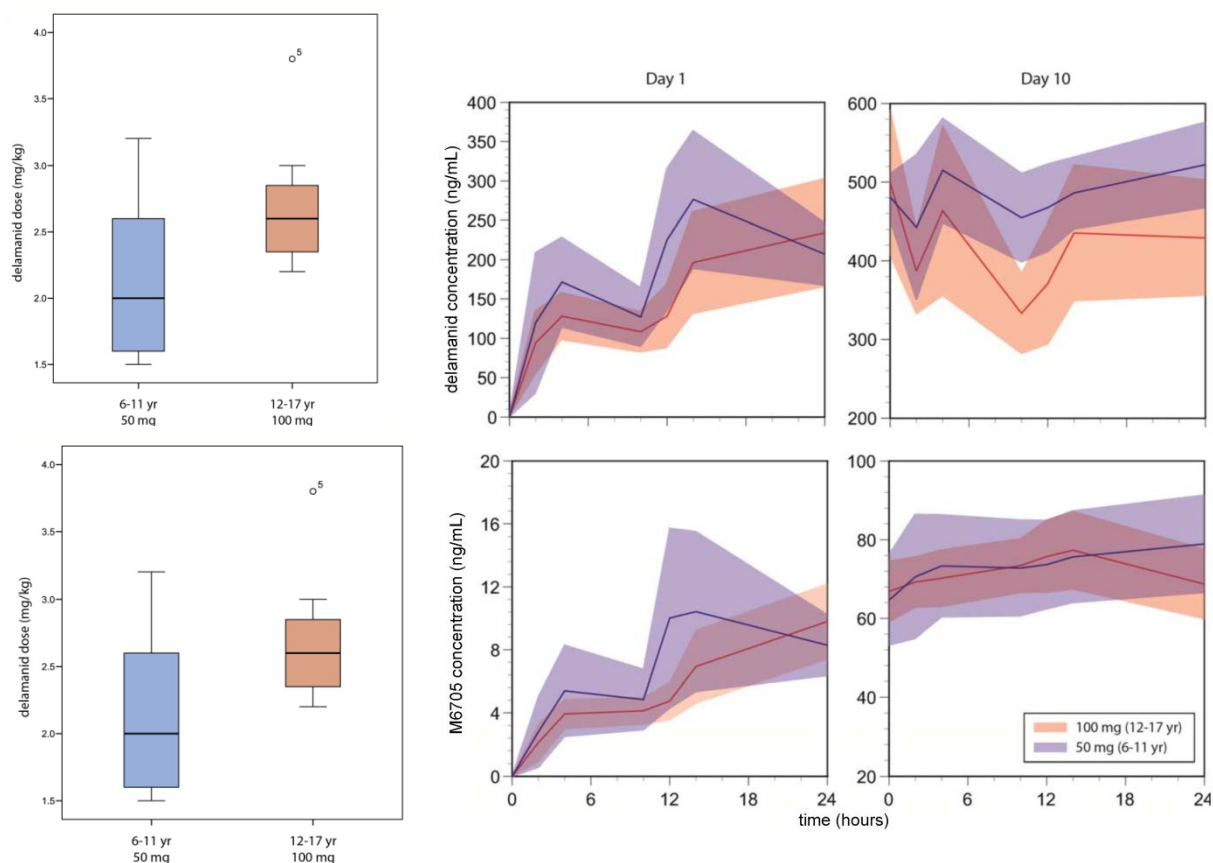


Inspecting the influence of age on delamanid disposition, a significant relationship between age and delamanid exposure was observed when exposure was adjusted for the mg/kg dose that was received. Both Cmax ($r^2 = 0.515$, $P < 0.01$) and $AUC_{0-24}$ ($r^2 = 0.319$, $P = 0.04$) on day 1 demonstrated significant associations with age. The association between age and dose-adjusted $AUC_{0-24}$ was still present on day 10, albeit less pronounced ($r^2 = 0.231$, $P = 0.10$); however, the association did not

persist for Cmax ($r^2 = 0.088$, $P = 0.325$). As expected, these associations between age and exposure were reproduced in the significant association between age and apparent oral clearance (Cl/F) for delamanid ($r^2 = 0.327$, $P = 0.04$). Notably, these age-dependent differences did not extend to delamanid half-life ($r^2 = 0.023$, $P = 0.62$) or DM-6705 half-life ($r^2 = 0.001$, $P = 0.93$), or to metabolite:parent ratios for Cmax ($r^2 = 0.058$, $P = 0.43$; $r^2 = 0.022$, $P = 0.63$) and $AUC_{0-24}$ ($r^2 = 0.063$, $P = 0.41$; $r^2 = 0.425$, $P = 0.02$) on days 1 and 10, respectively (**Fig. 3a**). Given the lack of any appreciable association between age delamanid biotransformation and the extensive apparent distribution volume reported for delamanid, the existing data appear to suggest that age-dependent changes in Cl/F are driven by changes in bioavailability. It is not clear whether this reflects ontogenic changes that occur as children mature or pathologic or environmental differences between the age cohorts.

**Fig. 3a.** Correlations between the age of children enrolled in Study 242-12-232 and selected disposition parameters for delamanid (n = 13)
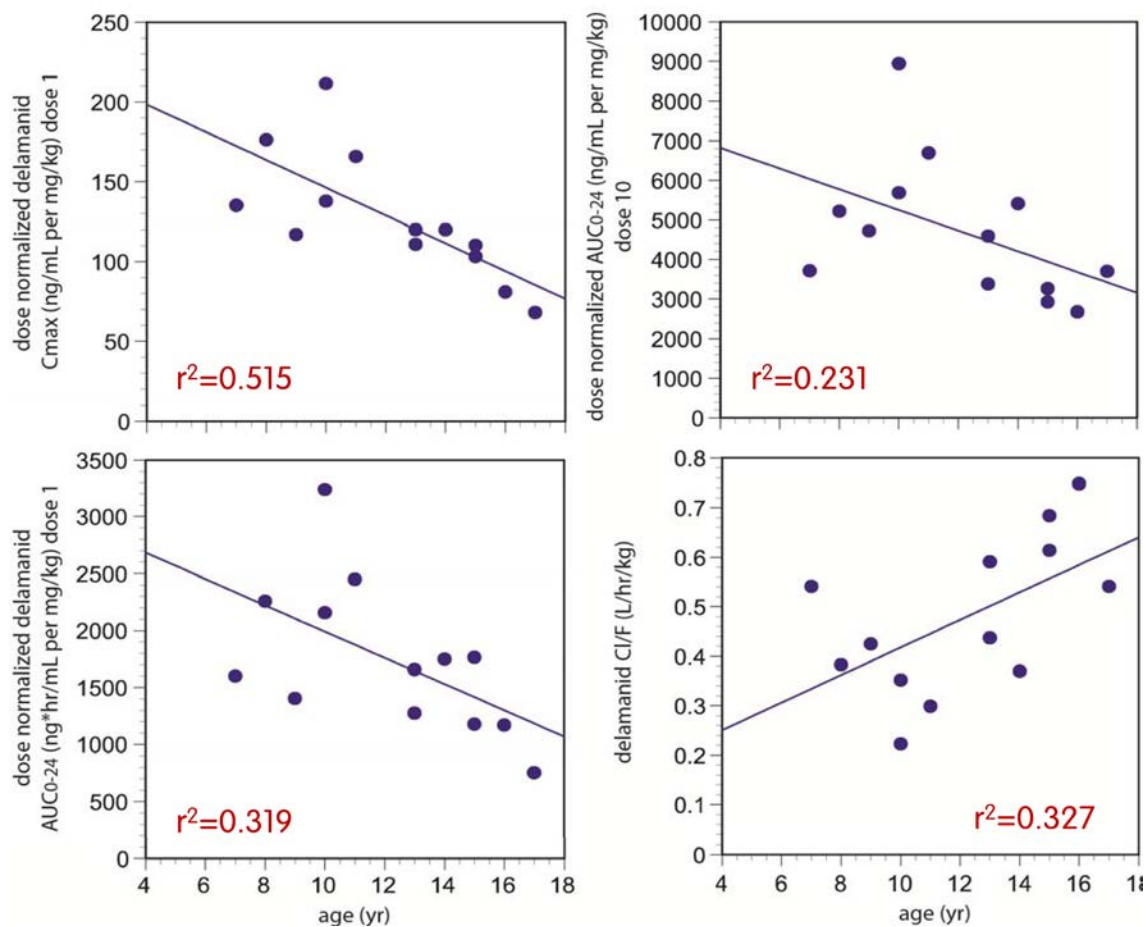


AUC, area under the curve; Cl/F, apparent oral clearance; Cmax, maximum plasma concentration; yr, years

**Fig. 3b. Correlations between delamanid Cl/F and BMI z-score (children (n = 13), left) or BMI percentile (adults (n = 321), right)**



