Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

A review of available evidence (2016)

28 - 29 June 2016

Geneva, Switzerland

World Health Organization

THE END TB STRATEGY

Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

A review of available evidence (2016)

28 - 29 June 2016

Geneva, Switzerland

Suggested citation. Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis, A review of available evidence (2016). Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

WHO/HTM/TB/2017.01

Table of Contents

List of boxes, figures and tables

Abbreviations and acronyms

aDSM	active TB drug safety monitoring and management
AE	adverse event
ART	antiretroviral therapy
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
ECG	electrocardiogram
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	WHO Guidelines Review Committee
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant tuberculosis
MDR-TB$_{+FQ}$	multidrug-resistant tuberculosis with additional resistance to fluoroquinolones
MDR-TB$_{+SLI}$	multidrug-resistant tuberculosis with additional resistance to injectable drugs
MIC	minimum inhibitory concentration
NTP	national tuberculosis control programme
OBR	optimised background regimen
PK/PD	pharmacokinetic/pharmacodynamic
PMDT	programmatic management of drug-resistant tuberculosis
RCT	randomised control trial(s)
SAE	serious adverse event
TB	tuberculosis
U.S. FDA	United States Food and Drug Administration
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Acknowledgements

This document was prepared by Christian Lienhardt and Lice González-Angulo, with the contribution of Ernesto Jaramillo, Dennis Falzon and Karin Weyer (World Health Organization (WHO) Global TB Programme), to report on the outputs of the Guideline Development Group meeting convened by WHO in Geneva on 28 - 29 June 2016, and subsequent Webinar conducted on 15 September 2016. WHO gratefully acknowledges the contributions made by the Chair of the Guideline Development Group (Holger J. Schünemann) and its members (Martien Borgdoff, Grania Brigden, Lucy Chesire, Daniela Cirillo, Gerry Davies, Poonam Dhavan, Peter Donald, Christopher Kuaban, Miranda Langendam, Mauricio Lima-Barreto, Anna Mandalakas, Beatrice Mutayoba, Payam Nahid, Viet Nhung Nguyen, Rohit Sarin, Alena Skrahina, Carlos Torres-Duque, and Carrie Tudor). WHO greatly acknowledges the work conducted by Lawrence Mbuagbaw, consultant to WHO, in the analysis and synthesis of evidence, as well as the contributions made by technical resource persons during discussions (Anneke Hesseling, Erica Lessem, Norbert Ndjeka, Kate Schnippel, and Fraser Wares).

Administrative and secretarial support: Lou Maureen Comia.

Funding

The Bill and Melinda Gates Foundation is acknowledged for its support to the process (meeting of the GDG and systematic review) through grant project number **OPP 1126615.**

Declarations of interest

The Declaration of Interest forms were completed by all non-WHO members of the Guideline Development Group (GDG), as well as the members of the academic centres who were involved in the reviews. Four members of the GDG declared interests that were judged to be non-significant (Grania Brigden; Daniela Cirillo; Gerry Davies; and Alena Skrahina). Three additional experts disclosed interests that were deemed to be conflicting for the partial review of the interim policy guidance on bedaquiline: (1) Anneke Hesseling is the principal investigator in two phase II, open-label, multiple-dose trials funded by Otsuka pharmaceuticals (Study 242-12-232 and Study 242-12-233). She also received research support to fund a multi-site phase I/II trial of bedaquiline in HIV infected and uninfected children with MDR-TB, through the IMPAACT network (P1108). Anneke Hesseling joined the meeting remotely through internet connection. (2) Erica Lessem disclosed that her employer (Treatment Action Group) received a total of $108 000 as means of general support from Janssen Pharmaceutical / Tibotec Therapeutics from 2010 – 2015. These funds were allocated to the Hepatitis C/HIV Programme and not for her work or the TB/HIV Project. (3) Fraser Wares's employer, KNCV, coordinates the USAID-Johnson & Johnson bedaquiline donation programme in those countries supported under the Challenge TB Project through its Challenge-TB project activities. In consultation with the WHO *Compliance, Risk Management and Ethics* and *Legal* departments and the Chairman of the GDG meeting, the WHO Guidelines Steering Group at the Global TB Programme decided to assign them the status of 'technical resource persons' allowing them to contribute in the technical discussions but not taking part in final decision making and in any vote if deemed necessary. The aforementioned, as well as the independent expert who performed the systematic review of evidence (Lawrence Mbuagbaw) and observers did not participate in the final decision making and formulation of recommendations.

Preface

The issuance of the WHO interim policy guidance for the use of bedaquiline represented a major milestone in the treatment and care of multidrug-resistant tuberculosis (MDR-TB)[1]. The implications and application of this 2013 policy guidance expanded treatment options for MDR-TB cases, namely MDR-TB patients with additional resistance or contraindication to fluoroquinolones (MDR-TB$_{+FQ}$) or second-line injectable drugs (MDR-TB$_{+SLI}$), as well as patients with extensively drug-resistant TB (XDR-TB). As the recommendations for the use of the drug were drawn upon phase II safety and efficacy data available at the time, the WHO recommended that ***bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB***, subject to the following five conditions being met: **i**) effective treatment and monitoring; **ii**) proper patient inclusion; **iii**) informed consent; **iv**) adherence to principles of designing a WHO-recommended regimen; and **v**) active pharmacovigilance and management of adverse drug reactions. The scope of this policy guidance was set to be *conditional*, promoting and ensuring the rational introduction and proper management and care of MDR-TB patients, including active TB drug safety monitoring and management, and additionally, due to the *interim* nature of the guidance document, allowing international and national authorities and key TB stakeholders to re-evaluate the use of the drug as new evidence becomes available.

In recent years, as the number of countries introducing and rolling out bedaquiline in combination with a WHO-recommended longer regimen has increased, data on the use of bedaquiline at a country level have become available from various settings. On that account - and in addition to the limited life span of the 2013 policy recommendations - the WHO convened a Guideline Development Group (GDG) meeting aiming at re-evaluating the added benefit of bedaquiline in conjunction with a WHO-recommended longer regimen for treatment of MDR-TB, and on this basis, updating the 2013 WHO interim policy guidance, should changes to the previous recommendation be deemed required. The GDG consisted of an international and multidisciplinary panel of experts from various technical and scientific fields who came together to review new evidence in Geneva on 28 - 29 June 2016[2]. As the WHO and the GDG became aware of existing new mortality data from South Africa at the time the first meeting was held, the panel decided to resume their evidence assessment in a subsequent Webinar conducted on 15 September 2016.

The current report describes the process carried out for the assessment of newly available data on the use of bedaquiline, and presents the recommendations made by the GDG panel for the use of bedaquiline in addition to a WHO-recommended longer regimen, along with the implications for implementation. Of note, the current document is a complement to – and it *does no*t supersede the newly available ***WHO Treatment Guidelines for Drug-resistant Tuberculosis (2016 update)*** [3] in which the use of a shorter MDR-TB treatment regimen for rifampicin-resistant or MDR-TB patients is recommended under certain conditions.

[1] World Health Organisation (WHO). The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance, 2013. **Available from**: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf

[2] Guideline Development Group (GDG) Meetings: Revision of the interim policy on bedaquiline for MDR-TB treatment and special session on delamanid use in children. Public notice, including GDG biographies. **Available from**: http://www.who.int/tb/areas-of-work/treatment/public_notice_gdg_new_drugs.pdf?ua=1

[3] World Health Organisation (WHO). WHO Treatment guidelines for drug-resistant tuberculosis, 2016 update. **Available from**: http://www.who.int/tb/MDRTBguidelines2016.pdf

Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

A review of available evidence (2016)

1. Background

The emergence of drug-resistant tuberculosis (TB) is of major concern to global TB control *(1)*. Annually, up to half a million persons are estimated to develop multidrug-resistant TB (MDR-TB), a form of TB that is resistant to isoniazid and rifampicin (two of the key first-line TB drugs) and which occurs in 3.9% of all newly diagnosed cases and in 21% of previously treated cases *(1)*. Up to 10% of MDR-TB cases are reported to have extensively drug resistant TB (XDR-TB), defined as additional resistance to any fluoroquinolone and at least one of three injectable second-line drugs (i.e. amikacin, kanamycin, or capreomycin*) (1)*. Treatment of MDR-TB is substantially more complex, more costly, and less effective than standard therapy, typically requiring a higher number of drugs, including injectable agents and a longer treatment duration than that of drug-susceptible TB cases. MDR- and XDR-TB can be, *per se*, incapacitating and life-threatening. Furthermore, current treatment options can be disabling and lead to medical complications. The need for new therapeutic options has been a critical area to combat the global drug-resistant TB epidemic. The advent of novel antibiotics such as bedaquiline represents an additional therapeutic option for treatment of a disease which is hindered by the limited efficacy and significant toxicity of second-line drugs.

Bedaquiline was approved by the United States Food and Drug Administration (FDA) for the treatment of adults with pulmonary MDR-TB on the basis of phase II trial data under the provisions of the accelerated approval regulations for serious or life-threatening conditions. Subsequently, the World Health Organization (WHO) convened a panel of experts in January 2013 to review the available evidence on the efficacy, safety and effectiveness of bedaquiline for MDR-TB treatment *(2)*. Although safety concerns including QT interval prolongation, hepatotoxicity, and excess mortality in patients treated with bedaquiline were reported and assessed, the panel concluded that benefits of using bedaquiline for the treatment of MDR-TB in patients with additional resistance or contraindication to fluoroquinolones (MDR-TB$_{+FQ}$) or second-line injectable drugs (MDR-TB$_{+SLI}$), outweighed these harms. Consequently, WHO issued an interim policy comprising a conditional recommendation indicating that bedaquiline may be added to a WHO-recommended regimen in adult MDR-TB patients under specific conditions (**Box 1**) *(3)*.

Since then, the drug has been registered and introduced in a number of countries. WHO estimates that, up to 2015, the drug had been introduced and used at least once in 70 countries worldwide, under various mechanisms of compassionate use, expanded access programmes, donation programmes, import waiver and registered market access *(1)*. As the interim guidance was issued in June 2013 for a duration of 2 years, WHO undertook, at the end 2015, a process of gathering available evidence with the view to inform any changes, if appropriate, to the interim guidance. The current report summarises the discussion and recommendations made by members of the Guideline Development Group (GDG) convened to reassess the evidence for the use of bedaquiline in the treatment of MDR-TB.

Box 1. Summary of the main recommendations of the WHO 2013 interim policy guidance on the use of bedaquiline in the treatment of MDR-TB

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*).

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. Proper patient inclusion (special caution in persons above 65 years of age or adults living with HIV; use not advised in pregnant women and children).
2. Signed patient informed consent obtained after detailed explanations on the novel nature of the drug, the reasons why it is added to the regimen, and its risks and benefits have all been provided to the patient.
3. Adherence to principles of designing a WHO-recommended MDR-TB regimen typically composed of at least pyrazinamide and four second-line drugs that are considered to be effective based on drug susceptibility test 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 para-aminosalicylic acid. Bedaquiline may be indicated if such a regimen is not feasible because of: (**i**) in vitro resistance to fluoroquinolones and/or second-line injectable drugs; (**ii**) known adverse reaction, poor tolerance or contraindication to any component of the combination regimen; or **(iii**) unavailability or lack of a guaranteed supply of a drug(s).
4. Treatment administered under closely monitored conditions to enable optimal drug effectiveness and safety (sound treatment and management protocols must be in place, preferably submitted and approved by the relevant national ethics authority; review of treatment and management programmes by an independent group of experts in clinical management and public health, such as the national MDR-TB advisory group is recommended).
5. Active pharmacovigilance and proper management of adverse drug reactions and prevention of complications from drug–drug interactions.

2. Preparation for the assessment of newly available evidence

In June 2016, the WHO convened a meeting of experts to discuss and evaluate new data on bedaquiline use arising from various expanded access/compassionate use programmes, as well as from observational studies. The preparation of this meeting included a series of activities described below.

2.1. Evidence retrieval and synthesis

The review of newly available evidence was prepared in accordance with the updated WHO standard methods for guideline development *(4)*. The process for retrieving and assessing the evidence was initiated and supported by a systematic search of literature, as well as the formal assessment of quality of evidence.

The following actions were conducted:

2.1.1. Literature search strategy

Bibliographic searches included MEDLINE®, Embase® and the Cochrane Central Register of Controlled Trials. Conference proceedings and reference lists were also searched to identify additional published studies that were not retrieved in the initial search. Concepts or "facets" (topic specific terms) included in the PICO question were combined with Boolean operators to develop an optimal search strategy.

