The use of delamanid in the treatment of multidrug-resistant tuberculosis

Interim policy guidance

World Health Organization

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Abbreviations

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BD	twice daily
CEA	cost effectiveness analysis
CEM	cohort event monitoring
CI	confidence interval
CHMP	Committee for Medicinal Products for Human Use
DDI	drug drug interaction
DoI	declaration of interests
DOT	directly observed treatment
DOTS	basic package that underpins the WHO Stop TB Strategy
DST	drug-susceptibility testing
ECG	electrocardiogram
EG	Expert Group
ERP	External Review Panel
EMA	European Medicines Agency
GTB	WHO Global TB Programme
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRC	Guidelines Review Committee
HIV	human immunodeficiency virus
ITT	intention to treat
MDR-TB	multidrug-resistant tuberculosis
MIC	minimal inhibitory concentration
MGIT	mycobacteria growth indicator tube liquid culture system
MITT	modified intention to treat
NTP	national tuberculosis programme
OBR	optimized background regimen
PICO	population, intervention, comparator, outcome
PLHIV	people living with HIV
PMDT	programmatic management of drug-resistant tuberculosis

QT	the interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram
QTcF	QT interval corrected for heart rate according to the Fridericia method
RCT	randomized controlled trial
RR	relative risk
SAE	severe adverse event
SCC	sputum culture conversion
SRA	stringent regulatory authority
SSM	sputum-smear microscopy
TB	tuberculosis
TEAE	treatment-emergent adverse effects
USAID	United States Agency for International Development
XDR-TB	extensively-drug resistant tuberculosis
WHO	World Health Organization

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Declarations of interest

All Expert Group members, consultants, technical resource persons, members of the External Review Panel and STAG-TB members submitted completed Declaration of Interest (DoI) forms. These were reviewed by the WHO Legal Department prior to the Expert Group meeting and preparation of the draft interim policy guidance, in keeping with WHO rules.

Two Expert Group members (Daniela Cirillo, Erica Lessem) declared having received support from pharmaceutical companies for work not related to the present guideline; and Dalene van Delft declared receiving compassionate use access to bedaquiline – all of these declarations were deemed to be insignificant. Three members (Frank Cobelens, Michael L. Rich, Francis Varaine) declared current discussions with the company (Otsuka) on potential access to delamanid for future studies on roll-out of new drugs under programmatic conditions (FC, MR) or for future clinical trial of new regimens for MDR-TB Treatment (FV). These declarations were deemed to be significant for a possible conflict of interest, and experts were requested not to contribute to deliberations on the recommendations. The other members of the Expert Group as well as the consultants and the members of the Expert Review Panel declared no interest.

With respect to the STAG-TB review, Chuck Daley declared serving as chair of the data monitoring board for Otsuka delamanid trials, and Francis Varaine declared participation in discussions between MSF and Otsuka to receive supplies of Delamanid for use in clinical trials along with other drugs. These two declarations were deemed significant for a possible conflict of interest and these STAG members did not participate in external review. Frank Cobelens, as a member of STAG-TB, had a revised declaration of interest noting no current or future planned work with Otsuka; he participated in the external review.

Executive summary

Background

Drug resistance is a major threat to global tuberculosis (TB) care and control. WHO estimates that around 480,000 new multidrug-resistant tuberculosis (MDR-TB)[a] cases occured in 2013. Current treatment regimens for drug-resistant TB are complex, lengthy, toxic and expensive. Only about one half of MDR-TB patients started on treatment globally are reported to be treated successfully, largely due to a high frequency of death and loss to follow-up, commonly associated with adverse drug reactions and high costs of treatment. In addition, it is estimated that up to a third of MDR-TB cases may have strains with additional resistance to fluoroquinolones and/or injectable second-line drugs (aminoglycosides or capreomycin), rendering their treatment even more difficult, with recourse only to highly toxic drugs.

The landscape of drug development for treatment of TB has evolved over the past ten years and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB. Considering the global MDR-TB crisis, the limited therapeutic options available for this life-threatening condition, and the need to promote safe and responsible use of TB drugs, WHO convened an Expert Group in April 2014 to review the available evidence on the efficacy, safety and effectiveness of delamanid, a new drug for the treatment of MDR-TB, with the view to issue interim recommendations on its use in conjunction with WHO-recommended MDR-TB treatment.

Evidence assessment

Data on the pre-clinical and clinical development of the drug provided by the manufacturer, as well as publicly available data were reviewed to assess efficacy, safety and tolerability of the drug. In addition, modeling work to assess the potential cost-effectiveness of programmatic implementation was commissioned to an independent expert. The comprehensive review of these data was conducted according to the GRADE process for evidence assessment, as required by WHO.

a Multidrug-resistant tuberculosis: tuberculosis with resistance to, at least, isoniazid and rifampicin.

Data on delamanid efficacy and safety resulted from three studies:

- Trial 204: A phase 2, multicentre, double-blind, randomized, placebo-controlled clinical trial conducted in nine countries.[a] A total of 481 patients aged 18 to 64 were randomized to receive two months of treatment with either delamanid 100mg twice daily (BD) on top of an optimized background regimen (OBR), delamanid 200mg twice daily+OBR, or placebo+OBR;
- Trial 208:[a] An open-label extension of Trial 204 that allowed continued or first-time access to delamanid in combination with OBR for an additional six months for patients who completed Trial 204 and consented to participate. A total of 213 (44.2%) of the 481 patients from Trial 204 were enrolled in this study;
- Study 116:[b] An observational study which captured the long-term treatment outcomes for patients who participated in Trial 204 and Trial 208. 421 patients who initially participated in Trial 204 were included, and 390 completed the 24 months follow-up.

Summary of results

Short-term efficacy: Data for efficacy analysis was provided by the manufacturer for various time periods and from a variety of patient populations. The *primary efficacy endpoint* (short-term efficacy) was two-month sputum culture conversion (SCC) as derived from Trial 204. Efficacy analysis was based on a modified intention to treat (MITT) population (N=402/481 patients) and involved randomized patients who had a positive sputum culture for TB and drug-resistance to isoniazid and rifampicin confirmed phenotypically at baseline, using the mycobacteria growth indicator tube (MGIT) liquid culture system. A higher proportion of patients treated with delamanid 100mg BD (the dose recommended by the manufacturer)+OBR achieved SCC at two months (Day 57) than patients treated with placebo+OBR: 64/141 (45.4%) *vs.* 37/125 (29.6%); p=0.008. The hazard ratio for time to conversion to a negative sputum culture was 0.58 (95% CI: 0.39 to 0.89) in the delamanid-100mg BD group.

Long-term efficacy: Data for efficacy beyond the first two months of treatment was provided by the manufacturer through analysis of *combined data* using solid culture from Trial 204, Trial 208 and Study 116, grouping patients according to the total duration of delamanid received in the various trials, irrespective of the dose received (100mg BD or 200mg BD). By the end of treatment, 90.9% (130/143) of patients who received delamanid+OBR for six months or more (≥6 months) achieved sustained SCC compared to 70.9% (112/158) of patients who received delamanid+OBR for two months (≤2 months) or less.

a China, Egypt, Estonia, Japan, Latvia, Peru, the Philippines, Republic of Korea, and the United States of America.

b Trial 208 and Study 116 are extensions of Trial 204. They are referred to by the terminology used in the published references and as provided by the manufacturer; it should be noted that these are not different/separate studies, but involved non-randomized and selected patients from the original Trial 204.

The proportion of patients reported with a *favourable treatment outcome* at the end of the 24-month treatment period (i.e. confirmed microbiological cure on solid culture or treatment completion) was significantly higher in the ≥6 month group (74.5%, 95% CI: 67.7–80.5) than in the ≤2 month group (55.0%, 95% CI: 48.3–61.6) (p<0.0001). The reported mortality rate was lower in the ≥6 month treatment group (2 deaths, 1%) compared to the ≤2 month treatment group (19 deaths, 8.3%) (p<0.001).

Safety: Pooled data provided by the manufacturer from 12 phase I trials in healthy subjects showed that treatment-emergent adverse effects (TEAEs) with the highest incidence in persons who received delamanid were headache, nausea and dizziness.

A total of 887 individuals have been exposed to delamanid in all trials, of which 22.1% (196/887) had a cumulative exposure longer than 6 months. The only clinically relevant TEAE with a difference in incidence between the delamanid+OBR treatment groups compared to the placebo+OBR group was prolongation of QT interval. Other TEAEs varied in occurrence but were present in similar proportions in the delamanid+OBR and the placebo+OBR groups. Most frequent were nausea, vomiting, and dizziness.

A total of 74 patients in Trial 204 and Trial 208 reported severe adverse events (SAEs). QTc interval prolongation occurred more frequently in the delamanid 100mg BD+OBR group (4.3%; 7/161) and the delamanid 200mg BD+OBR group (5.6%; 9/160) than in the placebo+OBR group (1.9%; 3/160).

Drug-drug interaction studies in healthy subjects showed no clinically-significant interactions when delamanid was co-administered with tenofovir, efavirenz or lopinavir/ritonavir.

Expert Group findings and recommendations

The Expert Group felt strongly that the main data to consider for evaluation of delamanid efficacy were those collected in the randomized controlled Trial 204. They were not convinced that the prognostic surrogates for cure used (i.e. two months SCC and time to SCC) were adequate or accurate for MDR-TB. They also noted that the duration of comparison between delamanid and placebo in Trial 204 did not allow an assessment of the potential benefit of adding delamanid to OBR for six months without interruption (as recommended by the manufacturer).The Expert Group noted a number of problems in the design and conduct of Trial 208, including absence of randomization; self-selection of patients; absence of blinding for treatment allocation; variable gaps between the end of Trial 204 and the beginning of Trial 208; and lack of consistency in the allocation of drug dosages (leading to wide variations in the dose, timing and duration of exposure to the drug for various subgroups of patients). There was also concern about risk of serious bias for the data arising from the observational Study 116 due to variability in follow-up procedures in the various sites, as well as un-blinded assessment of outcome, and serious inconsistency due to the variability in duration of drug exposure. They also agreed that the post hoc analysis of efficacy at the

end of treatment (Study 116) performed by the manufacturer had little value for the evaluation of effect, since this was a retrospective analysis relying on non-standardized follow-up procedures and conditions, and on artificial grouping of patients with wide variability of drug exposure in terms of timing, duration and doses of treatment.

The Expert Group therefore requested re-analyses of data for the estimate of effect beyond the two-month SCC, considering (i) only patients included in Study 116 who received delamanid from the start of treatment in Trial 204 and continued to receive delamanid during Trial 208, as this was felt to be more consistent with the manufacturer's instruction to use delamanid for 6 months (in addition to OBR) from the start of treatment; and (ii) using as controls only those *patients who did **not** receive delamanid at all* in either trial. The revised analyses showed a 35% increase in cure (according to WHO definition) when delamanid was added to an OBR *vs.* OBR alone (RR 1.35; 95% CI 1.03 – 1.63).

Of note, 4/205 patients seemed to have developed *in vitro* resistance to delamanid during treatment, although no discernible reasons could be established.

Final conclusion on efficacy: The Expert Group concluded that data on short-term or long-term efficacy of delamanid added to an OBR for MDR-TB were of 'very low' quality, i.e. *the Expert Group had very low confidence in the estimate of effect of delamanid.*

Final conclusion on safety: The Expert Group noted that the risk of any adverse event in the delamanid treatment arms in Trial 204 was not significantly different than in the placebo arm. They noted, however, that prolongation of the QT interval was the most serious adverse event, with a significantly higher risk of QT prolongation relative to baseline in the delamanid treatment arms compared to the placebo arm. Safety risks for patients receiving at least six months of treatment with delamanid+OBR compared to OBR alone could not be assessed in Trial 208 due to the absence of proper controls. The Expert Group also noted that there was no information on the potential synergy of cardiotoxic effects if delamanid was used in combination with other drugs which also prolong the QT interval (such as moxifloxacin); therefore, the overall evidence for safety was graded as 'low', despite the clear difference in mortality observed when delamanid was added to an OBR.

Cost-effectiveness: The Expert Group assessed the results of a cost-effectiveness analysis (CEA) conducted to model the incremental cost-effectiveness of adding delamanid to existing WHO-recommended MDR-TB regimens. This CEA was undertaken for various settings to allow for variation among countries in income level, the model of care used for MDR-TB treatment, and background patterns of drug resistance. It focused on the direct benefits to patients, but did not attempt to assess the indirect (and acquired) transmission benefits, nor did it assess the broader economic benefits to patients or society. Since several analyses were conducted by the manufacturer to assess efficacy (see above), a sensitivity analysis was performed on the cost-effectiveness of delamanid applying the different trial data and respective assumptions. Using a

conservative approach, delamanid was found to be cost-effective in most settings, but the quality of this evidence was considered 'very low', and the Expert Group concluded that further work was needed to evaluate cost-effectiveness once the final price of the drug is made public by the manufacturer.

Overall, balancing the potential benefits and risks of adding delamanid to an optimised MDR-TB regimen, the Expert Group concluded that the anticipated benefits probably outweighed anticipated undesirable effects. Therefore, the Expert Group recommended that delamanid (100mg BD for 6 months) may be added to a WHO recommended regimen in MDR-TB adult patients under specific conditions *(conditional recommendation, very low confidence in estimates of effect*).

WHO interim policy recommendations

Available data on delamanid efficacy and safety is very limited as assessed by the GRADE process; however, the overall benefits of the inclusion of delamanid in a WHO-recommended MDR-TB regimen appear to outweigh the observed harms. Therefore, considering the global MDR-TB crisis, the limited therapeutic options available for this life-threatening condition, and the need to promote safe and responsible use of TB drugs, WHO is making the following **interim policy recommendation** for the use of delamanid in the 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 under the different conditions that may be expected in treatment programmes, 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:

1. Proper patient inclusion

The current recommendation for the use of delamanid applies to adults (≥18yrs) with pulmonary MDR-TB disease, including people living with HIV. Special caution and proper clinical judgment should be applied when delamanid is used in persons 65 years and older, or in those with diabetes, hepatic or severe renal impairment, or those who use alcohol or substances, given that data on efficacy and safety under such conditions are extremely limited or unavailable.