Paediatric — Adult
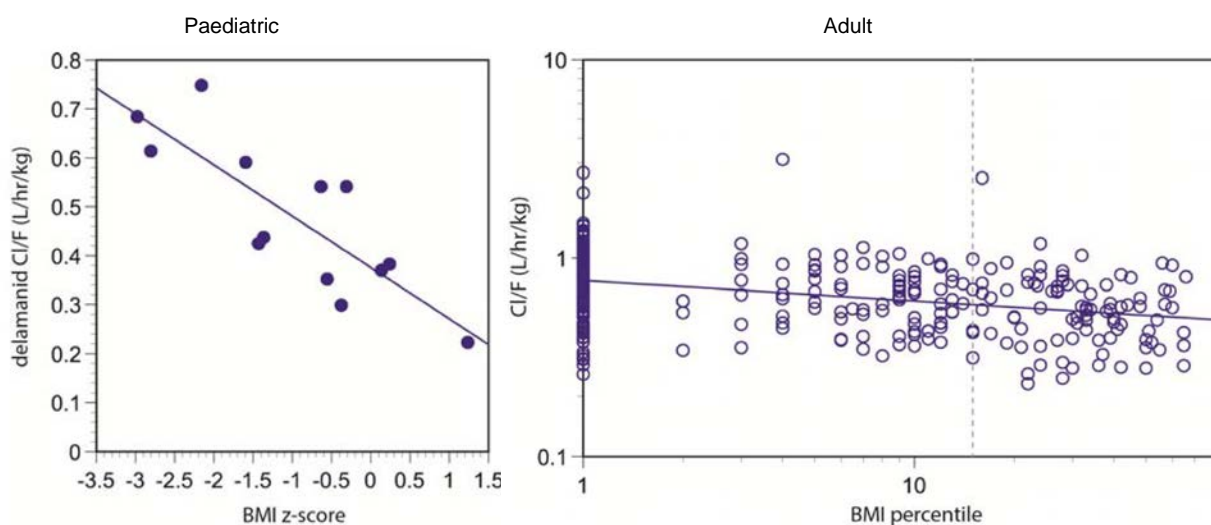
BMI, body mass index; Cl/F, apparent oral clearance

BMI percentile for adults was determined using the Third National Health and Nutrition Examination Survey (NHANES III) as the reference population; thus, the trend may be informative but individual percentile values may not be wholly accurate. Adults with a BMI percentile < 2 were arbitrarily assigned a value of 1 for the purpose of visualization.

When examining nutritional status as a potential confounder, BMI z-score had a more profound effect on apparent oral clearance ($r^2 = 0.683$, $P < 0.01$) than did age, raising the question as to whether underlying nutritional status plays a role in the biodisposition of delamanid in children (**Fig. 3b**). In multivariate analysis, age becomes insignificant (probably due to the effect of sample size) and BMI z-score remains the primary factor influencing variability in Cl/F. Using BMI percentiles (United States population reference) to determine whether the same results are observed in adults, the data analysis indicates that there is a much weaker, yet significant, relationship between BMI percentile in adults and their clearance of delamanid ($P < 0.01$) (**Fig. 3b**). Collectively, these findings suggest that both age and habitus probably influence Cl/F of delamanid.

*Paediatric–adult exposure comparison*

**Fig. 4** presents the raw plasma concentration time data on day 1 for children aged 6–11 years and 12–17 years overlaid on the range (±1.96 SD) of adult exposure profiles on day 1 (plotted in gray) for adults receiving 100 and 200 mg BID. At both doses (50 mg and 100 mg) nearly half of the children in these cohorts experienced delamanid concentrations in excess of adults receiving 100 mg. Findings were similar for DM-6705 concentrations. In all cases, delamanid exposure sits at the high end of the adult exposure range. At the doses evaluated in Study 242-12-232, paediatric exposures were more consistent with the profiles observed in adults receiving regimens of ≥ 200 mg BID as opposed to the labelled dose of 100 mg BID (**Fig. 5**).

**Fig. 4. Raw plasma concentration time.** Data on day 1 for children enrolled in Study 242-12-232 overlaid on the range (± 1.96 SD) of adult exposure profiles on day 1 for patients enrolled in Study 242-07-204.
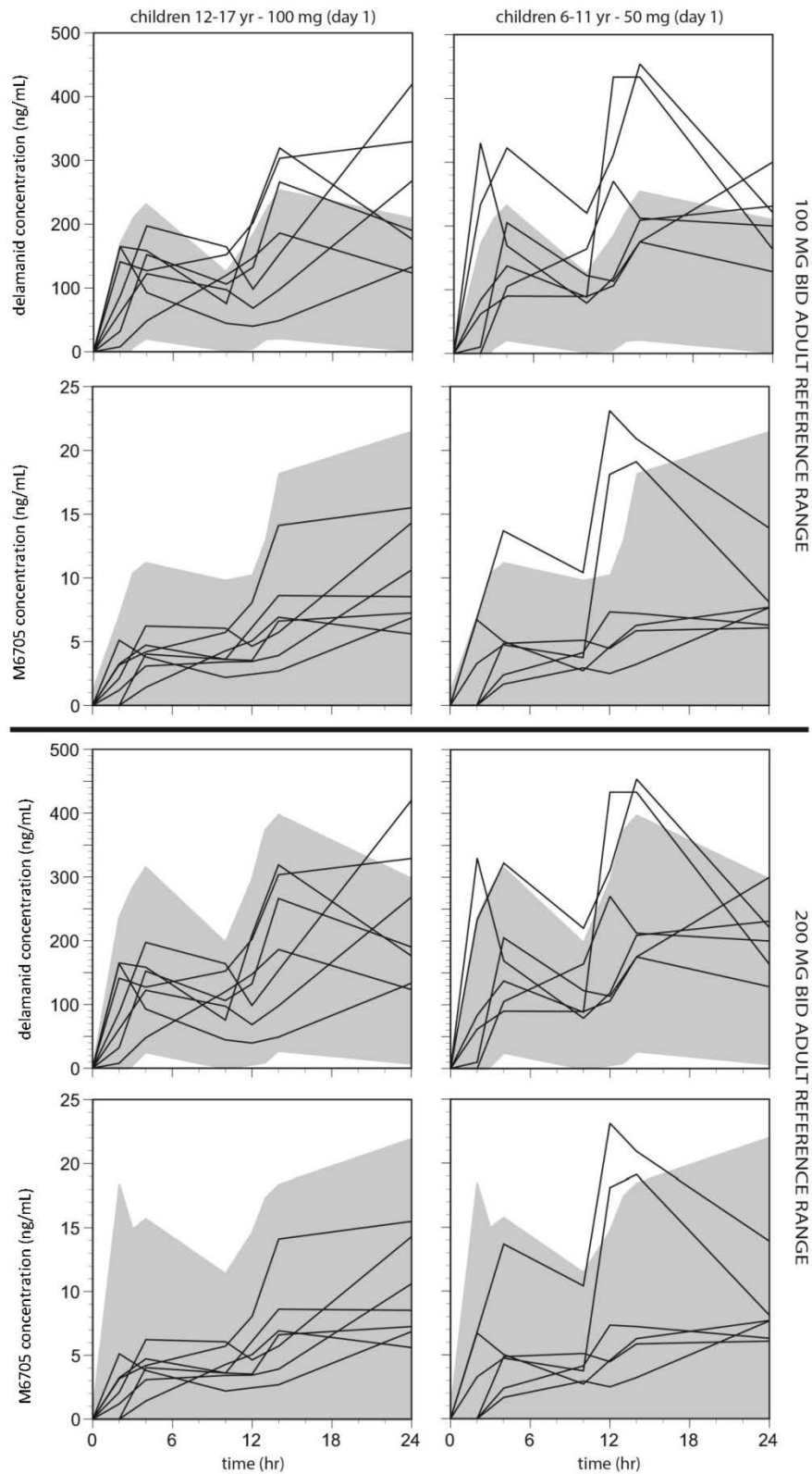


BID, twice a day; SD, standard deviation

Given that there are limited safety data, it is not yet known whether potential dose-dependent toxicities – which may or may not have been defined – would occur in paediatric populations.

**Fig. 5. Delamanid exposure.** 90% confidence intervals for delamanid exposure on day 1 and at steady-state in selected trials
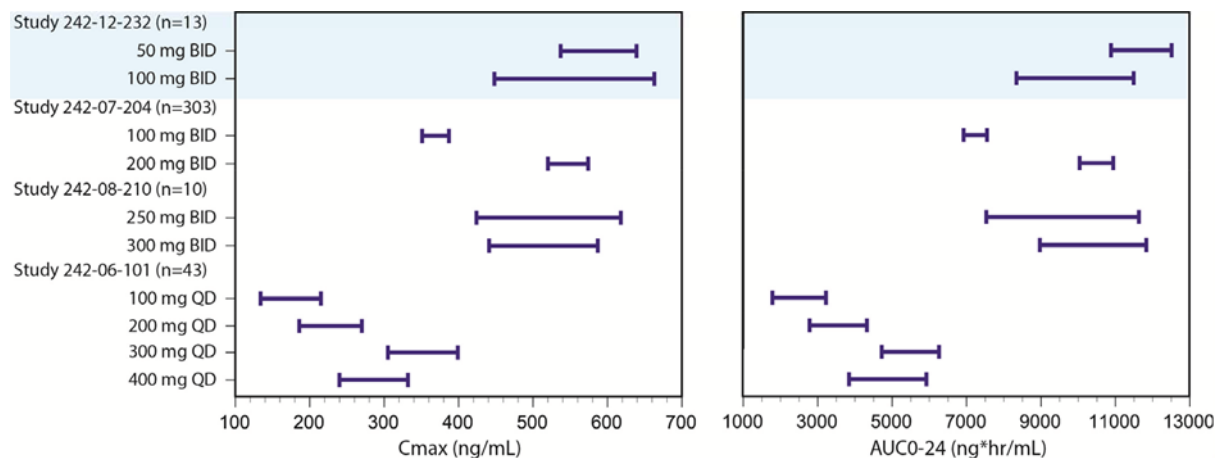


AUC, area under the curve; BID, twice a day; Cmax, maximum plasma concentration; QD, once a day

Adult summary data from 242-07-204 and 242-08-210 were available as mean (coefficient of variation %). Standard deviations were computed from the coefficient of variation.