Inclusion criteria

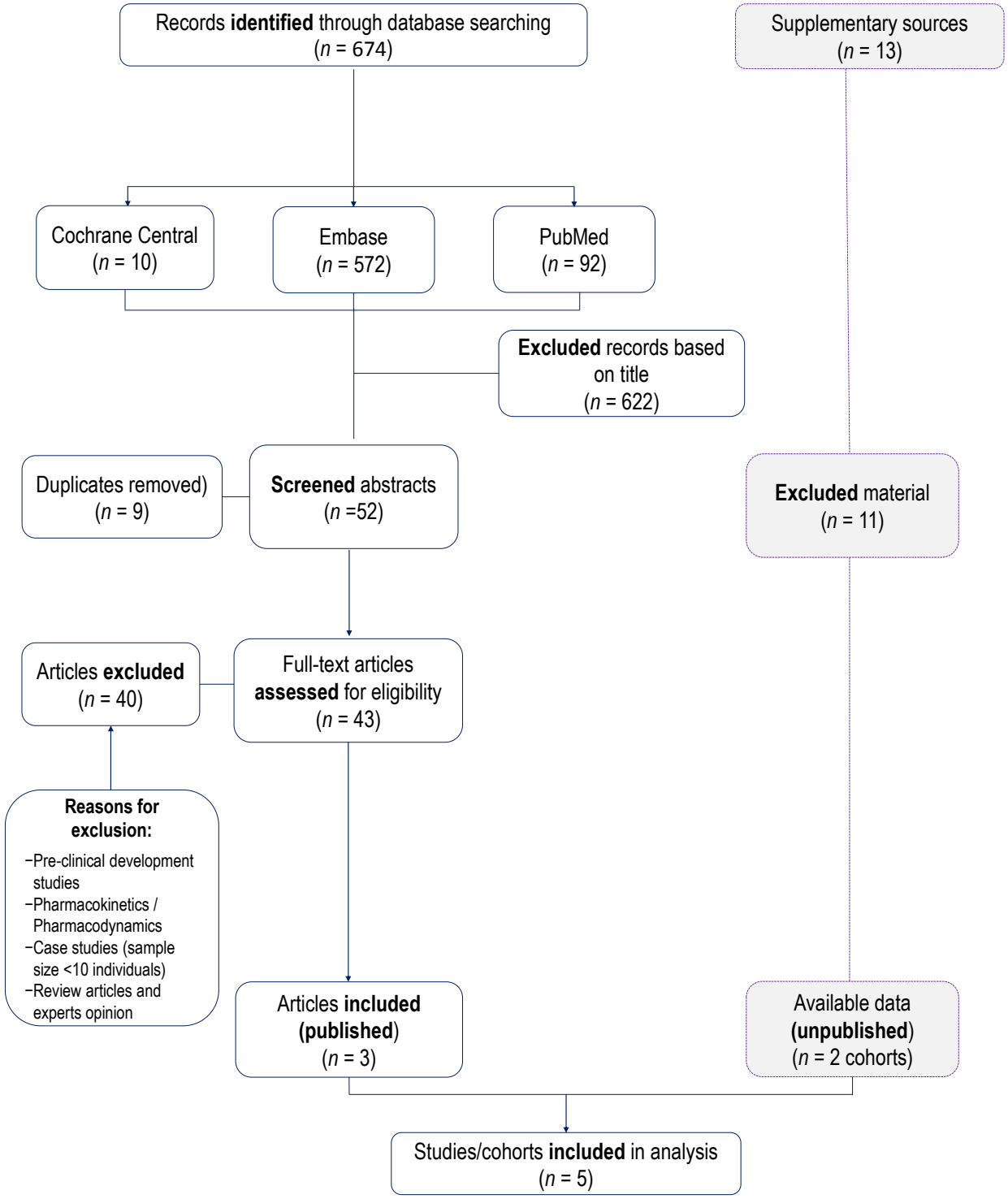
- Diagnosis of multi-drug resistant tuberculosis (pulmonary and extrapulmonary);
- Bedaquiline added to background regimen for at least 6 months; *and*
- Studies implementing drug-monitoring for bedaquiline, at least at baseline and at end of treatment.

Exclusion criteria

- Studies not relevant to the main subject (title-screened);
- Pharmacokinetics / Pharmacodynamics (PK-PD) studies;
- Studies of only-bedaquiline therapy;
- Studies not providing information on background therapy (WHO-recommended or any other);
- Studies not providing outcome information; *and*
- Samples size: Case reports or other observational studies with samples less than 10 participants.

A total of 674 studies were identified (CENTRAL, 10 records; PubMed/MEDLINE®, 92 records; and Embase®, 572 records). Further to this search, 13 additional studies were identified through supplementary sources, namely conference proceedings (**Fig. 1**).

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



As a result of this search, 5 studies (including those identified through supplementary sources) were selected:

- A phase II, single-arm, open-label multi-centre study conducted to confirm the safety and efficacy of bedaquiline: bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis (*Published data*) *(5)*.
- A retrospective cohort study describing results of the compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort (*Published data*) *(6)*.
- An interim cohort analysis to describe the safety and effectiveness of bedaquiline in the *South African Bedaquiline Clinical Access Programme* (*Published data*) *(7)*.
- Interim data from compassionate use and expanded access programmes in Armenia (*Unpublished data*) *(8)*.
- Interim data from compassionate use and expanded access programmes in Georgia (*Unpublished data*) *(9)*.

All data owners, including Janssen Therapeutics (*drug manufacturer*), were contacted by WHO to provide access to raw data from the selected studies and authorise their use for this guideline review.

An independent biostatistician was appointed by WHO to conduct a systematic review of these studies and to look specifically at the following aspects:

i. Effectiveness: Evaluation of culture conversion after 6 months of bedaquiline intake; and treatment outcomes in cohorts of patients treated with bedaquiline in addition to (optimised) background regimen; *and*,

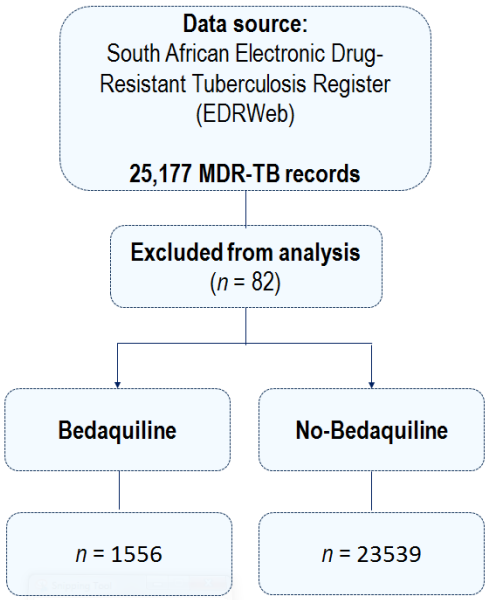
ii. Safety: Type, frequency, severity and seriousness of adverse events related to the use of bedaquiline; *and*

iii. Survival: evaluation of mortality rates when receiving bedaquiline (and related causes of death) in comparison with available data.

2.2. Further data for comparative mortality analysis

In addition, the WHO Guidelines Steering Group was informed in late May 2016 of the existence of a comparative study nearing completion in South Africa, in which data from a cohort of patients treated with bedaquiline were matched with data from the national South African Electronic Drug-Resistant Tuberculosis Register (EDRWeb) and vital registry data to assess mortality in MDR-TB patients treated or not with bedaquiline (**Fig. 2**). Access to these data was requested from the National Department of Health of South Africa, but data could not be made available in time for their inclusion in the systematic review presented at the GDG meeting on 28-29 June 2016. These were then included in a revision of the systematic review presented to the GDG panel in a webinar on 15 September 2016 *(10)*.

Fig. 2. EDRWeb patients' records included in analysis



3. Guideline Development Group Meeting

The GDG meeting took place in Geneva on 28-29 June 2016. Participants included field practitioners, TB specialists, clinical trialists, epidemiologists, methodologists, national TB programme managers and representatives from civil society organizations from both developed and developing countries. Experts appointed to serve as members of the GDG to review current evidence on bedaquiline were selected through consultation with the WHO Guidelines Steering Group established for the review of the 2013 interim policy guideline.

3.1. Meeting objectives

Overall aim

To re-evaluate the added benefit of bedaquiline to the treatment of MDR-TB, a life-threatening form of tuberculosis, and revise the WHO interim guidance issued in June 2013 in view of available evidence on its use in conjunction with WHO-recommended MDR-TB treatment regimens.

Specific objectives

1. To evaluate the harms/benefits ratio of bedaquiline in combination with currently recommended MDR-TB treatment regimen according to the following criteria:

   i. for safety, through the evaluation of the type, frequency and severity of adverse events related to the use of bedaquiline;

   ii. for effectiveness, through the evaluation of treatment outcomes in cohorts of patients treated with bedaquiline in addition to an optimised background regimen, in comparison with similar cohorts or programmatically available data;

   iii. for survival, through evaluation of the mortality rates when receiving bedaquiline (and related causes of death).

2. Based on this evaluation, to update the interim guidance on the use of bedaquiline as part of WHO-recommended MDR-TB treatment regimens, *as appropriate*, keeping in mind the attention to concerns relevant to the use of a medicine for which phase III clinical trial data are not yet available.

Each objective was addressed in different sessions during the GDG meeting, concluding with the development of recommendations based on quality of the evidence, balance between desirable and undesirable effects, resources, feasibility, values and preferences (**Annex 1**).

3.2. Meeting procedures: Management of conflicts of interest

GDG members were carefully selected based on their area of expertise, provided no conflicting interests were involved. All GDG members submitted a completed Declaration of Interest (DOI) form, which was reviewed by the WHO Guidelines Steering Group. For cases in which potential conflicts were unclear, the WHO *Compliance, Risk Management and Ethics* and *Legal* departments were consulted for further clarification and advice as to how to manage competing interests. For some experts, the declared interests were judged significant, but given that their technical expertise and potential contribution to the meeting were estimated of value, their status was changed to that of "Technical resource persons". Technical resource consultants participated in the meeting to provide specific information on technical issues, but were not involved in the deliberations and formulation of the actual recommendations. All participants signed a confidentiality agreement and were reminded of the need for confidentiality until the full WHO process is concluded. The list of participants for this GDG meeting as well as a summary of DOI statements are presented in **Annex 2** and **Annex 3.**

Additionally, in compliance with the procedures and practices established by the *WHO Guideline Review Committee*, as indicated in its 2014 Conflict of Interest Policy, the full list of GDG members and respective biographies were published on the WHO website[4] on 03 May 2016. This was followed by a public comment period, during which the WHO Global TB Programme allowed members of the public to provide comments pertinent to any competing interests that could have gone unnoticed or not reported during earlier assessments. No additional information on any competing interest was shared with WHO.

3.3. Assessment of evidence and its grading: The GRADE system

The quality of evidence and strength of the recommendations were assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (www.gradeworkinggroup.org). In this system, the quality of a body of evidence is defined as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The usefulness of an estimate of the effect (of the intervention) depends on the level of confidence in that estimate. The higher the quality of evidence, the more likely a strong recommendation can be made; however, the decision regarding the strength of the evidence also depends on other factors. The strength of the recommendations reflects the degree of confidence of the panel on whether the desirable effects of the recommendations outweigh the undesirable effects. Through the assessment of both the quality of

[4] Guideline Development Group (GDG) Meetings: Revision of the interim policy on bedaquiline for MDR-TB treatment and special session on delamanid use in children. Public notice, including GDG biographies. **Available from**: http://www.who.int/tb/areas-of-work/treatment/public_notice_gdg_new_drugs.pdf?ua=1

evidence and strength of recommendations, GRADE aims to provide a comprehensive and transparent approach for developing policy guidance. It serves to assess the impact of a particular intervention on patient-centered outcomes and the validity and generalisability of results to the target population, taking into consideration the comparator used and whether comparison was direct or indirect.

3.2.1. Review of the quality of evidence

Members of the GDG were requested to evaluate the available evidence using the GRADE system for grading quality of evidence and assessing strength of recommendations, based on the formulation of an *a priori* agreed-upon question, worded in the PICO (Population, Intervention, Comparator, Outcome) format:

In MDR-TB patients, does the addition of bedaquiline to WHO-recommended second-line drug therapy safely improve patient outcome, as reflected by sputum culture conversion at the end of 6 months, cure at the end of treatment, and patient survival?

3.2.2. Patient outcomes

The following outcomes were selected for evaluation of evidence.

Safety

Evaluation of the type, frequency, severity and seriousness of adverse events related to the use of bedaquiline. These included the following parameters:

- Gastrointestinal (nausea, diarrhea, vomiting, abdominal pain)
- Hearing
- Musculoskeletal and connective tissue (arthralgia, extremity pain, back pain)
- Respiratory (pleuritic pain, chest pain, pharyngolaryngeal pain)
- Dermatological (cutaneous rash, pruritus)
- Central nervous system (dizziness, headache)
- Ocular/visual
- Reproductive
- Cardiac (electrocardiogram (ECG) changes, specifically QTc prolongation)
- Major laboratory abnormalities (> grade II modifications)

Safety was assessed through identification and frequency of adverse events (whether mild; moderate; or severe) and serious adverse events (defined as an adverse event which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly).