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.

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

When an effective and reasonably well-tolerated MDR-TB regimen can be composed with conventional second-line drugs, the routine addition of delamanid may not be warranted and the implications of additional health service costs should be considered. MDR-TB patients in whom delamanid may have a particular role include those with:

- higher risk for poor outcomes (eg. drug intolerance or contraindication, extensive or advanced disease);
- additional resistance to fluoroquinolones or injectable drugs;
- XDR-TB (see 3.b for additional measures to apply when the drug is used in XDR-TB patients).

While patients with exclusive 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 harm that delamanid may cause is offset by the benefit expected.

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; the cardinal rules governing the general composition and duration of MDR-TB regimens remain the same:

a. The WHO-recommended MDR-TB treatment regimen *(1)* is typically composed of at least pyrazinamide and four second-line drugs considered to be effective (based on drug susceptibility testing (DST) and/or previous use and/or drug resistance surveillance data): a fluoroquinolone (preferably later-generation), a second-line injectable agent, and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or *p*-aminosalicylic acid.

b. MDR-TB patients with confirmed resistance or intolerance to either fluoroquinolones or the second-line injectable drugs 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 four, and reducing the risk of acquisition of additional resistance and progression towards XDR-TB.

c. There is as yet no standardized DST method for delamanid, nor a commercially available test. DSTs for second-line drugs other than fluoroquinolones and injectables (kanamycin, amikacin, capreomycin) are not accurate or reproducible, 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.

d. While experience in the use of delamanid in the management of XDR-TB is very 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 5 which have unproven anti-tuberculosis activity or a lower safety profile. However, special caution is necessary when delamanid is used with a fluoroquinolone or a Group 5 drug given the potential for synergistic drug-drug interactions effects, particularly on QT prolongation.[a]

e. 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.

f. 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 emergence of resistance to delamanid observed in the available data, all possible measures should be taken to protect the efficacy of the drug.

g. The recommended dose of delamanid in adults is 100mg twice a day, irrespective of body-weight, for a period of six months. As bioavailability was higher when given after a standard meal, delamanid should preferably be delivered after a meal. There was no evidence that delamanid 200mg twice a day was more effective than the 100mg dose and the higher dose was associated with higher rates of adverse events including QT interval prolongation. It should be particularly noted that supervision of delamanid intake should be adapted to twice a day.

3. Treatment is closely monitored

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

a. Sound treatment and management protocols, including clear patient eligibility criteria, locally appropriate procedures for informed consent *(see 5)*, and defined roles and responsibilities of all professionals involved. Safety concerns are best addressed through active pharmacovigilance *(2)*.

   The treatment protocols should allow for the prospective capture of data on key variables for both effectiveness and safety, making sure that the good practices, such as those applied in the conduct of observational studies, are adhered to *(3,4)*.

a A QTcF value greater than 440ms is considered prolonged. A value greater than 480ms (or an increase of greater than 60ms from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTcF interval of more than 500ms is considered dangerous and stopping QT-prolonging drugs is indicated.

b. Treatment protocols are preferably submitted to, and approved by the relevant national ethics authority in the country prior to patient enrolment on treatment.

c. 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).

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

4. Active pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.

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

a. Given that the results of Phase III trials are expected in the next few years, it is particularly important that the introduction of delamanid is accompanied by an enhanced monitoring for adverse events. For this purpose, spontaneous reporting is not expected to represent an appropriate level of care and active pharmacovigilance techniques, such as 'cohort event monitoring' (CEM), will be needed to improve the early detection of adverse drug reactions. Details on the methodologies for mounting CEM, particularly when new drugs are introduced, have already been published by WHO *(2)*.

b. Any adverse drug reaction attributed to delamanid should be reported to the national pharmacovigilance centre. As for 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 occurrences should also trigger a rapid response to manage these untoward effects in the patient.

c. When introducing delamanid into a regimen, there is also the potential for its interaction with other medications administered concurrently, with additive or synergic adverse effects. Other second-line drugs that are likely to be administered with delamanid, notably fluoroquinolones and clofazimine, may potentially increase the risk of cardiotoxicity. Although there are data showing QT interval prolongation when delamanid is administered simultaneously with levofloxacin, no data are available on concomitant use with moxifloxacin and/or clofazimine. Also, some antiretroviral medications can cause modest QT prolongation, especially ritonavir-containing regimens. Therefore, monitoring of patients for cardiac dysrhythmias or QT interval prolongation (i.e. using

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

d. Drug-drug interaction studies of delamanid with tenofovir, efavirenz and lopinavir/ritonavir, respectively, 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 anti-retroviral agents. However, there is no published evidence so far on the use of delamanid in HIV-infected MDR-TB patients 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 co-morbid conditions such as diabetes, liver and/or renal dysfunction, malignancies, alcohol and substance use, and therefore careful screening for these conditions prior to treatment initiation is advised. Hypersensitivity reactions to delamanid have not yet been described, but vigilance is nevertheless required.

5. Patient informed consent obtained

Health care workers should follow a due process for informed consent by ensuring that the patient: i) is aware of the novel nature of delamanid; ii) appreciates the reason why the drug is being proposed to be included in their treatment regimen; and iii) 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 compassionate use programmes. In some settings, as per national or local policy, it is required that the informed consent is made in writing for enrolment on MDR-TB treatment.

Validity of the interim policy guidance

This interim recommendation is valid for a maximum of two years and will be updated should additional data become available.

a It is imperative that ECGs are 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 greater than 440 ms is considered prolonged. A value greater than 480 ms (or an increase of greater than 60 ms from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTc interval of more than 500 ms is considered dangerous and should lead to stopping of the intake of the responsible QT prolonging drug(s).

INTERIM POLICY GUIDANCE

THE USE OF DELAMANID IN THE TREATMENT OF MULTIDRUG RESISTANT TUBERCULOSIS

1. Background

The emergence of drug-resistant tuberculosis is a major threat to global tuberculosis care and control. WHO estimates that around 480,000 new multidrug-resistant tuberculosis (MDR-TB)[a] cases occurred in the world in 2013 *(5)*. Current treatment regimens for drug-resistant TB are far from satisfactory. Whereas most patients with drug-susceptible TB can usually be cured with a six-month course of treatment, in most MDR-TB cases a treatment length of 20 months or more is used, requiring the daily administration of drugs that are more toxic, more expensive and less effective than those used to treat drug-susceptible TB. Only about half of MDR-TB patients started on treatment globally are treated successfully, as a result of loss to follow-up (28%), commonly associated with adverse drug reactions and high costs associated with treatment, and high frequency of death (15%). In addition, it is estimated that up to a third of MDR-TB cases may have strains with additional resistance to fluoroquinolones and/or injectable second-line drugs (aminoglycosides or capreomycin), rendering their treatment even more difficult, with recourse only to highly toxic drugs. Finally, the global deployment of rapid diagnostics for drug resistance, such as the Xpert MTB/RIF assay, has increased the demand for treatment of MDR-TB patients, and this has not been matched by a similar expansion in the provision of appropriate treatment for diagnosed cases. The increased global scale-up of rapid tests to diagnose MDR-TB cases is bound to make this gap even wider in the coming years. The lack of effective and affordable drugs for the treatment of MDR-TB is a critical factor in the inability of programmes to scale-up their treatment efforts to meet national and global targets.

The landscape of drug development for treatment of TB has evolved dramatically over the last ten years, and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB. Dossiers have been submitted to stringent regulatory authorities (SRAs) under procedures of "accelerated" or "conditional" approval for marketing these new drugs. Among these, bedaquiline, a diarylquinoline, was approved by the US Food and Drug Administration (FDA) in December 2012, and WHO issued interim guidance for its use in the treatment of MDR-TB in June 2013*(6)*. Delamanid, a nitro-imidazole, another new compound, has been granted a conditional marketing authorisation by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) on the 28th April 2014 *(7)*. Dossiers are currently

a Multidrug-resistant tuberculosis: tuberculosis with resistance to, at least, isoniazid and rifampicin.

being submitted to several national regulatory authorities and are being evaluated under procedures of "accelerated" or "conditional" approval based on early (Phase IIb) clinical data, and Member States have expressed the need for WHO to provide interim advice on the use of delamanid in MDR-TB treatment.

Considering the global MDR-TB crisis, the limited therapeutic options available for this life-threatening condition, and the need to promote safe and responsible use of TB drugs, WHO has evaluated the added value of delamanid within the context of existing guidelines on programmatic management of MDR-TB. An Expert Group Meeting was convened in April 2014 in Geneva to review the available evidence on the efficacy, safety and effectiveness of this new drug for the treatment of MDR-TB, and to recommend whether WHO interim guidance on the use of this drug in treatment of MDR-TB is warranted. As in the case of bedaquiline *(6)*, it is acknowledged that issuing interim guidance carries the responsibility to ensure that this guidance provides specific recommendations on the conditions for the use of the drug that reflect the limited data currently available. WHO will review, revise or update the interim guidance as additional substantive data on efficacy and safety become available. Acceleration of Phase III trials and completion at the earliest opportunity is imperative, as is timely analysis of emerging operational data on the use of the drug. It should also be noted that, in the absence of interim guidance from WHO, uncontrolled and potentially irresponsible use of the new drug may adversely affect TB care and control efforts overall – with emergence of additional drug resistance and the possible loss of a new drug for TB chemotherapy.

2. Guideline purpose and target audience

2.1. Purpose

The aim of this guidance is to provide the interim principles that should guide the use of delamanid in conjunction with WHO-recommended MDR-TB treatment. It also specifies the essential treatment and management conditions for use of this drug, in particular the patient's eligibility criteria and safety conditions, and presents the necessary caveats relevant to the use of this new drug for which Phase III clinical trial data are not yet available.

The interim guidance positions delamanid in the context of existing guidelines on MDR-TB treatment, as the drug cannot be used on its own and should be added to MDR-TB regimens designed according to WHO-recommended principles. This document should therefore be read in conjunction with the most recent documents on the programmatic management of drug-resistant tuberculosis:

- *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update*. (GRC-approved) *(1)*; and
- *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (3).*

It should also be read in conjunction with the detailed findings from the Expert Group meeting and the delamanid implementation manual, part of the 'Companion handbook' referenced above.

The planned date of review of this interim guidance is 2016, or earlier in case of significant development. It is expected that data emerging from a currently on-going Phase III clinical trial of delamanid will inform future review and possible refinement of the interim policy guidance.

2.2 Target audience

The main target audience of this interim guidance is national TB programmes (NTP), other public health agencies, and other public and private partners involved in planning, implementing and monitoring tuberculosis control activities. The principles and recommendations are also relevant for specialist clinicians, technical advisors, laboratory technicians, drug procurement managers, other service providers, other relevant government officials, and implementing partners involved in country-level strengthening of drug-resistant TB care and control. Individuals responsible for programme planning, budgeting, resource mobilization, and training activities for drug-resistant TB diagnostic services may also benefit from using this document.

3. Guideline development process

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

3.1 Expert Group meeting

An Expert Group (EG) was convened in Geneva by the Global TB Programme of the World Health Organization (WHO) on 15–16 April 2014 to assess available data on delamanid with a view towards developing interim policy recommendations on its use, if deemed appropriate. The EG (**Annex 2**) consisted of researchers, epidemiologists, end-users (clinicians and national TB and drug-resistant TB programme managers), community representatives and evidence synthesis experts. The meeting followed a structured agenda (**Annex 3**) and was chaired by a clinical epidemiologist/methodologist with extensive experience in evidence synthesis and guideline development.

The aim of this meeting was to evaluate the added benefit of delamanid for the treatment of MDR-TB and, if appropriate, provide recommendations to WHO for interim guidance to countries on its use in conjunction with WHO-recommended MDR-TB treatment regimens.

The *specific objectives* were:

- To evaluate the efficacy and safety of delamanid when given together with current WHO recommended MDR-TB treatment;
- To evaluate the balance between harms and benefits of the drug, its potential cost-effectiveness, patient and provider preferences and concerns, and the feasibility of introducing the drug in MDR-TB programmes; and
- To provide, as appropriate, recommendations on the use of the drug as part of WHO-recommended MDR-TB treatment regimens, including attention to concerns/constraints relevant to the use of a new drug for which Phase III clinical trial data are not yet available.

3.2 Management of conflicts of interest

WHO policies on conflicts of interest were applied in consultation with the WHO Legal Department. All EG members were asked to complete the WHO Declaration of Interest (DoI) form before their invitation was confirmed and data shared with them under non-disclosure agreements. All forms were reviewed by the WHO Guideline

Steering Group in conjunction with the WHO Legal Department prior to the EG meeting. Attention was given to potential conflicts of interest related to the appraisal of evidence, the formulation of recommendations and the external peer review process. Particular attention was also given to assessment of financial as well as intellectual DoIs. In addition, individuals were not considered for inclusion in the Expert Group if they had been involved in clinical trials conducted by the company, or in any entity or committee related to the conduct of any trial conducted by the company (e.g. trial steering committee, data monitoring committee, scientific advisory board), even if not remunerated, or if they had been involved in the development and testing of the new drug or other, potentially competing, drugs.

DoI statements were summarized by the WHO/GTB secretariat at the start of the meeting. A summary is attached in **Annex 4**.

Technical resource consultants participated in the meeting to provide specific information on technical issues, but were not involved in the deliberations and preparation of the actual recommendations.