## 4.2 Evidence for the safety of delamanid in the treatment of MDR-TB

*QT prolongation*

The drug manufacturer provided ECG data to be analysed as a safety end-point (focus on QT prolongation). ECG data were quality assured by independently calculating the corrected QT intervals (QTcF and QTcB) [a] from the manufacturer-provided ECG data according to the following: $QTcB = QT/\sqrt{RR}$ and $QTcF = QT/RR1/3$. Estimation of QTc at each time point reflected the mean of three QT values obtained at baseline or within a 10-minute window of PK sampling. Deviations observed between the sponsor-reported and consultant-calculated QTc values were insignificant across all measurements ($0.0 \pm 0.2\%$) and were probably the result of numerical rounding. [b]

ECG data on day 1 and day 10 for baseline-corrected QTcF indicated that there is no significant effect that is picked up early on therapy. However, time-dependent increases were noted during the first month of exposure to delamanid, and QTc remained elevated until exposure was discontinued. Between days 28 and 182, confidence intervals for the intercept of ΔQTcF versus time in both the 50 mg BID and 100 mg BID cohorts did not span zero, indicating that the QTc prolongation was significant (**Fig. 6a** and **Fig. 6b**).

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[a] The drug manufacturer provided both Bazett (QTcB) and Fridericia (QTcF) corrected QTc interval data from Study 242–12–232 and Study 242–12–233. To facilitate comparisons with the available adult data, QTcF interval data were used in this analysis.

[b] The ECG data provided in the source files report intervals were determined from one of two leads (either lead-II or lead-V5). Though the ultimate relevance of this fact is unclear, this inconsistency merits consideration when critically evaluating these data.

**Fig. 6a.** Mean (90% CI) QTcF versus time profiles during the 10-day 242-12-232 study period
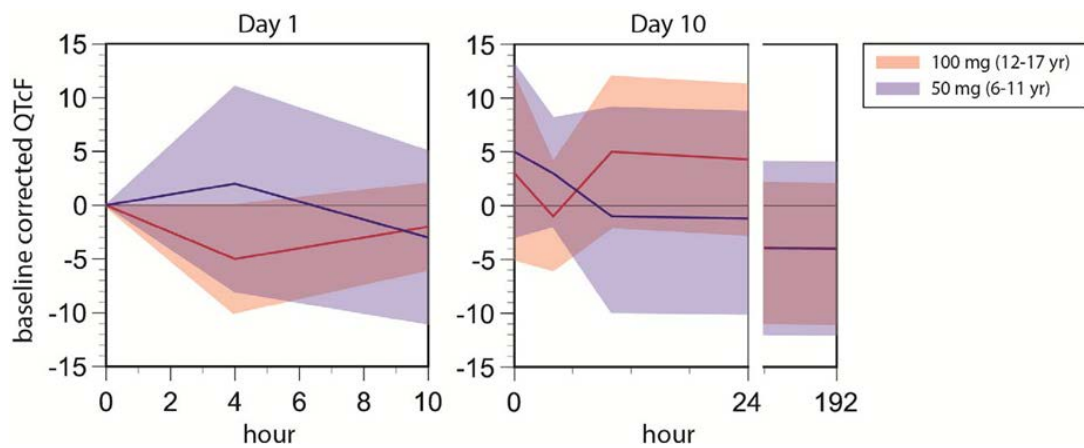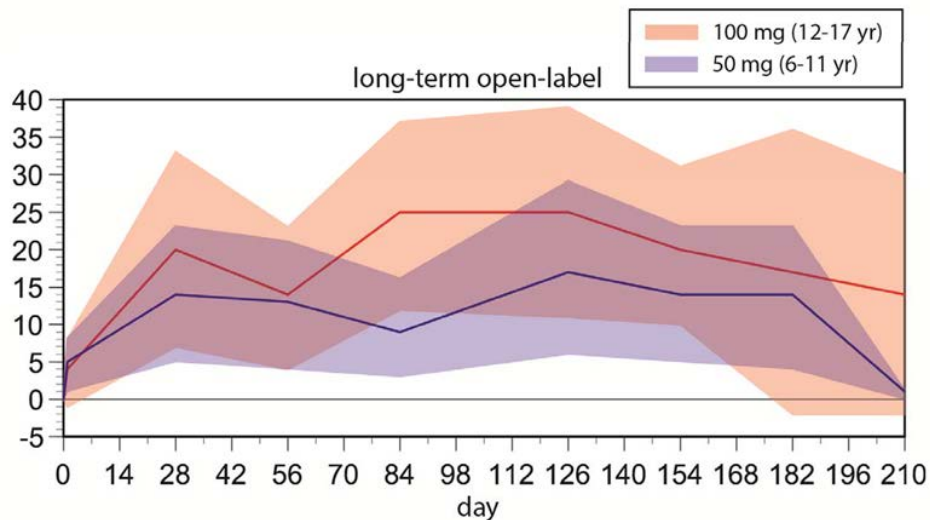


**Fig. 6b.** Mean (90% CI) QTcF versus time profiles during the 210-day 242-12-233 open-label extension



CI, confidence interval; QTcF, Fridericia corrected QTc

**Fig. 7** shows the relationship between delamanid plasma concentration and baseline-corrected QTcF. This relationship is more pronounced with plasma DM-6705 concentrations than with delamanid concentrations. In a multivariate analysis examining serum electrolytes and delamanid analyte concentrations, only metabolite DM-6705 and albumin remained significantly associated with the variation in QTcF from baseline (ΔQTcF).

**Fig. 7. Correlations between delamanid and DM-6705 concentrations with baseline-corrected QTcF for children enrolled in Study 242-12-232 and Study 242-12-233**
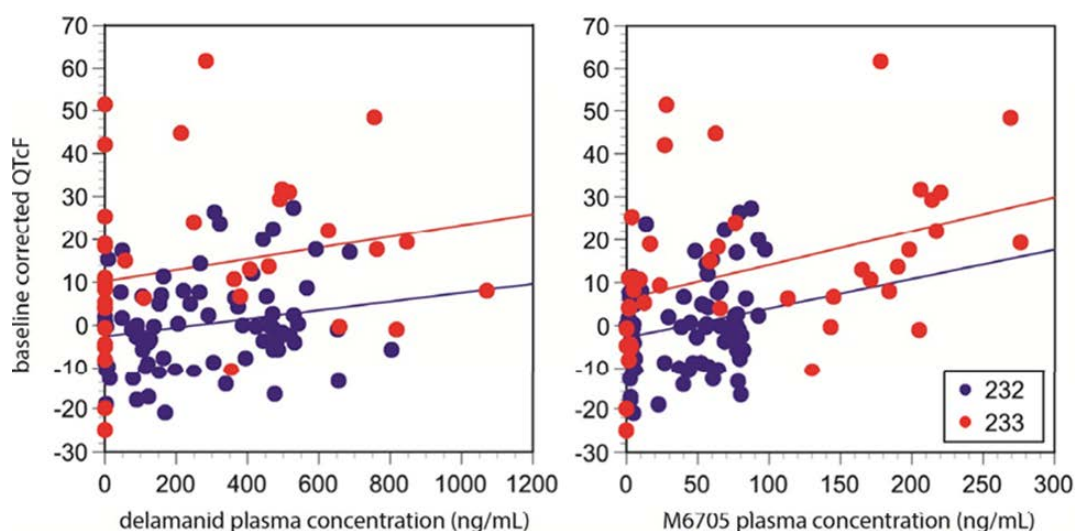


QTcF, Fridericia corrected QTc

When comparing delamanid-associated cardiac conduction changes in children with those of adults (**Table 3**) the data appear to suggest that the fraction of children at each "risk" threshold is comparable to that of adults; thus, relative risk appears comparable and putatively age independent. It is not known whether children have a higher risk of progressing to cardiac events than adults with the same QT prolongation.

**Table 3. Cardiac conduction changes reported for delamanid clinical studies in adults and children**

| ECG parameter | Paediatric data | | Adult data | |
|---|---|---|---|---|
| | 242-12-232 *n* (%) | 242-12-233 *n* (%) | 242-07-204 *n* (%) | 242-07-208 *n* (%) |
| QTcF > 500 msec | 0 (0) | 0 (0) | 2 (0.6) | 2 (0.9) |
| QTcF > 480 msec | 0 (0) | 0 (0) | | 4 (1.9) |
| QTcF > 450 msec | 0 (0) | 1 (7.7) | | 33 (15.5) |
| QTcF > 440 msec | 1 (7.7) | 7 (53.8) | | |
| $\Delta$QTcF $\geq$ 60 msec | 0 (0) | 1 (7.7) | 29 (9) | 8 (3.8) |
| $\Delta$QTcF $\geq$ 30 < 60 msec | 0 (0) | 4 (30.8) | | 66 (31) |

ECG, electrocardiogram; QTcF, Fridericia corrected QTc

Note: 440 msec was included in this table because it has been defined as the threshold for borderline long QTc in children.

Additional information from a recently published paper *(17)* reporting CU of delamanid in 16 children described one case with a QTcF elevation of > 500 msec, accompanied by vomiting, nausea and electrolyte imbalance. The QTcF resolved once the electrolyte imbalance was corrected in the child. Of note, the child described in this case was concurrently receiving clofazimine.