Effectiveness

In the absence of long-term clinical endpoints which are being assessed through phase III clinical trials, culture conversion at a prespecified time point during treatment or time to stable culture conversion have been proposed by the United States Food and Drug Administration (FDA) as surrogate markers of MDR-TB treatment outcome *(11)*. Since bedaquiline is prescribed for a duration of 6 months, to be given together with a WHO-recommended longer regimen, it is logical to measure culture conversion at 6 months as a marker of effectiveness. Furthermore, for cohorts of patients with longer follow-up (i.e. at least up to the end of treatment), effectiveness is measured using treatment success rate, defined as: 'treatment completed' *or* 'cured', the latter being defined programmatically

as 'treatment completed as recommended by the national policy without evidence of failure *and* three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Survival

One of the main concerns expressed by the GDG panel in the initial WHO interim guidance was the excess death rate observed in the investigational arm as compared to the control arm in the pivotal phase IIb C208 trial (10/79 (12.7%) *versus* 2/81 (2.5%) respectively, p = 0.017). As a consequence, it was considered essential to measure patient survival in cohorts of patients exposed to bedaquiline treatment, and if possible, to compare outcomes appropriate comparison groups.

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

- *Overall study design:* randomised control trial(s) (RCT), or observational studies. RCT start as high quality evidence, observational studies as low quality evidence
- *Risk of bias or limitations in study design and execution*
- *Inconsistency:* unexplained heterogeneity between studies' endpoints or treatment outcome estimates.
- *Indirectness:* interventions, population and outcomes on which the evidence is based differs from the interventions, populations and outcomes of interest.
- *Imprecision:* wide confidence intervals around treatment outcome estimates.
- *Other considerations:* possibility of publication bias, upgrading factors (applicable to observational studies).

GRADE categorises the quality of evidence as high, moderate, low or very low (**Table 1**) to reflect the overall confidence in the effect under evaluation:

Table 1. Significance of the four levels of evidence

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

3.4. Reviewing the 2013 policy recommendation

Overall, the process of revising the recommendation consisted of a series of interconnected steps involving multiple interdisciplinary experts, including the GDG members, technical resource persons and members of the WHO Guidelines Steering Group. In accordance with WHO procedures, the critical review and assessment of evidence and the formulation of recommendations was the responsibility of experts appointed as GDG members only. This fosters the development of independent, impartial, and unbiased recommendations. For the review of the interim policy guidance on bedaquiline, the GDG had been convened by the WHO to a meeting held on 28 – 29 June 2016, to assess the evidence arising from a systematic review of 5 observational studies (see **Table 2** and **section 4** below), and inform any changes, if appropriate, to the interim guidance. In addition, the GDG requested that new data on mortality – *as presented by representatives from South African Department of Health during the June GDG meeting* – be included in the systematic review of evidence informing the guideline development process, as this additional evidence could guide the re-formulation of the interim recommendations (**Section 1.4.4**). The GDG agreed to reconvene at a second meeting. With the quorum requirement met (14 out of 17 GDG members), the meeting took place remotely via a webinar on 15 September 2016. The GDG concluded the systematic assessment of the evidence and agreed upon the considerations for the use of bedaquiline described in this report.

4. Summary of main findings

4.1. Sample description and baseline characteristics

The selected studies comprised data from a total of 537 MDR-TB cases from the following five data sources: a phase II, single arm, open-label study conducted by the drug manufacturer (*n* = 205) (hereafter referred to as "multi-centre study"); the South African Bedaquiline Clinical Access Programme, BCAP (*n* = 195); a retrospective cohort of patients receiving bedaquiline under compassionate use in France (*n* = 45);), and the Medecins Sans Frontières (MSF) compassionate use programmes in Armenia (*n* = 62); and Georgia (*n* = 30) (**Table 2**). Sixty-four *per cent* of participants were males. There were no significant differences in age distribution among the various cohorts: the mean age for all the studies was 36.4 years (standard deviation = 11.8) (**Table 3**). Among cohorts reporting data on patients with history of previous TB (except South Africa), about three-quarters of patients (79.2%; 271/342) were reported to have had history of previous use of second-line TB treatment. With the exception of South Africa, extensive cavitary lung disease due to *Mycobacterium tuberculosis* was reported in 73.9% of the cases (253/342). The drug resistance profile varied across the cohorts[5]: in South Africa, 41.0% of cases had XDR-TB and 37.9% were reported as cases of MDR-TB$_{+FQ}$; more than half of the cases (53.3%) in the French study were identified as XDR-TB cases, whereas about half the cases (45.4%) in the multi-centre study had MDR-TB with no additional resistance. More than three-quarters (83.3%) of cases in Georgia were XDR-TB patients, followed by 16.7% of cases with MDR-TB$_{+SLI}$. In Armenia there was higher proportion of MDR-TB$_{+FQ}$ (48.4%) and XDR-TB (40.3%) cases (**Table 3**).

The composition of the baseline regimens was different across studies, with a high use of aminoglycosides in the French cohort (all patients), as well as in the drug manufacturer's multi-centre study. In the latter, and also in South Africa, high use of fluoroquinolones was observed (87.8% and 81.0% respectively). Amoxicillin-clavulanate was used in a large proportion of patients in Armenia and Georgia (80.6% and 96.7%), and clofazimine was administered to 82.3% and 80.0% of patients in these cohorts. 72.6% of patients in Armenia received cycloserine compared to only 43.3% in Georgia. The proportion of patients receiving imipenem-cilastatin was higher in Georgia than in Armenia, with 90.0% *vs*. 71.0% of patients receiving this antibiotic within their optimised background regimen. Most patients received bedaquiline for a duration of six months - along with a WHO-recommended longer regimen. In the French cohort, however, the average duration of treatment with bedaquiline was 12.3 months (standard deviation= 7 months) with 71.1% of patients, (32/45), receiving bedaquiline for more than 6 months (**Table 3**). All cohorts provided data on status of co-infection with human immunodeficiency virus (HIV) for the majority of patients (HIV status was not reported for 5.4% (29/537) of patients). Sixty-three *per cent* of cases in South Africa were HIV co-infected. In contrast, the proportion of HIV-infected cases was less prominent in the other cohorts: seven *per cent* of cases in Armenia, four *per cent* in France and in the multi-centre study, and three *per cent* in Georgia. About half of the HIV co-infected cases (110/195) in the South African cohort, as well as all HIV positive patients in the French (4/4) cohort and in the multi-centre study (8/8) were on antiretroviral (ARV) therapy at the time data were collected (**Table 3**). None of the HIV co-infected patients in the Armenian and Georgian cohorts received ARV therapy.

Out of all MDR-TB cases included in this analysis, eight cases (17.8%) in the French cohort were reported to have extrapulmonary TB. All cohorts, except South Africa reported history of previous TB treatment, with the majority of cases from the multi-centre study (94.1%), followed by France

[5] Missing data (South Africa (12 records); Multi-centre study (31 records); Armenia (1 record); Georgia (8 records).

(75.6%), Georgia (66.7%), and Armenia (38.7%) (**Table 3**). Overall, 86.3% of patients (except South Africa), had previous exposure to second line TB treatment: all cases in Armenia, 96.7% of patients in Georgia, followed by 86.3% and 60.0% of cases in the multi-centre and French cohorts had history of previous treatment with second line drugs (**Table 3**).

Table 2. Characteristics of included studies

	Multi-centre (*n* = 205)	**France** (*n* = 45)	**Armenia** (*n* = 62)	**Georgia** (*n* = 30)	**South Africa** (*n* = 195)
Design	A phase II, single arm open label trial	Retrospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Setting	31 sites, 11 countries*	Sanatorium of Bligny Hospital	MSF sites in Armenia	MSF sites in Georgia	Multi-sites
Inclusion criteria	Sputum smear-positive pulmonary infection with MDR-TB	MDR-TB receiving bedaquiline for compassionate use	MDR-TB patients with additional resistance to either a fluoroquinolone or both XDR-TB and failures of MDR-TB treatment	MDR-TB patients with additional resistance to either a fluoroquinolone or both XDR-TB and failures of MDR-TB treatment	Pulmonary XDR-TB, MDR-TB$_{+FQ}$ or MDR-TB$+_{SLI}$
Intervention	Weeks 1-2: bedaquiline 400mg once daily Weeks 3-24: bedaquiline 200mg thrice a week	Bedaquiline 400mg once daily for 2 weeks, then 200mg thrice a week	Bedaquiline for 24 weeks. 400mg once daily for 2 weeks, then 200mg thrice a week	Bedaquiline for 24 weeks. 400mg once daily for 2 weeks, then 200mg thrice a week	Bedaquiline 400mg once daily for 2 weeks, then 200mg thrice a week for 24 weeks
Composition of regimen	The intensive phase would include an injectable aminoglycoside with 3 or 4 other drugs, including a fluoroquinolone, and then followed by a continuation phase without an aminoglycoside and without pyrazinamide.†	Baseline regimens were tailored according to drug susceptibility results.	Baseline regimen was constructed according WHO recommendations: at least four effective drugs including a fluoroquinolone and injectable if possible, with linezolid and imipenem-cilastatin included when needed.	Baseline regimen was constructed according WHO recommendations: at least 4 effective drugs including a fluoroquinolone and injectable if possible, with linezolid and imipenem-cilastatin included when needed.	Regimens included at least three effective second line drugs, and according to availability. Levofloxacin was preferred over moxifloxacin, to mitigate QT effects.

Notes—.* China, Estonia, Republic of Korea, Latvia, Peru, Philippines, Russian Federation, South Africa, Thailand, Turkey, Ukraine. †In the multi-centre study, baseline regimens were selected in accordance with local treatment guidelines, although these typically were composed as described above. *Abbreviations:* TB= tuberculosis; MDR-TB=multidrug resistant TB; FQ= fluoroquinolone; SLI= second line drugs; XDR-TB= extensively drug resistant TB; MSF= Médecins Sans Frontières; WHO= World Health Organization.

Table 3. Baseline characteristics of participants in the included studies

Variable	Country / Data source					
	S. Africa (*n* = 195)	**France (*n* = 45)**	**Multi-centre (*n* = 205)**	**Armenia (*n* = 62)**	**Georgia (*n* = 30)**	**Total (*n* = 537)**
Age (years): mean (SD)	35.8 (11.2)	37.4 (12.1)	34.9 (12.2)	41.6 (12.6)	38.7 (11.9)	36.4 (11.8)
Male: n (%)	98 (50.3)	36 (80.0)	132 (64.4)	55 (88.7)	21 (70.0)	342 (63.7)
Female: n (%)	97 (49.7)	9 (20.0)	73 (35.6)	7 (11.3)	9 (30.0)	195 (36.3)
Duration on BDQ (months): mean (SD)	5.8 (1.2)	12.3 (7.0)	5.9 (1.1)	5.6 (1.6)	6.0 (1.3)	6.37 (2.3)
Duration on BDQ >6months: n (%)[†]	4 (2.1) [*]	32 (71.1)	0.0 (0.0)	6 (9.6) [*]	4 (13.3) [*]	46 (8.5)
Duration on treatment (months): mean (SD)	14.9 (6.7)	19.4 (4.7)	21.8 (7.6)	17.2 (8.4)	9.2 (3.6)	17.8 (7.0)
Received full treatment (18-20 months): n (%)	101 (51.8)	45 (100.0)	205 (100.0)	29 (46.7)	7 (23.3)	207 (38.5)
HIV status (positive): n (%)[‡]	123 (63.1)	2 (4.4)	8 (4.0)	4 (6.5)	1 (3.3)	138 (25.7)
On antiretroviral therapy: n (%)	110 (56.4)	2 (4.4)	8 (4.0)	0 (0.0)	0 (0.0)	120 (22.3)
Type of TB: Pulmonary	NR	44 (97.8)	205 (100.0)	62 (100.0)	30 (100.0)	341 (99.7)
Type of TB: Extra-pulmonary	NR	8 (17.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.3)
History of previous TB treatment	NR	34 (75.6)	193 (94.1)	24 (38.7)	20 (66.7)	271 (79.2)
History of previous second line TB treatment	NR	27 (60.0)	177 (86.3)	62 (100.0)	29 (96.7)	295 (86.3)
Cavities (yes): n (%)	NR	39 (86.7) [§]	135 (65.8)	55 (88.7)	24 (80.0)	253 (73.9)
Resistance profile: n (%)[‖]						
MDR-TB	0 (0)	7 (15.6)	93 (45.4)	0 (0.0)	0 (0.0)	100 (18.6)
MDR-TB$_{+FQ}$	73 (37.4)	8 (17.8)	31 (15.1)	30 (48.4)	5 (16.7)	147(27.3)
MDR-TB$_{+SLI}$	29 (14.9)	6 (13.3)	13 (6.3)	7 (11.3)	0 (0.0)	55 (10.2)
XDR-TB	77 (39.5)	24 (53.3)	37 (18.0)	25 (40.3)	25 (83.3)	188 (35.0)

Notes—.[*]Different approaches to computing duration on bedaquiline and incomplete data on interruptions led to certain patients in Armenia, Georgia and South Africa appearing to have received bedaquiline for more than 6 months. However, as per protocol, patients in these two cohorts received bedaquiline for 6 months only. [†]Missing data: South Africa=15; [‡]Missing data: South Africa=13; Multi-centre study=7; Georgia=8; Armenia =1; [§]Missing data: France=1; [‖]Missing data: South Africa=16; Multi-centre study =31; Armenia=1; Georgia=8. *Abbreviations:* SD= standard deviation; BDQ= bedaquiline; HIV=human immunodeficiency virus; TB= tuberculosis; MDR-TB= multidrug resistant TB; FQ= fluoroquinolone; SLI= second line drugs; XDR-TB= extensively drug resistant TB; NR= Not reported.

