# The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

## Interim policy guidance

World Health Organization

*This guidance was developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development on, 2012 available at http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf.*

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- *Cost-effectiveness of introducing bedaquiline in MDR-TB regimens – an exploratory analysis*, Anna Vassall, London School of Hygiene and Tropical Medicine, London, United Kingdom.

Available here:
http://www.who.int/tb/challenges/mdr/bedaquiline/en/index.html

# Acknowledgements

This document was prepared by Christian Lienhardt, Karin Weyer, Dennis Falzon, Fraser Wares, Ernesto Jaramillo, Diana Weil and Mario Raviglione (World Health Organization (WHO), Stop TB Department) on the basis of consensus at an international Expert Group meeting convened by WHO in Geneva, Switzerland on 29–30 January 2013.

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## Declarations of interest

All Expert Group (EG) members, technical resource consultants and members of the External Review Panel completed Declaration of Interest (DOI) forms. These were reviewed by the WHO Legal Department prior to the EG meeting and preparation of the current *Interim Policy Guidance*.

Two EG members (Erica Lessem and Andrew Vernon) declared receiving support from pharmaceutical companies for work not related to the present guidance. These declarations were deemed to be insignificant. The other members of the EG, as well as the technical resource consultants and the members of the External Review Panel, declared no interest.

# Executive summary

## Background

The emergence of drug resistance is a major threat to global tuberculosis (TB) care and control. The World Health Organization (WHO) estimates that up to half a million new cases of multidrug-resistant tuberculosis (MDR-TB) cases (i.e. resistant to, at least, rifampicin and isoniazid) occur each year globally. Current treatment regimens for MDR-TB are far from satisfactory: the overall duration is 20 months or more, requiring daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB, and have a high cost. Among MDR-TB patients started on treatment globally in 2009, only 48% were treated successfully, largely as a result of a high frequency of patient deaths (15%) and loss to follow-up (28%), which is commonly associated with adverse drug reactions, among other factors. In a subset of 200 extensively drug-resistant tuberculosis (XDR-TB) patients in 14 countries, treatment success reached only 33% overall and 26% of the patients died. New drugs that would help build a better, safer, less toxic, shorter and cheaper regimen are therefore urgently needed to reduce patient suffering and mortality.

The landscape of TB drug development has evolved dramatically over the past ten years, and novel drugs are entering Phase III trials for the treatment of MDR-TB. Among these, a new drug, bedaquiline, has recently (December 2012) been granted accelerated approval by the United States Food and Drug Administration (US-FDA) based on Phase IIb data. Similar submissions are currently being made to other national regulatory authorities worldwide. WHO Member States have requested the organization to provide interim policy guidance on the use of bedaquiline as part of the treatment of MDR-TB.

It is acknowledged that developing interim guidance on the use of a new TB drug on the basis of Phase IIb trial data is a novel step for WHO. Issuing interim guidance carries with it the responsibility of ensuring that it provides specific recommendations on the conditions for the use of the drug that reflect the limited data currently available. It will also be necessary for WHO to review, revise and/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 drug may adversely affect TB care and control efforts overall – potentially prompting the emergence of bedaquiline resistance and the possible loss of the first new TB chemotherapeutic drug in over 40 years.

## Objectives, rationale and methods used to develop the guidance

This document provides interim guidance for the use of bedaquiline in conjunction with other WHO-recommended MDR-TB treatments. It also specifies the essential treatment and management conditions for the use of this drug. The main audiences are national TB control programmes (NTP), other public health agencies, and other public and private partners involved in planning, implementing and monitoring MDR-TB 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 MDR-TB service strengthening. Individuals responsible for programme planning, budgeting, resource mobilization, and training activities for MDR-TB diagnostic services may also benefit from this guidance.

An Expert Group (EG) was convened by the WHO/Stop TB Department in Geneva, Switzerland from 29th to 30th January 2013 to assess all available data on bedaquiline, and with a view to issuing interim policy recommendations on its use, as appropriate. Since efficacy and safety data available for this drug, used for the treatment of MDR-TB, are results from Phase IIb studies only (i.e. not Phase III trials), the potential guidance could only be provisional, until further clinical trial and safety data are available.

The overall objective of the EG meeting was to evaluate the added benefit of bedaquiline for the treatment of MDR-TB and, if appropriate, to provide recommendations to WHO for interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment.

The specific objectives were:

(1) To evaluate the efficacy and safety of bedaquiline in addition to currently WHO-recommended MDR-TB treatments.

(2) 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 into MDR-TB programmes.

(3) 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 potential use of a new drug for which Phase III clinical trial data are not yet available.

The EG consisted of researchers, epidemiologists, end-users (clinicians and NTP officers), community representatives and experts in evidence synthesis. Declarations of Interest were managed according to WHO rules.

Publicly available data on the pre-clinical and clinical development of the drug were reviewed to assess efficacy, safety and tolerability of the drug, and complemented by modelling work to assess the potential cost-effectiveness of programmatic implementation. Issues to be addressed in future research were also discussed. In

addition, data on final outcomes of the pivotal proof-of-concept Phase II trial (that had not been evaluated by the US-FDA in their accelerated regulatory assessment) were provided to WHO by the manufacturer, allowing more comprehensive review by the EG. To comply with current standards for evidence assessment in formulation of policy recommendations, the GRADE system[1] adopted by WHO for policy and guidelines development was used.

A PICO question[2] was pre-defined in consultation with the EG: *"In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendations safely improve patient outcomes?"*

The following outcomes were selected by the EG for evaluation:

1. Cure by end of study – 120 weeks.
2. Serious adverse events during investigational 24 weeks treatment phase.
3. Mortality.
4. Time to culture conversion over 24 weeks.
5. Culture conversion at 24 weeks.
6. Acquired resistance to second-line drugs (fluoroquinolones, amino-glycosides and capreomycin) at 72 weeks.

## Summary of available data

Data were available from a series of studies and trials made public by the manufacturer, and supplemented with final outcome results made available to WHO. Main findings on efficacy and safety originated from two Phase IIb trials: (1) C208, a two-stage trial of which Stage 1 was an exploratory study, and Stage 2 was a multi-centre, stratified, randomized, double-blind placebo-controlled trial serving as a pivotal proof-of-efficacy study; and (2) C209, a single-arm, open label trial.

### *1. Evidence for the efficacy of bedaquiline in the treatment of MDR-TB*

Subjects aged 18 to 65 years with newly diagnosed pulmonary MDR-TB were enrolled in the C208 Stage 2 efficacy trial from 15 sites in Brazil, India, Latvia, Peru, the Philippines, the Russian Federation, South Africa and Thailand; 160 subjects were randomized to receive bedaquiline or placebo as well as a five-drug MDR-TB background regimen (BR), which consisted of various combinations of fluoroquinolones, aminoglycosides, pyrazinamide, ethionamide, ethambutol, and/or cycloserine/terizidone. Bedaquiline was given at 400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks. After 24 weeks, subjects continued the BR of MDR-TB therapy until a treatment duration of 96 weeks was achieved. The total duration of the study was 120 weeks. An interim analysis was done at 72 weeks.

1 GRADE: Grading of Recommendation Assessment, Development and Evaluation.

2 PICO: Population, Intervention, Comparator, Outcome.

The primary efficacy endpoint for the C208 Stage 2 trial was time to sputum culture conversion in commercial liquid culture (MGIT™ 960 Mycobacterial Detection System, Becton Dickinson Diagnostic systems, USA) during the 24-week investigational treatment period (subjects who discontinued before week 24 were considered as not having culture converted). The analysis was conducted on a 'modified' intention to treat population (mITT) of 132 subjects (66 in each of the bedaquiline and placebo groups).[3]

The median time to culture conversion was 83 days (95%CI: 56, 97) in the bedaquiline group versus 125 days (95%CI: 98, 168) in the placebo group. Using Cox proportional hazards model (adjusted for lung cavitation and pooled centre) there was a higher chance of faster culture conversion in the bedaquiline arm compared with the placebo arm (HR=2.44 [1.57, 3.80], p<0.0001). The proportion of subjects with culture conversion at Week 24 (secondary efficacy endpoint) was 78.8% in the bedaquiline group versus 57.6% in the placebo group (p=0.008). The percentage of responders at Week 72 (i.e. the time point attained by all Stage 2 subjects at the interim analysis) was 71.2% in the bedaquiline group versus 56.1% in the placebo group (p=0.069). Utilizing all available efficacy data up to end of study (Week 120), the percentage was 62.1% of respondents in the bedaquiline group versus 43.9% in the placebo group (p=0.035).

Efficacy was further evaluated by the EG using WHO-recommended treatment outcome definitions applied to Week 120 final data. The proportion of subjects defined as cured at 120 weeks was 57.6 % in the bedaquiline arm versus 31.8% in the placebo arm (p=0.003).

### *2. Evidence for the safety of bedaquiline in the treatment of MDR-TB*

Information was available from pooled data from C208 Stage 1 and Stage 2 trials, with 102 subjects in the 'Any bedaquiline' group and 105 subjects in the 'Any placebo' group: 96.1% of subjects in the Any bedaquiline group and 95.2% subjects in the Any placebo group experienced at least one adverse event (AE). The most frequently reported AEs in the Any bedaquiline group (>20.0% of subjects) were nausea (35.3%), arthralgia (29.4%), headache (23.5%), hyperuricaemia (22.5%), and vomiting (20.6%). The incidence of these AEs was generally similar in the Any bedaquiline and the Any placebo groups, except for headache (in 23.5% and 11.4% of subjects, respectively), nausea (35.3% and 25.7%, respectively), and arthralgia (29.4% and 20.0%, respectively). Additional AEs were, in order of frequency: dizziness, increased transaminases, myalgia, diarrhoea and QT prolongation on electrocardiogram (ECG). There was a higher incidence of events related to hepatic disorders (mostly increases in transaminases) in the Any bedaquiline group compared to the Any placebo group. QT prolongations were observed in both the bedaquiline and placebo groups, but were more pronounced in the bedaquiline

3 The mITT-excluded subjects who had drug-susceptible TB, XDR- or unconfirmed MDR-TB (based on susceptibility tests taken prior to randomization), or had missing or negative baseline cultures, or who were positive at baseline, but had no post-baseline culture results.

group: more patients had QTcF[4] values above 450 ms (26.6% versus 8.6%) and more patients had QTcF increases >60 ms from reference values (9.1 % versus 2.5%). The use of bedaquiline with other potential QT prolonging medications (e.g. clofazimine) was found to increase the risk of prolonged QT interval.

Twelve deaths were reported from the C208 Stage 2 trial in total (i.e. irrespective of when deaths occurred). Of these, 10/79 (12.7%) came from the bedaquiline group and 2/81 (2.5%) from the placebo group (p=0.017) (intention to treat analysis). In the bedaquiline group, 8 of the 10 deaths occurred in culture converters. TB was reported to be the cause of death in the two placebo-arm deaths and in 5 of the 10 bedaquiline-arm deaths (all occurred off bedaquiline treatment). Counting deaths strictly at the 120 weeks cut-off point revealed nine in the bedaquiline and one in the placebo group. There were no discernible associations between death and culture conversion, relapse, microbiological response, susceptibility to drugs used in the BR, human immunodeficiency virus (HIV) status, or severity of TB-related disease. Despite detailed descriptive line listings of all deaths, the reasons for the imbalance in deaths between the two arms were not identified.