Just prior to the EG meeting, some participants updated their DoIs with ongoing talks with the company for future studies involving delamanid. This was considered to be significant and possibly conflicting interest, so these participants were asked to serve as "technical resource persons" during the meeting – i.e. they provided technical input during discussions of the data but did not take part in the discussion and deliberations leading to the development of the recommendations. All participants signed a confidentiality agreement and were reminded of the need for confidentiality until the full WHO process was concluded.

3.3 Review of evidence

Published data on the pre-clinical and clinical development of the drug were assembled and reviewed to assess efficacy, safety and tolerability of the drug. In addition, a series of documents were submitted to WHO by the manufacturer, following the list of required data as stipulated in the "Information Note to developers of TB drugs" *(8)*. These data included preclinical toxicity evaluations, dosing and pharmacokinetic studies, drug-drug interaction studies, early bactericidal activity studies, safety studies, Phase IIb studies (including a Phase IIb randomized controlled trial (RCT) using sputum culture conversion (SCC) at two months as the primary endpoint, and an open-label Phase IIb trial) and subsequent observational studies. An independent consultant was contracted to review and synthetize all available data into a synthesis document and prepare the GRADE evidence tables that were reviewed by the EG. This was complemented by modeling work to assess the cost-effectiveness of implementation of the drug in MDR-TB programmes. A formal bibliographic search of information on the product was carried out, and all publications in English were made available to the EG.

To comply with current standards for evidence assessment in formulation of policy recommendations, the GRADE system (www.gradeworkinggroup.org), adopted by WHO for all policy and guidelines development was used *(9)*. The GRADE evaluation, assessing both the quality of evidence and strength of recommendations, aims to provide a comprehensive and transparent approach for developing policy guidance. It assesses the impact of a particular intervention on patient-important outcomes and the generalizability of results to the target population, taking into consideration the comparison used and whether this was direct or indirect.

A PICO (Population, Intervention, Comparator, Outcome) question was pre-defined in consultation with the WHO Expert Group: "*In MDR-TB patients, does the addition of delamanid to a background regimen based on WHO-recommendations safely improve patient outcomes?*"

PICO refers to four elements that should be in a question governing a systematic search of the evidence, and was defined for delamanid as follows:

- Population: targeted by the action/intervention: patients with MDR-TB, including newly diagnosed patients, patients treated empirically for MDR-TB, HIV-infected patients (+/- use of ARVs), and children;
- Intervention: addition of delamanid during the first 6 months of WHO-recommended background MDR-TB therapy;
- Comparator: addition of placebo to WHO-recommended MDR-TB treatment;
- Outcome: efficacy (as demonstrated by sputum culture conversion during treatment and final treatment outcomes based on WHO definitions), safety (toxicity, serious adverse events, mortality).

In order to preserve consistency in the evaluation of drugs that are being considered for the treatment of MDR-TB, it was proposed that the EG use the same patient outcomes for the GRADE evaluation as those that were used for the evaluation of bedaquiline and determined to be most important for patients *(6)*. These important outcomes were applied to the published results as well as data that were provided to WHO by the drug manufacturer (Otsuka). Subsequently, the following outcomes were evaluated for the evidence profile:

1. Sputum culture conversion at two months
2. Time to sputum culture conversion over the first two months of treatment
3. Sustained sputum culture conversion at 24 months
4. Cure at 24 months
5. Mortality at 24 months
6. Serious adverse events
7. Acquired resistance to delamanid.

These different outcomes were scored by the EG members on a scale from 1 to 9 based on their relative importance; all were considered "critical".

The review of evidence took place in three successive stages.

At the first stage, prior to the in-person meeting of the Expert Group, experts reviewed the evidence from available studies of delamanid, including data from a Phase IIb RCT using SCC at two months as the primary endpoint, an open-label Phase IIb trial and subsequent observational study, together with the synthesis document prepared by the external independent consultant.

At the second stage, experts evaluated the available evidence using the GRADE system for grading quality of evidence and assessing strength of recommendations, based on the PICO question. For each of the agreed outcomes (above), the **quality of evidence** was evaluated according to the following criteria:

- *Overall study design:* randomized trial(s), or consecutive selection of patients (observational), or selection of patients according to given reference standard (case-control).
- *Risk of bias or limitations in study design and execution*
- *Inconsistency:* unexplained inconsistency in study endpoints or estimates.
- *Indirectness:* absence of direct evidence of impact on patient-important outcomes and generalisability.
- *Imprecision:* wide confidence intervals for treatment outcome estimates.
- *Other considerations:* possibility of publications bias, etc.

A glossary of the GRADE terms used can be found in **Annex 5**.

In a third stage, as called for by GRADE and based on the PICO question, the EG developed a recommendation and considered the strength of the recommendation (strong or conditional), based on the quality of available evidence, the balance of effects (benefits weighed against harms), as well as patient values and preferences, resources and equity.

3.4 Decision-making during the Expert Group meeting

The EG meeting was chaired by a recognized methodologist/evidence synthesis expert. Decisions were based on consensus (preferred option). In one instance, consensus could not be achieved among members and the EG proceeded to a vote (with simple majority rule) – this decision related to the need for written informed consent prior to starting a delamanid-containing MDR-TB treatment (see section 5.2).

Concerns and opinions by EG members during the meeting were noted and included in the final meeting report. The detailed meeting report was prepared by the WHO Secretariat Steering Group and was revised based upon input and sign-off by all EG members.

3.5 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 by the EG. The ERP was composed of eight reviewers external to the Expert Group, including content experts, end-users from high TB and HIV burden countries, and representatives from WHO's Strategic and Technical Advisory Group for TB (STAG-TB). The list of members of the ERP can be found in **Annex 6**. Comments made by the members of the ERP are reflected in the final version of the present interim guidance document.

3.6 Financial support

Financial support for the EG meeting and related analyses was provided under a Sub-agreement under Cooperative Agreement (CA) No. AID-OAA-A-10–00020 for the TB CARE I project awarded to KNCV by the Office of Health of the US Agency for International Development (USAID). US Centers for Disease Control and Prevention (CDC) provided work pro bono on the evaluation of sputum culture conversion as a surrogate marker of MDRTB treatment outcome (work carried out by Ekaterina Kurbatova and colleagues).

4. Evidence base for policy formulation

Published data on the pre-clinical and clinical development of delamanid were reviewed.[a] Additional data were provided to WHO by the manufacturer with the understanding that these data would be available publically at the time that the interim policy guidance was issued by WHO. An independent consultant was contracted to prepare a concise synthesis report of the available evidence, and this report was circulated to the EG before the meeting. In addition, two technical resource consultants were requested to develop specific documents to assist the EG in their evaluation of delamanid:

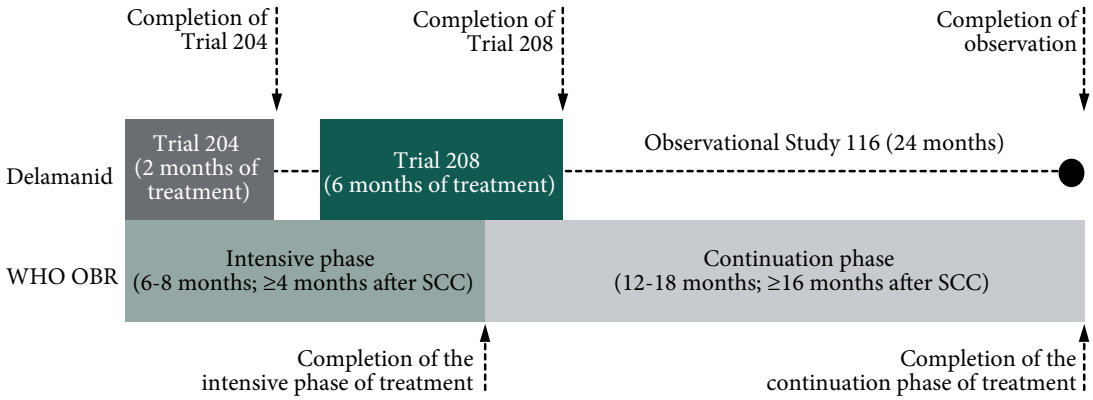
1. an assessment of the validity of sputum culture conversion at two and six months and time to culture conversion as surrogate markers of MDR-TB treatment outcomes; and
2. a cost-effectiveness analysis of introducing delamanid in MDR-TB regimens based on modeling.

The overall clinical development programme for delamanid included, in addition to 12 Phase I trials in healthy subjects, six trials conducted in patients with TB. During 2008–2011, the manufacturer launched and completed two trials and one observational study evaluating the efficacy and safety of delamanid for the treatment of MDR-TB when used in combination with an 'optimized background regimen' (OBR) designed according to WHO recommendations *(1)* – see **Figure 1**. To design an OBR, initial information was required on susceptibility of the individual patient *M.tuberculosis* isolates, the patient's previous treatment history for TB, drug resistance patterns of known MDR-TB contacts, and HIV status. According to the manufacturer, such a strategy was believed to offer individual patients the best opportunity for cure, irrespective of whether delamanid was added to the regimen. While this approach to treatment would inevitably result in greater variability in the regimens used in the delamanid and placebo arms, as opposed to a standardized regimen, the manufacturer considered that any benefit of delamanid observed in such heterogeneous population could be considered a closer approximation of real-world conditions.

According to the manufacturer, the objectives of the clinical development programme for delamanid were first to demonstrate increased SCC at two months of treatment when delamanid was added to background MDR treatment and then to show continued improved microbiologic outcomes with prolonged treatment by extending treatment for an additional six months (consistent with the WHO-recommended six to eight month initial intensive phase treatment for MDR-TB). Results from these two trials and a further observational study, were analysed together and served as the basis for submission of the Marketing Authorization Application for delamanid with the EMA.

a References for documents available on delamanid can be found at the website indicated in page 3 of this Guidance document.

Figure 1: Design of delamanid Trial 204, Trial 208 and Study 116 (Modified from Skripconoka et al, 2013) *(10)*



- WHO OBR refers to the optimised background regimen designed according to WHO recommended treatment for multidrug-resistant tuberculosis (MDR-TB)
- SCC: Sputum Culture Conversion
- Note: the time period between completion of Trial 204 and initiation of Trial 208 was variable

- Trial 204 was a phase II, multicentre, double-blind, randomized, stratified, placebo-controlled clinical trial conducted between May 2008 and June 2010 in nine countries.[a] A total of 481 patients aged 18 to 64 years were randomized to receive two months of treatment with either delamanid 100mg twice daily + OBR, delamanid 200mg twice daily + OBR, or placebo + OBR.
- Trial 208[b] was an open-label extension of Trial 204 that allowed continued or first-time access to delamanid in combination with OBR for an additional six months for patients who completed Trial 204 and consented to participate. Trial 208 was conducted between March 2009 and October 2011 at 14 of the 17 study sites that participated in Trial 204. In total, 213 (44.2%) of the 481 patients from Trial 204 were enrolled in this trial.
- The observational Study 116[b] captured the long-term treatment outcomes for patients who participated in Trial 204, irrespective of whether they participated in Trial 208. Treatment outcomes, as assessed by clinicians, were categorised as favourable or unfavourable, based on WHO recommendations *(1)*. A total of 421 patients who initially participated in trial 204 were included in study 116 and 390 completed the 24 month follow-up.

a China, Egypt, Estonia, Japan, Latvia, Peru, the Philippines, Republic of Korea, and the United States of America.

b Trial 208 and Study 116 are extensions of Trial 204. They are referred to by the terminology used in the published references and as provided by the manufacturer; it should be noted that these are not different/separate studies, but involved non-randomized and selected patients from the original Trial 204.

4.1 Evidence for the efficacy of delamanid in the treatment of MDR-TB

Data for efficacy analysis was provided by the manufacturer derived from the three trial/studies mentioned above, with data collected at various time periods and from a variety of patient populations. It should be emphasized that the study populations in Trial 208 and Study 116 are in fact derived from the cohort of Trial 204; accordingly, all three studies involved the same participants (or a subset thereof). According to published reports *(10) (11)* and results made available to WHO, the key endpoints used to assess the efficacy of delamanid were classified by the manufacturer as follows:

- **Short-term efficacy:** *endpoints were measured in the pivotal two months phase II, randomized placebo-controlled clinical trial 204*
  - Sputum culture conversion at two months (two-month SCC) – the primary endpoint, defined as a patient's achieving a series *of at least five consecutive weekly cultures negative for growth of M. tuberculosis (without subsequent positive cultures*). Assessment of two-month SCC using the MGIT liquid culture system served as the primary efficacy analysis;
  - Time to SCC – the time from treatment initiation to the first of the series of cultures that defined SCC; and
  - Time to detection of positive culture results using the MGIT system.