Table 4. Populations used in the various analyses

Analysis	Source of data (*n*)	Total number of patients included in the analysis	Data description
Description of baseline characteristics	South Africa (195); France (45); Multi-centre study (205); Armenia (62); *and* Georgia (30).	537	Total sample with baseline characteristics available.
Composition of OBR regimen	South Africa (195); France (45); Multi-centre study (205); Armenia (60); *and* Georgia (30).	535	Data missing from 2 patients from Armenia.
Composition of antiretroviral therapy	South Africa (110); France (2); *and* Multi-country study (8).	120	Data available only for HIV infected patients on antiretroviral therapy.
Effectiveness (sputum culture conversion at 6 months)	South Africa (72); France (45); ; Multi-centre study (205);Armenia (50); *and* Georgia 23.	391	Data on patients who had a culture done at 6 months.
Treatment outcomes (cure, death, lost to follow-up, treatment complete, treatment failure)	South Africa (101); France (45); *and* Multi-centre study (205).	351	Data on cohorts of patients with complete follow up (18 months and more) and available outcome data.
Safety (adverse events)	South Africa (195); France (45);; Multi-centre study (233); Armenia (62); *and* Georgia (30).	565	This analysis includes additional data from 28 patients from the Multi-centre study cohort who received bedaquiline, but were later found to be ineligible or withdrew.
Safety (QT prolongation)	South Africa (141); France (45); Multi-centre study (233); Armenia (62); *and* Georgia (30).	511	Data available only for 141 patients from South Africa who received complete follow-up.
Mortality (Causes of death)	South Africa (27); France (3); Multi-centre study (16); Armenia (6); *and* Georgia (4).	56	All deaths included in the stratifications by HIV status, resistance profile and time.
Mortality (Comparative data analysis)	South Africa: Treated with a bedaquiline containing regimen (1 556); and and treated with a non-bedaquiline containing regimen (23 539).	25 095	Mortality data on a total of 25 177 patients with MDR-TB was provided. Eighty-two (82) of them belonged to the BCAP cohort and were excluded from the analysis leaving 25 095.

4.2. Effectiveness of bedaquiline in the treatment of MDR-TB

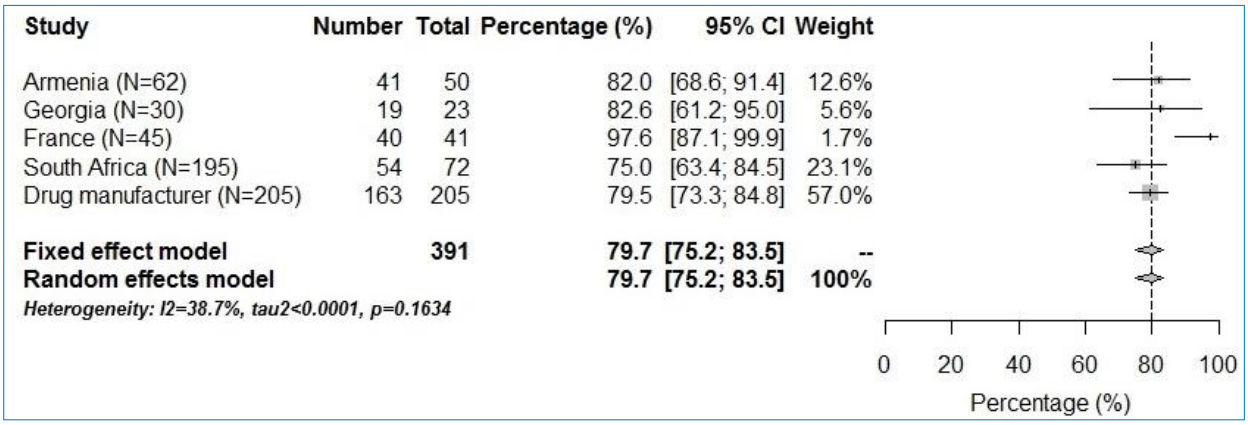
The clinical efficacy and side-effect profile of bedaquiline have been evaluated through two phase IIb studies, one being a randomized controlled trial conducted in two consecutive, but separate stages (C208 stage 1 and C208 stage 2) and the other was a single arm, open label study (C209)[6]. Although late-stage trials of bedaquiline in combination with other novel compounds or in optimized regimens are underway,[7,8,9,10] there were no additional clinical trial data provided to the GDG to further confirm the efficacy and safety of bedaquiline in conjunction with a WHO-recommended longer regimen. Thus, observational data, as indicated before, arising from various studies were used to inform estimates of treatment effectiveness, safety and mortality.

Of note, given that only two-thirds of patients (351/537) enrolled in these studies had completed treatment, and due to missing data on specific co-variates of interest, the denominators used for each outcome presented in this report vary depending on the availability of such data by the time the analysis was conducted. The respective denominators used in the analyses are provided in **Table 4**.

4.2.1. Effectiveness: Culture conversion after six months of treatment

In the reviewed studies, bedaquiline was administered as 400 mg once daily for 2 weeks, followed by 200 mg thrice weekly for up to 22 weeks or longer, together with multidrug background treatment. Effectiveness was calculated as the proportion of patients who had sputum culture conversion at the end of the initial six months of bedaquiline treatment. Overall, the effectiveness of bedaquiline was 79.7% (95% CI 75.2 to 83.5), with 75.0% to 97.6% of patients having conversion to negative cultures at the end of the initial six months of bedaquiline treatment (**Fig. 3**).

Fig. 3. Meta-analysis of culture conversion at six months of bedaquiline treatment



[6] Diacon *et al*. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. New England Journal of Medicine. 2009;360(23):2397-405. **Available from**: http://www.nejm.org/doi/pdf/10.1056/NEJMoa0808427

[7] A phase III study assessing the safety and efficacy of bedaquiline, PA-824 and linezolid in subjects with drug resistant tuberculosis. A**vailable from**: https://clinicaltrials.gov/ct2/show/NCT02333799?term=bedaquiline&rank=2

[8] A trial of the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid, alone and in combination, among participants taking multidrug treatment for drug-resistant pulmonary tuberculosis. **Available from**: https://clinicaltrials.gov/ct2/show/NCT02583048?term=bedaquiline&rank=7

[9] STREAM, stage 2: The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis drugs for patients with MDR-TB. **Available from**: https://clinicaltrials.gov/ct2/show/NCT02409290?term=stream+bedaquiline&rank=1

[10] NeXT trial: An Open-label RCT to Evaluate a New Treatment Regimen for Patients With Multi-drug Resistant Tuberculosis (NEXT). **Available from**: https://clinicaltrials.gov/ct2/show/study/NCT02454205

4.2.2. Treatment outcomes

Treatment outcomes (cure, death, lost to follow-up, treatment complete and treatment failure) were assessed on the basis of the definitions of treatment outcomes for drug-resistant patients *(12)*. In this analysis, outcomes were estimated for all patients who had at least 18 - 24 months of follow-up data available (**Table 5** and **Figs. 4** to **9**). Two cohorts (Armenia and Georgia) for which outcome data were either not available, of low quality, or contained up to 50% missing values, were excluded from the analyses of treatment outcomes.

Overall, although the proportion of MDR-TB patients who were classified as treatment success (i.e. cured or treatment completed) was 69.3% (95% CI: 59.7 to 78.2), the proportional rates of treatment outcomes varied across the studies: the proportion of cases who got cured was higher in the French cohort (75.5%; 34/45) than in the South African cohort (63.4%; 64/101) and in the drug manufacturer's multi-centre study (61.0%; 125/205) (**Table 5**). There were also a higher number of deaths in the South African cohort (19.8%; 20/101) while mortality rate was similar in the French (6.7%; 3/45) and the multi-centre studies (6.8%; 14/205). An exploratory subgroup analysis indicated that observed mortality rates were higher in patients co-infected with HIV (See **section 4.4**). Data on treatment failure remained unclear for the multi-centre study in which missing outcomes were interpreted as failures, diluting the true number of patients in whom treatment truly failed. For the remaining two cohorts, South Africa and France, 1.0% (1/101) and 2.2% (1/45) of patients were reported to have failed treatment (**Table 5**).

Table 5. Distribution of treatment outcomes

Outcome	S. Africa *n* = 101 (%)	France *n = 45* (%)	Multi-centre *n = 205* (%)	Overall*		
				n = 351	% (95%CI)	I^2
Cured	64 (63.4)	34 (75.5)	125(61.0)	223	63.8 (57.8-69.4)	39.5%
Death	20 (19.8)	3 (6.7)	14 (6.8)	37 †	10.6 (3.8-20.0)	81.7%
Lost to follow up	10 (9.9)	5 (11.1)	31 (15.1)	46	12.8 (9.2-16.8)	0%
Treatment complete	6 (5.9)	2(4.4)	3 (1.5)	11	3.3 (0.7-7.3)	58.7%
Treatment failure	1 (1.0)	1 (2.2)	32(15.6) ‡	34	5.2 (0.0-16.3)	92.2%
Treatment success	70 (69.3)	36 (80.0)	128 (62.4)	234	69.3 (59.7 – 78.2)	64.9%

Notes—. *Random effects meta-analysis of proportions for 3 studies; †Subgroup analysis for death rates by HIV status (HIV positive: 17.2% [95% CI 10.3-27.1), I^2=0%; HIV negative: 8.3% [95% CI 2.0-29.3, I^2=80.8%); ‡For the multi-centre study, a missing equals failure approach was used.

A meta-analysis of proportions to calculate the summary frequency of each treatment outcome was conducted. In this analysis, only lost-to-follow-up outcomes seemed to be homogeneous (consistent) throughout these studies (I^2 = 0%). Contrarily, there was moderate to considerable variation across studies as reflected in the measure of heterogeneity for cure (I^2 = 39.5%), treatment completion (I^2 = 58.7%), treatment failure (I^2 = 92.2%), and death (I^2 = 81.7%) outcomes. Such variability could be explained by the differences in the burden of disease in these cohorts, severity, individual patient characteristics (co-morbidities and other socio-demographic factors), differences in background MDR-TB regimen and health care services, which are by nature inherently heterogeneous. In addition, the quality of data was found to vary across settings. Results of the various random effects analyses for each outcome are presented in **Figs. 4** to **9**.