## Expert Group findings

The EG concluded that the randomized, double-blind, design of the pivotal study was of high quality, although information on the desired sample size and on the actual randomization process was not available. The EG was, however, concerned about the use of mITT analysis (and subsequent assumptions made), as well as the representativeness of the study population. Experts were also concerned about the low cure rate at 120 weeks observed in the placebo group, when compared to those reported from recent published reviews. This could indicate that the patients included in the trial were not representative of the MDR-TB population at large and that the effects observed in the bedaquiline arm may not be reproducible under programme conditions.

Concern was also expressed that, in the absence of patient data on drug susceptibility test status in the different arms, the BR used in various sites of the trial may not have been compliant with WHO recommendations. There was further concern on the generalizability of the data to the target patient group (e.g. a greater proportion of HIV co-infected TB cases occurred in the placebo arm; XDR-TB patients were excluded). Lastly, there was concern on the generalizability of study findings to all populations and to all regions in the world. The overall quality of evidence for efficacy was therefore graded as "Low", i.e. the EG had low confidence in the estimate of effect (or efficacy) of bedaquiline.

The EG expressed concern on the risk of QT prolongation and the additive effect in combination with other MDR-TB drugs reported to prolong QT. The EG also expressed concerns regarding co-morbidities (notably HIV infection and liver diseases), and the

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

effects of alcohol or substance use on the risk of severe adverse events. The evidence for safety as reflected by AEs was therefore graded as "Very low".

The EG was highly concerned with the observed difference in mortality between the bedaquiline and placebo arms in the C208 stage 2 trial. No clear pattern could be observed, and reason(s) for the imbalance were unclear. The quality of evidence for mortality as a measure of safety was therefore graded as "Very low".

Lastly, the EG had concerns about the available data on emergence of resistance, due to a high risk of bias, as serial drug susceptibility data on patient strains were not provided (i.e. at enrolment and during follow-up). The quality of evidence for acquisition of resistance to fluoroquinolones, aminoglycosides or capreomycin was, therefore, graded as "Very low".

Modelling of the incremental cost-effectiveness of adding bedaquiline to WHO-recommended MDR-TB regimens was conducted by an independent consultant contracted by WHO for review by the EG. The model assumed that bedaquiline would be added to treatments for all patients starting MDR-TB treatment. Data from WHO were available on current MDR-TB treatment costs (excluding programme costs) and effectiveness in several high TB burden settings. Several scenarios were explored to appraise the cost-effectiveness of bedaquiline in these settings. Under the model assumptions, the bedaquiline-containing regimens were assessed as relatively cost-effective in most settings, but results were ambiguous in low-income settings and highly dependent on the assumptions made about the generalizability of trial results to routine settings. The EG noted that further analysis would be needed to test the robustness of the assumptions in various settings and to separately assess affordability. As the recommendation of the EG was to use bedaquiline only for selected sub-groups of the full MDR-TB patient population, as opposed to all patients with MDR-TB that were considered in the cost-effectiveness analysis, the cost-effectiveness model needs to be further refined such that results are available for these sub-groups specifically.

The final grading of evidence for the use of bedaquiline in MDR-TB treatment was "Very low". There was modest agreement among the EG that the quality of evidence for possible benefits was "Low" due to imprecision and indirectness, and high agreement that the quality of evidence for possible harms was "Very low" due to imprecision, indirectness and risk of bias. The EG could not reach consensus, however, on the overall balance of harms and benefits and proceeded to a vote (observers and technical resources consultants were excluded). The results were as follows: 10 votes that benefits outweighed harms; 4 votes that harms outweighed benefits; and 2 abstentions (including the chair).

## Expert Group recommendations

The EG suggested that, as an interim recommendation, bedaquiline may be added to a WHO-recommended regimen in adult MDR-TB patients under the following

conditions *(conditional recommendation, very low confidence in estimates of effect, i.e. very low quality of evidence):*

- when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide according to WHO recommendations cannot be designed;
- when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance.

In addition, the EG recommended that:

- a duly informed decision-making process by patients should be followed;
- bedaquiline be used with caution in people living with HIV, as well as in patients with co-morbidities (e.g. diabetes) or people reporting alcohol or substance use, due to limited or no information;
- bedaquiline be used for a maximum duration of 6 months and at suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks);
- bedaquiline must not be added alone to a failing regimen;
- baseline testing and monitoring for QT prolongation and development of arrhythmia is imperative;
- clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place;
- spontaneous reporting of adverse drug reactions is reinforced at country level and active pharmacovigilance is established among patient groups treated with the drug;
- in the absence of a specific drug-susceptibility test, resistance to bedaquiline should be monitored through assessment of minimum inhibitory concentrations (MICs);
- resistance to other anti-TB drugs should be monitored following WHO recommendations.

The EG also recommended that these interim recommendations be re-assessed in 2015, or earlier if additional data of significance become available that increase the knowledge on safety, toxicity and/or efficacy of bedaquiline. In addition, the EG identified a number of research topics to be addressed to inform future guidance on the use of bedaquiline.

## WHO Interim policy recommendations

In view of the aforementioned evidence assessment and advice provided by the EG, WHO recommends that **bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB *(conditional recommendation, very low confidence in estimates of effects).*** Given the limited data available on bedaquiline and its use under the various situations that may be encountered in different clinical settings, adequate provisions for safe and effective use of the drug must be in place. Consequently, countries are advised to follow a phased approach to bedaquiline

implementation, ideally through observational cohorts, where the following measures are in place. The WHO recommendation for the inclusion of bedaquiline in the adult treatment regimen of MDR-TB is subject to the following five conditions being met:

1. **Treatment is administered under closely monitored conditions,** adhering to best practices in treatment delivery, to enable optimal drug effectiveness and safety. Given that the results of the Phase IIb trial showed an excess mortality in the bedaquiline arm versus placebo arm, and that results of Phase III trials are only expected a few years from now, it is particularly important that the introduction of bedaquiline is carefully monitored for safety. It is therefore recommended that the following measures are in place:
    a. Sound treatment and management protocols, including clear patient eligibility criteria, procedures for informed consent and defined roles and responsibilities of all professionals involved. The treatment protocols should allow for the prospective capture of data on key variables for both effectiveness and safety. Safety concerns are best addressed using the cohort event monitoring methodology employed for active pharmacovigilance. Electronic systems will facilitate efficient data management and generation of key indicators.
    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 and management programmes is provided by an independent group of experts in clinical management and public health – for instance, such as a national MDR-TB advisory group.

2. **Proper patient inclusion.** The current recommendation for the use of bedaquiline applies to adults (≥18yrs) with pulmonary disease. Special caution is needed when bedaquiline is used in persons aged 65 years and older, and in adults living with HIV, as data on efficacy and safety are extremely limited. Use of the drug in pregnant women and children is not advised due to a lack of evidence on safety and efficacy. While patients with exclusive extrapulmonary disease were not included in the bedaquiline trial, the use of the drug in extrapulmonary TB patients may be considered, extrapolating from the data in patients with pulmonary TB.

3. **Patient informed consent obtained.** Health-care providers should ensure that the patient is: (i) aware of the novel nature of bedaquiline; (ii) appreciates the reason why the drug is being proposed to be included in the regimen; and (iii) recognizes the benefits and potential harms. In addition, health-care workers should obtain the patient's agreement on the inclusion of bedaquiline in the prescribed treatment regimen. This informed consent process must be documented and signed by the patient, and applies to all situations where bedaquiline is employed, including under compassionate use programmes.

4. **Adherence to principles of designing a WHO-recommended MDR-TB regimen.** As uncertainties remain about the relative benefits and harms when using bedaquiline, caution is advised when other options to compose an effective MDR-TB

regimen using conventional second-line medication still exist. In addition, the shortcomings of conventional drug-susceptibility testing (DST) of second line anti-TB drugs must be taken into account: DST of second-line drugs is only considered to be accurate and reproducible for fluoroquinolones, aminoglycosides (kanamycin, amikacin) and capreomycin (a polypeptide).

a. The WHO-recommended MDR-TB treatment regimen 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. Bedaquiline may be indicated if such a regimen is not feasible because of:
   i) *in vitro* resistance to a drug (see b. and c. below );
   ii) known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen; or
   iii) unavailability or lack of a guaranteed supply of a drug(s).

b. MDR-TB patients with strains resistant to fluoroquinolones or the second-line injectable drugs (kanamycin, amikacin, capreomycin) represent a particular concern given that these are the two most effective classes of second-line drugs. In such cases, bedaquiline may have a crucial role to play to strengthen a regimen, bringing the number of drugs likely to be effective to a minimum of four, and averting the acquisition of additional resistance and progression towards XDR-TB.

c. While experience in the use of bedaquiline in the management of XDR-TB is limited, it may have an indication in such patients given the limitations in designing an effective regimen based on existing recommendations in many situations. In patients resistant to both classes of injectable drugs and also to fluoroquinolones (i.e. XDR-TB), bedaquiline may lower the need to include drugs belonging to Group 5, some of which have unproven anti-TB activity, high cost, and/or high toxicity.[5] Bedaquiline may thus be used with or instead of a Group 5 drug. In these cases, special caution is advised on the potential increase of adverse drug reactions due to potential drug–drug interactions, particularly the synergistic cardiotoxic effect on QT prolongation, necessitating close ECG monitoring.

d. In line with general principles of TB therapeutics, bedaquiline 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 implies that bedaquiline should not be added alone to a failing regimen, and should be introduced well before the regimen fails completely.

e. Bedaquiline should be used strictly at the dose recommended by the manufacturer, i.e. 400mg daily for the first two weeks, followed by 200mg three times per week

5 Group 5 drugs belong to different classes of medicines and are not recommended by WHO for routine use in DR-TB patients.

at least 48 hours apart, for a total maximum duration of 24 weeks. Available data suggest better uptake of bedaquiline when administered with food.

5. **Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.**
    a. Special measures need to be put in place to ensure the early detection and timely reporting of adverse events using active pharmacovigilance methods, such as 'cohort event monitoring'. Any adverse drug reaction attributed to bedaquiline should also be reported to the national pharmacovigilance centre as part of the spontaneous reporting mechanism in the country. As for any other drug in the 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.
    b. When introducing bedaquiline 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 bedaquiline, particularly clofazimine and moxifloxacin, may increase the risk of cardiotoxicity. Thus, if the drug is introduced into the MDR-TB treatment regimen, monitoring of patients for cardiac dysrhythmias or QT prolongation (i.e. using ECG), liver dysfunction, renal impairment, and other effects as denoted in the product briefing package is mandatory.
    c. Caution should be exercised when giving bedaquiline together with accompanying drugs that may inhibit liver function (e.g. the effect of ketoconazole or lopinavir/ritonavir on the enzyme CYP3A4), as these could increase bedaquiline concentrations, resulting in toxicity, or with accompanying drugs that may induce liver function (e.g. the effect of rifampicin on the enzyme CYP3A4), as these could result in sub-therapeutic bedaquiline concentrations, resulting in reduced efficacy. Of note, very limited data are available on drug–drug interactions with antiretroviral medicines, and these are based on single dose studies conducted in healthy normal volunteers. Therefore, people living with HIV who will be receiving bedaquiline as part of MDR-TB treatment should have their antiretroviral therapy (ART) regimens designed in close consultation with HIV clinicians and ART specialists.
    d. Lastly, caution is advised in patients with pre-existing health conditions that may be exacerbated or worsened by bedaquiline. Currently there are no data on the efficacy and safety of bedaquiline 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 required.