Apart from the risks associated with underlying cardiac conduction abnormalities, and the additive risk contributed by concomitant medications that prolong QT (e.g. bedaquiline, clofazimine and moxifloxacin), other considerations include genetic, developmental and pathophysiologic factors that may alter disposition of DM-6705, the delamanid metabolite implicated in QTc changes. DM-6705 formation is mediated by the interaction between delamanid and albumin *(21)*. Interspecies data support a clear role for albumin sequence variations contributing to differences in M6075 formation

*(21)*. This raises the question as to whether DM-6705 formation rates differ among individuals with different albumin isoform distributions (e.g. neonates) or individuals with genetic variations in their albumin sequence. Formation of DM-6705 is also greater at alkalotic pH. While clear differences in formation rate can be observed from pH 6 to pH 8 (0.0% at pH 6.0, 4.8% at pH 7.0, 12.7% at pH 7.5, and 20.1% at pH 8.0 after 4 hours at 37 $^{\circ}$C in 10% human plasma) *(21)*, it is unclear whether any appreciable differences would be observed within the range of physiologically relevant pH.

### *Other adverse events*

Neurologic toxicities such as paraesthesia, tremor and anxiety were identified by the drug manufacturer *(12)*. Other risks, including depression, insomnia, tinnitus and blurred vision, were deemed important and listed by the drug manufacturer in the summary of product characteristics.

## 4.3    Evidence for the efficacy of delamanid in the treatment of MDR-TB

PK data were used as a surrogate for efficacy. Evidence for efficacy derives from the two PK studies presented above *(18, 19)*. Early bactericidal activity (EBA) studies – for which data were collected at various time periods and from a variety of patient populations – suggested that maximal EBA correlated with an AUC of between 3500 ng· h/mL and 5500 ng· h/mL *(20, 22)*. When the exposures attained in paediatric studies are compared to the pre-established AUC threshold range for maximum efficacy (3500–5500 ng· h/mL) *(12)* – and if that surrogate is adopted for children with the understanding that these data are derived from sputum data for adults with pulmonary TB – 70% of children achieve the lower limit of this exposure range after the first dose. All children attained exposures in excess of the lower limit of these PK surrogates by day 10 (**Table 4**). Day 1 findings are in slight contrast to data from adults receiving the labelled 100 mg dose, where a greater fraction of participants fell below the lower limit of this threshold. The findings are more consistent with the adults receiving 200 mg, where most participants exceeded the lower threshold *(12)*.

Additional efficacy data from the CU programme referenced earlier indicated that [at the time of the interim analysis] 13 of 16 patients were *Mycobacterium tuberculosis* culture negative, with the remaining three patients having received treatment for an insufficient duration to determine interim treatment response. Final outcomes were only available for one patient, with the remaining cases still undergoing treatment at the time of writing *(17)*.

**Table 4.** **Baseline PK characteristics of paediatric and adult participants**

| Study 242-12-232 | AUC$_{0-24}$ day 1 (ng · h/mL) | AUC$_{0-24}$ day 10 (ng · h/mL) |
|---|---|---|
| Overall mean | 4082 | 10735 |
| SD | 1309 | 2164 |
| 90% CI | 3485, 4680 | 9748, 11722 |
| 100 mg BID mean | 3709 | 9911 |
| SD | 1241 | 2534 |
| 90% CI | 2937, 4480 | 8336, 11487 |
| 50 mg BID mean | 4518 | 11695 |
| SD | 1357 | 1214 |
| 90% CI | 3607, 5429 | 10879, 12511 |

AUC, area under the curve; BID, twice a day; CI, confidence interval; PK, pharmacokinetics; SD, standard deviation

# 5. Clinical and scientific factors related to the recommendation

The GRADE system was used to rate the quality of evidence (as high, moderate, low or very low) and to determine the strength of the recommendations (as strong or conditional) *(23)*. The GDG evaluated the quality of evidence to determine whether, based on the available data, delamanid should be added to a WHO-recommended background MDR-TB regimen for children aged 6–11 years and adolescents aged 12–17 years. For each outcome, the quality of the body of evidence was assessed based on the design of the studies; study limitations and risk of bias; precision, consistency and directness of findings; and completeness of the evidence (e.g. publication bias).

Regarding the analysis of these data, members of the panel agreed with the quality assurance procedures performed by the consultant to validate PK parameters established by the drug manufacturer. They also agreed with as the statistical methods used to determine relationships between these parameters and relevant factors.

In general, provided that efficacy data from adults are considered relevant, and drug exposures associated with favourable outcomes in adults are known, PK/PD data from adults coupled with PK data from children can be used to find drug doses in children that achieve adult PK targets. Safety and efficacy can then be extrapolated from adults to the paediatric population. However, the GDG recognized the limitations of current data, particularly the use of [partial] extrapolation of PK/PD adult efficacy and safety data to inform the development of recommendations for the paediatric population. The panel acknowledged that, in terms of drug development, collecting paediatric data represents a significant challenge. Members also recognized that thorough PK/PD data can – to a certain degree – inform the relationship between concentrations and efficacy and safety. However, with regard to estimating the efficacy and safety of delamanid for children, the panel expressed low confidence in these data. Given that current data mainly address concerns about QT prolongation but do not provide information about other unstudied toxicities, the panel had little confidence in the extrapolation from adult data, especially for the evaluation of safety markers. When discussing efficacy endpoints, the panel stated that although the microbiology of the organism and the histology of the lesions do not differ between adults and children, the actual lesions observed in children are more likely to be of the extrapulmonary TB type. Thus, drug penetration in children can vary from that in adults and might be more problematic. Members agreed that evidence was lacking on this topic, and that this was not related to the concentrations of the drug that were going to be achieved according to the PK/PD data presented. In terms of safety issues, the GDG was also in agreement that unexpected toxicities are more likely to occur in younger children. The PK data – and the association between PK and efficacy – show a wide range of concentrations. Based on these data, with the high concentrations that children were exposed to (exceeding those of the labelled adult dose), the GDG agreed that the concentration could be decreased through dose adjustment, and advised that further research to identify the optimal dose for children be undertaken; however, the panel also noted that different nutritional conditions could affect the drug concentrations.

The GDG discussed each outcome of interest based on the GRADE evidence profile defined in 2014 for adult data, and made changes to the profile to adopt specific considerations for the paediatric population.

The GDG also discussed whether any of the effect estimates should differ based on the evidence presented during the meeting. In the absence of any additional information, the GDG agreed to make no modification to the following outcomes: *sputum culture conversion at 2 months*; *time to sputum culture conversion over 2 months*; *sustained sputum culture conversion at 24 months*; *cure at 24 months*; *mortality at 24 months*; and *acquired resistance to delamanid* (see the *GRADE evidence profile summary* (**Table 5**) and the *GRADE evidence to decision framework* (**Table 6**)).

Regarding whether the occurrence of adverse events was similar in children and adults, the panel considered that it would be necessary to adjust drug levels in children. It was emphasized that adult data cannot be extrapolated to predict the toxic effects of drugs in children and infants for several

reasons (e.g. different drug metabolism in children). The panel decided that confidence in the evidence of safety in children, with regard to the occurrence of serious adverse events, was to be rated from "low" to "very low" because of concern about indirectness.

QT prolongation was the main observation on safety. When comparing with data from children to that of adults (with delamanid intake associated with a 2.6-fold increase in QT prolongation), the experts decided on lower certainty in the relevance of the estimate because of indirectness. The panel also noted that the extrapolation was limited due to the small sample size and low number of observations, and expressed concern that only QT prolongation was examined, leaving uncertainty on other potential toxicities.

On the whole, members of the panel considered that none of the judgements on the relevance and confidence in effect estimates examined in 2014 would differ, except for an additional uncertainty on the assessment of QT prolongation (**Table 5**).

Thus, the GDG rated the quality of the evidence for the efficacy and safety of the use delamanid in children aged 6–11 years and adolescents aged 12–17 years as "very low".

For values and preferences, the GDG considered that the initial interim guidance for adults still stood for children and adolescents. The panel noted, however, that requirements for ECG before and during treatment may reduce *operational feasibility*, as the availability of ECG machines is not a given in all settings and because interpretation of ECG results may require referral to specialists or extension of ECG access (implying additional resources). Twice-daily dosing may also affect feasibility, and would require additional resources to ensure drug administration under observation. However, oral (in comparison to injectable medication) use may increase feasibility. On the whole, the EG estimated that the use of delamanid on top of a longer MDR-TB treatment regimen would be feasible in most MDR-TB treatment settings.

## 6. WHO interim policy recommendations for the use of delamanid in children and adolescents

Available data on delamanid efficacy and safety in children aged 6 years and over are very limited as assessed by the GRADE process. However, based on the newly available PK/PD and safety data, the overall anticipated benefits of the inclusion of delamanid in a longer WHO-recommended MDR-TB regimen (see below) appear to outweigh the potential harms in that population. Therefore, considering the global MDR-TB crisis, the limited therapeutic options available for this life-threatening condition, the unsatisfactory treatment outcomes achieved using regimens composed solely of older medications, and the need to promote safe and rational use of TB medicines, WHO is revising the 2014 *interim policy guidance* for the use of delamanid in the treatment of MDR-TB in adults issued in October 2014 *(2)* to include this population:

**Delamanid may be added to the WHO-recommended longer regimen in children and adolescents (aged 6–17 years) with multidrug- or rifampicin-resistant TB (MDR/RR-TB) who are not eligible for the shorter MDR-TB regimen[a], under specific conditions** (*conditional recommendation; very low confidence in estimates of effect*): *(24)*

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[a] Frequently asked questions about the implementation of the new WHO recommendation on the use of the shorter MDR-TB regimen under programmatic conditions. Available at: http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regimen.pdf. Geneva, World Health Organization. 2016.