Fig. 4. Meta-analysis of cure rates

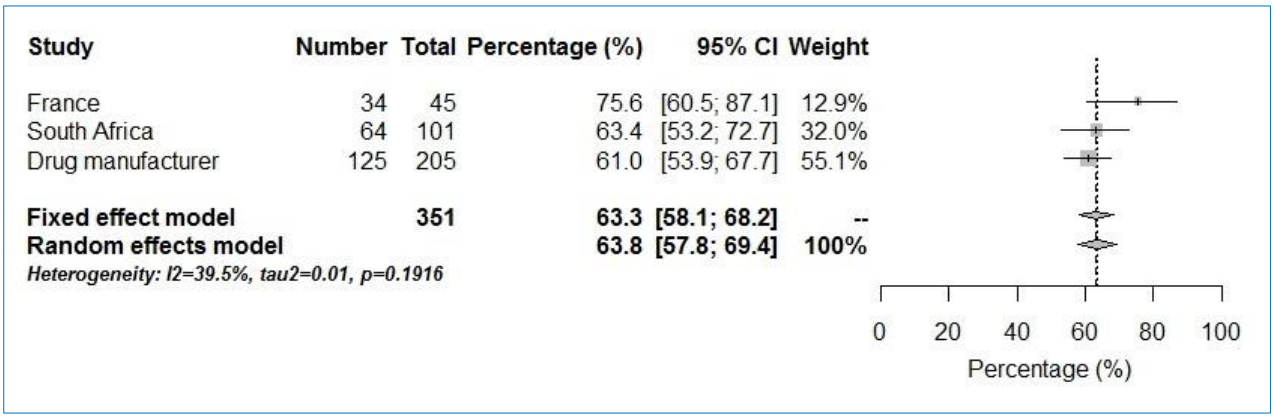


Fig. 5. Meta-analysis of treatment completion rates

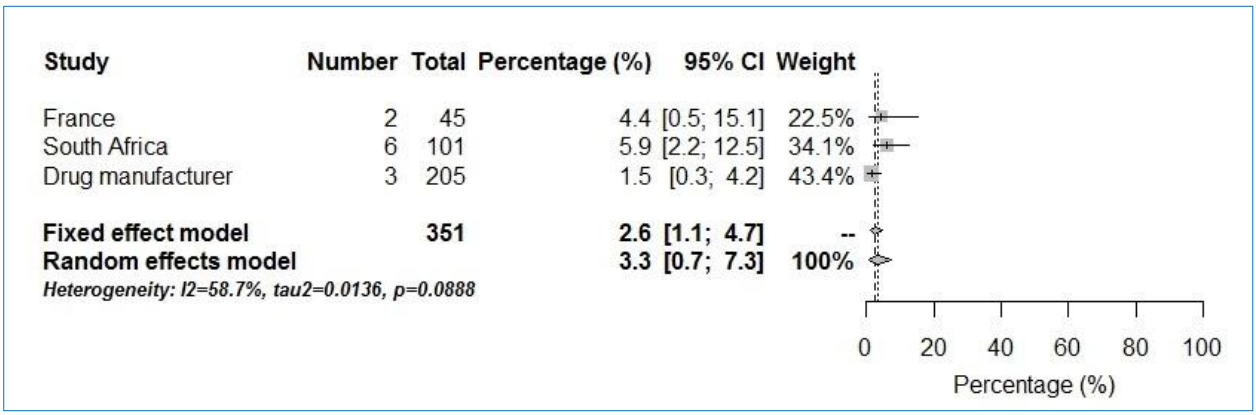


Fig. 6. Meta-analysis of failure rates

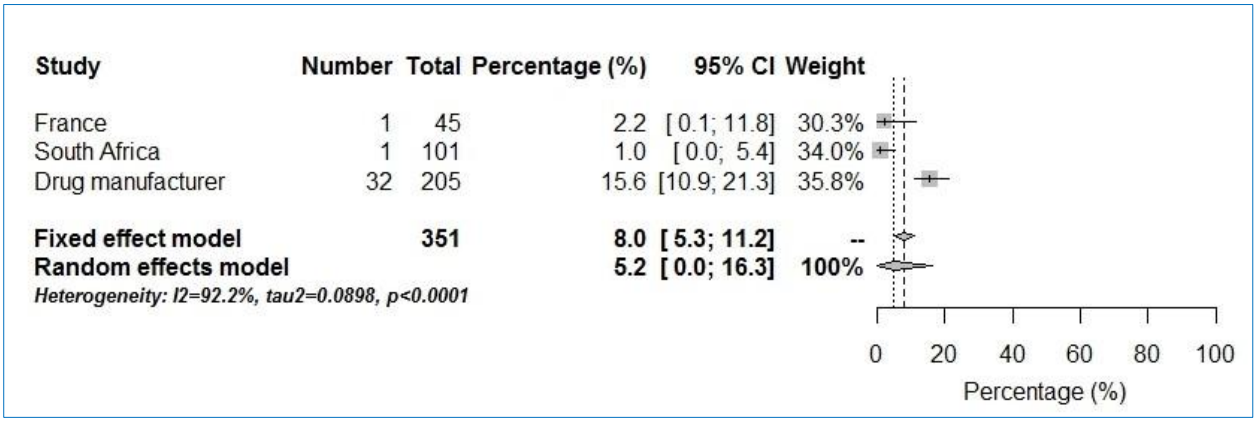


Fig. 7. Meta-analysis of death rates

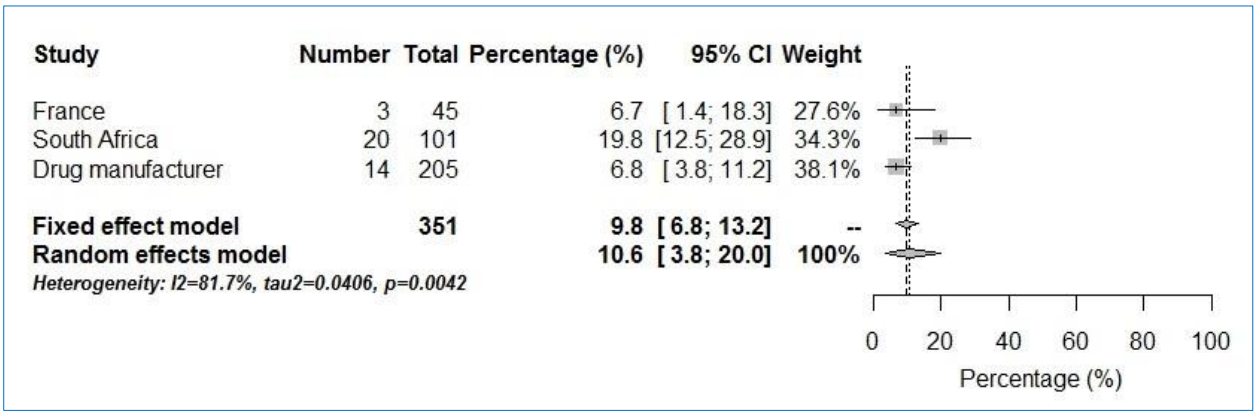


Fig. 8. Meta-analysis of lost-to-follow-up rates

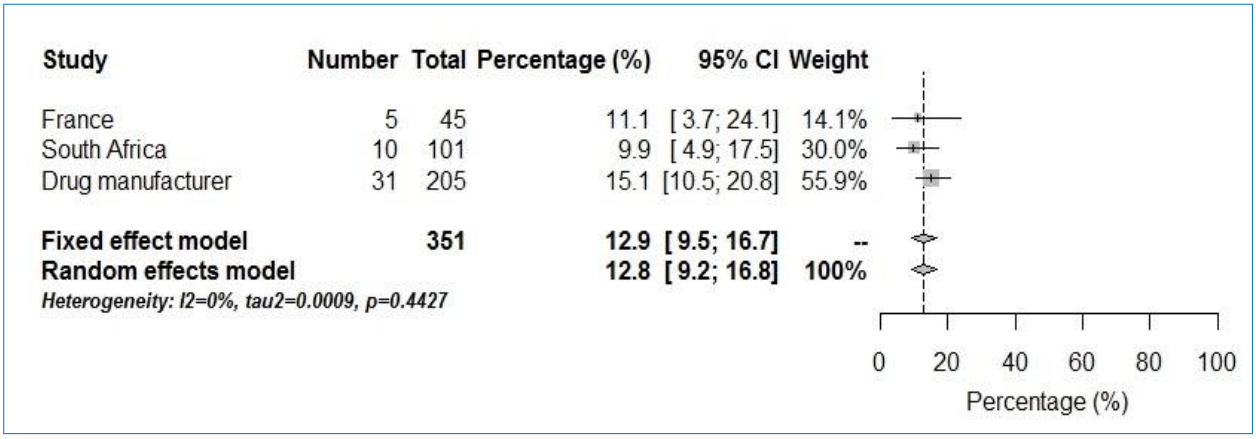
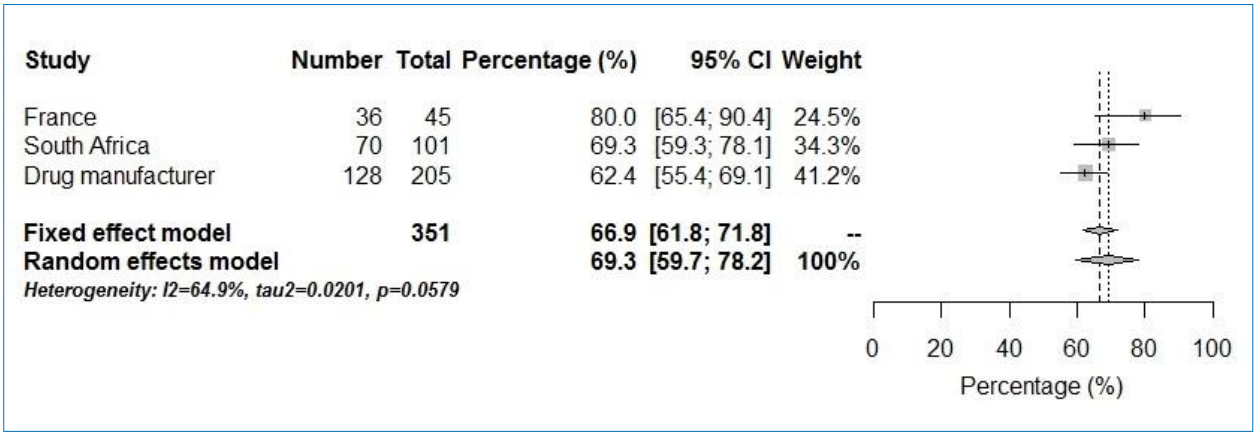


Fig. 9. Meta-analysis of success rates



4.3. Safety

Data were grouped according to system, based on available information, e.g.: gastrointestinal adverse events include events reported as gastrointestinal or related to the gastrointestinal system (such as nausea, vomiting, diarrhoea etc.); hepatic adverse events include events reported as such by the authors or including liver enzyme elevation and clinical reports; cardiovascular adverse events included events reported by authors as cardiovascular or other clinical and ECG reports.

A total of 520 patients were reported to have experienced at least one adverse event (all cases in the retrospective cohort from France, Armenia and Georgia, 93.9% in the open-label multi-centre study and 84.1% in the South African cohort, respectively). Additionally, 118 patients presented severe adverse events, and 42 patients experienced at least one *serious adverse event (SAE)* (**Table 6**).

A total of 2622 adverse events were reported among all cohorts (*n* = 565). A large proportion of adverse events (74.1%; 1943/2622) were reported among patients in the drug manufacturer multi-centre study. Close to 10 *per cent* (9.7%; 256/2622) of these events were reported in patients from the South African cohort, followed by the MSF Armenia cohort with 205 adverse events (7.8%; 205/2622), France with 179 events (6.8%; 179/2622), and the MSF Georgia cohort reporting 39 adverse events (1.4%; 39/2 622) (**Table 7**). *The difference in the number of adverse events presented in each cohort may be attributed to various factors, including recording and reporting systems, and implicit bias*[11]. The most prevalent adverse events were gastrointestinal (14.0%), followed by metabolic disorders (8.5%), nervous system disorders (8.5%) and musculoskeletal and connective tissue disorders (6.8%) (**Table 7**). A total of 48 SAE were notified among 42 patients in all cohorts; the most common SAE were respiratory (25.0%), followed by cardiac (16.7%) and laboratory signs of hepatitis (14.6%) (**Table 8**). Of the SAE classified as life-threatening (Grade IV) and fatal (Grade V)[12], 16.7% were attributed to respiratory, thoracic and mediastinal disorders, followed by a similar distribution of cardiac events, including ECG changes and QT prolongation (10.0%), and signs of nervous system toxicities (10.0%) (**Table 9**).

Table 6. Number of patients who experienced adverse events

Country/study	At least one adverse event *n* (%)	Any severe adverse event *n* (%)	Any serious adverse event *n* (%)
France (*n* = 45)	45 (100.0)	28 (62.2)	7 (15.6)
South Africa (*n* = 195)	164 (84.1)	32 (16.4)	6 (3.1)
Drug manufacturer (*n* = 233)*	219 (93.9)	50 (21.5)	15 (6.4)
Armenia (*n* = 62)	62 (100.0)	5 (8.1)	11 (17.7)
Georgia (*n* = 30)	30 (100.0)	3 (10.0)	3 (10.0)
Total (*n* = 565)	520 (92.0)	118 (20.8)	42 (7.4)

Note—.* Includes patients (*n* = 28) who were later found to be ineligible or withdrew consent.

[11] Implicit bias refers to bias in clinical decision-making (by the provider) which can result in the provision of unequal treatment or other health inequalities.
[12] Only the multi-centre study from the drug manufacturer as well as the French and South African cohorts reported data on life-threatening and fatal adverse events.

Table 7. Distribution of all adverse events by system affected and study

System	South Africa	France	Multi-centre study	Armenia	Georgia	Total
Gastrointestinal symptoms	22 (8.6)	37 (20.7)	251 (12.9)	46 (22.4)	11 (28.2)	367 (14.0)
Metabolisms and nutrition disorders	36 (14.1)	3 (1.7)	185 (9.5)	0 (0)	0 (0)	224 (8.5)
Musculoskeletal, connective tissue, and arthralgia	19 (7.4)	7 (3.9)	147 (7.6)	5 (2.4)	0 (0)	178 (6.8)
Nervous system disorders (dizziness, headache)	34 (13.3)	42 (23.5)	111 (5.7)	34 (16.6)	3 (7.7)	224 (8.5)
Skin and subcutaneous tissue disorders	17 (6.6)	8 (4.5)	90 (4.6)	5 (2.4)	0 (0)	120 (4.6)
Respiratory, thoracic and mediastinal disorders	3 (1.2)	2 (1.1)	125 (6.4)	5 (2.4)	2 (5.1)	137 (5.2)
Ear and labyrinth disorders, Eye	23 (9.0)	10 (5.6)	90 (4.6)	10 (4.9)	1 (2.6)	134 (5.1)
Psychiatric disorders	9 (3.5)	12 (6.7)	60 (3.1)	0 (0)	0 (0)	81 (3.1)
Blood and lymphatic system disorders	20 (7.8)	12 (6.7)	65 (3.3)	0 (0)	1 (2.6)	98 (1.9)
Cardiac (incl. ECG changes and QT prolongation)	5 (2.0)	8 (4.5)	31 (1.6)	4 (2.0)	1 (2.6)	49 (1.9)
Laboratory signs of hepatitis	2 (0.8)	20 (11.2)	24 (1.2)	35 (17.1)	7 (17.9)	88 (3.4)
Laboratory signs of pancreatitis	2 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.1)
Renal failure	9 (3.5)	7 (3.9)	14 (0.7)	5 (2.4)	3 (7.7)	38 (1.4)
Other*	55 (21.5)	11 (6.1)	750 (38.6)	56 (27.3)	10 (25.6)	882 (33.6)
Total	256 (100.0)	179 (100.0)	1 943 (100.0)	205 (100.0)	39 (100.0)	2 622 (100.0)

Notes—. Other includes congenital, familial and genetic, general disorders and admin site conditions, injury, poisoning and procedural complications, investigations, neoplasms and events reported as 'other'. *Abbreviation (s)*: ECG= electrocardiogram.