WHO strongly recommends the acceleration of Phase III trials in order to generate a more comprehensive evidence base to inform future policy guidance on bedaquiline. WHO strongly urges the development of accurate and reproducible DST methods for bedaquiline and other second-line drugs.

# List of abbreviations

| | |
|---|---|
| **AE** | adverse events |
| **ART** | antiretroviral therapy |
| **BR** | background regimen |
| **DDI** | drug–drug interaction |
| **DOI** | declaration of interest |
| **DST** | drug-susceptibility testing |
| **ECG** | electrocardiogram |
| **EG** | Expert Group |
| **ERP** | External Review Panel |
| **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 |
| **mITT** | modified intention to treat |
| **NTP** | national tuberculosis control programme |
| **PLHIV** | people living with HIV |
| **PMDT** | programmatic management of drug-resistant tuberculosis |
| **STAG-TB** | Strategic and Technical Advisory Group for TB |
| **TB** | tuberculosis |
| **USAID** | United States Agency for International Development |
| **US-FDA** | United States Food and Drug Administration |
| **XDR-TB** | extensively drug-resistant tuberculosis |
| **WHO** | World Health Organization |

# Interim policy guidance

## The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

## 1. Background

The emergence of drug resistance is a major threat to global tuberculosis (TB) care and control. The World Health Organization (WHO) estimates that up to half a million cases of multidrug-resistant tuberculosis (MDR-TB) cases (i.e. resistant to, at least, rifampicin and isoniazid) occur each year globally.[6] Of these, less than 20% were reported to WHO, largely as a result of critical gaps in diagnostic and treatment capacity in most countries. Furthermore, 84 countries have now reported at least one case of extensively drug-resistant tuberculosis (XDR-TB), a form of TB that is resistant to at least four of the core anti-TB drugs (rifampicin, isoniazid, fluoroquinolones and second-line injectable agents), and associated with high mortality, particularly among people living with human immunodeficiency virus (PLHIV).

The global deployment of new, rapid diagnostic tests for drug resistance, such as the Xpert MTB/RIF assay, is increasing the demand for treatment of MDR-TB patients. Current treatment regimens for drug-resistant TB are far from satisfactory. Whereas most drug-susceptible TB patients can usually be treated successfully 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 2009, only 48% were treated successfully, as a result of high frequency of mortality (15%) and loss to follow-up (28%), commonly associated with adverse drug reactions, among other factors.[7] In a subset of 200 XDR-TB patients in 14 countries, treatment success only reached 33% overall and 26% of cases died. Effective new drugs and treatment regimens are therefore urgently needed to improve safe and effective treatment to reduce patient suffering and deaths.



6 *Global tuberculosis control: WHO report 2010* (WHO/HTM/TB/2010.7). Geneva, World Health Organization, 2010.

7 *Global tuberculosis control: WHO report 2012* (WHO/HTM/TB/2012.6). Geneva, World Health Organization, 2012.

The landscape of TB drug development has evolved dramatically over the past ten years, and novel drugs are presently, or will soon be, entering Phase III trials for the treatment of MDR-TB. Among these, the bedaquiline compound, proposed for use in the treatment of MDR-TB, has been granted license by the United States Food and Drug Administration (US-FDA) in December 2012. Files have been submitted to a number of other national regulatory authorities, which are currently being evaluated under procedures of 'accelerated' or 'conditional' approval based on early (Phase IIb) clinical data. Several WHO Member States have requested the organization to provide interim advice on the use of bedaquiline in MDR-TB treatment. For these reasons, WHO convened an Expert Group (EG) meeting from 29th to 30th January 2013 in Geneva, Switzerland 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 as part of the treatment of MDR-TB is warranted.

It is acknowledged that developing interim guidance on the use of a new TB drug on the basis of Phase IIb data only is a novel step by WHO, and one made in response to requests from WHO Member States for specific guidance. Issuing interim guidance carries with it the responsibility of ensuring that it provides specific recommendations on the conditions for the use of the drug, which reflect the limited data that is currently available. It will also be necessary for WHO to review, revise or update the interim guidance as additional substantive data on efficacy and safety of bedaquiline 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 drug may adversely affect TB care and control efforts overall – potentially prompting the emergence of bedaquiline resistance and the possible loss of the first new TB drug in over 40 years.

# 2. Guidance purpose and target audience

## 2.1. Purpose

The overall objective of this guidance is to provide the interim principles that should guide the use of bedaquiline – a newly available drug for the treatment of MDR-TB, a life-threatening form of tuberculosis – in conjunction with other WHO-recommended MDR-TB treatment regimens. It also specifies the essential treatment and management conditions for use of this drug, in particular patient eligibility criteria and safety conditions, and presents the necessary caveats relevant to the use of a new drug for which Phase III clinical trial data are not yet available.

WHO guidelines are already available for the programmatic management of drug-resistant tuberculosis (PMDT), and the current document should be read in conjunction with those guidelines.[8, 9]

This document should be read in conjunction with the detailed findings included in the EG meeting report. The interim guidance positions bedaquiline 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.

Manuals and tools to operationalize the interim guidance and introduce bedaquiline within a programmatic context will be provided in subsequent WHO publications.

The planned date of review of this interim guidance is 2015, or earlier in case of significant developments. It is expected that data emerging from planned Phase III clinical trial(s) and early implementing countries will inform future review and possible refinement of the interim policy guidance.

### 2.2 Target audience

The main target audiences are national TB control 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 MDR-TB service strengthening. Individuals responsible for programme planning, budgeting, resource mobilization, and training activities for TB diagnostic services may also benefit from this guidance.

## 3. Guidance 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 EG (see below), the areas requiring evidence synthesis.



8 *Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008*. (WHO/HTM/TB/2008.402). Geneva, World Health Organization, 2008.

9 *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update*. Geneva: World Health Organization, 2011.

## 3.1 Expert Group meeting

An EG meeting was convened by the WHO Stop TB Department from 29th to 30th January 2013 to assess all available data on bedaquiline, and with a view to developing interim policy recommendations on its use, as appropriate. The EG (Annex 2) comprised researchers, epidemiologists, end-users (clinicians and national TB programme officers), community representatives and evidence synthesis experts. The EG meeting followed a structured agenda (Annex 3) and was chaired by a clinical epidemiologist/methodologist with expertise and extensive experience in evidence synthesis and guideline development.

The overall objective of the EG meeting was to evaluate the added benefit of bedaquiline for the treatment of MDR-TB and, if appropriate, to provide recommendations to WHO for interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment.

The specific objectives were:

1. To evaluate the efficacy and safety of bedaquiline in addition to currently WHO recommended MDR-TB treatment regimens.
2. 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 into MDR-TB programmes.
3. 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 developed and applied in consultation with the WHO Legal Department. Every member of the EG was 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 completed forms were reviewed by the WHO Guideline Steering Group in conjunction with the WHO Legal Department prior to the EG meeting. Particular 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 interests. In addition, individuals who were involved in clinical trials conducted by the bedaquiline manufacturer, 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, as well as individuals who had been involved in development and testing of the new drug or other, potentially competing, drugs were not considered for inclusion in the EG.

DOI statements were summarized by the WHO/Stop TB Department (STB) secretariat at the start of the meeting. A summary is attached in Annex 4.

Technical resource consultants participated in the meeting and provided specific information on selected technical issues but were not involved in the decision-making process, or in the preparation of the actual recommendations. Observers participated only at the request of the Chair and did not contribute to the preparation of the recommendations. All participants signed a confidentiality agreement and were reminded of the need for confidentiality until the full WHO process had been concluded.

## 3.3 Review of evidence

Publicly available data on the pre-clinical and clinical development of the drug were assembled and reviewed to assess efficacy, safety and tolerability of the drug,[10] and complemented by modelling work to assess the cost-effectiveness of implementation of the drug in MDR-TB programmes. Issues to be addressed in future research were also discussed. In addition, data on final outcomes of the pivotal proof-of-efficacy Phase II trial (that were not available at the time of US-FDA review) were provided to WHO by the manufacturer.

An independent consultant was contracted to review and synthesize all available data into a comprehensive document that was made available to all members of the EG, and prepare the draft GRADE[11] evidence tables that were reviewed by the EG.

To comply with current standards for evidence assessment in formulation of policy recommendations, the GRADE system, adopted by WHO for all policy and guidelines development,[12] was used. The GRADE approach, assessing both the quality of evidence and strength of recommendations, aims to provide a comprehensive and transparent approach for developing policy guidance. The GRADE process assesses the impact of a particular intervention on patient-important outcomes and the generalizability of results to the target population, taking into consideration the comparator used and whether comparison was direct or indirect.

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



10 All available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm

11 GRADE: Grades of Recommendation Assessment, Development and Evaluation (www.gradeworkinggroup.org).

12 WHO *Handbook for Guideline Development, 2012*. Geneva, World Health Organization, 2012. Available at: http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf

The following outcomes were selected by the EG for evaluation:

1. Cure by end of study – 120 weeks.
2. Serious adverse events during investigational 24 weeks treatment phase.
3. Mortality.
4. Time to culture conversion over 24 weeks.
5. Culture conversion at 24 weeks.
6. Acquired resistance to second-line drugs (fluoroquinolones, amino-glycosides and capreomycin) at 72 weeks.

In a first stage, experts evaluated the **quality of evidence** for each of the above outcomes according to the following criteria:

- 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 generalizability.
- Imprecision: wide confidence intervals for treatment outcome estimates.
- Other considerations: possibility of publication bias, etc.

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

In the second 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 a balance of effects (benefits weighed against harms), patient values and preferences, resources and equity. The system used to establish the strength and ranking of the recommendations involved assessing each intervention on the basis of: (1) desirable and undesirable effects; (2) quality of available evidence; (3) values and preferences related to interventions in different settings; and (4) cost options for different epidemiological settings.

## 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). Only exceptionally, when a consensus could not be achieved among members, did the EG proceed to a vote (with simple majority rule) – this was resorted to in only one instance (see page 27). Concerns and opinions of EG members 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 on 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 10 reviewers external to the EG, including content experts, end-users from high TB and HIV burden countries, and representatives from the WHO 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 were reflected in the final version of the guidance document.

### 3.6 Financial support

Financial support for the EG meeting and related analyses were provided under the USAID consolidated grant to the WHO Stop TB Department (project number: US 2012 0392). The US Centers for Disease Control (CDC) completed the evaluation of sputum culture conversion as a surrogate marker of MDR-TB treatment outcome (work carried out by Ekaterina Kurbatova and colleagues).

## 4. Evidence base for policy formulation

Publicly available data on the pre-clinical and clinical development of bedaquiline were reviewed. These included toxicity, dosing and pharmacokinetic studies, drug–drug interaction (DDI) studies, an early bactericidal activity study, safety studies, a pivotal Phase IIb clinical trial and an (ongoing) single arm open-label trial.[13,14]

A total of 265 subjects participated in 11 Phase I trials with bedaquiline (208 subjects were enrolled in eight single-dose trials evaluating bedaquiline doses up to 800 mg; and 57 subjects were enrolled in three multiple-dose trials evaluating bedaquiline doses up to 400 mg daily with a maximum treatment duration of 15 days). The Phase I trials provided a basic understanding of bedaquiline's pharmacokinetic characteristics, DDI potential, and short-term safety/tolerability in healthy subjects and in a special population of moderately hepatic-impaired subjects. A double-blind, single-dose trial was conducted to evaluate the effect of a single supra-therapeutic (800 mg) dose of bedaquiline on the QT corrected (QTc) interval.