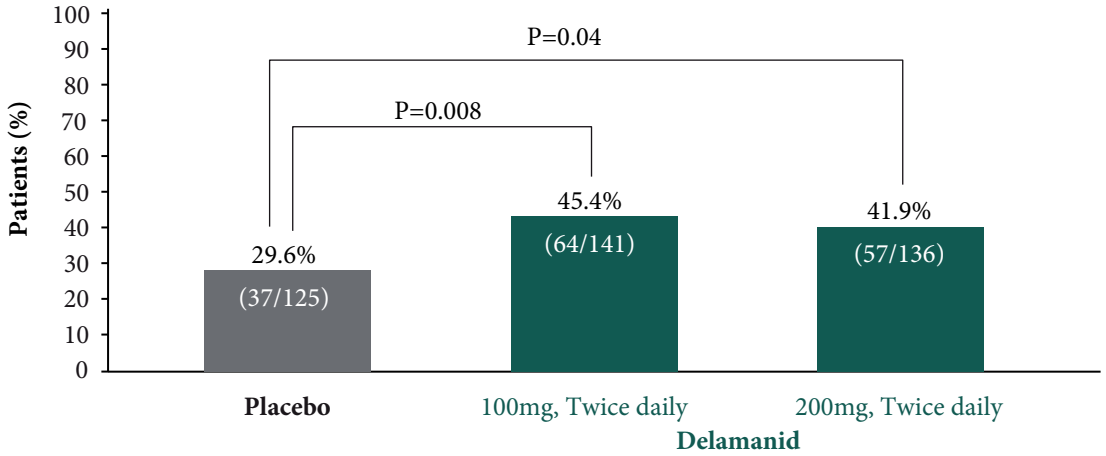
- **Longer term efficacy:** *endpoints were measured through combination of data* (using solid culture) *from Trial 204, Trial 208 and Study 116, grouping patients according to the total duration of delamanid received in the various trials, irrespective of the dose received (100mg BD or 200mg BD).*
  - Sustained SCC – Proportion of patients with no positive culture results throughout the remaining course of treatment after SCC has been achieved (consistently negative sputum cultures during the continuation phase of MDR-TB treatment ultimately defined a favorable outcome);
  - Favorable outcome – as assessed by the managing clinician at 24 months based on WHO treatment outcome definitions (cure, treatment completion, failure, death); and
  - Mortality – assessed as all-cause mortality per WHO guidelines.[a]

The ***primary efficacy endpoint, two-month sputum culture conversion (SCC)***, arose from the pivotal Trial 204. Overall, 434 patients completed the trial and the percentage of patients who completed or discontinued the trial was evenly distributed across groups. Efficacy analysis was based on a modified intent to treat (MITT) population (N=402), including randomized patients who had a positive sputum culture for TB at baseline using the MGIT culture system and who were resistant to isoniazid and rifampicin.

a Generally high among MDR-TB patients with 15% reported in a large meta-analysis of MDR-TB treatment *(12)*.

A higher proportion of patients treated with delamanid + OBR achieved SCC by Day 57 using the MGIT culture system than patients treated with placebo + OBR: 64/141 (45.4%) [p=0.008] in the delamanid 100mg group, 57/136 (41.9%) [p=0.04] in the delamanid 200mg BD + OBR group, and 37/125 (29.6%) in the placebo + OBR group – **see Figure 2**. Similar results were obtained when using solid culture (data not shown).

Figure 2: Proportion of patients with sputum-culture conversion by Day 57



Source: Gler et al, 2012 *(11)*.

A secondary efficacy endpoint was time to SCC. Although the median time to SCC (sustained SCC achieved by Day 57) could not be calculated because fewer than 50% of patients in each group met the criteria, the Kaplan-Meier curves for time to SCC using the MGIT system showed clear separation between each delamanid BD + OBR group and the placebo + OBR group from Day 36 to Day 57 (Weeks five to eight). By the end of the two-month treatment period, the difference in SCC between the delamanid groups (both doses) and the placebo group was significant (p=0.001). The hazard ratio for increased time to conversion to a negative sputum culture as assessed with MGIT was 0.58 (95% CI: 0.39 to 0.89) in the 100mg BD group and 0.63 (95% CI: 0.42 to 0.96) in the 200mg BD group. When using solid medium, the hazard ratio for increased time to conversion to a negative sputum culture was 0.54 (95% CI, 0.36 to 0.81) in the 100mg BD group and 0.44 (95% CI, 0.29 to 0.64) in the 200mg BD group.

To assess the ***long-term efficacy of delamanid for MDR-TB beyond the first two months of treatment***, the manufacturer combined data from Trial 204, Trial 208 and Study 116 to evaluate the proportion of patients who achieved sustained SCC and final treatment outcomes at 24 months (including mortality). In total, follow-up could be assessed in 421 (87.5%) out of the 481 patients initially randomized in Trial 204. To compare treatment outcomes, patients were grouped as follows:

- Patients treated with delamanid 100mg BD or 200mg BD (+ OBR) were grouped together. The rationale for this was that short-term treatment results (two-month SCC) were similar for those participants who received 100mg BD and 200mg BD;

- Patients who participated in Trial 208 and received six months of delamanid (any dose) were grouped together with those who had received placebo, delamanid 100mg BID, or delamanid 200mg BD during Trial 204 and designated as the "**≥6month**" administration group. Individuals in this group thus received six or eight months of delamanid. The manufacturer's rationale for this was that treatment outcomes and sustained SCC results were similar among those who had received six *vs.* eight months of delamanid.
- Patients who only contributed to trial 204 and received delamanid for two months or who received placebo were pooled to make a delamanid "**≤2 month"** administration group, because of comparable demographics and baseline characteristics and similar final treatment outcome. Hence individuals in this group received two months of delamanid or no delamanid at all.

Analyses performed by the manufacturer to evaluate the long-term efficacy of delamanid compared patients who received delamanid for ≥6 months with patients receiving delamanid for ≤2 months. The key endpoints for assessing longer term efficacy included:

- ***Sustained SCC:*** By the end of treatment, 90.9% (130/143) of patients in the delamanid ≥6months treatment group achieved sustained SCC compared to 70.9% (112/158) of patients in the delamanid ≤2months treatment group.
- ***Favourable outcome:*** The proportion of patients who showed a favourable treatment outcome (i.e. confirmed microbiological cure by solid culture or treatment completion) at the end of the 24-month treatment period was significantly higher in the ≥6 month group (74.5%, 95% CI: 67.7–80.5) than in the ≤2 month group (55.0%, 95% CI: 48.3–61.6) ($p < 0.0001$)**.**
- ***Mortality:*** The reported mortality rate was lower in the delamanid ≥6 months treatment group (two deaths, 1%) compared to the delamanid ≤2 months treatment group (19 deaths, 8.3%) ($p < 0.001$).

Table 1: Favourable treatment outcome and mortality at 24 months for MDR-TB patients treated with delamanid

Delamanid exposure	Total ITT patients N	24 months outcome			
		favourable		deaths	
		N (%)	95% CI	N (%)	95% CI
≥ 6 months*	192	143 (74.5)	67.7–80.5	2 (1.0)	0.1–3.7
≤ 2 months**	229	126 (55.0)	48.3–61.6	19 (8.3)	5.1–12.7

*Patients participating in Trial 208 and treated with delamanid or placebo in Trial 204

**Patients not participating in Trial 208 and treated with delamanid or placebo in Trial 204

In order to clarify the participation of patients in the above analysis, WHO requested the manufacturer to provide treatment outcomes at 24 months (using WHO-recommended treatment outcome definitions) stratified by delamanid dose and duration of exposure for patients who had been followed up within Study 116. The results are provided in **Table 2**.

Table 2: Outcome at 24 months for patients consenting to participate in Study 116 who were treated with delamanid 100mg BD or 200mg BD + OBR for two, six or eight months or with OBR alone, using WHO treatment outcome categories (N=421)

Trial 204 Assignment (2 months DLM+OBR or OBR alone)	Trial 208 Participation (6 months DLM+OBR or OBR alone)		ITT patients in Study 116 (N)	Cured		Completed		Failed		Died		Lost to Follow-up	
				n	%	n	%	n	%	n	%	n	%
100-BD	1	100-BD	38	24	63%	9	24%	2	5%	0	0%	3	8%
	2	200-BD	21	13	62%	2	10%	2	10%	1	5%	3	14%
	3	No	80	31	39%	17	21%	12	15%	9	11%	11	14%
200-BD	4	100-BD	45	25	56%	16	36%	3	7%	0	0%	1	2%
	5	200-BD	22	15	68%	3	14%	4	18%	0	0%	0	0%
	6	No	76	36	47%	14	18%	12	16%	4	5%	10	13%
Placebo	7	100-BD	39	27	69%	7	18%	3	8%	0	0%	2	5%
	8	200-BD	27	18	67%	2	7%	4	15%	1	4%	2	7%
	9	No	73	33	45%	12	16%	13	18%	6	8%	9	12%
Total			421	222	53%	82	19%	55	13%	21	5%	41	10%

Note: this table was used for the estimate of efficacy of delamanid on ultimate treatment outcomes in the GRADE table – i.e. cure and mortality (see table 4). In the test arms, patients receiving delamanid (irrespective of dose) from the start of treatment only were considered, as a clearer proxy of the manufacturer's recommendation for delamanid use of 6 months – i.e. groups 1, 2, 4 and 5. For controls, only patients who did not receive any delamanid (i.e. placebo only on top of OBR in Trial 204 and 208) were considered (group 9). Total population is N=199.

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

Twelve phase I trials in healthy subjects have been conducted. Pooled data provided by the manufacturer showed that treatment-emergent adverse effects (TEAEs) with the highest incidence in subjects who received delamanid were headache (20.9%, 88/422), nausea (11.6%, 49/422), and dizziness (8.8%, 37/422).

In total, 887 individuals have been exposed to delamanid in clinical trials. Overall, 22.1% (196/887) of delamanid-treated patients had a cumulative exposure of longer than six months (180 days). Most frequent were headache, abdominal pain and insomnia. The incidence and distribution of TEAEs occurring in 10% of patients in the two delamanid groups in *Trial 204* are shown in **Table 3.** The only clinically relevant TEAE with a difference in incidence between the delamanid+OBR treatment groups compared to the placebo+OBR group was QT prolongation.[a] Other TEAEs varied in occurrence but were present in similar proportions in the delamanid+OBR and the placebo+OBR groups. Most frequent were nausea, vomiting, and dizziness.

In Trial 204 and Trial 208, 74 patients experienced severe adverse events (SAEs), including death. The only clinically relevant SAE with a difference in incidence among treatment groups was QT interval prolongation, which was significantly higher in the delamanid 100mg BD + OBR group (4.3%, 7/161) and the delamanid 200mg BD + OBR group (5.6%, 9/160) than the placebo + OBR group (1.9%, 3/160). In Trial 204, the placebo-corrected, change-from-baseline QTcF[b] increased with duration of dosing and reached 11.3 to 13.1 msec in delamanid 100mg BID + OBR and 14.1 to 15.6 msec in delamanid 200mg BID + OBR over all time points on Day 56. In Trial 208, four of 131 patients treated with delamanid 100mg BID + OBR and four of 73 patients treated with delamanid 200mg BID + OBR) had a change from baseline QTcF exceeding 60 msec. Only patients on delamanid exhibited QTcF prolongation exceeding 60 msec from baseline.

Delamanid is metabolized by cytochrome P450 enzymes like CYP3A4, and formation of its main metabolite is regulated by plasma albumin. It is neither an inducer nor an inhibitor of key drug metabolizing enzymes so is unlikely to have a significant impact on concentrations of companion drugs. Studies in healthy subjects showed no clinically-significant interactions when delamanid was co-administered with tenofovir, efavirenz or lopinavir/ritonavir.

a The heart's electrical cycle can be measured on an electrocardiogram (ECG); the QT interval is a measure of the time between the start of the Q wave and the end of the T wave representing the electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for potential ventricular tachy-arrhythmias (such as 'torsades de pointes') and a risk factor for sudden death. Concomitant use of drugs that prolong the QT interval may cause additive QT prolongation, and should be avoided if possible. Of note, some of the other second-line anti-TB drugs are known to prolong the QT interval.

b QTcF: QT interval corrected for heart rate according to the Fridericia method.

Table 3: Incidence of adverse events (occurring in 10% of patients in either delamanid group and with greater frequency than in the placebo group)*

Adverse Event	Delamanid, 100mg Twice Daily	Delamanid, 200mg Twice Daily	Placebo
	(N = 161)	(N = l60)	(N = 160)
	n (percent)		
Haematopoietic			
Anaemia	18 (11.2)	10 (6.2)	14 (8.8)
Reticulocytosis	19 (11.8)	20 (12.5)	17 (10 6)
Gastrointestinal			
Nausea	58 (36.0)	65 (40.6)	53 (33.1)
Vomiting	48 (29.8)	58 (36.2)	44 (27.5)
Upper abdominal pain	41 (25.5)	36 (22.5)	38 (23.8)
Cardiovascular			
Palpitations	13 (8.1)	20 (12.5)	10 (6.2)
Prolonged QT interval	16 (9.9)	21 (13.1)	6 (3.8)
Respiratory: hemoptysis	19 (11.8)	15 (9.4)	17 (10.6)
Nervous system			
Headache	36 (22.4)	41 (25.6)	30 (18.8)
Paresthesias	17 (10.6)	20 (12.5)	12 (7.5)
Tremor	19 (11.8)	16 (10.0)	13 (8.1)
Insomnia	42 (26.1)	51 (31.9)	42 (26.2)
General			
Tinnitus	16 (9.9)	22 (13.8)	12 (7.5)
Asthenia	20 (12.4)	27 (16.9)	20 (12.5)
Malaise	12 (7.5)	16 (10.0)	12 (7.5)
Anorexia	23 (14.3)	34 (21.2)	24 (15.0)
Hyperhidrosis	9 (5.6)	17 (10.6)	8 (5.0)
Hyperuricaemia	31 (19.3)	38 (23.8)	35 (21.9)
Hypokalaemia	20 (12.4)	31 (19.4)	24 (15.0)

*With pairwise comparisons of the frequency of adverse events, only QT prolongation on electrocardiography (ECG) was significant (P = 0.048 for the comparison of the 100mg group with the placebo group and P = 0.005 for the comparison of the 200-mg group with the placebo group). Furthermore, the Cochran–Armitage trend test used to evaluate for a dose–response trend in the incidence of adverse events across the three dose groups (0mg, 100mg, and 200mg twice daily) yielded a P value of 0.004 for QT prolongation detected by means of ECG.

Source: Gler et al, 2012 *(11)*.

4.3 Cost-effectiveness

The EG assessed the results of a cost-effectiveness analysis (CEA) conducted to model the incremental cost-effectiveness of adding delamanid to existing WHO-recommended MDR-TB regimens. This CEA was undertaken for different settings to allow for variation among countries across income level, the model of care used for MDR-TB treatment, and background patterns of drug resistance. It focused on the direct benefits to patients, but did not attempt to assess the indirect (and acquired) transmission benefits, nor did it assess the broader economic benefits to patients or society.