Table 8. Distribution of number of serious adverse events by system in all studies

System	Total *n* (%)
Gastrointestinal symptoms	1 (2.1)
Metabolisms and nutrition disorders	2 (4.2)
Musculoskeletal and connective tissue disorders, arthralgia	0 (0.0)
Nervous system disorders (dizziness, headache)	4 (8.3)
Skin and subcutaneous tissue disorders	0 (0.0)
Respiratory, thoracic and mediastinal disorders	12 (25.0)
Ear and labyrinth disorders, Eye	0 (0.0)
Psychiatric disorders	2 (4.2)
Blood and lymphatic system disorders	0 (0.0)
Cardiac disorders (including ECG changes and QT prolongation)	8 (16.7)
Laboratory signs of hepatitis	7 (14.6)
Laboratory signs of pancreatitis	0 (0.0)
Renal failure	2 (4.2)
Other*	10 (20.8)
Total	48 (100.0)

Notes—.* Includes some deaths. *Abbreviation (s)*: ECG= electrocardiogram.

Table 9. Distribution of serious adverse events by system affected for all cohorts

System	Life-threatening	Fatal	SAE, non-categorised†	Total
	n (%)	*n* (%)	*n* (%)	*n* (%)
Gastrointestinal symptoms	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.1)
Metabolisms and nutrition disorders	1 (7.1)	0 (0.0)	1 (4.5)	2 (4.2)
Musculoskeletal and connective tissue disorders, arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders (dizziness, headache)	2 (14.3)	1 (8.3)	1 (4.5)	4 (8.3)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3 (21.4)	2 (16.7)	7 (31.8)	12 (25.0)
Ear and labyrinth disorders, Eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (7.1)	0 (0.0)	1 (4.5)	2 (4.2)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac disorders (including ECG changes and QT prolongation)	2 (14.3)	1 (8.3)	5 (22.7)	8 (16.7)
Laboratory signs of hepatitis	1 (7.1)	0 (0.0)	6 (27.3)	7 (14.6)
Laboratory signs of pancreatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure	1 (7.1)	1 (8.3)	0(0.0)	2 (4.2)
Other*	3 (21.4)	7 (58.3)	NR	10 (20.8)
Total	14 (100.0)	12 (100.0)	22 (100.0)	48 (100.0)

Notes—.* Other includes congenital, familial and genetic, general disorders and admin site conditions, injury, poisoning and procedural complications, investigations, neoplasms, events reported as 'other', and some deaths .† Armenia and Georgia provided non-categorised data on serious adverse events. *Abbreviation (s)*: ECG= electrocardiogram.

Additionally, to further explore signs of cardiotoxicity, QTc prolongation was calculated using Fredericia corrected QT intervals (QTcF). Emphasis was placed on absolute QTc interval (worse outcomes) greater than 500 milliseconds (ms) and increases of 30 and 60 or more ms compared to baseline. Out of 511 patients with ECG data, more than two thirds of cases (69.7%; 356/511) did not experience QTc prolongation. Approximately 20% of the patients (20.5%; 105/511) had a QTc between 450 - 480ms, and 5.1% (26/511) experienced a QTc prolongation between 481 - 500ms. QTc was prolonged to greater than 500ms in 24 patients (4.7%) (**Table 10**). About 46% of patients (238/511) had an increase of 0-30 ms; 33% (172/511) had an increase between 30 to 60 ms and 14% (76/511) had an increase greater than 60ms (**Table 11**). Data from the French cohort allowed to assess whether the duration of bedaquiline treatment had an effect on QTc prolongation. Data seemed to indicate an absence of effect of duration of bedaquiline exposure [higher than six months] on QTc prolongation >480 ms (**Table 12**). However, the very limited sample size needs to be noted.

Table 10. Distribution of worst QTcF measurements

Worst QTcF measurement (ms)	**France** *n* = 45 (%)	**S. Africa** *n* = 141 (%)	**Armenia** *n* = 62 (%)	**Georgia** *n* = 30 (%)	**Multi-centre study** *n* = 233 (%)	**Total** *n* = 511(%)
≤450	14 (31.1)	105 (74.5)	34 (54.8)	13 (43.3)	190 (81.5)	356 (69.7)
>450-480	16 (35.6)	24 (17.0)	15 (24.2)	14 (46.7)	36 (15.5)	105 (20.5)
>480-500	7 (15.6)	6 (4.3)	6 (9.7)	2 (6.7)	5 (2.1)	26 (5.1)
>500	8 (17.8)	6 (4.3)	7 (11.3)	1 (3.3)	2 (0.9)	24 (4.7)
Total	45 (100.0)	141 (100.0)	62 (100.0)	30 (100.0)	233 (100.0)	511

Notes.—Safety data includes records of additional 28 patients who received bedaquiline, but where later found to be ineligible or withdrew from the drug manufacturer's multi-centre study. Additionally, 54 QTc records of patients from the South African cohort were missing, therefore, only 141 South African patients were included in analysis of cardiotoxicity. *Abbreviation (s)*: QTcF= baseline-corrected QTcF (where the "F" denotes Fridericia corrected QTc); ms= milliseconds.

Table 11. Increase in QTc from baseline to longest measurements

QTc increase from baseline at end of follow- up (ms)	**France** *n* = 45 (%)	**S. Africa** *n* = 141 (%)	**Armenia** *n* = 62 (%)	**Georgia** *n* = 30 (%)	**Multi-centre study** *n* = 233 (%)	**Total** *n = 511(%)*
0-30	17 (37.8)	68 (48.2)	17 (27.4)	9 (30.0)	127 (54.5)	238 (46.6)
>30-60	6 (13.3)	46 (32.6)	15 (24.2)	9 (30.0)	96 (41.2)	172 (33.7)
>60	8 (17.8)	26 (18.4)	24 (38.7)	8 (26.7)	10 (4.3)	76 (14.8)
Missing	14 (31.1)	1 (0.7)	6 (9.7)	4 (13.3)	0 (0.0)	25 (4.9)
Total	45 (100.0)	141 (100.0)	62 (100.0)	30 (100.0)	233 (100.0)	511

Note—.*Abbreviations*: QTcF= baseline-corrected QTcF (where the "F" denotes Fridericia corrected QTc); ms= milliseconds.

Table 12. Average QTcF prolongation by duration on bedaquiline

QTcF length (ms)	France		Total *n* (%)
	BDQ 0-6mo *n* (%)	BDQ >6mo *n* (%)	
≤450	7 (53.8)	23 (71.9)	30 (66.6)
>450-480	6 (46.2)	9 (28.1)	15 (33.3)
>480-500	0 (0.0)	0 (0.0)	0 (0.0)
>500	0 (0.0)	0 (0.0)	0 (0.0)
Total	13 (100.0)	32 (100.0)	45 (100.0)

Note—.*Abbreviations*: QTcF= baseline-corrected QTcF (where the "F" denotes Fridericia corrected QTc); ms= milliseconds; BDQ= bedaquiline; mo= months.

4.4. Mortality

A total of 56 patients died among the five cohorts. Sixty-six (37/56) *per cent* of these patients were reported to have died among cohorts with complete treatment outcome data, i.e. patients with 18 - 24 month follow-up data. The remaining 19 deaths were reported among patients with incomplete treatment outcome data. Close to one third of patients (32.1%; 18/56) died within the first six months of treatment whereas an additional 57.1% died between month 6 to month 26. An additional 10.7% of patients died outside follow-up period (6/56). Furthermore, in the drug manufacturer's multi-centre study in which patients were followed-up beyond 26 months, two deaths were reported between 26 and 30 months (3.6%), and 4 deaths after 30 months (7.1%). The proportion of deaths seemed to be higher in HIV positive patients (13.0%; 18/138) than in patients with known HIV-negative status (8.8%; 36/405). Nine *per cent* (9.0%; 2/22) of patients with unknown HIV status died. Looking at deaths by drug-resistance profile, a higher proportion of deaths seemed to have occurred among MDR-TB$_{+FQ}$ patients (16.3%; 24/147); this was followed by 10.9% of deaths in MDR-TB$_{+SLI}$ patients (6/55), and 10.1% of XDR-TB patients reported to have died (19/188). Only three MDR-TB patients (2.9%; 3/105) without additional resistance patterns died.

Among the 56 fatalities reported, the leading underlying cause of death in 39.2% of cases was related to respiratory system (22/56), including a high proportion of respiratory failures attributed to TB (15 out of 22); seven *per cent* of patients died as consequence of cardiovascular disorders (4/56). There were three patients whose death was attributed to sputum culture reversion (7.1%); 5.3% of cases died as result of other (major) infections (3/56); 4% presented neuropsychiatric disorders (2/56); 2% renal disorders (1/56); and 2% were attributed to sudden death (1/56). The causes and circumstances of death were reported as unclear in 7% of the cases, and for 34% of the cases, the cause of death was not reported (19/56).

A comparative mortality analysis was conducted in South Africa using retrospective data from the South African Electronic Drug-Resistant Tuberculosis Register (EDRWeb)[13] complemented with data from the national vital statistics record system. The data analysis included 25 177 MDR-TB records of patients treated under programmatic conditions in South Africa from 2014 to 2016 (**Fig. 2**). A survival analysis using Cox regression was conducted using propensity score adjustment. Propensity scores in the dataset were constructed using the following variables: Gender, age, province, HIV and

[13] The EDRWEb is a web-based software used in the surveillance and management of drug resistant TB in South Africa (https://edrweb.net/). It is used in 22 drug resistant TB units in all the 9 provinces of South Africa.

antiretroviral therapy status, site of TB (pulmonary or extra pulmonary), history of TB, year of treatment initiation, drug resistance pattern, diagnostic method and weeks of exposure to regimen. The propensity scores were divided into quintiles to create comparable groups of patients with similar characteristics other than their exposure to bedaquiline. After using propensity scores to adjust for selection bias, data from 82 patients who received bedaquiline under the *Bedaquiline Clinical Access Programme* were excluded from the analysis, leaving a total of 25 095 records. Among these, 23 539 of MDR-TB cases (93.8%) received treatment with a WHO-recommended longer regimen. The remaining 1556 patients (6.2%) included in this analysis received bedaquiline under the following indications:

- Patients ≥ 18 years of age; *and*
- Laboratory-confirmed RR-TB (at least resistance to RIF) by culture-based phenotypic drug sensitivity testing or genotypic line probe assay or PCR testing (Xpert MTB/RIF) from pulmonary and/or extrapulmonary sites; *and*
- No history or family history of QT prolongation; *and*
- Baseline QTcF< 450 msec;

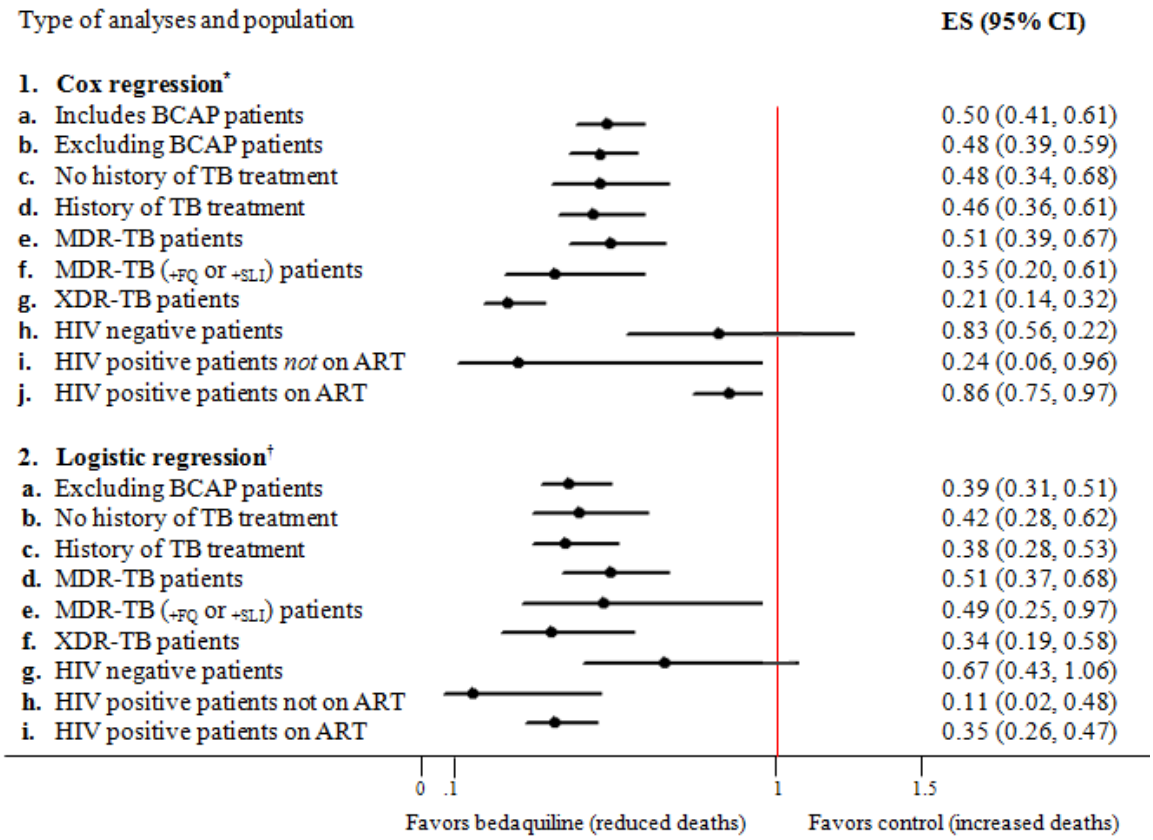
and any one of the following three conditions:

- Drug resistance in addition to RR-TB: XDR-TB; MDR-TB$_{+FQ}$ or MDR-TB$_{+SLI}$; or both inhA and katG mutations;
- Documented / recorded intolerance to second line anti-TB treatment at baseline (prior to treatment initiation) or during RR-TB treatment, e.g. hearing loss, renal dysfunction;
- History of, or surgical candidate for pneumonectomy or lobectomy; *and*
- Patients who meet the above criteria, regardless of HIV infection status or concomitant treatment with ARVs can be considered eligible for the 6 months of bedaquiline treatment without review by the National or Provincial DR-TB Committees. Patients not meeting the above criteria could also be eligible for bedaquiline upon review by a *Drug-Resistant Tuberculosis Clinical Advisory Committee* prior to prescribing.