A Phase IIa, 7-day extended early bactericidal activity trial in 75 patients with drug-susceptible TB (evaluating doses up to 400 mg bedaquiline daily) was conducted to evaluate clinical antimycobacterial activity of bedaquiline.

13 Janssen Pharmaceutical Companies, 2012. *TMC207 (bedaquiline) treatment of patients with MDR-TB (NDA 204–384)*. Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012. All documents available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm

14 References for all documents available on bedaquiline can be found at the website indicated in page 1 of this document.

The bedaquiline Phase II programme encompassed 2 Phase IIb clinical trials: C208 and C209. Trial C208 consisted of two stages, of which Stage 1 was an exploratory study and Stage 2 was a multi-centre, stratified, randomized, double-blind placebo-controlled trial, serving as a pivotal proof-of-efficacy study. Study C209 is a single-arm, open label trial (ongoing).

## 4.1 Evidence for the efficacy of bedaquiline in the treatment of MDR-TB

Evidence for efficacy derives from the C208 Stage 2 trial, in which subjects aged 18 to 65 years with newly diagnosed MDR-TB – enrolled from 15 sites in Brazil, India, Latvia, Peru, the Philippines, the Russian Federation, South Africa and Thailand – were randomized in a 1:1 ratio to receive bedaquiline 400 mg, or placebo, daily for the first two weeks, followed by 200 mg bedaquiline, or placebo, three times per week for the remaining 22 weeks.[15] In both the bedaquiline and placebo arms, patients received a five-drug MDR-TB background medication regimen (BR) consisting of fluoroquinolones (mainly ofloxacin), aminoglycosides (mainly kanamycin), pyrazinamide, ethionamide, ethambutol, and cycloserine/terizidone in various combinations. After 24 weeks, subjects continued the BR of MDR-TB therapy until a total treatment duration of 96 weeks was achieved. The total duration of the study was 120 weeks. All subjects presented in the data sets completed Week 72 (the pre-determined study data cut-off point) and also Week 120 (end of study).

The ***primary efficacy endpoint for C208 Stage 2 was time to sputum culture conversion***[16] in commercial liquid culture (MGIT™ 960 Mycobacterial Detection System, Becton Dickinson Diagnostic systems, USA) during the 24-week investigational treatment period, evaluated after all subjects had completed the 24-week investigational treatment period, or discontinued earlier. In the primary efficacy analysis, subjects who discontinued before week 24 were considered as not having culture converted (censored at the last culture visit, i.e. missing = failure). Primary efficacy analysis was based on a modified intention to treat (mITT) population, which excluded subjects who had drug-susceptible TB, XDR-TB or unconfirmed MDR-TB (based on susceptibility tests taken prior to randomization), or had missing or negative baseline cultures, or who were positive at baseline, but had no post-baseline culture results. The mITT population was composed of 132 subjects (66 in each of the bedaquiline and placebo groups). The median time to culture conversion was 83 days (95%CI: 56, 97) in the bedaquiline group compared to 125 days (95%CI: 98, 168) in the placebo group. Primary analysis at Week 24 using the Cox proportional hazards model (adjusted for lung cavitation and pooled centre) showed a statistically significant difference in time to culture conversion

15 This dose regimen was selected based on non-clinical safety and microbiology data as well as safety and pharmacokinetic results from several Phase I clinical trials with bedaquiline, and early bactericidal activity results from the earlier Phase IIa trial C202.

16 Defined as: "two consecutive negative cultures from sputa collected at least 25 days apart (as well as all intermediate cultures), and this culture negativity was not followed by a confirmed positive MGIT culture (or a single positive sputum result after the subject completed the trial), and the subject did not discontinue up to the time point being analyzed".

between the two treatment groups in favour of bedaquiline: HR=2.44 [1.57, 3.80] (p<0.0001).

The ***secondary endpoint for C208 Stage 2 was the proportion of patients with culture conversion.*** The proportion of subjects with culture conversion at Week 24 (i.e. 24-week responders [missing = failure]) was 78.8% in the bedaquiline arm and 57.6% in the placebo arm (p = 0.008, based on a logistic regression model with only treatment as covariate). Similar analyses were conducted at Week 72 and Week 120. The percentage of responders (missing = failure) at Week 72 (i.e. the time point attained by all Stage 2 subjects at the interim analysis who were ongoing in the trial) was 71.2% in the bedaquiline group and 56.1% in the placebo group (p= 0.069). Utilizing all available efficacy data up to end of study (Week 120), the percentage was 62.1% in the bedaquiline group and 43.9% in the placebo group (p= 0.035).

Efficacy was further evaluated using ***WHO-recommended treatment outcome definitions*** applied to Week 120 final data. Cure was defined as: "at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment; if only one positive culture is reported during that time, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart". In the bedaquiline arm, 38/66 (57.6%) subjects were categorized as cured, compared to 21/66 (31.8%) in the placebo arm (p=0.003).

**Table 1. Summary of evidence for the efficacy of bedaquiline in the treatment of MDR-TB**

| Parameters | Bedaquiline | Placebo | p value |
|---|---|---|---|
| Median time to sputum conversion | 83 days (95% CI: 56,97) | 125 days (95% CI: 98,168) | <0.0001 |
| Proportion of patients with culture conversion | | | |
| Week 24 | 78.8 % | 57.6% | 0.008 |
| Week 72 | 71.2% | 56.1% | 0.069 |
| Week 120 | 62.1% | 43.9% | 0.035 |
| Proportion cured | 57.6% (38/66) | 31.8% (21/66) | 0.003 |



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

The safety database covered non-clinical aspects (pharmacology and toxicology) during pre-clinical development, and human experience in Study C208 (pivotal randomized control trial, double-blind placebo-controlled) and Study C209 (single arm, open label). The intention to treat (ITT) population in each of these studies was used for the description of safety. A total of 160 subjects contributed to ITT analysis, 79 in the bedaquiline arm and 81 in the placebo arm.

Similar numbers of patients in the bedaquiline group and placebo group reported adverse events (AEs) (Table 2). The most frequently reported AEs in the bedaquiline group (from both controlled and uncontrolled trials) were nausea, arthralgia, headache and vomiting. Additional AEs identified were, in order of frequency: dizziness, increased transaminases, myalgia, diarrhoea and QT prolongation on electrocardiogram (ECG). AEs of at least grade 3 were similar in both groups: 28/102 (27.5) in the bedaquiline group and 24/105 (22.9) in the placebo group. Main safety concerns included QT prolongation and cardiac events, hepatic events, and deaths.

**Table 2. Summary of adverse events of interest**

| | Bedaquiline/BR N=79 (%) | Placebo/BR N=81 (%) |
|---|---|---|
| Musculoskeletal and connective tissue | 39 *(49.4)* | 40 *(49.4)* |
| *Myalgia* | *6 (7.6)* | *7 (8.6)* |
| *Musculoskeletal pain* | *4 (5.1)* | *4 (4.9)* |
| *Rhabdomyolysis/Myopathy* | *0* | *0* |
| Gastrointestinal disorders | 53 (67.1) | 53 (65.4) |
| *Pancreatitis* | *1 (1.3)* | *0* |
| *Increased amylase* | *2 (2.5)* | *1 (1.2)* |
| *Nausea* | *32 (40.5)* | *30 (37.0)* |
| *Vomiting* | *23 (29.1)* | *22 (27.2)* |
| *Upper abdominal pain* | *10 (12.7)* | *7 (8.6)* |
| *Gastritis* | *7 (8.9)* | *16 (19.8)* |

## *Cardiovascular safety (Trial C208: pooled experience Stage 1 and Stage 2)*

Mean QTcF [17] increases were observed in both the pooled bedaquiline ('Any bedaquiline') and pooled placebo ('Any placebo') groups, but they were more pronounced in the Any bedaquiline group: more patients had QTcF values above 450 ms (26.6% versus 8.6%) and more patients had QTcF increases >60 ms from reference values (9.1 % versus 2.5%). There were no reports of Torsade de Pointes events, and no reported fatalities from sudden death. Bedaquiline, in multiple dosing, can prolong the QT interval and the risk is highest during the treatment phase, but could extend beyond the treatment period. The use of bedaquiline with QT-prolonging medications increases the risk of prolonged QT interval, i.e. QTcF prolongation from multiple QTcF prolonging drugs could be additive (e.g. clofazimine).

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

**Table 3. QT prolongation during treatment as reflected by worst QTcF**

| ECG parameter, abnormality | Investigational treatment phase: pooled controlled trials | |
|---|---|---|
| | Bedaquiline (Any) N (%) | Placebo (Any) N (%) |
| QTcF calc (ms) | 102 | 105 |
| 450 ms – ≤480 ms | 23 (22.5) | 7 (6.7) |
| 480 ms – ≤500 ms | 3 (2.9) | 1 (1.0) |
| More than 500 ms | 1 (1.0) | 0 |
| QTcF calc (ms) | 99 | 101 |
| Increase by 30–60 ms | 52 (52.5) | 33 (32.7) |
| Increase by >60 ms | 10 (10.1) | 4 (4.0) |

N = number of ITT subjects with data; QTcF: QT interval corrected for heart rate to the Fridericia method.

## *Hepatic events (Trial C208: pooled experience Stage 1 and Stage 2)*

There was a higher incidence of events related to hepatic disorders in the Any bedaquiline group (9 subjects, 8.8%) compared to the Any placebo group (2 subjects, 1.9 %). Increases in transaminases accounted for the majority of these reported events. An analysis to identify cases of severe liver toxicity revealed 1 case of a patient who experienced concurrent >3-fold elevation of aspartate aminotransferase (AST) and >2-fold elevation in total bilirubin, but was confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background medications.

**Table 4. Investigator-reported hepatic events**

| Investigator-reported events | Bedaquiline 24 weeks (N=79) | Placebo 24 weeks (N=81) |
|---|---|---|
| Liver-related signs/symptoms | 8 (10%) | 3 (3.7%) |
| Hepatic disorders | 10 (12.5%) | 5 (6.7%) |
| Possible hepatic-related disorders | 10 (12.5%) | 5 (6.7%) |
| Hepatitis (non-infectious) | 2 (2.5%) | 1 (1.23%) |
| Hepatic failure, fibrosis, cirrhosis, liver damage-related conditions | 1 (1.25%) | 0 |

## *Mortality*

Four deaths were reported from the C208 Stage 1 trial: 2 out of 23 subjects (8.7%) in the bedaquiline arm and 2 out of 24 subjects (8.3 %) in the placebo arm. In the C208 Stage 2 trial, twelve deaths were reported in total (irrespective of when deaths occurred). Of these, 10/79 (12.7%) came from the bedaquiline group and 2/81 (2.5%) from the placebo group (p=0.017) (ITT analysis). In the bedaquiline group, 8 of the 10 deaths occurred in culture converters. TB was the cause of death in the two placebo-arm deaths and in 5 of the 10 bedaquiline-arm deaths (all occurred off bedaquiline treatment). Counting deaths strictly at the 120 weeks cut-off point reveal nine deaths in

the bedaquiline and one death in the placebo group. There was no discernible pattern between death and culture conversion, relapse, microbiological response, susceptibility to drugs used in the BR, HIV status, or severity of disease. Despite detailed descriptive line listings of all deaths, the reason(s) for the imbalance were not clear.