## Condition 1. Proper patient inclusion

The population to whom this recommendation applies is children and adolescents with RR-TB or MDR-TB aged 6–17 years who are not eligible for the WHO-recommended shorter MDR-TB regimen *(4)*. The population includes those patients who have previously received treatment with second-line anti-TB medicines, or who have isolates with additional resistance to fluoroquinolones or second-line injectable agents (including XDR-TB), or in whom components of the shorter MDR-TB regimen are contraindicated. The shorter MDR-TB regimen is also not recommended in pregnancy and extrapulmonary TB. Delamanid is thus only indicated as a component of longer regimens that have been individualized to increase a patient's likelihood of success.

The recommended dose of delamanid *in children (aged 6–11 years) is 50 mg twice a day (BID) for 6 months*, and *in adolescents (aged 12–17 years) it is 100 mg BID for 6 months*. Because bioavailability was found to be higher when given after a standard meal, delamanid should preferably be delivered after a meal. Given that TB regimens are generally administered once a day, any observation of treatment needs to be adapted to ensure supervision of the BID intake of delamanid in patients on this medication.

Because delamanid is shown to cause prolongation of the QT interval, children with a QTcF > 500 msec should not receive the drug.

Children and adolescent with MDR-TB/RR-TB in whom delamanid may have a particular role include those with the following:

- higher risk for poor outcomes (e.g. drug intolerance or contraindication, extensive or advanced disease);
- additional resistance to fluoroquinolones or injectable drugs; or
- XDR-TB (see **Condition 2.d** below for additional measures to apply when the drug is used in XDR-TB patients).

While patients with exclusively extrapulmonary disease were not included in the delamanid trials, there is no absolute contraindication for its use in such patients, and inclusion may be considered where any potential harms that delamanid may cause are offset by the benefits expected. However, the effectiveness of delamanid in the treatment of TB of the central nervous system is as yet unestablished. Of note, there are no data on the safety of delamanid in pregnancy; hence, this medication is not currently indicated in pregnant females.

## Condition 2. Adherence to the principles of designing a WHO-recommended longer MDR-TB regimen

Delamanid is indicated as an add-on agent to a longer MDR-TB regimen designed using a minimum of core second-line anti-TB drugs, as per the updated WHO treatment guidelines *(4)*. The cardinal rules governing the inclusion of delamanid in a MDR-TB regimen are as follows:

a. The WHO-recommended longer MDR-TB treatment regimen is composed of at least pyrazinamide and four core second-line drugs considered to be effective *(4)* (based on DST and/or previous use and/or drug resistance surveillance data): if the minimum number of five effective TB medicines cannot be composed as indicated, delamanid *may be added to bring the total to at least five*. The regimen may be further strengthened with high-dose isoniazid or ethambutol (or both).

b. The WHO-recommended longer MDR-TB treatment regimens usually last 20 months or more *(25)*. Delamanid is, however, only to be used for a maximum of 6 months, preferably at the start of the initial (intensive) phase.

c. *In view of the absence of evidence on its effectiveness and safety as part of, or in addition to, a shorter regimen for the treatment of MDR-TB, no recommendation on the use of delamanid in addition to or as part of the WHO-recommended 9–12 month shorter regimen can be made.*

d. MDR-TB patients with confirmed resistance or intolerance to either fluoroquinolones or the second-line injectable agents represent a particular treatment challenge. In such cases, delamanid may have a crucial role to play in strengthening a regimen, bringing the number of drugs likely to be effective to a minimum of five, and reducing the risk of acquisition of additional resistance and progression towards XDR-TB.

e. Although experience in the use of delamanid in the management of XDR-TB is limited, there may be a benefit given the limitations in designing an effective regimen. In such patients, delamanid may lower the need to include other drugs belonging to group D3,[a] which either have an unclear role in MDR-TB regimens or a higher harm-to-benefit potential. However, special caution is necessary when delamanid is used with a fluoroquinolone or other medicines with the potential for synergistic drug–drug interactions effects, particularly on QT prolongation.[b]

f. *There are currently no data on the simultaneous use of bedaquiline and delamanid in the same patient. Until such data become available, no recommendation on the joint administration of these two medicines is possible within the scope of this interim guidance. Moreover, bedaquiline is only recommended for use in adults.*

g. There is as yet no standardized drug-susceptibility testing (DST) method for delamanid, nor a commercially available test. DSTs for second-line drugs other than fluoroquinolones and injectable agents (kanamycin, amikacin and capreomycin) are not accurate or reproducible. Moreover, and MDR-TB patients may respond poorly to treatment for reasons other than drug resistance. A change in medication may, therefore, have to be based on persistence of positive sputum culture, or reversion to positive following initial culture conversion, rather than DST.

h. In line with general principles of TB therapeutics, delamanid should not be introduced into a regimen in which the other companion drugs are known or believed to be ineffective, or are failing to show effectiveness. This means that delamanid should not be added alone to a failing regimen. Given the risk of emergence of resistance to delamanid, all possible measures should be taken to protect the efficacy of the drug through rational use.

i. *Although studies are under way, there are so far no data on the use of delamanid in children aged under 6 years, so no recommendation can be made on the use of delamanid in that age group.*

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[a] WHO treatment guidelines for drug-resistant tuberculosis – 2016 update. Drug classification: Group A = levofloxacin, moxifloxacin, gatifloxacin; Group B = amikacin, capreomycin, kanamycin (streptomycin); Group C = ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine; Group D2 = pyrazinamide, ethambutol, high-dose isoniazid; Group D2 = bedaquiline, delamanid; Group D3 = *p*-aminosalicylic acid, imipenem-cilastatin, meropenem, amoxicillin-clavulanate (thioacetazone)

[b] A QTcF value of > 440 msec is considered prolonged. A value of > 480 msec (or an increase of > 60 msec from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTcF interval of > 500 msec is considered dangerous and an indication to stop QT-prolonging agents.

## Condition 3. Close monitoring of patients

Adherence to best practices when administering treatment is imperative to ensure optimal drug effectiveness and patient safety. It is therefore recommended that the following measures be in place:

a. Sound treatment and management protocols, including clear patient eligibility criteria, locally appropriate procedures for informed consent (see **Condition 5** below), and defined roles and responsibilities of all professionals involved. Measures to safeguard patients from avoidable harms are best addressed by observing the principles of active TB drug safety monitoring and management *(26)*.

b. National guidance on the implementation of MDR-TB/RR-TB treatment should allow for the prospective capture of key variables for both the effectiveness and safety of delamanid-containing regimens, ensuring that the good practices equivalent to those applied in the conduct of observational studies, are adhered to *(13)*.

c. Treatment guidelines are preferably submitted to and approved by the relevant national ethics authority in the country before patient enrolment on treatment.

d. Preferably, oversight of treatment programmes is provided by an independent group of experts in clinical management and public health (e.g. a national MDR-TB advisory group).

e. The potential for emergence of delamanid resistance during the course of therapy requires that all measures to enable the patient's adherence are in place before starting treatment.

## Condition 4. Active TB drug safety monitoring and management

Alongside the measures in **Condition 3** above, in order to monitor treatment adherence and effectiveness, special vigilance is needed for adverse events, including potential reactions to delamanid that are as yet undescribed.

a. Given that the results of Phase III trials are not yet available, it is particularly important that the introduction of delamanid be accompanied by enhanced monitoring for adverse events. For this purpose, spontaneous reporting is insufficient; instead, active TB drug safety monitoring and management is needed to improve the early detection of adverse drug events.

b. Any adverse drug reaction attributed to delamanid should be reported to the national pharmacovigilance centre. As with any other drug in an MDR-TB regimen, the patient should be encouraged to report to the attending health worker any adverse event that occurs during the time the drug is being taken. Such occurrence should also trigger a rapid response to manage these untoward effects in the patient.

c. Delamanid may interact with other medications administered concurrently, with synergistic or antagonistic action resulting in additive or lowered effects. Other second-line drugs that are likely to be administered with delamanid, notably fluoroquinolones or clofazimine, may increase the risk of cardiotoxicity. Although there are data showing QT prolongation when delamanid is administered simultaneously with levofloxacin, no data are available on concomitant use with moxifloxacin or clofazimine (or both). Also, some antiretroviral medications can cause modest QT prolongation, especially ritonavir-containing regimens. Therefore, it is imperative to monitor patients for cardiac dysrhythmias or QT prolongation

(using ECG), and for electrolyte imbalances (especially serum potassium) that can predispose to cardiotoxicity.[a]

    **d.** Drug–drug interaction studies of delamanid with tenofovir, efavirenz and lopinavir/ritonavir, conducted among healthy individuals who did not have HIV or TB, suggested that no dose adjustments were needed when delamanid was used with any of these antiretroviral agents. However, there is no published evidence so far on the use of delamanid in HIV-infected MDR-TB children on ART. Therefore, people living with HIV who will be receiving delamanid as part of MDR-TB treatment should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

    **e.** Lastly, caution is advised in patients with pre-existing health conditions that may be exacerbated or worsened by delamanid. Currently, there are no data on the efficacy and safety of delamanid in patients with comorbid conditions such as diabetes, liver or renal dysfunction, malignancies, and alcohol and substance use; therefore, careful screening for these conditions before treatment initiation is advised. Hypersensitivity reactions to delamanid have not yet been described, but vigilance is nevertheless required.