Since several analyses were conducted by the manufacturer to assess efficacy (see above), a sensitivity analysis was performed on the cost-effectiveness of delamanid when different trial data and assumptions about the translation of trial results to current practice were applied. Results showed that delamanid would be cost-effective in most environments studied. However, this interpretation needs to take into account the quality of clinical evidence as assessed by the EG (i.e. if the quality of clinical evidence is viewed as low, then likewise the evidence supporting cost-effectiveness should be regarded as low), as well as all limitations related to the assumptions made above. Of note, in settings where cure/treatment success rate is currently high, delamanid may not be cost-effective, as it may result in limited additional benefit. However, the incremental cost of delamanid introduction will not only depend on price, but also on the cost savings for retreatment as a result of an expected reduction in treatment failures. Using a conservative approach, delamanid was thus found to be cost-effective in most settings, but the quality of this evidence was considered very low, and further work would be needed to evaluate cost-effectiveness and to test the robustness of the assumptions in various settings.

5. Expert Group recommendations

5.1 Summary of evidence for the recommendation

The GRADE process was used to evaluate the quality of evidence presented to the EG to determine whether delamanid should be added to WHO recommended background MDR-TB regimen. For each identified critical endpoint, the quality of evidence was assessed based on the criteria of study limitations/risk of bias, inconsistency, indirectness, and imprecision.

The EG members agreed that key data to consider for evaluation of efficacy were those collected in the pivotal **Trial 204**, since this trial was using a randomized controlled design with proper selection of controls. The experts took note that two months SCC and time to SCC were assessed as surrogates for cure, but they were not convinced of the prognostic adequacy or accuracy of these endpoints for MDR-TB cure. The experts also noted that the duration of comparison between delamanid and placebo in Trial 204 did not allow an assessment of the potential benefit of adding delamanid (at either 100mg or 200mg BD dose) to OBR for six months duration without interruption (as recommended by the manufacturer).

Trial 208 investigated six months exposure to delamanid. Here, the experts noted a number of problems in the design and conduct of this trial hampering the collection of high quality data, including: absence of randomization; self-selection of patients; absence of blinding for treatment allocation; a variable gap period between the end of Trial 204 and the beginning of Trial 208; and a lack of consistency in the allocation of drug dosages. As a result, there were wide variations in the doses, timing and duration of exposure to the drug for various subgroups of patients. Furthermore, the experts considered that there was a serious risk of bias for all data arising from the observational **Study 116** due to variability in follow-up procedures as well as un-blinded assessment of outcome, and serious inconsistency due to the variability in duration of drug exposure. Experts were also in agreement that the post hoc analysis performed by the manufacturer of efficacy at the end of treatment in Study 116 had little value for the evaluation of effect: this was a retrospective analysis relying on non-standardized follow-up procedures and conditions, and the grouping of patients in those who received ≥6 versus ≤2 months of delamanid was considered not appropriate due to lack of randomization to the various treatment arms and the high variability of exposure (in terms of timing, duration and doses of treatment).

The experts noted that the duration of exposure to delamanid in the pivotal RCT was too short to be able to discern a benefit of adding delamanid (at either 100mg or 200mg BD dose) to OBR for six months, and the subsequent enrolment of patients in Trial 208 and Study 116 did not allow for a controlled assessment of efficacy endpoints over the

proposed duration of use of delamanid (six months), nor a robust assessment of cure rates by the end of treatment.

Experts also noted that the risk of any adverse event in the delamanid arms was not significantly different than in the placebo arm. They noted, however, that QT interval prolongation was the most concerning serious adverse event, and were concerned about the lack of information on the potential synergy of cardiotoxic effects if delamanid was used in combination with other QT prolonging drugs, such as moxifloxacin or clofazimine. The experts also noted that there was no evidence that delamanid 200mg twice a day was more effective than 100mg twice a day and that the higher dose was associated with higher rates of adverse events, including QT prolongation.

Overall, the EG had **a very low level of confidence** in the short- or long-term efficacy of delamanid given that the available evidence was very limited and of low or very low quality (for efficacy and safety, respectively).

The EG also discussed the potential to draw conclusions for different subcategories of MDR-TB patients, such as patients with strains resistant to either fluoroquinolones or injectable drugs or both. Limited evidence for use of the drug in XDR-TB patients was available, but members of the EG felt that delamanid in MDR-TB patients with isolates that have additional resistance to fluoroquinolones or injectables or XDR-TB could potentially benefit from delamanid, given that treatment options for these patients are severely limited. The EG also expressed concern about the potential for emergence of resistance following exposure to delamanid.

In view of the shortcomings of the analyses of long-term efficacy performed by the manufacturer and submitted to WHO (**Tables 1** and **2**), the EG requested a re-analysis of the estimate of efficacy beyond the two-month SCC considering: (i) only patients included in Study 116 who received delamanid from the start of treatment in Trial 204 and continued to receive delamanid during Trial 208 (as a clearer proxy of the manufacturer's recommendation for delamanid use of 6 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 (**Table 2**), the EG further 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 reasons for this observation were not clear but the sensitivity analysis would suggest that, as patients were not randomized during Trial 208 and Study 116 and default was a non-random outcome, treatment outcomes may have been correlated with default. For example, patients who defaulted could have been more likely to fail or die had they completed treatment, and the observed treatment success of 1.35 (95% CI: 1.03 to 1.63) (**Table 4**) could therefore be an over-estimation of effect.

Of note, 4/205 patients seemed to have developed in vitro resistance to delamanid during treatment, although no discernible reasons could be established.

Overall, although the experts had very low confidence in the quality of evidence available, they agreed that *the anticipated benefit of adding the drug to OBR could outweigh the anticipated undesirable effects.* The experts considered that any potential harm associated with using the drug would be offset by the benefits which can be expected in most settings, given that clinicians treating MDR-TB patients often face limited treatment options, that outcomes for MDR-TB patients on second-line treatment are very unsatisfactory, and that ineffective regimens could increase the likelihood of acquisition of additional resistance or chronicity.

The EG felt that there were *potentially large variations in patient values and preferences* for each outcome. Most members felt that patients would place high value on treatment success/cure, serious adverse events and mortality but that it was less clear that patients would similarly value mycobacterial culture conversion. The expert group assumed that there was minimal variation for values related to death, but larger variation for other outcomes, in particular about how much value patients would place on the side effects (e.g. QT interval prolongation).

EG members expressed the view that *patient acceptance of delamanid* would depend on the severity of their disease and the likelihood that an effective background regimen could be designed for them – e.g. XDR-TB patient groups might be more likely to accept the risk of taking a new drug with uncertain efficacy than patients with newly diagnosed MDR-TB without additional drug resistance. The EG felt, however, that a duly informed decision making-process by patients should be followed; this would require that the intervention be presented as an option and that information be provided on uncertainty about the effects. The decision about requesting signed informed consent was submitted to a vote (5:5 vote, 2 missing). Subsequently, as written informed consent is mandatory for MDR treatment in some settings, the EG noted that local practice should be observed.

With respect to required resources, the EG took the cost perspective of a TB programme and focused on direct benefits to patients. The cost-effectiveness analysis showed that while incremental cost varied relative to the net benefits, there were a number of sources of uncertainty including the costs of the drug, related additional treatment costs, efficacy and long-term outcomes. The EG noted that indirect transmission benefits were not considered, and that the analysis was based on drug cost parameters provided by the manufacturer. The EG also noted that relative cost-effectiveness does not necessarily translate into affordability or country readiness to pay, given the potential high relative cost of adding delamanid. Resource implications related to training of health care staff and establishing pharmacovigilance systems were not considered but were felt to be important. The EG concluded that the resource implications of introducing delamanid in addition to MDR-TB treatment may be more substantial than those presented in the cost-effectiveness study.

The EG felt that the direction or impact on *equity* was uncertain based on present knowledge about resource requirements for the drug and companion regimen, and additional resource requirements of the TB programme. Experts recognized that implementation of any new intervention may be associated with trade-offs in the absence of additional resource mobilization.

The EG considered that treatment should be *acceptable* overall to the patient, given the likely benefits, tolerability and limited harms. The EG pointed that, while the other companion drugs of the MDR-TB regimen are administered in a single daily dose, delamanid should be given twice daily. This may affect acceptability and adherence, given the need for directly observed therapy to prevent acquisition of further resistance. However, acceptability may be improved by the fact that delamanid is only used for six months.

The EG felt 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 OBR would be feasible in most MDR-TB treatment settings.

Based on the available evidence, the EG concluded that delamanid may only be *given in addition to* a current WHO-recommended regimen, and *not as a substitute* for any of the currently recommended second-line drugs unless they are considered to be ineffective or cannot be used because of severe intolerance *(3)*. There was no evidence at present that addition of delamanid could allow for any shortening of treatment duration.

5.2 Expert Group recommendations

Based on the available evidence, and recognizing the limits of available clinical data, the EG recommended that delamanid (100mg BD for six months) may be added to a WHO recommended regimen in MDR-TB adult patients under specific conditions and taking into account the following remarks *(conditional recommendation, very low confidence in estimates of effects*):

- The population to whom this recommendation applies is MDR-TB patients. This may also include those with additional resistance or intolerance to fluoroquinolones or second line injectable drugs, those with extended lesions, advanced disease and others deemed at higher baseline risk for poor outcomes, as well as patients with XDR-TB.
- The population excludes patients with QT prolongation.
- Adherence to principles of designing a WHO-recommended regimen is required. As with all TB treatment regimens, delamanid should never be added as a single drug

to an already failing regimen. Rather, it should be part of a multi-drug regimen, in which the other companion drugs are selected based on WHO MDR-TB treatment recommendations.

- This recommendation includes PLHIV, as individuals with HIV co-infection were included in the RCT.
- Delamanid has not been tested in pregnant and breastfeeding women, children, and patients with extra-pulmonary MDR-TB, and there are limited or no data describing the effects of substance abuse, advanced age and diabetes, on treatment outcomes or safety. Because of uncertainty regarding safety and efficacy in these patient populations, particular caution is suggested for use of delamanid in these situations.
- The use of the drug in patients with extra-pulmonary MDR-TB may be considered, extrapolating from the data in patients with pulmonary TB.

Implementation considerations:

- A duly informed decision making-process by patients should be followed; this includes presenting the intervention as an option and providing information on uncertainty about the effects.
- With regard to QT prolongation, data were available for simultaneous use with levofloxacin only. No evidence was available on the effect on QT prolongation when delamanid was used in combination with other fluoroquinolones or clofazimine. Delamanid should be given under strict monitoring of QT intervals, particularly if given in combination with other QT prolonging drugs. Active pharmacovigilance is recommended.
- No data for the simultaneous use of bedaquiline and delamanid (that can both prolong QT) were available. Without this data, no recommendation about the simultaneous use of delamanid and bedaquiline can be made.

Monitoring and evaluation:

- The EG recommends that QT and serum potassium levels be regularly monitored during treatment with delamanid
- The risk of emergence of resistance to delamanid should be a key guiding principle when the drug is being used, and appropriate DST should be in place, when available.

In addition, based on the available evidence, the EG considered that culture conversion at two months should not be used as a surrogate marker for treatment outcome in MDR-TB patients.

The Expert Group proposed that interim recommendations should be valid for a maximum of two years and be updated should additional data become available.

6. WHO interim policy recommendations

Available data on delamanid efficacy and safety is very limited as assessed by the GRADE process; however, the overall benefits of the inclusion of delamanid in a WHO-recommended MDR-TB regimen appear to outweigh the observed harms. Therefore, considering the global MDR-TB crisis, the limited therapeutic options available for this life-threatening condition, and the need to promote safe and responsible use of TB drugs, WHO is making the following **interim policy recommendation** for the use of delamanid in the 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 under the different conditions that may be expected in treatment programmes, 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:

1. Proper patient inclusion

The current recommendation for the use of delamanid applies to adults (≥18yrs) with pulmonary MDR-TB disease, including people living with HIV. Special caution and proper clinical judgment should be applied when delamanid is used in persons 65 years and older, or in those with diabetes, hepatic or severe renal impairment, or those who use alcohol or substances, given that data on efficacy and safety under such conditions are extremely limited or unavailable.

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.

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

When an effective and reasonably well-tolerated MDR-TB regimen can be composed with conventional second-line drugs, the routine addition of delamanid may not be warranted and the implications of additional health service costs should be considered. MDR-TB patients in whom delamanid may have a particular role include those with:

- higher risk for poor outcomes (eg. drug intolerance or contraindication, extensive or advanced disease);
- additional resistance to fluoroquinolones or injectable drugs;

- XDR-TB (see 3.b for additional measures to apply when the drug is used in XDR-TB patients).

While patients with exclusive 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 harm that delamanid may cause is offset by the benefit expected.