**Table 5. Trial C208 Stage 2: Causes of death**

| Subject | Treatment arm | Category | Cause of death |
|---|---|---|---|
| *Deaths while followed during trial* | | | |
| 208–4041 | BDQ | Non-responder; converted; discontinued | Alcohol poisoning |
| 208–4153 | BDQ | Non-responder; relapse | TB-related illness |
| 208–4224 | BDQ | Non-responder; relapse | TB-related illness |
| 208–5069 | BDQ | Non-responder; converted; discontinued | Cirrhosis, hepatitis, anaemia |
| 208–4399 | BDQ | Responder; converted | Cerebrovascular accident |
| 208–5067 | BDQ | Responder; converted | Peritonitis and septic shock |
| 208–4120 | Placebo | Non-responder; failure to convert | Haemoptysis (TB) |
| *Deaths during long-term survival follow-up of prematurely withdrawn subjects* | | | |
| 208–4127 | BDQ | Non-responder; failure to convert | TB-related illness |
| 208–4145 | BDQ | Non-responder; relapse | TB-related illness |
| 208–4378 | BDQ | Non-responder; relapse | Motor vehicle accident |
| 208–4464 | BDQ | Non-responder; failure to convert | TB-related illness |
| 208–4155 | Placebo | Non-responder; failure to convert | TB-related illness |

## 4.3. Cost effectiveness

Modelling of the incremental cost-effectiveness of adding bedaquiline to WHO-recommended MDR-TB regimens was conducted by an independent consultant contracted by WHO for review by the EG. The model assumed that bedaquiline would be added to treatment for all patients starting MDR-TB treatment. Data from WHO were available on current MDR-TB treatment costs (excluding programme costs) and effectiveness in several high TB burden settings. Several scenarios were explored to appraise the cost-effectiveness of bedaquiline in these settings. Under the model assumptions, the bedaquiline-containing regimens were assessed as relatively cost-effective in most settings, but results were ambiguous in low-income settings, and highly dependent on the assumptions made about the generalizability of trial results to routine settings. The EG noted that further analysis would be needed to test the robustness of the assumptions in various settings and to separately assess affordability. As the recommendation of the EG is to use bedaquiline for only selected sub-groups of the full MDR-TB patient population (as opposed to all patients with MDR-TB that were considered in the cost-effectiveness analysis), the cost-effectiveness model needs to be further refined such that results are available for these sub-groups specifically.

# 5. Expert Group recommendations

## 5.1. Summary of evidence to recommendation

Based on the GRADE process, the EG had a low level of confidence in using the available data for global decision-making, given that the available evidence was limited. There were concerns about imprecision and indirectness due to the small sample size, the use of mITT (i.e. not ITT) analysis, and the low quality of evidence for the background MDR-TB treatment regimens used in the trial. In particular, the EG was concerned about the low cure rate at 120 weeks observed in the placebo group when compared to those reported from recent published reviews.[18,19,20] This could indicate that the patients included in the trial were not representative of the MDR-TB population at large and that the effects observed in the bedaquiline arm may not be reproducible under programme conditions.

The EG also discussed the potential to draw conclusions for different sub-categories of MDR-TB patients, such as patients with strains resistant to either fluoroquinolones or injectable drugs. No evidence for use of the drug in XDR-TB patients was available, since these patients were excluded from the mITT analysis. No information, aside from MDR-TB status, was available on drug susceptibility testing at diagnosis. Members of the EG did, however, feel that the use of bedaquiline in XDR-TB patients or those with resistance or contraindication to fluoroquinolones or injectables may have added benefit, given that treatment options for these patients are severely curtailed.

The EG also concluded that recommendations could only be made on the use of bedaquiline in addition to current WHO-recommended regimens. Bedaquiline should not replace drugs generally recommended for MDR-TB treatment unless these are considered ineffective.[21]

There was modest agreement that the quality of evidence for benefits was "low" due to imprecision and indirectness, and high agreement that the quality of evidence for harms was "low" or "very low" due to imprecision, indirectness and risk of bias. The EG expressed particular concern about mortality risk, with a high degree of uncertainty about the evidence.



18 Ahuja SD et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Medicine* 2012;9(8):e1001300.

19 Orenstein EW et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infectious Diseases* 2009 Mar;9(3):153–61.

20 Johnston JC, Shahidi NC, Sadatsafavi M and Fitzgerald JM. Treatment Outcomes of Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis. *PLoS ONE*. 2009 Sep 9;4(9):e6914.

21 WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update.* (WHO/HTM/TB/2011.6). Geneva, World Health Organization, 2011.

**Table 6. Anti-tuberculosis agents for treatment of drug-susceptible and drug-resistant tuberculosis**

| | |
|---|---|
| Group 1 First-line oral agents | isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z); rifabutin (Rfb) [a] |
| Group 2 Injectable agents | kanamycin (Km); amikacin (Am); capreomycin (Cm); viomycin (Vm); streptomycin (S) |
| Group 3 Fluoroquinolones | moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Ofx) |
| Group 4 Oral bacteriostatic second-line agents | ethionamide (Eto); prothionamide (Pto); cycloserine (Cs); terizidone (Trd); *p*-aminosalicylic acid (PAS) |
| Group 5 Agents with unclear role in DR-TB treatment (not recommended by WHO for routine use in DR-TB patients) | clofazimine (Cfz); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H);[b] clarithromycin (Clr) |

[a] Rifabutin is not on the WHO Essential Medicines List. It has been added here as it is used routinely in many settings, among patients taking protease inhibitors.

[b] High-dose H is defined as 16–20 mg/kg/day.

The need for caution in prescribing bedaquiline was stressed, as well as the importance of clear and understandable communication with patients prior to drug prescription. Mention was made of the need to support this by informed consent, ideally in writing.

The EG could not reach consensus on the overall balance of harms and benefits and proceeded to a vote (observers and technical resources consultants were excluded). The results were as follows: 10 votes that benefits outweighed harms; 4 votes that harms outweighed the benefits; and 2 abstentions (including the chair).

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 survival but that it was less clear that patients would value microbiological culture conversion in the same way. EG members expressed the view that patient acceptance of bedaquiline would depend on the severity of their disease and the likelihood of designing an effective background regimen – e.g. XDR-TB patient groups might be more likely to accept the risk of taking a new drug with apparent increased risk of death than patients with uncomplicated MDR-TB without additional drug resistance.

The EG had difficulty reaching consensus on the resource requirements of the proposed recommendation. While the cost-effectiveness modelling showed overall benefit, there were concerns about the simplifying assumptions used (e.g. no accounting for the difference in serious adverse events, no accounting for effect on transmission, uncertainty about application of trial outcomes – including deaths – to routine programmatic conditions, etc.). The EG also felt that cost effectiveness would not necessarily translate into affordability or country readiness to pay given the potentially high cost of bedaquiline. Resource implications related to programme costs, training of health care staff, and establishing active pharmacovigilance systems were not explicitly

discussed due to time constraints. The EG nevertheless concluded that the resource implications of introducing bedaquiline would probably involve "small cost relative to net benefits".

Lastly, the EG felt that effects on equity of bedaquiline addition to WHO-recommended MDR-TB treatment was difficult to assess, due to the uncertainly of affordability and country willingness to pay, as well as the difference in opinion on the balance of benefits and harms discussed above.

## 5.2. Expert Group recommendations

The EG suggested that, as an interim recommendation, bedaquiline may be added to a WHO-recommended regimen in MDR-TB adult patients under the following conditions (conditional recommendation, very low confidence in estimates of effects):

- when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide, according to WHO recommendations, cannot be designed;
- when there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance.

In addition, the EG recommended that:

- a duly informed decision-making process by patients should be followed;
- bedaquiline be used with caution in people living with HIV, as well as in patients with co-morbidities (such as diabetes) or people reporting alcohol or substance use, due to limited or no information;
- bedaquiline be used for a maximum duration of 6 months and at the suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks);
- bedaquiline must not be added alone to a failing regimen;
- baseline testing and monitoring for QT prolongation and development of arrhythmia is imperative;
- clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place;
- spontaneous reporting of adverse drug reactions is reinforced at country level and active pharmacovigilance is established among patient groups treated with the drug;[22]
- in the absence of a specific drug-susceptibility test, resistance to bedaquiline should be monitored through assessment of minimum inhibitory concentrations (MICs);
- resistance to other anti-TB drugs should be monitored following WHO recommendations.

22 For more details see: *A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: enhancing the safety of the TB patient.* Geneva, World Health Organization, 2012. Available from: http://www.who.int/medicines/publications/pharmacovigilance_tb/

The EG also recommended that these interim recommendations be re-assessed in 2015, or earlier if additional data of significance become available increasing the knowledge on safety, toxicity and efficacy of bedaquiline (e.g. post-marketing studies, ongoing trials and other studies).

## 5.3. Research implications

The EG strongly supported the need for an acceleration of Phase III trials to expand knowledge on safety and efficacy of bedaquiline, with particular attention to mortality (including causes of death), in the treatment of MDR-TB. The EG identified further research gaps, including:

- development of a reliable drug susceptibility test for bedaquiline;
- pharmacokinetics, safety and efficacy studies in specific populations (infants and children, HIV patients – especially those on antiretroviral therapy (ART), alcohol and substance users, elderly people, pregnant or nursing women, people with extrapulmonary TB, people with diabetes);
- safety studies, including type, frequency and severity of adverse events (short and long term), and mortality (including cause of death);
- drug–drug interactions, including with other existing and newly developed TB drugs and ART;
- acquisition of resistance to bedaquiline and to other TB drugs;
- identification of optimal combination of drugs including bedaquiline and determination of optimal duration and dosing of treatment;
- patient acceptability;
- appropriate cost-effectiveness studies.

# 6. WHO Interim policy recommendations

In view of the aforementioned evidence assessment and advice provided by the EG, WHO recommends that ***bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB (conditional recommendation, very low confidence in estimates of effects).***

Given the limited data available on bedaquiline and its use under the various situations that may be encountered in different clinical settings, adequate provisions for safe and effective use of the drug must be in place. Consequently, countries are advised to follow a phased approach to bedaquiline implementation, ideally through observational cohorts, where the following measures are in place. The WHO recommendation for the inclusion of bedaquiline in the adult treatment regimen of MDR-TB is subject to the following five conditions being met:

1. **Treatment is administered under closely monitored conditions,** adhering to best practices in treatment delivery to enable optimal drug effectiveness and safety. Given that the results of the Phase IIb trial showed an excess mortality in the bedaquiline arm versus placebo arm, and that results of Phase III trials are only expected a few years from now, it is particularly important that the introduction of bedaquiline is carefully monitored for safety. It is therefore recommended that the following measures are in place:
    a. Sound treatment and management protocols, including clear patient eligibility criteria, procedures for informed consent, and defined roles and responsibilities of all professionals involved. The treatment protocols should allow for the prospective capture of data on key variables for both effectiveness and safety. Safety concerns are best addressed using the cohort event monitoring methodology employed for active pharmacovigilance.[23] Electronic systems will facilitate efficient data management and generation of key indicators.[24]
    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 and management programmes is provided by an independent group of experts in clinical management and public health – for instance, a national MDR-TB advisory group.
2. **Proper patient inclusion.** The current recommendation for the use of bedaquiline applies to adults (≥18yrs) with pulmonary disease. Special caution is needed when bedaquiline is used in people aged 65 years and older, and in adults living with HIV, as data on efficacy and safety are extremely limited. Use of the drug in pregnant women and children is not advised due to a lack of evidence on safety and

23 *A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: enhancing the safety of the TB patient*. Geneva, World Health Organization, 2012. Available from: http://www.who.int/medicines/publications/pharmacovigilance_tb/

24 *Electronic recording and reporting for tuberculosis care and control* (WHO/HTM/TB/2011.22). Geneva, World Health Organization, 2012.

efficacy. While patients with exclusive extrapulmonary disease were not included in the bedaquiline trial, the use of the drug in extrapulmonary TB patients may be considered, extrapolating from the data in patients with pulmonary TB.