The remaining 93.8% of patients (23 539) received a longer regimen following WHO-recommendations. Close to eight *per cent* of patients on bedaquiline treatment died (7.6%; 119/1 556) compared to 18.2% of the patients who were not on bedaquiline (4 288/23 539), a crude odds ratio of 0.37 (0.30-0.45) and an adjusted Hazard Ratio (aHR) of 0.50 (0.41-0.61), i.e. 40-60% reduction in mortality when receiving bedaquiline. Although mortality rate seemed to increase as resistance patterns amplified, reductions in mortality were present irrespective of resistance profile groups or history of TB. More precisely, bedaquiline use was associated with lower mortality in patients with MDR-TB$_{+FQ}$ and MDR-TB$_{+SLI}$ (aHR: 0.35; 95% CI 0.20 - 0.61; p-value <0.001), and in patients with XDR-TB (aHR: 0.21; 95% CI: 0.14 - 0.32; p-value <0.001). The aHR for HIV positive patients who were receiving ARV therapy was 0.86 (0.75-0.97; p-value 0.020) compared to an aHR of 0.24 for HIV positive patients *not* receiving ARV (0.06-0.96; p-value 0.044) (**Fig. 10**).

Additionally, further sub-analysis focused on exploring mortality among patients 12 – 17 years of age who received bedaquiline out of protocol. Out of the 669 adolescents on MDR-TB treatment, 5.6% (39/669) received bedaquiline with a background regimen. A total of 47 deaths were observed among adolescents who did not receive bedaquiline in addition to a background regimen (7.4%; 47/630). No deaths were observed among adolescents who did receive bedaquiline.

Fig. 10. Forest-plot of adjusted Hazard Ratios on a number of co-variates for Cox regressions and Logistic regression analyses



Notes—. *Cox regression analysis with propensity score matching; †Logistic regression with adjustment for age, gender, HIV status, type of TB, history of TB, type of drug resistance, year of treatment, duration of treatment, province and type of resistance confirmation. *Abbreviations:* ART= antiretroviral therapy; BCAP= South African Bedaquiline Clinical Access Programme; HIV=human immunodeficiency virus; TB= tuberculosis; MDR-TB= multidrug resistant TB; FQ= fluoroquinolone; SLI= second line drugs; XDR-TB= extensively drug resistant TB; NR= Not reported.

5. GRADE Evidence Profile and Guideline Development Group findings

The GDG panel concurred that in the absence of late-stage phase III clinical trial data, a key advantage of using observational studies was that these could provide substantial "natural setting" data from patients receiving bedaquiline under programmatic conditions. More so, in such settings, bedaquiline use was determined by the needs of patients, field practitioners' preferences, practice patterns, or policy decisions, hence, providing more "real-life" data about the implications for its use, from an effectiveness and safety standpoint. For the review of new data, the GDG panel opted for preserving the GRADE evidence profile and evidence to decision framework initially developed in 2013 (**Table 13**), completing these as appropriate with the estimates calculated using observational data captured in the current analysis. Judgments and discussion of the panel were added to the GRADE evidence profile summary and evidence to decision tables for the 2016 evidence assessment (**Table 14** and **15**).

Experts agreed that observational cohort studies can help evaluate the effectiveness of a therapy relative to the standard-of-care practice and additionally provide information on the "real-world" applicability of such therapy. However, they recognized that these studies face methodological challenges, including selection bias and confounding, due to the absence of a control group, the absence of randomization, and systematic selection of patients receiving care. Although data reviewers did attempt to find a suitable comparator, only two heterogeneous studies were identified: The Preserving Effective TB Treatment Study (PETTS) and an individual patient data (IPD) meta-analysis of 9 153 patients to assess various MDR-TB treatment regimens and patient outcomes were initially identified and used in a comparative data analysis *(13, 14)*. The PETTS study was intended to be used as the primary comparator group due to being a more homogenous cohort in terms of participants, interventions, outcomes and follow-up time, whereas the IPD was planned to be used to test the robustness of the analyses. However, data access was restricted to aggregated data only, and therefore it was not possible to run an individual patient comparison, making it difficult to adjust for potentially important confounders. During the 28 - 29 June meeting, it became clear that these problems, together with the observed substantial differences in study characteristics, and substantial heterogeneity in measurement of outcomes were major obstacles for comparability purposes. As a result the GDG considered that using these comparators could potentially dilute the beneficial or harmful effects of using bedaquiline and decided to not include these studies (as potential comparators) in this review.

In addition, GDG members discussed the approaches in selecting denominators for each of the measured outcomes. The panel emphasized that, although some of the patients in these cohorts were still under follow-up by the time the analyses were conducted, using the total sample size of these cohorts could induce 'immortal time bias', limiting the chances for any event or any outcome (e.g. death) to occur, that is, limiting the temporal nature of the exposure-outcome relationship *(15, 16)*. For instance, as less than half of the participants in the Armenian and Georgian cohorts had yet completed treatment, these studies were likely to contribute spuriously to the evaluation of treatment outcome, including mortality.

Furthermore, as mentioned above (See **section 4.4**), comparative data assessing mortality only in South African patients were shared by the National Department of Health of South Africa during the June meeting. This retrospective analysis of a large national drug-resistant TB database suggests that patients who received bedaquiline experienced an estimated 50% to 80% reduction in risk of mortality, with a possible trend for greater reduction in patients with the worst resistance profile. However, as

these data had not been included in the review by the independent biostatistician appointed by the WHO Guidelines Steering Group, the GDG suggested these data be added to the analysis and presented to the panel at a succeeding meeting.

The GDG was later convened through a webinar on 15 September to review and discuss results from the updated analysis, which focused on the meta-analysis of the cohort studies and included the South African mortality data. At this second meeting, the GDG re-emphasized both, the respective limitations and interests of the revised data analysis and their implications. Experts commented that the treatment outcomes described in this review suggested a beneficial effect attributable to bedaquiline, but there remained underlying biases and confounders. Selection bias may have played a role in all of the observational cohort studies - with healthcare workers or study personnel in some cohorts potentially selecting patients **i)** with less severe TB disease, **ii)** less co-morbidities, and/or **iii)** with a less extensive drug resistance profile and/or more likely to survive, although the possibility of recruiting sicker patients for bedaquiline treatment cannot be excluded. However, the selection of patients to receive bedaquiline could have also been directly influenced by the burden of disease and healthcare services infrastructure in each of the countries where patients were selected from. It is also worth noting that data collected from patients receiving bedaquiline constitute data on the programmatic use of bedaquiline. As such, while the GDG panel recognizes the methodological limitations that can result (e.g. bias from misclassification of outcomes for safety endpoints and treatment), experts also agreed that this type of data may reflect results from actual clinical practice and public health services which can be applicable to settings with similar health infrastructure or services as those presented in South Africa. Additionally, these programmatic data can more closely describe how bedaquiline will perform in a broader, more representative population over a longer timeframe, and can provide real-life data on treatment outcome, which can in turn, present an opportunity for public health programmes to adopt strategies to increase treatment adherence. Nonetheless, the GDG panel continued to advise caution in the interpretation and generalization of these results, given the various limitations described above.

When analysing the overall treatment outcomes, members of the GDG reflected on the estimates presented in this analysis, which indicate improved treatment success in 69.1% of the cases, surpassing global estimates of ~50%. However, panel members also highlighted that for treatment outcomes as well as for safety aspects, there could be confounding factors of significance. As an example, the panel discussed the higher proportion of cured patients in the French cohort (75.5% compared to 63.4% in South African patients and 61.0% in the multi-centre study, respectively), and the potential link with a higher duration of treatment (71.1% (32/45) of patients received bedaquiline for more than six months). Of note, patients recruited in this cohort experienced a higher occurrence of adverse events and SAEs, as compared to other cohorts, but conversely, had a lower death rate when compared to South African patients alone. Although the analysis of these data has been stratified on a number of co-variates (i.e. HIV status; resistance profile; duration on bedaquiline), members of the panel acknowledged the importance of independent factors at the local and country level which may influence treatment outcomes and which may not have been captured or reported for this evidence review.

Additionally, members of the panel also assessed observational data on bedaquiline in South African adolescents (12 – 17 years). Out of the 669 adolescents on MDR-TB treatment, 5.6% (39/669) received bedaquiline with a background regimen. Though no deaths were observed in adolescents being treated with bedaquiline (compared to 7.4% (47/630) deaths in adolescents who did not receive the drug), the overall quality of the evidence for this subpopulation was questioned due to risk of bias (incomplete outcome data; prevalence-incidence bias), as well as the limited number of cases.

GDG members, however, highlighted a number of limitations associated with observational studies, their interpretation and considerations for generalization. One important limitation was the absence of a comparison group, which would have allowed examining the comparative effectiveness and safety of the drug. Additionally, the GDG noted that inclusion criteria varied across the cohorts: although data were gathered from either compassionate and extended use programmes, or routine control programmes, the strategy for recruiting and selecting patients eligible to receive bedaquiline could have been mostly at the discretion of field practitioners. Equally important was the understanding of which patients were excluded from each of these cohorts, as it is possible that patients with high chances of getting cured or *vice versa* could (or could not) have received the drug, depending on the severity of their disease, presence of co-morbidities, as well as other unexplored factors, leading to ascertainment bias.

Although the main safety concerns include cardiotoxicity (i.e. QTc prolongation) and hepatotoxicity, members of the GDG panel also noted that the limited sample size in these observational studies makes it insufficient for evaluating unstudied toxicities. In addition, the panel was much concerned with the quality and consistency of measurements for adverse events in these cohorts, as the data collection was not consistent across study sites, for instance, the Armenian and Georgian cohorts did not report safety data using standard toxicity grading scales. The differences in the occurrence of adverse events may have also been influenced by reporting practices within each site as well as by the length of follow-up, which was different across study groups.

The GDG judged that the effect of bedaquiline on culture conversion after six months of treatment (or longer) was large enough to outweigh the harms for most patients. Additionally, the panel found no higher risk of mortality for patients receiving bedaquiline and noted that in the observational study from South Africa, the risk of all-cause mortality during treatment *appeared* to be reduced in patients receiving bedaquiline in addition to a background MDR-TB regimen, as compared to patients receiving a standard WHO-recommended MDR-TB regimen only.

Overall, the GDG panel agreed to rate the quality of the evidence for the use of bedaquiline in MDR-TB treatment as "*very low*" due to imprecision, indirectness, inconsistency, and risk of bias (**Tables 14** and **15**). The panel emphasised that due to limitations in the design of these observational studies, potential *serious* biases could have been introduced, especially for outcome assessment. Inconsistency across the various studies, especially in relation to patient selection criteria as well as the various treatment regimens and health service delivery had influenced the panel's decision to downgrade the quality in the evidence, and subsequently, quantifying important uncertainty in this evidence. Additionally, the panel commented on the high degree of heterogeneity as measured in specific outcomes (treatment complete (58.7%), treatment failure (92.2%), and death (81.7%)). Members of the GDG discussed that although the pooling of estimates was done through random effects models, sources of heterogeneity were not completely understood requiring careful interpretation and generalization of effect estimates as calculated in these observational studies due to this inconsistency (inappropriate representation and mixing of variabilities).