## Condition 5. Informed decision-making process ensured

Health-care workers should follow due process for informed consent by ensuring that the parent or legal guardian is aware of the novel nature of delamanid; appreciates why is it proposed that the drug be included in their treatment regimen; and recognizes the possible benefits and potential harms, including the uncertainties that surround outcomes. This informed consent process applies to all situations where delamanid is employed, including under CU programmes, and follows the rules and conditions for MDR-TB treatment as stipulated.

Parental or legal guardian permission as well as child or adolescent assent to receive the delamanid should be at the discretion of national TB control programmes. National authorities must ensure adequate protection for minors, including parental permission and assent of able children, assurance of direct benefit for the child and minimization of any risks.

# 7.   Implementation considerations

- Key stakeholders, especially end-users and policy-makers, must consider that the design of these paediatric studies was highly optimized as a means to maximize drug exposure in the selected sample of patients, as well as to enhance drug absorption. Data seen in adults have provided information on the effect of meals with a high fat content, which is more pronounced than the effect of standard low-fat meals on delamanid bioavailability. Therefore, dietary fat intake can alter bioavailability of delamanid. The implications for health-care settings in terms of drug introduction and service delivery relate to requirements to evaluate nutritional status in all children, especially those at risk, and to provide sustainable food support for children who have a low body weight and those with limited access to food.

- With regard to special populations, such as people living with HIV, implementers are to exercise caution. Although drug–drug interactions between ART and delamanid have been studied in healthy volunteers, studies suggest that the CYP3A4 inhibitor lopinavir/ritonavir increases delamanid total body exposure by, on average, 22% (geometric mean ratio: 1.22 [90%

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[a] It is imperative that ECG is used to monitor the QT interval regularly during delamanid use. QT interval monitoring should preferably be done using ECG machines that directly report the QTc interval. A value of $> 440$ msec is considered prolonged. A value of $> 480$ msec (or an increase of $> 60$ msec from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTc interval of $> 500$ msec is considered dangerous and should lead to stopping of the intake of the responsible QT prolonging drug(s).

confidence interval: 1.06–1.40]) *(27)*. In the currently reviewed studies, children infected with HIV were excluded. Thus, special attention must be given to this subgroup. Potential drug–drug interaction with specific antiretroviral drugs in paediatric populations is to be further investigated.

▪ The risk of emergence of resistance to delamanid should be a key consideration when the drug is being used, and appropriate DST should be conducted, when available.

# 8. Updates and further research

The recommendation on the use of delamanid in people aged 6–17 years with MDR-TB/RR-TB is valid for a maximum of 2 years unless additional data become available earlier that would prompt a revision of the guidance.

While the results of the ongoing Phase III trial investigating the use of delamanid in adults with MDR-TB are eagerly awaited, further research on the use of delamanid in children and adolescents will still be needed, including:

▪ PK, safety and efficacy studies in specific subpopulations such as children aged under 6 years, paediatric cases with HIV coinfection (especially those on ART) in order to confirm drug–drug interactions; once daily dosing; adjustment of doses, applying optimal designs in clinical dose finding studies (e.g. dose–response models);
▪ substitution of a second-line injectable agent with delamanid within the MDR-TB regimen;
▪ appropriate child-friendly formulations of medicines (i.e. age-adapted dosage forms and taste masking); and
▪ further research on the potential cardiotoxicity of the drug and its effect on QT prolongation, and its clinical significance, is also advisable.

*This WHO interim policy recommendation is valid for a maximum of 2 years, unless additional PK/PD and safety data become available sooner – particularly data relating to children aged under 6 years – that would prompt a revision of the guidance.*

## Table 5. Quality assessment, the GRADE evidence profile summary

| Author(s): | WHO GDG on Delamanid for MDR-TB | Date: | | 29 June 2016 |
|---|---|---|---|---|
| Question: | In children with MDR-TB aged six years and above, does the addition of delamanid to a WHO-recommended second-line drug therapy improve efficacy of treatment without increasing safety concerns? | | | |
| Settings: | Blinded, placebo-controlled trial (204) for two months, followed by an open observational trial (208) for six (6) months with reassignment of patients | | | |
| Bibliography: | Data extrapolated from adults to children (trial 242-07-204; trial 242-07-208; and obs. study 242-10-116). Confidential raw data supplied by Otsuka on trials 242-12-232 and 242-12-233. | | | |

| | Quality assessment | | | | | Summary of findings | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Patients (*n*) | | Effect | | | |
| № studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Delamanid plus OBR | OBR alone | Relative (95% CI) | Absolute (95% CI) | Quality | Importance |
| **Sputum culture conversion at 2 months as surrogate for cure (assessed with Solid culture - MITT population)** | | | | | | | | | | | |
| 1 | Randomised trials | Serious | Not serious | Serious | Serious | 64/119 (53.8%) | 38/113 (33.6%) | **RR 1.60** (1.18 to 2.18) | **202 more per 1,000** (from 61 more to 397 more) | ⊕□□□ Very low | Critical |
| **Sputum culture conversion at 2 months as a surrogate for cure (assessed with: MGIT liquid culture system - MITT population)** | | | | | | | | | | | |
| 1 | Randomised trials | Serious | Not serious | Serious | Serious | 64/141 (45.4%) | 37/125 (29.6%) | **RR 1.53** (1.10 to 2.12) | **157 more per 1,000** (from 30 more to 332 more) | ⊕□□□ Very low | Critical |
| **Time to culture conversion at 2 months as surrogate for cure (assessed with: MGIT liquid culture system - MITT population)** | | | | | | | | | | | |
| 1 | Randomised trials | Serious | Not serious | Serious | Serious | 49/119 (41.2%) | 27/113 (23.9%) | **HR 0.58** (0.39 to 0.89) | **92 fewer per 1,000** (from 23 fewer to 138 fewer) | ⊕□□□ Very low | Critical |
| **Sustained SCC at 24 months (after treatment for full 8 months) (assessed with: solid culture)** | | | | | | | | | | | |
| 1 | Observational studies | Serious | Not serious | Serious | Serious | 89/95 (93.7%) | 37/48 (77.1%) | **RR 1.22** (1.09 to 1.27) | **170 more per 1,000** (from 69 more to 208 more) | ⊕□□□ Very low | Critical |
| **Cure at 24 months (assessed with: Solid culture, clinical)** | | | | | | | | | | | |
| 1 | Observational studies | Serious | Not serious | Serious | Serious | 77/126 (61.1%) | 33/73 (45.2%) | **RR 1.35** (1.03 to 1.63) | **158 more per 1,000** (from 14 more to 285 more) | ⊕□□□ Very low | Critical |

**Table 5. Quality assessment, the GRADE evidence profile summary (*cont*)**

| № studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Delamanid plus OBR | OBR alone | Relative (95% CI) | Absolute (95% CI) | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **Quality assessment** | | | **Patients (*n*)** | | **Effect** | | | |
| **Mortality at 24 months** | | | | | | | | | | | |
| 1 | Observational studies | Serious | Not serious | Serious | Serious | 1/126 (0.8%) | 6/73 (8.2%) | **RR 0.10** | **74 fewer per 1,000** | ⊕◯◯◯ | Critical |
| | | | | | | | | (0.01 to 0.77) | (from 19 fewer to 81 fewer) | Very low | |
| **Serious Adverse Events (assessed with: clinical and laboratory measurements over 2 months in T204 - Safety population)** | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | Very serious | Serious | 16/161 (9.9%) | 14/160 (8.8%) | **RR 1.23** | **20 more per 1,000** | ⊕◯◯◯ | Critical |
| | | | | | | | | (0.61 to 2.33) | (from 34 fewer to 116 more) | Very low | |
| **Electrocardiogram QT prolongation (assessed with: ECG over 2 months in T204 - Safety population)** [*] | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | <u>Serious</u> | <u>Serious</u> | 16/161 (9.9%) | 6/160 (3.8%) | **RR 2.65** | **62 more per 1,000** | ⊕◯◯◯ | Critical |
| | | | | | | | | (1.08 to 5.99) | (from 3 more to 187 more) | Very low* | |
| **Electrocardiogram QT prolongation by more than 60 msec (assessed with: ECG over 2 months in T204 - Safety population)** [*] | | | | | | | | | | | |
| 1 | Randomised trials | Not serious | Not serious | <u>Serious</u> | <u>Serious</u> | 12/161 (7.5%) | 0/160 (0.0%) | **OR 12.81** | **0 fewer per 1,000** | ⊕◯◯◯ | Critical |
| | | | | | | | | (1.65 to 99.70) | (from 0 fewer to 0 fewer) | Very low* | |
| **Acquired resistance to delamanid (follow-up range 24 weeks) (assessed with: MGIT culture system (Trial 208 baseline) and solid media (Trial 208 follow-on))** | | | | | | | | | | | |
| 1 | Observational studies | Serious | Not serious | Serious | Serious | | | Not estimable | Not estimable | ⊕◯◯◯ | Critical |
| | | | | | | | | | | Very low | |

* The above table has been adopted and adapted from the GRADE table for evidence in adults to incorporate changes made to the GRADE evidence profile during the 2016 data assessment. Similarly to data in adults, indirectness and imprecision were considered to be *serious* for data on electrocardiogram QT prolongation that has been subsequently downgraded to *very low*.