3. **Patient informed consent obtained.** Health-care providers should ensure that the patient is: (i) aware of the novel nature of bedaquiline; (ii) appreciates the reason why the drug is being proposed to be included in the regimen; and (iii) recognizes the benefits and potential harms. In addition, health-care workers should obtain the patient's agreement on the inclusion of bedaquiline in the prescribed treatment regimen. This informed consent process must be documented and signed by the patient, and applies to all situations where bedaquiline is employed, including under compassionate use programmes.
4. **Adherence to principles of designing a WHO-recommended MDR-TB regimen.** As uncertainties remain about the relative benefits and harms when using bedaquiline, caution is advised when other options to compose an effective MDR-TB regimen using conventional second-line medication still exist. In addition, the shortcomings of conventional drug-susceptibility testing (DST) of second-line anti-TB drugs must be taken into account: DST of second-line drugs is only considered to be accurate and reproducible for fluoroquinolones, aminoglycosides (kanamycin, amikacin) and capreomycin (a polypeptide).[25] Evidence for accuracy and reproducibility of DST to other second-line drugs is very limited and value for clinical decision-making is uncertain. DST for bedaquiline has not yet been standardized. Laboratory testing of the minimal inhibitory concentration (MIC) of bedaquiline seems to suggest a breakpoint for susceptibility at <0.5µg/ml in agar medium; however, until a specific DST assay for bedaquiline is developed, clinicians will not be able to be guided by MIC values or DST results when composing a regimen. Furthermore, 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 reversal to positive following initial culture conversion.
    a. The WHO-recommended MDR-TB treatment regimen 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.[26] Bedaquiline may be indicated if such a regimen is not feasible because of:

        i) *in vitro* resistance to a drug (see b. and c. below );

25 *Policy guidance on drug susceptibility testing (DST) of second-line anti-tuberculosis drugs*. Geneva, World Health Organization, 2008. (WHO/HTM/TB/2008.392). Available from: whqlibdoc.who.int/hq/2008/WHO_HTM_TB_2008.392_eng.pdf

26 *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update*. (WHO/HTM/TB/2011.6). Geneva, World Health Organization. 2011.

ii) known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen; or

iii) unavailability or lack of a guaranteed supply of a drug.

b. MDR-TB patients with strains resistant to either fluoroquinolones or the second-line injectable drugs (kanamycin, amikacin, capreomycin) represent a particular concern given that these are the two most effective classes of second-line drugs. In such cases, bedaquiline may have a crucial role to play to strengthen a regimen, bringing the number of drugs likely to be effective to a minimum of four, and averting the acquisition of additional resistance and progression towards XDR-TB.

c. While experience in the use of bedaquiline in the management of XDR-TB is limited, it may have an indication in such patients given the limitations in designing an effective regimen based on existing recommendations in many situations.[27] In patients resistant to both classes of injectable drugs and also to fluoroquinolones (i.e. XDR-TB), bedaquiline may lower the need to include drugs belonging to Group 5, some of which have unproven anti-tuberculosis activity, high cost, or high toxicity. Bedaquiline may thus be used with or instead of a Group 5 drug. In these cases, special caution is advised on the potential increase of adverse drug reactions due to potential drug–drug interactions, particularly the synergistic cardiotoxic effect on QT prolongation, necessitating close ECG monitoring.

d. In line with general principles of TB therapeutics, bedaquiline 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 implies that bedaquiline should not be added alone to a failing regimen, and should be introduced well before the regimen fails completely.

e. Bedaquiline should be used strictly at the dose recommended by the manufacturer, i.e. 400mg daily for the first two weeks, followed by 200mg three times per week at least 48 hours apart, for a total maximum duration of 24 weeks. Available data suggest better uptake of bedaquiline when administered with food.

**5. Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions.**

a. Special measures need to be put in place to ensure the early detection and timely reporting of adverse events using active pharmacovigilance methods, such as 'cohort event monitoring'. Any adverse drug reaction attributed to bedaquiline should also be reported to the national pharmacovigilance centre as part of the spontaneous reporting mechanism in the country. As for any other drug in the 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

27 *Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008.* (WHO/HTM/TB/2008.402). Geneva, World Health Organization. 2008.

taken. Such occurrences should also trigger a rapid response to manage these untoward effects in the patient.

b. When introducing bedaquiline 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 bedaquiline, particularly clofazimine and moxifloxacin, may increase the risk of cardiotoxicity. Thus, if the drug is introduced into the MDR-TB treatment regimen, monitoring of patients for cardiac dysrhythmias or QT prolongation (i.e. using ECG), liver dysfunction, renal impairment, and other effects as denoted in the product briefing package is mandatory.[28]

c. Caution should be exercised when giving bedaquiline together with accompanying drugs that may inhibit liver function (e.g. the effect of ketoconazole or lopinavir/ritonavir on the enzyme CYP3A4), as these could increase bedaquiline concentrations, resulting in toxicity, or with accompanying drugs that may induce liver function (e.g. the effect of rifampicin on the enzyme CYP3A4), as these could result in sub-therapeutic bedaquiline concentrations, resulting in reduced efficacy. Of note, very limited data are available on drug–drug interactions with antiretroviral medicines, and these are based on single dose studies conducted in healthy normal volunteers. Therefore, people living with HIV who will be receiving bedaquiline as part of MDR-TB treatment should have their ART regimens designed in close consultation with HIV clinicians and ART specialists.

d. Lastly, caution is advised in patients with pre-existing health conditions that may be exacerbated or worsened by bedaquiline. Currently there are no data on the efficacy and safety of bedaquiline 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 required.

WHO strongly recommends the acceleration of Phase III trials in order to generate a more comprehensive evidence base to inform future policy on bedaquiline.

WHO strongly urges the development of accurate and reproducible DST methods for bedaquiline and other second-line drugs.

## 7. Dissemination and implementation

WHO interim policy guidance, as well as the systematic review reports and the EG meeting report, will be published online (www.who.int/tb/en) and disseminated

28 It should be noted that bedaquiline has a very large apparent volume of distribution and has a markedly prolonged terminal half-life (about 5.5 months), which reflects the slow release of the compound from peripheral tissue compartments. See: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf

through WHO/STB listserves to all WHO Regional and Country Offices, Member States, the Stop TB Partnership, donors, technical agencies and other stakeholders. As stated above, this interim guidance will be re-assessed in 2015, or earlier if additional data of significance become available increasing the knowledge on safety, toxicity and efficacy of bedaquiline (e.g. post-marketing studies, ongoing trials and studies). In this respect, it is noted that the US-FDA made the following requests to the company:

"- A phase III trial in MDR-TB cases, with assessment of long-term outcomes of failure or relapse at least 6 months after all MDR-TB treatment is completed (to be submitted by March 2022).

- Establishment of a patient registry for all bedaquiline-treated patients to assess the incidence of safety concerns (with annual reporting until 2018).

- Studies to define MIC methods for bedaquiline (by 2014), and assessment of actual MICs in clinical use (by 2019).

- An *in-vitro* study to assess the potential of bedaquiline and its metabolite as substrate, inducers or inhibitors of OATP1B1 and OATP1B3 drug transporters (by December 2013)."

To facilitate the implementation of this guidance, a derivative product (i.e. operational 'how-to' document) will be developed. WHO will provide guidance to programmes on monitoring and evaluation aspects as well as on essential data to be collected.

## Table 7. The GRADE evidence profile summary

**Author(s):** WHO Expert Group on bedaquiline for MDR-TB
**Date:** 2013–01–30
**Question:** In MDR-TB patients, does the addition of a bedaquiline to a background regimen based on WHO recommendations safely improve patient outcomes?
**Bibliography:** 1. Janssen Pharmaceutical Companies, 2012. TMC207 (bedaquiline) treatment of patients with MDR-TB (NdA 204–384). Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 (document available for public disclosure without redaction). 2. US-FDA AIDAC Meeting 28 Nov 2012. Slide presentations by Janssen R&D; Slide presentations by US-FDA. (http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm).
**Definitions of study population:**
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.

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bedaquiline added to BR | BR alone | Relative (95%CI) | Absolute | | |
| **Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT) [1,2]** | | | | | | | | | | | | |
| 1[3] | randomized trials | no serious risk of bias[4] | no serious inconsistency | serious[5] | serious[5] | none | 38/66[1] (57.6%) | 21/66[1] (31.8%) | RR 1.81 (1.26 to 2.31)[3,6] | 26 more per 100 (from 8 more to 42 more) | ++OO Low | Critical |
| **Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)** | | | | | | | | | | | | |
| 2[8] | randomized trials | no serious risk of bias | no serious inconsistency | Serious[9] | very serious[5] | none | 7/102[10] (6.9%) | 2/105 (1.9%) | RR 3.6 (0.77 to 14.00) | 5 more per 100 (from 0 to 25 more) | +OOO Very Low | Critical |
| **Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)** | | | | | | | | | | | | |
| 1[11] | randomized trials | no serious risk of bias | no serious inconsistency | serious[12] | very serious[3] | none | 9/79[11] (12.7%) | 1/81[11] (2.5%) | RR 9.23 (1.20 to 72.95)[13,14] | 10 more per 100 (from 0 more to 53 more) | +OOO Very Low | Critical |
| **Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)** | | | | | | | | | | | | |
| 1[15] | randomized trials | no serious risk of bias[4] | no serious inconsistency | serious[16] | serious[5] | none | n=66[1] median=83 days | n=66[1] median=125 days | | median 42 days lower[17] | ++OO Low | Critical |

1 The mITT modified intention to treat population in C208 trial consisted of 66 subjects in each randomization group after excluding 13 subjects (16.5%) treated with bedaquiline and 15 subjects (18.5%) with placebo who did not have MDR or pre-XDR-TB at baseline or for whom MGIT results were considered not evaluable.
2 Cure defined as 5 consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment , OR if only 1 culture is reported positive during that period, then a further 3 consecutive negative cultures from samples taken at least 30 days apart.
3 End of study data slide supplied by Janssen subsequent to US-FDA meeting. In this slide, mention is made of 'treatment success', but the company further clarified that the strict WHO definition of 'cure' was being used.
4 Representativeness of the mITT population (assumptions made for ITT population).
5 Small sample size and resulting large confidence interval limits precision: few (= serious) or very few (= very serious) observations.
6 This difference is statistically significant (Fisher p=0.005; Pearson p=0.003).