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; the cardinal rules governing the general composition and duration of MDR-TB regimens remain the same:

a. The WHO-recommended MDR-TB treatment regimen *(1)* is typically composed of at least pyrazinamide and four second-line drugs considered to be effective (based on DST and/or previous use and/or drug resistance surveillance data): a fluoroquinolone (preferably later-generation), a second-line injectable agent, and two bacteriostatic drugs, preferably prothionamide or ethionamide plus cycloserine or *p*-aminosalicylic acid.

b. MDR-TB patients with confirmed resistance or intolerance to either fluoroquinolones or the second-line injectable drugs 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 four, and reducing the risk of acquisition of additional resistance and progression towards XDR-TB.

c. There is as yet no standardized DST method for delamanid, nor a commercially available test. DSTs for second-line drugs other than fluoroquinolones and injectables (kanamycin, amikacin, capreomycin) are not accurate or reproducible, 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.

d. While experience in the use of delamanid in the management of XDR-TB is very 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 5 which have unproven anti-tuberculosis activity or a lower safety profile. However, special caution is necessary when delamanid is used with a fluoroquinolone or a Group 5 drug given the potential for synergistic drug-drug interactions effects, particularly on QT prolongation.[a]

e. There are currently no data on the simultaneous use of bedaquiline and delamanid in the same patient. Until such data become available, no

a A QTcF value greater than 440ms is considered prolonged. A value greater than 480ms (or an increase of greater than 60ms from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTcF interval of more than 500ms is considered dangerous and stopping QT-prolonging drugs is indicated.

recommendation on the joint administration of these two medicines is possible within the scope of this interim guidance.

f. 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 emergence of resistance to delamanid observed in the available data, all possible measures should be taken to protect the efficacy of the drug.

g. The recommended dose of delamanid in adults is 100mg twice a day, irrespective of body-weight, for a period of six months. As bioavailability was higher when given after a standard meal, delamanid should preferably be delivered after a meal. There was no evidence that delamanid 200mg twice a day was more effective than the 100mg dose and the higher dose was associated with higher rates of adverse events including QT interval prolongation. It should be particularly noted that supervision of delamanid intake should be adapted to twice a day.

3. Treatment is closely monitored

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

a. Sound treatment and management protocols, including clear patient eligibility criteria, locally appropriate procedures for informed consent *(see 5)*, and defined roles and responsibilities of all professionals involved. Safety concerns are best addressed through active pharmacovigilance *(2)*.

   The treatment protocols should allow for the prospective capture of data on key variables for both effectiveness and safety, making sure that the good practices, such as those applied in the conduct of observational studies, are adhered to *(3,4)*.

b. Treatment protocols are preferably submitted to and approved by the relevant national ethics authority in the country prior to patient enrolment on treatment.

c. 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.

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

4. Active pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.

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

a. Given that the results of Phase III trials are expected in the next few years, it is particularly important that the introduction of delamanid is accompanied by an enhanced monitoring for adverse events. For this purpose, spontaneous reporting is not expected to represent an appropriate level of care and active pharmacovigilance techniques, such as 'cohort event monitoring' (CEM), will be needed to improve the early detection of adverse drug reactions. Details on the methodologies for mounting CEM, particularly when new drugs are introduced, have already been published by WHO *(2)*.

b. Any adverse drug reaction attributed to delamanid should be reported to the national pharmacovigilance centre. As for 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 occurrences should also trigger a rapid response to manage these untoward effects in the patient.

c. When introducing delamanid into a regimen, there is also the potential for its interaction with other medications administered concurrently, with additive or synergic adverse effects. Other second-line drugs that are likely to be administered with delamanid, notably fluoroquinolones and clofazimine, may potentially increase the risk of cardiotoxicity. Although there are data showing QT interval prolongation when delamanid is administered simultaneously with levofloxacin, no data are available on concomitant use with moxifloxacin and/or clofazimine. Also, some antiretroviral medications can cause modest QT prolongation, especially ritonavir-containing regimens. Therefore, monitoring of patients for cardiac dysrhythmias or QT prolongation (i.e. using ECG), and for electrolyte imbalances (especially serum potassium) that can predispose to cardiotoxicity is imperative.[a]

d. Drug-drug interaction studies of delamanid with tenofovir, efavirenz and lopinavir/ritonavir, respectively, 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 anti-retroviral agents. However, there is no published evidence so far on the use of delamanid in HIV-infected MDR-TB patients on ART. Therefore, people living with HIV who will be receiving

a It is imperative that ECGs are 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 greater than 440ms is considered prolonged. A value greater than 480ms (or an increase of greater than 60ms from baseline) should trigger electrolyte testing and more frequent ECG monitoring. A QTc interval of more than 500ms is considered dangerous and should lead to stopping of the intake of the responsible QT prolonging drug(s).

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 co-morbid conditions such as diabetes, liver and/or renal dysfunction, malignancies, alcohol and substance use, and therefore careful screening for these conditions prior to treatment initiation is advised. Hypersensitivity reactions to delamanid have not yet been described, but vigilance is nevertheless required.

5. Patient informed consent obtained

Health care workers should follow a due process for informed consent by ensuring that the patient: i) is aware of the novel nature of delamanid; ii) appreciates the reason why the drug is being proposed to be included in their treatment regimen; and iii) 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 compassionate use programmes. In some settings, as per national or local policy, it is required that the informed consent is made in writing for enrolment on MDR-TB treatment.

Validity of the interim policy guidance

This interim recommendation is valid for a maximum of two years and will be updated should additional data become available.

It is noted that an ongoing Phase III trial is underway and timely completion, analysis and availability of results will be critical for the future revision of this interim guideline.

7. Further research

Several research areas were identified in the course of the development of these guidelines:

- Pharmacokinetics, safety and efficacy studies in specific populations (infants and children, PL HIV (especially those on ART), alcohol and drug users, elderly persons, pregnant or breastfeeding women, persons with extrapulmonary TB, persons with diabetes);
- Safety studies, including type, frequency and severity of adverse events (short term and long term), and mortality (including cause of death);
- Drug-drug interaction studies with other existing and newly developed TB drugs (including Group 5 second line drugs) and ARVs; and the most frequently used drugs to manage adverse effects and other TB co-morbidities;
- Optimal dosing studies (including once daily dosing) and treatment duration studies;
- Acquisition of resistance to delamanid and to other TB drugs during treatment;
- Accurate, reproducible and affordable DST methods for delamanid;
- Effectiveness studies performed in various programmatic settings.

8. Dissemination and implementation

WHO interim policy guidance (as well as Expert Group meeting report) will be published online (www.who.int/tb/en) and disseminated through WHO listserves to WHO regional and country offices, Member States, the Stop TB Partnership, donors, technical agencies and other stakeholders.

To facilitate the implementation of this guidance, derivative products have been developed to complement existing guidance and tools for the management of MDR-TB, including monitoring and evaluation. In particular, a "How-to-use delamanid" document is part of the Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis *(3)*. Of note, this document will include comparative tables on bedaquiline and delamanid, the two newest drugs for MDR-TB treatment, and a guide on how to use these drugs respectively.

This interim recommendation is valid for a maximum of two years and will be updated should additional data become available.

Table 4: The GRADE evidence profile summary

Author(s): WHO Expert Group on delamanid for MDR-TB
Date: 2014–06–12 (Final update)
Question: In MDR-TB patients, does the addition of delamanid to a background regimen based on WHO-recommendations safely improve patient outcomes?
Settings: Blinded, placebo-controlled trial (204) for two months, followed by an open observational trial (208) for six months with reassignment of patients
Bibliography (systematic reviews): data supplied by Otsuka + references *(10,11)*.

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delamanid + OBR	OBR alone	Relative (95% CI)	Absolute (95% CI)		
Sputum culture conversion at 2 months as surrogate for cure (assessed with: solid culture - MITT population)												
1	randomized trial [1]	serious [2]	not serious	serious [3,4]	serious [5]	none	64/119 (53.8%) [6]	38/113 (33.6%)	RR 1.6 (1.18 to 2.18) [6]	202 more per 1000 (from 61 more to 397 more) [6]	⊕○○○ VERY LOW	CRITICAL
Sputum culture conversion at 2 months as a surrogate for cure (assessed with: MGIT liquid culture system - MITT population)												
1	randomized trial [1]	serious [2]	not serious	serious [3,4]	serious [5]	none	64/141 (45.4%) [7]	37/125 (29.6%)	RR 1.53 (1.1 to 2.12) [7]	157 more per 1000 (from 30 more to 332 more) [7]	⊕○○○ VERY LOW	CRITICAL
Time to culture conversion at 2 months as surrogate for cure (assessed with: MGIT liquid culture system - MITT population)												
1	randomized trial [1]	serious [2]	not serious	serious [3,4]	serious [5]	none	49/119 (41.2%)	27/113 (23.9%)	HR 0.58 (0.39 to 0.89) [8]	92 fewer per 1000 (from 23 fewer to 138 fewer)[8]	⊕○○○ VERY LOW	CRITICAL
Sustained SCC at 24 months (assessed with: solid culture)												
1	observational study [9]	serious [10]	not serious	serious [3]	serious [5]	none	89/95 (93.7%)	37/48 (77.1%)	RR 1.22 (1.09 to 1.27) [11]	170 more per 1000 (from 69 more to 208 more)[11]	⊕○○○ VERY LOW	CRITICAL
Cure at 24 months (assessed with: solid culture, clinical)												
1	observational study [9]	serious [10]	not serious	serious [3]	serious [5]	none	77/126 (61.1%)	33/73 (45.2%)	RR 1.35 (1.03 to 1.63) [11]	158 more per 1000 (from 14 more to 285 more)[11]	⊕○○○ VERY LOW	CRITICAL

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delamanid + OBR	OBR alone	Relative (95% CI)	Absolute (95% CI)		
Mortality at 24 months												
1	observational study [9]	serious [10]	not serious	serious [3]	serious [5]	none	1/126 (0.8%)	6/73 (8.2%)	RR 0.1 (0.01 to 0.77) [12]	74 fewer per 1000 (from 19 fewer to 81 fewer) [12]	⊕○○○ VERY LOW	CRITICAL
Serious Adverse Events (assessed with: Clinical and laboratory measurements over 2 months in Trial 204 - ITT population)												
1	randomized trial [1]	not serious	not serious	serious [12]	serious [5]	none	16/161 (9.9%)	14/160 (8.8%)	RR 1.23 (0.61 to 2.33) [13,14]	20 more per 1000 (from 34 fewer to 116 more) [13,14]	⊕⊕○○ LOW	CRITICAL
Electrocardiogram QT prolongation in >=3% of patients and incidence at least 3% higher than in placebo (assessed with: ECG and MedDRA criteria - ITT population)												
1	randomized trial [1]	not serious	not serious	not serious	serious [5]	none	16/161 (9.9%)	6/160 (3.8%)	RR 2.65 (1.08 to 5.99) [15]	62 more per 1000 (from 3 more to 187 more)[15]	⊕⊕⊕○ MODERATE	CRITICAL
Electrocardiogram QT prolongation by more than 60 msec (assessed with: ECG - ITT population)												
1	randomized trial [1]	not serious	not serious	not serious	serious [5]	none	12/161 (7.5%) [16,17]	0/160 (0.0%)	OR 12.81 (1.65 to 99.7) [16]	0 fewer per 1000 (from 0 fewer to 0 fewer) [16]	⊕⊕⊕○ MODERATE	CRITICAL
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 study [9]	serious [10,18]	not serious	serious	serious [5]	none	[19]		not estimable	not estimable	⊕○○○ VERY LOW	CRITICAL

ITT = intention to treat population (all randomized subjects who had received at least one dose of treatment); conventionally used to assess safety parameters in drug trials;
MITT = modified intention to treat population (all missing or discontinued subjects are regarded as failures); conventionally used to assess efficacy parameters in drug trials
RR: Relative Risk

Footnotes:

1. Trial 204: blinded, placebo-controlled, duration two months; delamanid 100mg BD + OBR vs OBR alone
2. Rated serious because of uneven proportions available for analysis (12.4% and 21.9% in the intervention and control groups respectively)
3. Serious indirectness when intended duration of the intervention (6 months) is compared to the one that was actually administered in Trial 204 (2 months)
4. Indirect outcome (uncertain prognostic accuracy) of 2 month SCC; however, Expert Group (EG) did not downgrade further
5. Number of events and sample size limited, wide confidence intervals that lead to uncertainty about the balance of benefits and harms

6. 2-month sputum culture conversion among MDR-TB patients (Solid); Odds for achieving SCC at Day 57 using solid media in Trial 204 (MITT population); Cochran-Mantel-Haenzel test stratified by cavitation, placebo group as reference (Refer to Figure 2 and Table 5 in the EG Synthesis Document)
7. 2-month sputum culture conversion among MDR-TB patients (MGIT); Odds for achieving SCC at Day 57 using MGIT in Trial 204 (MITT population); Cochran-Mantel-Haenzel test stratified by cavitation, placebo group as reference; RR based on regression analysis is 1.753 (0.996 to 3.084) (Refer to Figure 4 and Tables 4 and 6 in the EG Synthesis Document)
8. Adjusted for presence of cavities, degree of cavitation, drug resistance
9. The 24-month observational period refers to any delamanid exposure (100mg BD or 200mg BD vs OBR only in both Trials 204 and 208 (total duration 8 months) and followed to end of 24 months
10. Treatment interruption between Trial 204 and Trial 208, minimum 28 days and approximately one-third >4 months later; outcome assessment not blinded, clinician's opinion
11. Sustained SCC refers to patients with sequential sputum culture results remaining negative after initial conversion until the 24 months observation point in patients who received any dose of delamanid during Trial 204 and Trial 208 *vs.* OBR alone for the full duration of 8 months comprising these two trials; Cure at 24 months refers to patients who met the criterion of at least 5 consecutive negative sputum cultures over the previous 12 months;
12. Measured after 2 months only – long term outcomes may differ; downgraded for indirectness of the outcome
13. Serious adverse events reported by more than one patient in the delamanid 200mg BD group showed slightly more events (20/160), but not significantly different from control: RR 1.43 (0.74 to 2.59)
14. Further explanation can be obtained from Table 19 in the EG Synthesis Document
15. Clinically significant event; QT prolongation defined as above 460 msec in men and above 480 msec in women (Gler et al NEJM 2012 describes the same frequencies of occurrence for the 100mg BD + OBR *vs*. OBR alone groups in their Table 2 under the heading: Incidence of adverse events occurring in >=10% of patients in either delamanid group and with greater frequency than in the placebo group); All AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 13.1 coding system
16. Relative risk for prolongation of more than 60 msec is greater than 12 and statistically highly significant; for the purpose of calculating RR, a numerator of 1/160 instead of 0/160 was used for the control group in order to quantify the magnitude of the effect (also see Table 21 in the EG Synthesis Document)
17. Also note that QT prolongation >=60 msec in the delamanid 200mg BD group = 17/160 (10.6%)
18. There is not enough information on the denominator for intervention and placebo patients
19. Four patients (4/205, 2.0%), 2 in each treatment group, had confirmed resistance to delamanid (defined as growth on solid media in the presence of 200 ng/mL delamanid, the epidemiologic break-point). The clinical significance of resistance as defined in this trial has not yet been established; however, in all four cases, the exposure to delamanid exceeded the optimal threshold established in EBA trials suggesting that the development of resistance to delamanid in these cases was not due to delamanid exposure but rather likely to treatment history and initial drug resistance profile.