## Table 6. The GRADE Evidence to decision framework

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| **PROBLEM**<br><br>**Is the problem a priority?**<br>○ No<br>○ Probably no<br>○ Uncertain<br>○ Probably yes<br>● Yes<br>○ Varies | The emergence of drug-resistant tuberculosis is a major threat to global tuberculosis care and control. WHO estimates that about 480,000 new multidrug-resistant tuberculosis (MDR-TB) cases occurred in the world in 2014. Of these, only 123,000 were reported to WHO, largely as a result of critical gaps in diagnostic and treatment capacity in most countries. Furthermore, 105 countries have now reported at least one case of extensively drug-resistant tuberculosis (XDR-TB) (Global Report 2015). Current treatment regimens for drug-resistant TB are far from satisfactory. Whereas most drug-susceptible TB patients can usually be cured with a 6-month course of treatment, in most MDR-TB cases a treatment duration of 20 months or more is used, requiring the daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB. Among MDR-TB patients started on treatment globally in 2014, only half of MDR-TB reported cases were treated successfully, as a result of high frequency of death (16%), treatment failure (10%) and loss to follow-up (16%). | The expert group considered children, people living with HIV and pregnant and breastfeeding women as subgroups.<br><br>*2016 Update*<br>The expert group considered the expansion of the interim guidance for children aged 6 years and above. Data for children were obtained through two preclinical studies:<br>Trial 232: Phase 1, Open-label, multiple-dose, age de-escalation trial to assess the pharmacokinetics, safety, and tolerability of delamanid (OPC 67683) in paediatric multidrug-resistant tuberculosis patients on therapy with an optimised background regimen of anti-TB drugs.<br>Trial 233: Phase 2, Open-label, multiple-dose trial to assess the safety, tolerability, pharmacokinetics, and efficacy of delamanid (OPC 67683) in paediatric multidrug-resistant tuberculosis patients on therapy with an optimised background regimen of anti-tuberculosis drugs over a 6-month treatment period. |

**BENEFITS & HARMS OF THE OPTIONS**

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| **What is the overall certainty of this evidence?**<br>○ No included studies<br>● Very low<br>○ Low<br>○ Moderate<br>○ High<br><br>**Is there important uncertainty about how much people value the main outcomes?**<br>○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability<br>○ No known undesirable outcomes | (see table below) | Treatment success (cure), serious adverse events and mortality were considered most critical to patients while time to culture conversion, culture conversion and resistance were somewhat less important. The expert panel assumed that there is minimal variation for values related to death, larger variation for other outcomes. There is larger variation about how much value patients would place on the side effects (e.g. QT prolongation). It is to note that QT prolongation was possibly associated with hypokalemia. Although the indication for delamanid use is for 6 months, the review of the data indicated that those patients who received 6 months of delamanid did so in various combinations of doses and after an initial period of at least 2 months of OBR alone. The patients who received delamanid from the very start of treatment did receive it either for 2 or 2+6 months depending on their contribution to trials. For this reason, the experts decided to consider only the patients who received a full course of 2+6 months delamanid from start of treatment. Of note, all those patients experienced a gap in allocation of delamanid in-between the 2 trials of at least 28 days duration.<br><br>In view of the shortcomings of the analyses of long-term efficacy performed by the manufacturer and submitted to WHO, the EG performed a re-analysis of the data (i) considering patients receiving delamanid from the start of treatment only (as a clearer proxy of the manufacturer's recommendation for delamanid use of six months), and (ii) using a stricter definition of the control group (restricted to patients who did not receive any delamanid - i.e. placebo only on top of OBR). Due to the uneven distribution of defaulters in the respective arms, the EG conducted a sensitivity analysis, including and excluding patients who defaulted from treatment. The measured effects for cure were in the same direction irrespective of whether defaulters were included or excluded, and in the same direction as in the manufacturer's analysis. However, when the analysis was restricted to exclude defaulters (n=183), the relative risk of treatment success was smaller and did not reach statistical significance (RR: 1.25; 95% CI: 0.96–1.65). The odds ratio of male to female QTc prolongation (greater 60 msec) is: 0.33 (95% 0.15 to 0.62) - based on RCT 204  QTc prolongation is considered more common in women in general. No specific data indicating a higher risk of QT prolongation in women related to delamanid was provided. |

| Outcome | Relative importance | Certainty of the evidence (GRADE) |
|---|---|---|
| Cure at 24 months (assessed with: Solid culture) | Critical | ⊕○○○ VERY LOW |
| Serious Adverse Events | Critical | ⊕○○○ VERY LOW |
| Mortality at 24 months | Critical | ⊕○○○ VERY LOW |
| Sputum culture conversion at 2 months as surrogate for cure (assessed with Solid culture - MITT population) | Critical | ⊕○○○ VERY LOW |
| Sputum culture conversion at 2 months as a surrogate for cure (assessed with: MGIT liquid culture system - MITT population) | Critical | ⊕○○○ VERY LOW |
| Time to culture conversion at 2 months as surrogate for cure (assessed with: MGIT liquid culture system - MITT population) | Critical | ⊕○○○ VERY LOW |
| Cure at 24 months (after treatment for full 8 months) (assessed with: solid culture) | Critical | ⊕○○○ VERY LOW |
| Electrocardiogram QT prolongation | Critical | ⊕○○○ VERY LOW |
| Acquired resistance to delamanid (follow-up range 24 weeks) | Critical | ⊕○○○ VERY LOW |

# Table 6. The GRADE Evidence to decision framework (*cont*)

| JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|
| **BENEFITS & HARMS OF THE OPTIONS**<br><br>**Are the undesirable anticipated effects small?**<br>○ No<br>○ Probably no<br>○ Uncertain<br>○ Probably yes<br>○ Yes<br>● Varies<br><br>**Are the desirable effects large relative to undesirable effects?**<br>○ No<br>○ Probably no<br>○ Uncertain<br>○ Probably yes<br>● Yes<br>○ Varies | <br><br>Note: Certainty in the evidence is graded from "Moderate" to "Low" for QT prolongation. | Inconsistencies between published and submitted data have been noted, for example in the number of deaths. Data presented here are those submitted by the manufacturer or those of published data as noted.<br><br>*2016 Update*<br>For subgroup of children aged 6-17 years: the expert group expressed concern on directness for safety (but not for efficacy).<br>Extrapolation limited by low sample size in the observed studies.<br><br>• The evaluation of drug in adults is based on microbiology. In children this becomes very difficult because of the natural history of disease and specifics of physiopathology in this population. Microbiological endpoints are very difficult to generate and follow. When looking at first-line TB drugs, good correlation was observed between concentration of the drugs in children and in adults and associated treatment success in adults.<br>• Efficacy trials in children would take a very long time to enrol patients, follow them up and find adequate microbiological endpoints. In that sense, it is appropriate to rely on PK values (in adults) that are associated with efficacy and apply these to children. No concern about the level of extrapolation or indirectness.<br>• Concerns were expressed on safety. The younger the child, the more likely it is to find unexpected toxicities in this population. The PK data seen - and its association with efficacy - show very wide range of drug concentrations, and the dose-exposure relation showed that children were at the highest range. Looking at these data, with the high concentrations children were exposed to and the uncertainty about toxicity, the experts considered that dosing would have to be adapted so as to decrease drug concentration in children.<br>• For efficacy data, there is less concern about extrapolation from adult data. For safety, there are concerns due to the nature of disease in this population.<br>   ○ Directness is not a problem for efficacy outcomes, but is of concern for safety, especially regarding SAEs.<br>   ○ If want to be conservative, dosages should be decreased<br>*Certainty in the quality of evidence:* Very low<br><br>**QT aspects:** Current data might address concerns about QT prolongation, but it does not address unstudied toxicities.<br>• The extrapolation is limited due to the imprecision of the data (very small sample size – few observations). Adult data cannot be extrapolated to predict the toxic effects of drugs in children and infants for a variety of reasons; including the fact that drug metabolism may involve different pathways.<br>Certainty in the quality of the evidence in adults was MODERATE. The experts downgraded it to VERY LOW in children, due to indirectness and imprecision. |
| **RESOURCE USE**<br><br>**Are the resources required small?**<br>○ No<br>○ Probably no<br>○ Uncertain<br>○ Probably yes<br>● Yes<br>○ Varies | Using a conservative approach, and based on limited evidence (and therefore likely to be uncertain), delamanid is found to be cost-effective in most settings. The two main exceptions are in settings with a very high current cure/treatment success rate, where defaults rates are high; and low income settings, where uncertainty about outcomes impacts cost-effectiveness. In these settings further work needs to be done to evaluate cost-effectiveness, in particular examining any impact on transmission, and improving the assessment of uncertainty.<br>Of note, the application of different trial results impacts cost-effectiveness, and may in some cases double the incremental cost-effectiveness ratio. In all cases, further country based work, placing delamanid in a broader framework of investment prioritisation including considerations on equity and budget impact would be recommended from an economic perspective before country adoption. | The expert panel took the perspective of a TB programme (costs) and focused on direct benefits to patients.<br>Indirect transmission benefits were NOT considered.<br>The analysis excludes any broader economic benefits (productivity) to patients and society beyond health benefits. One of the key considerations is that defaulters are accounted for and there is an assumption that 80% die when defaulted.<br>The analysis is based on drug cost parameters provided by the manufacturer for the cost effectiveness analysis. |