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Bedaquiline added to BR | BR alone | Relative (95%CI) | Absolute | | |
| **Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGIT960)** | | | | | | | | | | | | |
| 1[18] | randomized trials | no serious risk of bias[4] | no serious inconsistency | serious [16] | serious[5] | none | 52/66[1] (78.8%) | 38/66[1] (57.6%) | RR 1.37 (1.1 to 1.77)[19] | 21 more per 100 (from 6 more to 44 more) | ++OO Low | Critical |
| **Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT) 20 (assessed with: Microbiological endpoints)** | | | | | | | | | | | | |
| 1[21] | randomized trials | serious[22] | no serious inconsistency | serious [16] | very serious[5] | none | 2/10[20] (20%) | 14/27[20] (51.9%) | RR 0.39 (0.11 to 1.40)[23] | 32 fewer per 100 (from 46 fewer to 21 more) | +OOO Very Low | Critical |
| | | | | | | | | 7/27 (25.9%)[24] | | 6 fewer (22 fewer to 34 more) [24] | | |

7 Analysis on ITT population, C208 Stages 1 and 2 combined (n=102 in bedaquiline arm, 105 in placebo arm).
8 See: Janssen, Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 (NdA 204–384), (referred to as 'BD'). BD Table 2 Page 14, Table 51, Page 184; and Slide set prepared by Janssen and presented at the US-FDA Anti-Infective Drugs Advisory Committee Meeting, DC, 28 November 2012 (referred to as 'JRd'), JRd Slide 71 – See: http://workspace.who.int/sites/stb/Expert-GroupMeetingBedaquiline/default.aspx
9 Risk of side-effects (e.g. prolonged QT) could be higher if clofazimine were used; concern about follow-up being short in spite of the long half-life of BDQ.
10 See JRd Slide 63.
11 See BD Table 45, Appendix 4; Analysis on ITT population, C208 Stage 2 trial only (n=79 in bedaquiline arm, 81 in placebo arm); Mortality amongst all subjects exposed to BDQ in the C208 Phase 2 study, irrespective of when deaths occurred (i.e. including deaths post-120 weeks), count 10 deaths in the BDQ and 2 deaths in the Placebo group. Counting deaths strictly at the 120 weeks cut-off point reveal 9 in the BDQ and 1 in the placebo group.
12 Concern that if, in HIV patients, ARV treatment was given, there might have been drug-drug interactions affecting SAE and mortality.
13 Fisher Exact p=0.017; Pearson p=0.014.
14 The imbalance in deaths is unclear; clinical factors (such as HIV-status or severity of disease) and clinical outcome (disease improved or not) do not seem associated with higher/lower risk for death.
15 See BD Figure 22.
16 Concern re. extrapolating to general population; background treatment regimen was considered sub-optimal and not in line with WHO recommended regimens (PZA plus 4 active second-line drugs).
17 Cox proportional hazards model: HR 2.44 [95%CI 1.57, 3.80] p<0.0001 (BD p106).
18 See JRd slide EF-142.
19 Fisher Exact p=0.015; Pearson p=0.009.
20 Analysis on paired samples, mITT population (n=10 in bedaquiline arm, 27 in placebo arm).
21 See JRd Slide 52;
22 Selected and differential ascertainment of acquired resistance to bedaquiline. Last available positive culture interrogated against baseline for all patients would have been useful; acquired resistance to bedaquiline as seen in non-responders in the bedaquiline arm (using the indicative breakpoint for susceptibility) should also be stated.
23 Fisher Exact p=0.14; Pearson p=0.08.
24 The Expert Group assumed that the true baseline risk for developing resistance would be substantially lower, i.e. approximately 25%, if all samples had been tested at last available positive sample

## Table 8. The GRADE Evidence to Recommendation

**In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendation safely improve patient outcomes?**

**Population:** MDR TB patients
**Intervention:** bedaquiline + background MDRTB treatment
**Comparison:** background MDRTB treatment alone
**Setting:** global, MDR clinics

| DOMAIN | | JUDGEMENT | DETAILS OF JUDGEMENT | EVIDENCE/EXPLANATION |
|---|---|---|---|---|
| QUALITY | **What is the overall confidence in effect estimates?**<br>Is there high or moderate quality evidence?<br>The higher the quality of evidence, the more likely is a strong recommendation | ☐ High<br>☐ Moderate<br>☐ Low<br>☒ Very low | *Critical Outcomes:* — *High* / *Moderate* / *Low* / *Very low*<br>1. Cure by 120 weeks. ☐ ☐ ☒ ☐<br>2. Serious adverse events by 24 weeks ☐ ☐ ☐ ☒<br>3. Mortality ☐ ☐ ☐ ☒<br>4. Time to culture conversion ☐ ☐ ☒ ☐<br>5. Culture conversion at 24 weeks ☐ ☐ ☒ ☐<br>6. Acquired resistance to fluoroquinolones and injectable drugs ☐ ☐ ☐ ☒<br><br>*Agree* / *Somewhat agree* / *Uncertain* / *Somewhat disagree* / *Disagree*<br>High confidence in the typical values ☐ ☒ ☐ ☐ ☐ | *All critical outcomes measured*<br><br>*There were concerns about imprecision (due to small sample size and few events), and indirectness (due to (1) background MDR-TB treatment not being consistent with currently recommended regimens and (2) to the use of a surrogate outcome, i.e. culture conversion). There were also concerns on the risk of bias (due to the inappropriate exclusion of 19 randomized patients with unconfirmed MDR-TB from mITT analysis).* |
| BENEFITS & HARMS | **What is the balance between benefits and risks/ burden? Are you confident that the benefits outweigh the harms and burden or vice versa?**<br>The larger the difference between the benefits and harms, the more likely is a strong recommendation.<br>The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional/weak recommendation. | ☐ Benefits outweigh harms/ burden<br>☒ Benefits slightly outweigh harms/ burden<br>☐ Benefits and harms/ burden are balanced<br>☐ Harms/ burden slightly outweigh benefits<br>☐ Harms/ burden outweigh benefits | *Critical Outcomes:* — *Large/ Modest benefit* / *Small benefit* / *No effect* / *Small harm/ burden* / *Modest/ Large harm/ burden*<br>1. Cure by 120 weeks. ☒ ☐ ☐ ☐ ☐<br>2. Serious adverse events by 24 weeks ☐ ☐ ☐ ☐ ☒ mod<br>3. Mortality ☐ ☐ ☐ ☐ ☒ large<br>4. Time to conversion ☒ large ☐ ☐ ☐ ☐<br>5. Culture conversion at 24 weeks ☒ large ☐ ☐ ☐ ☐<br>6. Acquired Resistance to fluoroquinolones and injectable drugs ☒ large ☐ ☐ ☐ ☐<br><br>*The issue is to balance a 23% increase in success (low confidence) vs. 5% increase in serious adverse events (very low confidence) and 10% increase in deaths (very low confidence)* | **See evidence profile**<br>*QoE for benefits: Low due to imprecision and indirectness*<br>*QoE for harms: Low or very low (resistance to BDQ) due to imprecision and indirectness (and risk of bias)*<br><br>*No consensus was found on the balance of respective harms and benefits of addition of bedaquiline to MDRTB treatment. So a vote took place:*<br>*- 10 experts evaluated that the benefits did outweigh the harms*<br>*- 4 experts evaluated that the harms did outweigh the benefits*<br>*- 2 abstained (including the chair)* |

| | | | | |
|---|---|---|---|---|
| VALUES AND PREFERENCES | **What are the patient's values and preferences?**<br>Are the assumed or identified relative values similar across the target population?<br>The greater the similarity in values and preferences, the more likely is a strong recommendation. | ☐ Similar values<br>☐ Some variation<br>☒ Large variation | Values and preferences likely similar<br>*Agree* ☐ *Somewhat agree* ☐ *Uncertain* ☐ *Somewhat disagree* ☒ *Disagree* ☐ | *Treatment success, serious adverse events and mortality were considered important to patients while time to conversion culture conversion and resistance were less so.*<br><br>*The likelihood that patients would accept an effective treatment regimen would depend on subgroups of the MDR-TB population – e.g. patients with MDR-TB plus additional resistance to fluoroquinolone and/or injectable drugs may be more likely to accept the risk of taking a new drug with potential increase in mortality than patients suffering from newly diagnosed and proven MDR-TB. There is minimal variation for death, larger variation for other outcomes* |
| RESOURCES | **Is the incremental cost (or resource use) small relative to the benefits?**<br>**Are the resources worth the expected net benefit from following the recommendation?**<br>The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention. | ☐ Cost is very small relative to the net benefits<br>☒ Cost is small relative to the net benefits<br>☐ Cost is borderline relative to the net benefits<br>☐ Cost is high relative to the net benefits<br>☐ Cost is very high relative to the net benefits | *No accounting of serious adverse events* | *There are variations of cost effectiveness across settings based on data and assumptions used in the model – that may not reflect real life situations. In addition, there were a series of limitations in the model being used for analysis of cost-effectiveness (e.g. no accounting of serious adverse events, no accounting for effect on transmission, etc.)* |
| EQUITY | **What would be the impact on health inequities?** | ☐ High<br>☐ Moderate<br>☐ Low<br>☐ Very low<br>☒ Uncertain | | *Difficult to assess whether intervention will reduce inequities because of uncertainty on affordability.* |

| **Recommendation** | | | | | | |
|---|---|---|---|---|---|---|
| *In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendation safely improve patient outcomes?* | | | | | | |
| Overall balance of consequences | *Undesirable consequences clearly outweigh desirable consequences* | *Undesirable consequences probably outweigh desirable consequences* | The balance between desirable and undesirable consequences is too uncertain* | The balance of desirable and undesirable consequences indicates they are very similar* | *Desirable consequences probably outweigh undesirable consequences* | *Desirable consequences clearly outweigh undesirable consequences* |
| | ☐ | ☐ | ☐ | ☐ | ☒ | ☐ |
| | *We recommend against the option or for the alternative* | *We suggest not to use the option or to use the alternative* | *No recommendation* | | *We suggest using the option* | *We recommend the option* |
| | ☐ | ☐ | | | ☒ | ☐ |
| Panel decisions | *There was no consensus among the panel as per the 'balance of harms and benefits', hence a vote: 10 experts evaluated that the benefits did outweigh the harms, 4 experts evaluated that the harms did outweigh the benefits and 2 (including chair) abstained* | | | | | |
| Recommendation | *The Expert Group Panel suggests that bedaquiline may be added to a WHO recommended regimen in MDR-TB adult patients under the following conditions (conditional recommendation, very low confidence in estimates of effect)* | | | | | |
| Remarks and justifications | Conditions:<br>• When an effective treatment regimen containing 4 recommended second line drugs in addition to pyrazinamide, according to WHO-recommendations cannot be designed<br>• When there is documented evidence of resistance to any fluoroquinolone in addition to MDR<br>• A duly informed decision making-process by patients should be followed;<br>• Bedaquiline should be used with caution in persons living with HIV infection, as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol use, due to limited or no information.<br>• Bedaquiline should be used for a maximum duration of 6 months and at suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks)<br>• Bedaquiline must not be added alone to a failing regimen;<br>• Baseline testing and monitoring for QT prolongation and development of arrhythmia is imperative<br>• Clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place<br>• Spontaneous reporting of adverse drug reactions is reinforced at country level and active pharmacovigilance is established among patient groups treated with the drug;[29]<br>• In the absence of a specific bedaquiline DST assay, resistance to bedaquiline should be monitored through assessment of Minimum Inhibitory Concentrations (MICs)<br>• Resistance to other anti-TB drugs should be monitored following WHO recommendations. | | | | | |