Table 5: The GRADE evidence to recommendation

<table>
<tr><th></th><th>Criteria</th><th>Judgments</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr><td>Problem</td><td>Is there a problem priority?</td><td>○ No
○ Probably no
○ Uncertain
○ Probably yes
● Yes
○ Varies</td><td>The emergence of drug-resistant tuberculosis is a major threat to global tuberculosis care and control. WHO estimates that around 500,000 new multidrug-resistant tuberculosis (MDR-TB) cases occurred in the world in 2012. Of these, only 94,000 were reported to WHO, largely as a result of critical gaps in diagnostic and treatment capacity in most countries. Furthermore, 92 countries have now reported at least one case of extensively drug-resistant tuberculosis (XDR-TB) (Global Report 2013). 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 2010, only 48% were treated successfully, as a result of high frequency of death (15%) and loss to follow-up (28%).</td><td>The expert group considered children, people living with HIV and pregnant and breastfeeding women as subgroups.</td></tr>
<tr><td rowspan="2">Benefits & harms of the options</td><td>What is the overall certainty of this evidence?</td><td>○ No included studies
● Very low
○ Low
○ Moderate
○ High</td><td rowspan="2">The relative importance or values of the main outcomes of interest:
<table>
<tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr>
<tr><td>Cure at 24 months assessed with solid culture)</td><td>CRITICAL</td><td>⊕○○○
VERY LOW</td></tr>
<tr><td>Serious Adverse Events</td><td>CRITICAL</td><td>⊕⊕○○
LOW</td></tr>
<tr><td>Mortality at 24 months</td><td>CRITICAL</td><td>⊕○○○
VERY LOW</td></tr>
<tr><td>Sputum culture conversion at two months as a surrogate for cure (assessed with solid culture, MITT population)</td><td>CRITICAL</td><td>⊕○○○
VERY LOW</td></tr>
<tr><td>Sputum culture conversion in at two months as surrogate for cure (assessed with MGIT liquid culture, MITT population)</td><td>CRITICAL</td><td>⊕○○○
VERY LOW</td></tr>
<tr><td>Cure at 24 months (after treatment for full 8 months) (assessed with: solid culture)</td><td>CRITICAL</td><td>⊕○○○
VERY LOW</td></tr>
<tr><td>Electrocardiogram QT prolongation</td><td>CRITICAL</td><td>⊕⊕⊕○
MODERATE</td></tr>
<tr><td>Acquired resistance to delamanid (follow-up range 24 weeks)</td><td>CRITICAL</td><td>⊕○○○
VERY LOW</td></tr>
<tr><td>Time to culture conversion at two months as surrogate for cure (assessed with MGIT liquid culture, MITT population)</td><td>CRITICAL</td><td>⊕○○○
VERY LOW</td></tr>
</table></td><td rowspan="2">Treatment success (treatment completion and 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). QT prolongation was possibly associated with hypokalemia.

Although the indication for delamanid use is six months, the review of the data indicated that those patients who received six months delamanid did so in various combinations of doses and after an initial period of at least two 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.</td></tr>
<tr><td>Is there important uncertainty about how much people value the main outcomes?</td><td>○ Important uncertainty or variability
○ Possibly important uncertainty or variability
● Probably no important uncertainty of variability
○ No important uncertainty of variability
○ No known undesirable</td></tr>
</table>

<table>
<tr><th></th><th>Criteria</th><th>Judgments</th><th>Research evidence</th><th>Additional considerations</th></tr>
<tr>
<td></td>
<td>Are the desirable anticipated effects large?</td>
<td>○ No
○ Probably no
○ Uncertain
● Probably yes
○ Yes
○ Varies</td>
<td rowspan="3">Summary of findings: Control: OBR alone
<table>
<tr><th>Outcome</th><th>Without Delamanid plus OBR</th><th>With Delamanid plus OBR</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr>
<tr><td>Cure at 24 months (assessed with solid culture)</td><td>452 per 1000</td><td>610 per 1000 (466 to 737)</td><td>158 more per 1000 (from 14 more to 285 more)</td><td>RR 1.35 (1.03 to 1.63)</td></tr>
<tr><td>Serious Adverse Events</td><td>88 per 1000</td><td>108 per 1000 (53 to 204)</td><td>20 more per 1000 (from 34 fewer to 116 more)</td><td>RR 1.23 (0.61 to 2.33)</td></tr>
<tr><td>Mortality at 24 months:</td><td>82 per 1000</td><td>8 per 1000 (1 to 63)</td><td>74 fewer per 1000 (from 19 fewer to 81 fewer)</td><td>RR 0.1 (0.01 to 0.77)</td></tr>
<tr><td>Sputum culture conversion at two months as a surrogate for cure (assessed with MGIT liquid culture, MITT population)</td><td>296 per 1000</td><td>453 per 1000 (326 to 628)</td><td>157 more per 1000 (from 30 more to 332 more)</td><td>RR 1.53 (1.1 to 2.12)</td></tr>
<tr><td>Sputum culture conversion at two months as surrogate for cure (assessed with solid culture, MITT population)</td><td>336 per 1000</td><td>538 per 1000 (397 to 733)</td><td>202 more per 1000 (from 61 more to 397 more)</td><td>RR 1.6 (1.18 to 2.18)</td></tr>
<tr><td>Cure at 24 months (after treatment for full eight months) (assessed with: Solid culture)</td><td>771 per 1000</td><td>940 per 1000 (840 to 979)</td><td>170 more per 1000 (from 69 more to 208 more)</td><td>RR 1.22 (1.09 to 1.27)</td></tr>
<tr><td>Electrocardiogram QT prolongation</td><td>19 per 1000</td><td>51 per 1000 (11 to 152)</td><td>33 more per 1000 (from 8 fewer to 133 more)</td><td>RR 2.74 (0.6 to 8.1)</td></tr>
<tr><td>Acquired resistance to delamanid (follow-up range 24 weeks)</td><td>0 per 1000</td><td>0 per 1000 (0 to 0)</td><td>not estimable</td><td>not estimable</td></tr>
<tr><td>Time to culture conversion at two months as surrogate for cure (assessed with MGIT liquid culture, MITT population)</td><td>239 per 1000</td><td>146 per 1000 (101 to 216)</td><td>92 fewer per 1000 (from 23 fewer to 138 fewer)</td><td>HR 0.58 (0.39 to 0.89)</td></tr>
</table>
</td>
<td>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 <u>not</u> 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).</td>
</tr>
<tr>
<td></td>
<td>Are the undesirable anticipated effects small?</td>
<td>○ No
○ Probably no
○ Uncertain
● Probably yes
○ Yes
○ Varies</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Are the desirable effects large relative to undesirable effects?</td>
<td>○ No
○ Probably no
○ Uncertain
○ Probably yes
○ Yes
● Varies</td>
<td>Inconsistencies between published and submitted data have been noted, for example in the number of death. Data presented here are those submitted by the manufacturer or those of published data as noted.</td>
</tr>
</table>

	Criteria	Judgments	Research evidence	Additional considerations
Resource use	**Are the resources required small?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ● 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. 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 . Indirect transmission benefits were NOT considered. 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. The analysis is based on drug cost parameters provided by the manufacturer for the cost effectiveness analysis.
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ● 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. 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 prioritization including considerations on equity and budget impact would be recommended from an economic perspective before country adoption. 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. 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. There are many sources of uncertainty: parameters (costs, prices, efficacy, long term outcomes) 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.

	Criteria	Judgments	Research evidence	Additional considerations
Equity	**What would be the impact on health inequities?**	○ Increased ○ Probably increased ● Uncertain ○ Probably reduced ○ Reduced ○ 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). Implementation of any new intervention may be associated with trade-offs in the absence of additional resource mobilization.
Acceptability	**Is the option acceptable to key stakeholders?**	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ 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. Twice-daily dosing may affect acceptability, including DOT.
Feasibility	**Is the option feasible to implement?**	○ No ○ Probably no ○ Uncertain ● Probably yes ○ Yes ○ 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 - this may require referral to specialist or extension of ECG access and mobilizing resources to monitor ECG. Twice-daily dosing may also affect feasibility, including DOT. Oral (in comparison to injectable medication) use may facilitate use. Careful monitoring of 'early adopters' would be required to ensure that cost-effectiveness can be achieved in 'real world' settings.

Recommendation
In MDR-TB patients, does the addition of delamanid to a background regimen based on WHO-recommendations safely improve patient outcomes?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	○	○	○	●	○

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	○	○	●	○

Recommendation	The Expert Group recommends that delamanid (100mg BD for 6 months) may be added to a WHO recommended regimen in MDR-TB adult patients under the following conditions (conditional recommendation, very low certainty in estimates of effect)
Justification	The Expert Group felt that there were more benefits than harm because harmful effects were less important and less frequent. A conditional recommendation was proposed because the evidence is of very low quality overall, leaving uncertainty about the actual effects. Considerations for use of delamanid in different populations settings: **Population:** The population to whom this recommendation applies includes MDR-TB patients. The population excludes patients with QT interval prolongation, i.e. delamanid should not be used in patients with QT interval prolongation. Considerations for appropriate patient selection in whom delamanid may be used include patients who do not tolerate injectables, those with additional resistance to fluoroquinolones or injectables or XDR-TB, those with extended lesions, advanced disease and others deemed at higher baseline risk for poor outcomes. Delamanid should not be used as a single drug addition in patients on a failing regimen and should only be used in situations of pharmacovigilance with close ECG monitoring **Intervention:** Adherence to principles of designing a WHO recommended regimen is required). **Outcomes**: Based on the available evidence, the Expert Group considered that culture conversion at two months should **not** be used as a surrogate marker for treatment outcome in MDR-TB patients.
Subgroup considerations	The recommendation includes PLHIV, as these were included in the RCT and treated alongside non-HIV patients. There is no data on children. There is also no data on pregnant and breastfeeding women, substance abuse (drug and alcohol) and the elderly. There is no data on patients with diabetes and or extrapulmonary TB.
Implementation considerations	A duly informed decision making-process by patients should be followed -this includes that the intervention be presented as an option and includes information about uncertainty about the effects. In some settings, informed consent is mandatory for MDR treatment and local practice should be observed. Local practice requiring written informed consent should be observed (5:5 vote, 2 missing). With regard to QT prolongation, data were available for simultaneous use with levofloxacin, but not with moxifloxacin. No evidence is available on combined use with clofazimine. In particular, no data for the simultaneous use of bedaquiline and delamanid are available. Therefore, for this interim guidance, no recommendation about the simultaneous use of delamanid and bedaquiline or other QT prolonging drugs is being made until further data are available. This recommendation is valid for a maximum of two years and will be updated should additional data become available.

Monitoring and evaluation	Monitor QT and serum potassium levels. Caution should be exercised with combined use of QT prolonging drugs (particularly moxifloxacin, clofazimine, levofloxacin). Active pharmacovigilance should be established for these patients. Protection of delamanid (resistance) should be a key consideration when used. DST testing should be in place.
Research possibilities	Data are needed in specific sub-groups/populations: children, pregnant and breastfeeding women, people with substance abuse (drug and alcohol) and elderly persons, patients with diabetes (other comorbidities), PLHIV on ART, Further research is needed on drug-drug interactions and optimal dosing, as well as on DST testing for delamanid and pharmacokinetic data for once-daily dosing.

References

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Annex 3: Expert Group meeting on interim guidance for the use of delamanid in the treatment of multidrug-resistant tuberculosis

15–16 April 2014, Geneva

MEETING OBJECTIVES and AGENDA

Background:

The emergence of drug-resistant tuberculosis is a major threat to global tuberculosis care and control. WHO estimates that about 450,000 new multidrug-resistant tuberculosis (MDR-TB) cases occurred in the world in 2012. Of these, only 94000 were reported to WHO, largely as a result of critical gaps in diagnostic and treatment capacity in most countries. Furthermore, 92 countries have now reported at least one case of extensively drug-resistant tuberculosis (XDR-TB) (Global Report 2013).

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 2010, only 48% were treated successfully, as a result of high frequency of death (15%) and loss to follow-up (28%) commonly associated with adverse drug reactions and high costs associated with adherence to treatment. In addition, it is estimated that up to a third of MDR-TB cases may have strains with additional resistance to fluoroquinolones and/or injectable drugs (aminoglycosides or capreomycin), rendering their treatment even more difficult, with recourse to highly toxic drugs. Finally, the global deployment of new, rapid diagnostics for drug resistance, such as the Xpert MTB/RIF assay, has increased the demand for treatment of MDR-TB patients, that has not been matched by a similar expansion in the provision of appropriate treatment for diagnosed cases. While 94,000 cases were reported to WHO as having been diagnosed in 2012, only 77,000 patients were known to have been placed on treatment for MDR-TB. The increased global scale-up of rapid tests to diagnose such cases is bound to make this gap even wider in the coming years. The lack of effective and affordable drugs for the treatment of MDR-TB is known to weigh heavily among the reasons why programmes cannot scale up their treatment efforts to the required level.

The landscape of drug development for treatment of TB has evolved dramatically over the last ten years, and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB. Dossiers have been submitted to stringent regulatory authorities (SRAs) under procedures of "accelerated" or "conditional" approval for marketing these new drugs. Among these, delamanid, a nitro-imidazole, has been recommended for conditional marketing authorisation by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) on the 26th November 2013. For this reason, WHO aims to evaluate the added value of this compound within the context of existing guidelines on programmatic management of MDR-TB and issue interim guidance on the use of delamanid as and if appropriate.