**Table 6. The GRADE Evidence to decision framework (*cont*)**

| | JUDGEMENT | RESEARCH EVIDENCE | ADDITIONAL CONSIDERATIONS |
|---|---|---|---|
| **RESOURCE USE** | **Is the incremental cost small relative to the net benefits?** ○ No<br>○ Probably no<br>○ Uncertain<br>○ Probably yes<br>○ Yes<br>● Varies | Using a simple model, conservative approach, based on limited evidence (and therefore likely to be uncertain), delamanid in addition to the WHO-recommended baseline regimen is found to be cost-effective in most settings. The two main exceptions are in settings with a very high current cure/treatment success rate, where defaults rates are high; and low income settings, where uncertainty about outcomes impacts cost-effectiveness. Results of modelling in various country settings show that the application of different trial results do not move the ICER above the willingness to pay thresholds in any of these but one (Nepal). However they do make a 2-3 fold difference in the ICER.<br><br>Of note, the application of different trial results impacts cost-effectiveness, and may in some cases double the incremental cost-effectiveness ratio. In all cases, further country based work, placing delamanid in a broader framework of investment prioritisation including considerations on equity and budget impact would be recommended from an economic perspective before country adoption.<br><br>Further work is also required to fully take into account transmission and patient cost consequences and to understand the efficacy of delamanid in settings where the OBR already achieves high cure/treatment success rates.<br>Further work is required also in low income settings to fully take into account transmission and patient cost consequences. | Willingness to pay (WTP) thresholds (one GNI per capita) and DALYs were used.<br>There are many sources of uncertainty: parameters (costs, prices, efficacy, long term outcomes)<br>Mortality differences are based on assumptions in the original trial (204) and this is the key driving factor for cost-effectiveness - based on assumptions including that it is based on the modified Intention to treat analysis. There is likely imprecision in the cost effectiveness estimates because of the imprecision of the mortality estimates. It is also based on the assumption that 80% of defaulters are dying. ICER increased up to threefold in sensitivity analyses but cost effectiveness is maintained based on WTP thresholds.<br><br>*2016 Update*<br>Cost-effectiveness evidence was not presented during this GDG meeting. However, given the public-private partnership between the drug manufacturer (Otsuka) and the Stop TB Partnership's Global Drug Facility (GDF), countries will be able to access delamanid the GDF. Delamanid will be supplied for Global Fund eligible countries at a price of US$ 1700 for each full-course treatment of six months' duration. |
| **EQUITY** | **What would be the impact on health equity?**<br>○ Increased<br>○ Probably increased<br>● Uncertain<br>○ Probably reduced<br>○ Reduced<br>○ Varies | No research evidence was searched for. | Direction or impact on inequity is uncertain based on present knowledge about resource requirements (of delamanid) and additional resource requirements (to a program to use delamanid).<br><br>Implementation of any new intervention may be associated with trade-offs in the absence of additional resource mobilization. |
| **ACCEPTABILITY** | **Is the intervention acceptable to key stakeholders?**<br>○ No<br>○ Probably no<br>○ Uncertain<br>● Probably yes<br>○ Yes<br>○ Varies | No research evidence was searched for. | The recommendation below refers to using delamanid as part of the recommended WHO regimen. Treatment should be acceptable given effects on benefits, tolerability and harms.<br><br>BID dosing may affect acceptability, including DOT. |
| **FEASIBILITY** | **Is the intervention feasible to implement?**<br>○ No<br>○ Probably no<br>○ Don't know<br>● Probably yes<br>○ Yes<br>○ Varies | No research evidence was searched for. | Requirements for ECG may reduce feasibility although cost effectiveness is present and given that resource estimates in the CEA included this requirement for ECG monitoring. Availability of ECG machines is not given in all settings - may require referral to specialist or extension of ECG access and mobilizing resources to monitor ECG.<br><br>BID dosing may also affect feasibility, including DOT. Oral (in comparison to injectable medication) use may facilitate use.<br><br>Careful monitoring of 'early adopters' would be required to ensure that cost-effectiveness can be achieved in 'real world' settings. |

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**Annex 1:** List of participants

# Guideline Development Group (GDG) meeting to update the WHO policy guidance on the use of delamanid in children

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5. **Dr Ernesto Jaramillo**, GTB/LDR
6. **Dr Karin Weyer,** GTB/LDR
7. **Matteo Zignol**, GTB/TME

| Declaration of interest |
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| **Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents**<br>**None declared** |

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| Holger Schünemann (Chairman) | Mauricio Lima-Barreto |
| Martien Borgdoff | Anna Mandalakas |
| Lucy Chesire | Beatrice Mutayoba |
| Geraint Davies | Payam Nahid |
| Poonam Dhavan | Viet Nhung  Nguyen |
| Peter Donald | Carlos Torres-Duque |
| Christopher Kuaban | Carrie Tudor |
| Miranda Langendam | Rohit Sarin |

| Declaration of interest |
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| **Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents**<br>**Declared: Insignificant** |

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| Daniela Maria Cirillo | (1b) Participation in expert writing group […] establishing recommendations on the use of delamanid and bedaquiline in Italy. €1000 sponsored by pharmaceutical company.<br><br>(2a) Her laboratory was involved in the standardization of the agar and microtitre-based DST for bedaquiline in 2014. €1000 sponsored by Janssen Italy.<br><br>COI Management: Recommendations were in line with the WHO policy. The focus was not only on the selection of cases, but on who should be prescribing the drugs, where the DST was going to be performed and on data collection. |

| Declaration of interest |
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| **Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents** <br> <u>Declared: Significant</u> |

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| Grania Brigden | MSF received a donation of 400 treatments of Delamanid (programmatic use) from Otsuka in Feb 2016. This was a one off donation and is not expected to be repeated with MSF now procuring delamanid directly from the GDF. <br><br> The MSF Access Campaign, for whom she works, did not directly receive the donation, but it is a department within MSF. Dr Brigden participated as a Technical Resource Person on the discussion regarding delamanid use in children and adolescents. |

| Declaration of interest |
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| **Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents** <br> <u>Declared: Significant</u> |

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| Alena Skrahina | (5b) […] held a position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work. <br><br> Participation in the development of «Rapid Clinical Advice – The use of delamanid and bedaquiline for children with drug-resistant tuberculosis». Document publically made available on 20 May 2016 via the TB Online Weekly Newsletter. <br><br> *COI Management:* Competing interests for development of any WHO GDG recommendations (present and future) on the use of bedaquiline and delamanid in children. Dr Skrahina participated as a Technical Resource Person during the discussion regarding delamanid use in children. |

| Declaration of interest |
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| **Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents** <br> **Declared: Significant – Technical Resource Person Status** |

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| Anneke Hesseling | (2a) Research support. NIH (DAIDS) would fund a multi-site phase I/II trial of bedaquiline in HIV infected and uninfected children with MDR-TB, through the IMPAACT network (P1108). <br><br> (2a) PI of two phase II, open-label, multiple-dose trials funded by Otsuka pharmaceuticals (Study 242-12-232 and Study 242-12-233). <br><br> *COI Management:* Prof Hesseling participated as a Technical Resource Person on the discussion regarding delamanid use in children and adolescents. |

| Declaration of interest |
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| **Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents** <br> **Declared: Significant – Technical Resource Person Status** |

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| Erica Lessem | (2a) Stop TB Partnership – Non-commercial support to track investments in TB R&D ($46,000) in 2015. <br><br> (2a) Bill & Melinda Gates Foundation – Non-commercial support to advocate for increased funding for TB R&D, research and access to evidence-based interventions ($2,937,759) from January 2014 to March 2017 <br><br> (2a) US Department of Veterans Affairs (on behalf od US CDC TB Trials Consortium) – Non-commercial support to manage the Community Research Advisors Group ($75,000), fiscal year 2015. <br><br> (2a) TB Alliance – Non-commercial support for work to tract resources invested in TB R&D and primarily paediatric TB R&D. <br><br> (2a) Janssen Pharmaceutical / Tibotec Therapeutics – General support to Treatment Action Group's Hepatitis C/HIV Programme (not for her work or the TB/HIV Project) Various funds (Total $108,000) from 2010 to 2015. <br><br> *COI Management:* Ms Lessem participated as a Technical Resource Person on the discussion regarding delamanid use in children and adolescents. |

| Declaration of interest |
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| **Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents** <br><br> <u>**Declared: Significant – Technical Resource Person Status**</u> |

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| Fraser Wares | (1a) Employment – Technical input into the development of the WHO's interim policy guidance on bedaquiline in 2013 and provisional technical assistance to India in the development of their bedaquiline implementation plan. <br><br> (6b) KNCV role in the USAID bedaquiline donation programme through Challenge-TB. <br><br> *COI Management:* Dr Wares participated as a Technical Resource Person on the discussion regarding delamanid use in children and adolescents. |

# Guideline Development Group (GDG) meeting to develop recommendations for the use of delamanid in children and adolescents

UNAIDS Building, D-46025 (HTM65), Geneva, Switzerland
29 June 2016

| Interim recommendations for use of delamanid in children and adolescents | | |
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| 13:30 – 14:00 | Objectives of the meeting and presentation of participants & DOI | Christian Lienhardt |
| 14:00 – 14:20 | Recap on WHO interim guidance on delamanid | Christian Lienhardt |
| 14:20 – 14:50 | Review of pediatric PK/PD and safety data in children aged 6 – 17 years. | Susan M. Abdel-Rahman |
| 14:50 – 15:30 | Discussion | All |
| *Coffee break* | | |
| 15:45 – 17:00 | Establish draft recommendations based on quality of the evidence, balance between desirable and undesirable effects, resources, feasibility, values and preferences. | All |
| 17:00 – 17:30 | Final recommendations, next steps, implementation and conclusion on interim guidance review process | Holger Schünemann |
| 17:30 – 17:45 | Conclusions and closing | Mario Raviglione |