29 For more details see : A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis: enhancing the safety of the TB patient. Geneva, World Health Organization, 2012. Available from: http://www.who.int/medicines/publications/pharmacovigilance_tb/

| **Recommendation** | |
|---|---|
| *In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendation safely improve patient outcomes?* | |
| Explanation | The expert group judged that the impact on culture conversion was large enough to outweigh the harms for most patients |
| Implementation and feasibility | • Monitor resistance to bedaquiline through assessment of MIC in the absence of a specific bedaquiline DST assay<br>• Monitor resistance to other anti-TB drugs<br>• Management of co-morbidities (cardiac diseases, etc.)<br>• Clinical monitoring<br>• Concerns on scale-up due to costs and/or local regulatory constraints |
| Research gaps | • Phase 3 clinical trial(s) of safety and efficacy of bedaquiline, with particular attention to mortality (including causes of death), in the treatment of MDR-TB should be accelerated<br>• Development of a reliable test for bedaquiline resistance<br>• Pharmacokinetics, safety and efficacy studies in specific populations (paediatrics, HIV patients, alcohol and drug users, elderly, pregnant women, extrapulmonary TB, persons with diabetes)<br>• Safety studies, including type; frequency and severity of adverse events (short term and long term)<br>• Drug-drug interactions, including with other existing and newly developed TB drugs and ARVs<br>• Mortality (including cause of death)<br>• Acquisition of resistance to bedaquiline and to other TB drugs<br>• Duration and dosing of treatment<br>• Patient acceptability<br>• Further research on the validity of culture conversion as a surrogate marker of treatment outcome |
| Revision planned | • By 2015 or earlier if substantial data become available increasing the knowledge on safety, toxicity and efficacy (e.g. post marketing studies, on-going trials and studies) |

* In this situation no recommendation could be reasonable

# Annexes

# Annex 1

## WHO Guideline Steering Group members

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# Annex 2

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Brenda Waning, UNITAID

**GRC (observers)**
Charles Penn, WHO/AIP
Susan Norris

# Annex 3

## Expert Group meeting on interim advice for the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

**29–30 January 2013, Geneva**
**Meeting objectives and agenda**

### Background:

The emergence of drug-resistant tuberculosis is a major threat to global tuberculosis care and control. The World Health Organization (WHO) estimates that about 310 000 multidrug-resistant tuberculosis (MDR-TB) cases (i.e. resistant to rifampicin and isoniazid) occurred among notified TB patients in 2011. Of these, only 19% were reported to WHO, largely as a result of critical gaps in diagnostic and treatment capacity in most countries. Furthermore, 85 countries have now reported at least one case of extensively drug-resistant tuberculosis (XDR-TB), a form of TB that is resistant to at least four of the core anti-TB drugs, and associated with high lethality among people living with HIV.[30]

The global deployment of new, rapid diagnostics for drug resistance, such as the Xpert MTB/RIF assay, is expected to increase the demand for treatment of MDR-TB patients. Current treatment regimens for drug-resistant TB are far from satisfactory. Whereas most drug-susceptible TB patients can usually be treated successfully 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 archaic 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 2009, only 48% were treated successfully, as a result of high frequency of death (15%) and loss to follow-up commonly associated with adverse drug reactions (28%). Among a subset of 200 (XDR-TB) patients in 14 countries, treatment success only reached 33% overall and 26% of cases died.[31]

The landscape of TB drug development has evolved dramatically over the past ten years, and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB. WHO intends to convene an Expert Group (EG) to review the available evidence on the efficacy, safety and effectiveness of a new drug, bedaquiline, for the treatment of MDR-TB, and recommend whether WHO guidance on the treatment of MDR-TB should be supplemented with interim guidance on the use of this drug. Of

30 *Global tuberculosis control: WHO report 2010* (WHO/HTM/TB/2010.7). Geneva, World Health Organization. 2010.

31 *Global tuberculosis control: WHO report 2010* (WHO/HTM/TB/2010.7). Geneva, World Health Organization. 2010.

note, dossiers have been submitted to several regulatory authorities and are currently being evaluated under procedures of 'accelerated' or 'conditional' approval.

## Overall objective:

The EG will evaluate the added benefit of bedaquiline, a new agent developed for the treatment of MDR-TB, a life-threatening form of TB, and provide recommendations to WHO for provision of interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment if appropriate.

## Specific objectives:

1. To evaluate the harms/benefits of bedaquiline 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 versus placebo in addition to optimised background therapy, using the surrogate markers of 'culture conversion at 6 months' and 'time to culture conversion' and other outcomes as suitable.
   - 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 affordability, including through the estimated cost and cost-effectiveness of MDR-TB treatment with the new drug based on modelling studies.

2. Based on this evaluation, to provide, as appropriate, provisional 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. This will include describing the additional data to collect and minimum parameter to put in place when new regimens are being used in programmes.

The *interim advice* will aim at reaching policy-makers, national TB programmes, health workers, academics, donors and technical partners.

## 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 – 29th January 2012 | *Chair: Holger Schünemann* |
|---|---|---|
| 9h00 – 9h15 | Welcome and Introduction | Mario Raviglione |
| 9h15 – 9h45 | Objectives of the meeting<br>Presentation of participants<br>Declaration of Interest statements | Christian Lienhardt |
| | ***Session 1: Background and procedures*** | |
| 9h45 – 10h00 | WHO requirements for evidence-based guidelines | Mary Lyn Gaffield |
| 10h00 – 10h30 | GRADE approach for WHO guidelines | Holger Schünemann |
| 10h30 – 10h45 | Review of MDR-TB treatment guidelines | Dennis Falzon |
| 10h45 – 11h00 | The PICO question for provisional guidance on use of bedaquiline in the treatment of MDR-TB | Holger Schünemann |
| *11h00 – 11h30* | *Coffee break* | |
| | ***Session 2: Review of available data on bedaquiline*** | |
| 11h30 -11h50 | Review of pre-clinical, toxicology and pharmacokinetic data | Bernard Fourie |
| 11h50 – 12h30 | Discussion | All |
| *12h30 –13h30* | *Lunch* | |
| 13h30 – 14h15 | Review of key efficacy and safety results | Bernard Fourie |
| | ***Session 3: The efficacy aspects*** | |
| 14h15 – 14h30 | Culture conversion as proxy of treatment outcome | Katya Kurbatova (remotely) |
| 14h30 – 15h45 | Discussion | Discussant (Andrew Vernon)<br>All |
| *15h45 – 16h15* | *Tea break* | |
| | ***Session 4: The safety and mortality aspects*** | |
| 16h15 – 17h30 | Discussion | Discussant (Michael Rich)<br>All |
| 17h30 – 18h00 | Re-cap and key points | Holger Schünemann |
| *18h00* | *End Day 1* | |

| | DAY 2 – 30th January 2012 | *Chair: Holger Schünemann* |
|---|---|---|
| | ***Session 5: The cost-effectiveness aspects*** | |
| 8h00 – 8h20 | Presentation of CE modelling analysis | Anna Vassall (remotely) |
| 8h20 – 9h00 | Discussion | All |
| | ***Session 6: Interim recommendations for use of bedaquiline in MDR-TB treatment*** | All |
| 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 bedaquiline in MDR-TB treatment*** (contd) | All |
| 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* | |
| | ***Session 6: Interim recommendations for use of bedaquiline*** (contd) | All |
| 13h30 – 15h30 | Review recommendations as a whole (contd), including conditions associated with potential recommendations. Complete decision grid and determine the strength of recommendation. | |
| *15h30 – 16h00* | *Tea break* | |
| 16h00 – 16h30 | Recommendation for further data and future research, including on various populations (PLHIV, children) | All |
| 16h30 – 17h30 | Re-cap and review of final recommendations | All |
| 17h30 – 18h00 | Next steps, implementation and conclusion | Karin Weyer/Diana Weil/Mario Raviglione |
| *18h00* | *Adjourn* | |

# Annex 4

## Expert Group meeting on interim advice for the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

### Declarations of Interest

| Expert Group meeting on interim advice for the use of bedaquiline in the treatment of MDR-TB<br>None declared | | |
|---|---|---|
| Elie Akl<br>Adekunle Victor Babawele<br>Mauricio Baretto<br>Dr Martien W. Borgdorff<br>Erlina Burhan | Richard E. Chaisson<br>Ms Lucy Chesire<br>Norbert Ndjeka<br>Nguyen Viet Nhung | Michael L. Rich<br>Simon Schaaf<br>Holger Schünemann<br>Francis Varaine<br>Susan Van Den Hof<br>Piret Viiklepp |

1 | World Health Organization

### Declarations of Interest

| Expert Group meeting on interim advice for the use of bedaquiline in the treatment of MDR-TB<br>Declared: insignificant | |
|---|---|
| Andrew Vernon | Supervises a branch at CDC that supports a consortium conducting clinical trials in TB that receives modest support (e.g., drug supplies for studies) from several manufacturers. One company, Sanofi-Aventis, has provided $1.7 million to the CDC Foundation to support work on rifapentine. Neither I nor any of my staff has received any personal benefit from these funds. |

2 | World Health Organization

## Declarations of Interest

| Expert Group meeting on interim advice for the use of bedaquiline in the treatment of MDR-TB<br>Declared: insignificant | |
|---|---|
| Erica Lessem | 1. TAG's TB/HIV Project receives funding from the Bill & Melinda Gates Foundation to conduct advocacy to accelerate research and development into new tools to fight TB and TB/HIV coinfection, and to promote universal access to effective tools and services. Activities supported by this funding include TB/HIV Project team operations, participation in meetings with key researchers and policymakers, attendance to scientific conferences, writing publications such as the Pipeline Report which provides an overview of all new drugs, diagnostics and vaccines in the pipeline for TB and other diseases, and coordinating a global TB community advisory board which provides input in the development and roll-out of tools to fight TB.<br>2. In addition, TAG's Hepatitis C program received from Janssen Therapeutics/Tibotec Therapeutics $10,000/year in 2011 and 2012 (not for any of my word or the TB/HIV project) |



World Health Organization

## Declarations of Interest

| Expert Group meeting on interim advice for the use of bedaquiline in the treatment of MDR-TB<br>Technical Resource Persons – None declared | | |
|---|---|---|
| Bernard Fourie<br>Ekaterina Kurbatova | Charles Peloquin | Anna Vassall |



World Health Organization

# Declarations of Interest

| Expert Group meeting on interim advice for the use of bedaquiline in the treatment of MDR-TB<br>Observers | |
|---|---|
| Xiumin Huo | Chief Pharmacist, State Food and Drug Administration, Beijing, China |
| Mukadi Ya-Diul | Works for a funding organization supporting drug research and development |



World Health Organization

# 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 is 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 is 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 External Review Panel members

*(area of expertise in brackets)*

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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, 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).

Ashok Kumar, Deputy Director General, Head Central TB Division & Project Director RNTCP, Directorate General Of Health Services, Ministry of Health and Family Welfare, New Delhi, India – (Programme management, end-user).

Helen McIlleron, Division of Clinical Pharmacology, Department of Medicine, University of Cape Town – (Clinical pharmacologist).

Richard Menzies, Director Respiratory Division, MUHC and McGill University, Montreal, Canada – (Epidemiologic and clinical research in TB).

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Alena Skrahina, Scientific Director, Republican Research and Practical Centre for Pulmonology and TB, Minsk, Belarus – (Clinical management and research, TB, M/XDR-TB, HIV/TB, end-user).

Maarten van Cleeff, KNCV Tuberculosis Foundation, The Hague, The Netherlands – (TB, TB/HIV, poverty and ethics, diagnosis, health system strengthening, operational research, monitoring and programme evaluation).

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