Overall Objective:

To evaluate the added benefit of a newly available drug, delamanid, to the treatment of MDR-TB, a life-threatening form of tuberculosis, and provide recommendation to WHO for provision of interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment as and if appropriate.

Specific objectives:

1. To evaluate the added value of this new drug in combination with currently recommended MDR-TB drugs according to the following criteria:
   1.1 for efficacy, through the evaluation of the performance of the new drug *vs.* placebo in addition to optimised background therapy, using the surrogate markers of "culture conversion at 2 months" and "time to culture conversion" and survival;

   1.2 for safety, through the evaluation of the type, frequency and severity of adverse reactions related to the new drug and mortality;

   1.3 for feasibility and affordability, through the estimated cost and cost-effectiveness of MDR-TB treatment including the new drug based on modeling studies.

2. Based on this evaluation, to provide recommendation for interim guidance on the use of the drug as part of WHO-recommended MDR-TB treatment regimens, including attention to all concerns relevant to the use of a new drug for which Phase III clinical trial data are not yet available.

Expected outcomes

1. Draft a recommendation based on the quality of the evidence, health impact, feasibility, cost-effectiveness, patients values, as well judgments about trade-offs between benefits and harms, including the description of parameters to be put in place at programme level to monitor and evaluate the introduction and use of the drug within recommended MDR–TB regimens;
2. Identify further needs in terms of data and future research during the interim period until final phase III data become available.

	DAY 1 – 15th April 2014	*Chair: Holger Schünemann*
9h00 – 9h15	Welcome and Introduction	Mario Raviglione
9h15 – 9h45	Objectives of the meeting Presentation of participants Declaration of Interest statements	Christian Lienhardt

Session 1: Background and procedures

9h45 – 10h15	GRADE approach for WHO guidelines	Holger Schünemann
10h15 – 10h30	Review of MDR–TB treatment guidelines	Dennis Falzon
10h30 – 10h45	The PICO question for provisional guidance on use of delamanid in the treatment of MDR–TB	Holger Schünemann
10h45 – 11h15	*Coffee break*	

Session 2: Review of available data on delamanid

11h15 -11h45	Review of pre-clinical, toxicology and PK data	Bernard Fourie
11h45 – 12h30	Discussion	All
12h30 -13h30	*Lunch*	

Session 3: The efficacy aspects

13h30 – 14h00	Review of key efficacy results	Bernard Fourie
14h00 – 14h15	Culture conversion as proxy marker of treatment outcome	Katya Kurbatova (remotely)
14h15 – 15h30	Discussion	All
15h30 – 16h00	*Tea break*	

Session 4: The safety and mortality aspects

16h00 – 16h15	Review of key safety results	Bernard Fourie
16h15 – 17h30	Discussion	All
17h30 – 18h00	Recap and Key points	Holger Schünemann
18h00	*End Day 1*	

DAY 2 – 16th April 2014		*Chair: Holger Schünemann*
Session 5: The cost-effectiveness aspects		
8h00 – 8h20	Presentation of CE modeling analysis	Anna Vassall
8h20 – 9h00	Discussion	All
Session 6: Interim recommendations for use of delamanid in MDR–TB treatment		
9h00 – 10h15	Establish draft recommendations based on quality of the evidence, balance between desirable and undesirable effects, resources, feasibility, values and preferences.	All
10h15 – 10h45	*Coffee break*	
Session 6: Interim recommendations for use of delamanid in MDR–TB treatment (contd)		
10h45 – 12h30	Establish draft recommendations based on quality of the evidence, balance between desirable and undesirable effects, resources, feasibility, values and preferences.	All
12h30 -13h30	*Lunch*	
13h30 – 15h30	Review recommendations as a whole (continued), including conditions associated with potential recommendations. Completes decision grid and determine the strength of recommendation.	All
15h30 – 16h00	*Tea break*	
16h00 – 16h30	Recommendation for further data and future research, including on various populations (PLHIV, children, other)	All
16h30 – 17h30	Recap and review of final recommendations	All
17h30 – 18h00	Next steps, implementation and Conclusion	Diana Weil/Karin Weyer
18h00	*Adjourn*	

Annex 4: Declarations of interest

Declarations of interest		
Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB **None declared**		
Mauricio Barretto Erlina Burhan Lucy Chesire Dick Menzies	Norbert Ndjeka Nguyen Viet Nhung Alena Skrahina	Holger Schünemann Piret Viiklepp

Declarations of interest	
Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB **Declared: insignificant**	
Daniela M. Cirillo	6e. I was invited to participate to a restricted one day meeting where Otsuka shared the agar protocol and results from DST for delamanid. I have an MTA for using the pure substance for DST if requested and I participated to EQA with other SRLs. Non-monetary involvement.

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Declared: insignificant

Erica Lessem	2a. 1. TAG's TB/HIV Project receives funding from the Bill & Melinda Gates Foundation – non commercial support - tUSD963,312 2. General support to Treatment Action Group's Hepatitis C /HIV program (not for any of my work or the TB/HIV project): $10k received for Hepatitis C fact sheets; $18k for HIV R&D Tracking; $20k for AIDS and Aging, Pathogenesis Report and HCV/HIV co-infection report; $30k for the HIV chapters of Pipeline, the HIV sections of TAGline and the National HIV/AIDS Strategy report

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Declared: insignificant

James Seddon	6b: I undertook my PhD (3 years) with the Desmond Tutu TB center in Cape Town. I continue to have active collaborations with this group. I am aware that they will be carrying out research into the use of delamanid in children. I have no role in these studies

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Declared: insignificant

Dalene Van Delft	6e: I am an MDR TB survivor - received compassionate use of a new drug, bedaquiline.

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Declared: significant – Technical resource person status

Frank Cobelens	2a: Subcontractor on a research grant to evaluate cost-effectiveness of shortened moxifloxacin-based first-line regimens (TB Alliance). 6e: KNCV Tuberculosis Foundation has submitted a research proposal for funding by Otsuka. This proposal is for a desk study that is not specifically about delamanid and is currently under consideration. It does not involve any drugs. No contract has been signed, no payments have been made.

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Declared: significant – Technical resource person status

Kelly Dooley	6e: I am one of the lead investigators on an ACTG proposal for a clinical trial evaluating the safety of delamanid and bedaquiline given alone or together to patients with MDR-TB taking background MDR treatment. […]. Support and funding will be provided by the DAIDS at NIH, not the drug companies. I have not and will not receive financial support directly or indirectly from any drug company for participation in this trial.

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Declared: significant – Technical resource person status

Michael Rich	6e. I am the co-leader on a multi-million dollar grant to UNITAID (under review and not yet approved) which deals with promoting the use of new TB drugs, including delamanid, the subject of this meeting, in 17 different countries. The grant also includes request for money for a trial of different regimens using new TB drugs, also including delamanid in some of the proposed regimens. The grant assumes possible future negotiation with drug produces on cost of new TB drugs for use within the grant.

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Declared: significant – Technical resource person status

Francis Varaine	MSF has an agreement with Otsuka for the compassionate use of Delamanid. MSF is in discussion with Otsuka for the potential use of Delamanid with other new and repurposed drugs in a clinical trial. Not linked to the outcome of the meeting.

Declarations of interest

Expert Group meeting on interim guidance for the use of delamanid in the treatment of MDR-TB

Technical Resource Persons - None declared

Bernard Fourie Ekaterina Kurbatova	Anna Vassall	

Annex 5: GRADE glossary

Absolute effect:

The absolute measure of intervention effects is the difference between the baseline risk of an outcome (for example, in patients receiving control interventions or estimated in the observational studies) and the risk of outcome after the intervention is applied; that is, the risk of an outcome in people who were exposed to or received an intervention. Absolute effect is based on the relative magnitude of an effect and baseline risk.

Bias:

A systematic error or deviation in results or inferences from the truth. In studies of the effects of health care, the main types of bias arise from systematic differences in the groups that are compared (selection bias), the care that is provided, exposure to other factors apart from the intervention of interest (performance bias), withdrawals or exclusions of people entered into a study (attrition bias) or how outcomes are assessed (detection bias). Systematic reviews of studies may also be particularly affected by reporting bias, where a biased subset of all the relevant data are available.

Critical outcome:

An outcome that has been assessed as 7–9 on a scale of 1–9 for the importance of the outcome when making decisions about the optimal management strategy.

Dose response gradient:

The relationship between the quantity of treatment given and its effect on outcome. This factor may increase confidence in the results.

Evidence profile:

A table summarizing the quality of the available evidence, the judgements that bear on the quality rating and the effects of alternative management strategies on the outcomes of interest. It includes an explicit judgement of each factor determining the quality of evidence for each outcome. It should be used by guideline panels to ensure that they agree about the judgements underlying the quality assessments and to establish the judgements.

High quality evidence:

We are very confident that the true effect lies close to that of the estimate of the effect.

Important outcome:

An outcome that has been assessed as 4–6 on a scale of 1–9 for the importance of the outcome when making decisions about the optimal management strategy. It is important but not critical.

Imprecision:

Refers to whether the results are precise enough. When assessing imprecision, guideline panels need to consider the context of a recommendation and other outcomes, whereas authors of systematic reviews need only to consider the imprecision for a specific outcome. Authors should consider width of confidence intervals, number of patients (optimal information size) and number of events.

Inconsistency:

Refers to widely differing estimates of the treatment effect (that is, heterogeneity or variability in results) across studies that suggest true differences in underlying treatment effect. When the magnitude of intervention effects differs, explanations may lie in the patients (e.g. disease severity), the interventions (e.g. doses, co-interventions, comparison interventions), the outcomes (e.g. duration of follow-up) or the study methods (e.g. randomized trials with higher and lower quality risk of bias).

Indirectness:

Refers to whether the evidence directly answers the health-care question. Indirectness may occur when we have no direct or head-to-head comparisons between two or more interventions of interest; it may occur also when the question being addressed by the guideline panel or by the authors of a systematic review is different from the available evidence regarding the population, intervention, comparator or an outcome.

Low quality evidence:

Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Moderate quality evidence:

We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Quality of evidence:

Refers to a body of evidence not to individual studies (that is, means more than risk of bias of studies). It includes consideration of risk of bias, imprecision, inconsistency, indirectness and publication bias, as well as the magnitude of treatment effect and the presence of a dose– response gradient. In the context of a systematic review, the ratings of the quality of evidence reflect the extent of our confidence that the estimates of the effect are correct. In the context of making recommendations, the quality ratings reflect

the extent of our confidence that the estimates of an effect are adequate to support a particular decision or recommendation.

Randomized controlled trial:

An experimental study in which two or more interventions are compared by being randomly allocated to participants. In most trials, one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals (for example, in a household) or interventions are assigned within individuals (for example, in different orders or to different parts of the body).

Relative effect:

The relative effect for a dichotomous outcome from a single study or a meta-analysis will typically be a risk ratio (relative risk), odds ratio or, occasionally, a hazard ratio.

Strength of a recommendation:

The degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. Either strong or weak/conditional.

Strong recommendation:

Most patients would want the recommended course of action, and only a small proportion would not; therefore, clinicians should provide the intervention. The recommendation can be adapted as policy in most situations.

Study limitations (risk of bias):

The risk of misleading results as a result of flawed design or conduct of randomized or observational studies. It is one of the five categories of reasons for downgrading the quality of evidence. It includes lack of allocation concealment; lack of blinding; incomplete accounting of patients and outcomes events; selective outcome reporting bias; and other limitations, such as stopping early for benefit, use of non- validated outcome measures, carryover effects in crossover trials, and recruitment bias in cluster-randomized trials.

Surrogate outcome:

Outcome measure that is not of direct practical importance but is believed to reflect an outcome that is important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate outcomes are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow- up. Also called: intermediary outcomes or surrogate end-points.

Very low quality evidence:

We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Weak/conditional recommendation:

The majority of patients would want the suggested course of action, but many would not. Clinicians should recognize that different choices will be appropriate for individual patients, and that they must help each patient arrive at a management decision consistent with his or her values and preferences. Policy-making will require substantial debate and involvement of various stakeholders.

Annex 6: List of Expert Review Panel members

(Area of expertise in parentheses)

- Jose A. Caminero, University General Hospital of Gran Canaria Dr Negrin, Las Palmas, Spain and MDR-TB Unit Coordinator, The UNION, Paris, France – (Clinical practice, representative from gGLC)
- Richard E. Chaisson, Johns Hopkins University School of Medicine, USA (trialist, clinician, HIV/TB specialist)
- Gavin Churchyard, Chief Executive Officer, Aurum Institute for Health Research, Johannesburg, South Africa – (STAG-TB member, Clinical practice, TB, TB/HIV, research, drug and vaccine development)
- Anna Marie Celina Garfin, Department of Health – National Center for Disease Prevention and Control, Philippines – (Programme management, end-user)
- Giovanni Battista Migliori, Director of WHO Collaborating Centre for TB and Lung Diseases Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy – (STAG-TB member, pulmonologist/MDR-/XDR-TB expert and TB technical adviser)
- Rohit Sarin, Director, National Institute of TB & Respiratory Diseases (NITRD), Sri Aurobindo Marg, New Delhi, India – (Clinical consultant in TB and Respiratory Diseases, member of rGLC SEAR, end-user).
- Maarten van Cleeff, KNCV Tuberculosis Foundation, The Hague, The Netherlands – (STAG-TB member, TB, TB/HIV, poverty and ethics, diagnosis, health system strengthening, operational research, monitoring and programme evaluation).
- Andrew Vernon, US Centers for Disease Control and Prevention (CDC), USA (trialist, clinician, surveillance)

World Health Organization