Table 13. Quality assessment, the GRADE evidence profile summary (2013)

Author(s): WHO GDG on bedaquiline for MDR-TB **Date**: 2013-01-30 (First GRADE evidence profile, 2013)
Question: In MDR-TB patients, does the addition of a bedaquiline to a background regimen based on WHO recommendations safely improve patient outcomes?
Bibliography: TMC207 (bedaquiline) treatment of patients with MDR-TB. Briefing document to the Anti-Infective Drugs Advisory Committee Meeting *(17)*. US FDA AIDAC Meeting *(18)*.
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							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline + background MDR-TB treatment	Background MDR-TB treatment alone (regimen of drugs recommended by WHO)	Relative (95% CI)	Absolute (95% CI)		
Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT) [1,2]												
1 [3]	randomised trials	not serious [4]	not serious	serious [5]	serious [5]	none	38/66 (57.6%) [1]	21/66 (31.8%) [1]	RR 1.81 (1.26 to 2.31) [3,6]	**26 more per 100** (from 8 more to 42 more)	⨁⨁◯◯ 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 [7,8]	randomised trials	not serious	not serious	serious [9]	very serious [5]	none	7/102 (6.9%) [7,10]	2/105 (1.9%) [7]	RR 3.60 (0.77 to 14.00)	**5 more per 100** (from 0 fewer to 25 more)	⨁◯◯◯ VERY LOW	CRITICAL
Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)												
1 [11]	randomised trials	not serious	not serious	serious [12]	very serious [3]	none	9/79 (11.4%) [11]	1/81 (1.2%) [11]	RR 9.23 (1.20 to 72.95) [13,14]	**10 more per 100** (from 0 fewer to 53 more)	⨁◯◯◯ VERY LOW	CRITICAL
Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)												
1 [15]	randomised trials	not serious [4]	not serious	serious [16]	serious [5]	none	n=66[1] median=83 days	n=66[1] median=125 days		**Median 42 days lower** [17]	⨁⨁◯◯ LOW	CRITICAL
Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGIT960)												
1 [18]	randomised trials	not serious [4]	not serious	serious [16]	serious [5]	none	52/66 (78.8%) [1]	38/66 (57.6%) [1]	RR 1.37 (1.10 to 1.77) [19]	**21 more per 100** (from 6 more to 44 more)	⨁⨁◯◯ LOW	CRITICAL
Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT) 20 (assessed with: Microbiological endpoints)												
1 [20]	randomised trials	serious [21]	not serious	serious [16]	very serious [5]	none	2/10 (20.0%) [22]	14/27 (51.9%) [22]	RR 0.39 (0.11 to 1.40) [24]	**32 fewer per 100** (from 46 fewer to 21 more)	⨁◯◯◯ VERY LOW	CRITICAL
								7/27 (25.9%) [23]		**6 fewer** (22 fewer to 34 more) [23]		

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio

Notes

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).
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/ExpertGroupMeetingBedaquiline/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 II 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. See JRd Slide 52;
21. 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
22. Analysis on paired samples, mITT population (n=10 in bedaquiline arm, 27 in placebo arm).
23. 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.
24. Fisher Exact p=0.14; Pearson p=0.08.

Table 14. Quality assessment, the GRADE evidence profile summary (2016)

Author(s): WHO GDG on bedaquiline for MDR-TB **Date**: 2016-12-20 (2016 review)
Question: In MDR-TB patients, does the addition of bedaquiline to WHO-recommended second-line drug therapy safely improve patient outcome, as reflected by sputum culture conversion at the end of 6 months, cure at the end of treatment, and patient survival?
Bibliography: The following studies were used in the 2016 review: (i) a phase II, single-arm, open-label multi-centre study conducted to confirm the safety and efficacy of bedaquiline (Published data) *(5)*; (ii) a retrospective cohort study on the use of bedaquiline for the treatment of MDR/XDR-TB in France (Published data) *(6)*; (iii) an interim cohort analysis to describe the safety and effectiveness of bedaquiline in the *South African Bedaquiline Clinical Access Programme* (Published data) *(7)*; (iv) interim data from compassionate use and expanded access programmes in Armenia and Georgia (Unpublished data) *(8, 9);* and individual patient and comparative control data on mortality from from the South African Electronic Drug-Resistant Tuberculosis Register (EDRWeb) *(10)* .

Quality assessment							№ of patients		Effect		Quality	Importance	Comments
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline + background MDR-TB treatment	Background MDR-TB treatment alone (regimen of drugs recommended by WHO)	Relative (95% CI)	Absolute (95% CI) [1]			
Effectiveness (Proportion with sputum conversion after initial 6 months of Bedaquiline) (follow up: 6 months)													
5	observational studies	serious [1,2]	not serious	not serious	not serious	none	311/395 (78.7%)	–	Percentage -- (74.8 to 83.0)	No comparator data	⨁◯◯◯ VERY LOW	CRITICAL	Risk of bias downgraded to *serious*
Cure up to end of treatment at 20 to 24 months													
3	observational studies	serious [1,2]	not serious	very serious [3]	not serious	none	221/351 (63.0%)	–	Percentage -- (57.9 to 68.1)	No comparator data	⨁◯◯◯ VERY LOW	CRITICAL	Risk of bias downgraded to *serious*. Indirectness downgraded to *very serious*.
Serious adverse events (number of people experiencing at least one SAE over total number of patients)													
5	observational studies	serious [1,2]	not serious	serious [4]	not serious	none	42/565 (7.4%)	–	Percentage -- (3.8 to 15.8)	No comparator data	⨁◯◯◯ VERY LOW	CRITICAL	Risk of bias downgraded to *serious*
Serious adverse events (total number of SAE over total number of patients)													
5	observational studies	serious [1,2]	not serious	serious [4]	not serious	none	48/565 (8.5%)	–	percent -- (6.4 to 11.0)	No comparator data	⨁◯◯◯ VERY LOW	CRITICAL	Risk of bias downgraded to *serious*
QTFc prolongation >60ms from baseline													
5	observational studies	serious [1,2]	not serious	not serious	serious [5]	none	24/488 (4.9%)	–	percentage -- (3.2 to 7.1)	No comparator data	⨁◯◯◯ VERY LOW	CRITICAL	Risk of bias downgraded to *serious*
Mortality (all cause during treatment)													
1	observational studies	serious	not serious	not serious	not serious	none	119/1556 (7.6%)	4288/23539 (18.2%)	OR 0.39 (0.31 to 0.51)	**10 fewer per 100** (from 8 fewer to 12 fewer) [6]	⨁◯◯◯ VERY LOW	CRITICAL	Risk of bias downgraded to *serious*

Notes

1. No control data
2. Downgrading for risk of bias / serious risk of bias due to (i) comparability between groups being studied; (ii) ascertainment (inconsistent data collection); and/or confounding effects.
3. Downgrading two levels for indirectness because the effects of other factor such as HIV status and resistance profile on cure is unclear
4. Downgrading for indirectness because the definition and (inconsistency in) reporting of all adverse events.
5. Downgrading for imprecision due to large amounts of missing and unusable data.
6. The Absolute effect estimate may not be reliable because of the adjustment.

Table 15. The GRADE evidence to decision framework

Assessment:

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>PROBLEM</td><td>Is the problem a priority?
○ No
○ Probably no
○ Probably yes
● Yes
○ Varies
○ Don't know</td><td>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 (28%), commonly associated with adverse drug reactions, among other factors [2].</td><td></td></tr>
<tr><td>DESIRABLE EFFECTS</td><td>How substantial are the desirable anticipated effects?
○ Trivial
○ Small
○ Moderate
● Large
○ Varies
○ Don't know</td><td rowspan="2">Bedaquiline + background MDR-TB treatment compared to Background MDR-TB treatment alone (regimen of drugs recommended by WHO) in Multidrug-resistant tuberculosis (MDR-TB)
<table><tr><th rowspan="2">Outcomes</th><th colspan="2">Anticipated absolute effects (95% CI)</th><th rowspan="2">Relative effect (95% CI)</th><th rowspan="2">№ of participants (studies)</th><th rowspan="2">Quality of evidence (GRADE)</th></tr><tr><th>Risk without Bedaquiline + background MDR-TB treatment</th><th>Risk with Bedaquiline + background MDR-TB treatment</th></tr><tr><td>Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)</td><td>Study population
31.8%
Moderate
45.0%</td><td>57.6% (40.1 to 73.5)
81.5% (56.7 to 100)</td><td>RR 1.81 (1.26 to 2.31)</td><td>132 (1 RCT)</td><td>⨁⨁◯◯ LOW</td></tr><tr><td>Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)</td><td>1.9%</td><td>6.9% (1.5 to 26.7) 9</td><td>RR 3.60 (0.77 to 14.00)</td><td>207 (2 RCTs)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>Mortality (all cause during treatment)
№ of participants: 25095
(1 observational study)</td><td>18.2%</td><td>8.0% (6.5 to 10.2)</td><td>OR 0.39 (0.31 to 0.51)</td><td>25095 (1 observational study)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)</td><td>1.2%</td><td>11.4% (1.5 to 90.1)</td><td>RR 9.23 (1.20 to 72.95)</td><td>160 (1 RCT)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>not estimable</td><td>(1 RCT)</td><td>⨁⨁◯◯ LOW</td></tr><tr><td>Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGIT960)</td><td>57.6% 1</td><td>78.9% (63.3 to 100.0)</td><td>RR 1.37 (1.10 to 1.77)</td><td>132 (1 RCT)</td><td>⨁⨁◯◯ LOW</td></tr><tr><td>Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT) 20 (assessed with: Microbiological endpoints)</td><td>51.9%</td><td>20.2% (5.7 to 72.6)</td><td>RR 0.39 (0.11 to 1.40)</td><td>37 (1 RCT)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>Effectiveness (Proportion with sputum conversion after initial 6 months of Bedaquiline) (Effectiveness)
follow up: 6 months</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>Percentage -- (74.8 to 83.0)</td><td>395 (5 observational studies)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>Cure up to end of treatment at 20 to 24 months (Cure)</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>Percentage -- (57.9 to 68.1)</td><td>351 (3 observational studies)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>Serious adverse events (proportion of SAEs - number of people experiencing at least one SAE) (SAE)</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>Percentage -- (3.8 to 15.8)</td><td>565 (5 observational studies)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>Serious adverse events (total number of SAE over all patients experiencing an SAE)</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>percent -- (6.6 to 11.6)</td><td>537 (5 observational studies)</td><td>⨁◯◯◯ VERY LOW</td></tr><tr><td>QTFc prolongation >60ms from baseline</td><td>0.0%</td><td>0.0% (0.0 to 0.0)</td><td>percentage -- (3.2 to 7.1)</td><td>488 (5 observational studies)</td><td>⨁◯◯◯ VERY LOW</td></tr></table></td><td>See evidence profile:
Quality of evidence (QoE) for benefits: Low due to imprecision and indirectness
QoE for harms: Low or very low (resistance to bedaquiline) due to imprecision and indirectness (and risk of bias)
No consensus was found on the balance of respective harms and benefits of addition of bedaquiline to MDRTB treatment. So a vote took place:
- 10 experts evaluated that the benefits did outweigh the harms
- 4 experts evaluated that the harms did outweigh the benefits
- 2 abstained (including the chair)

Update: Based on lack of higher quality data the judgments will not be changed</td></tr>
<tr><td>UNDESIRABLE EFFECTS</td><td>How substantial are the undesirable anticipated effects?
○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know</td><td>Update: The new data analyzed under programmatic conditions indicate lower mortality in the bedaquiline group compared to the initial RCT results. SAEs still observed but risk of bias may be important.
Update: Panel changed the judgement about undesirable effects to moderate based on that additional data.
If mortality is reduced, then the judgement for undesirable anticipated effects would still be moderate given the SAE.</td></tr>
</table>

<table>
<tr><th colspan="2">JUDGEMENT</th><th>RESEARCH EVIDENCE</th><th>ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>CERTAINTY OF EVIDENCE</td><td>What is the overall certainty of the evidence of effects?
● Very low
○ Low
○ Moderate
○ High
○ No included studies</td><td>The relative importance or values of the main outcomes of interest:
<table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Subjects cured by end of study: 120 weeks (C208 Stage 2: mITT)</td><td>CRITICAL</td><td>⊕⊕○○ LOW</td></tr><tr><td>Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) 7 (assessed through clinical and laboratory results)</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>Time to conversion over 24 weeks (C208 Stage 2: mITT1) (measured with microbiological endpoints - MGIT960)</td><td>CRITICAL</td><td>⊕⊕○○ LOW</td></tr><tr><td>Culture conversion at 24 weeks (C208 Stage 2: mITT1) (assessed with microbiological endpoint - MGIT960)</td><td>CRITICAL</td><td>⊕⊕○○ LOW</td></tr><tr><td>Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT) 20 (assessed with: Microbiological endpoints)</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>Effectiveness (Proportion with sputum conversion after initial 6 months of Bedaquiline)</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>Cure up to end of treatment at 20 to 24 months</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>Mortality up to end of treatment at 20 to 24 months</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>Serious adverse events (proportion of SAEs)</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>Serious adverse events (number of SAEs per patient)</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr><tr><td>QTFc prolongation >60ms from baseline</td><td>CRITICAL</td><td>⊕○○○ VERY LOW</td></tr></table></td><td>All critical outcomes measured 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).

Update: The previous pessimistic view of the mortality data is moderated by data that are of similar low quality and indicate an opposite effect. The overall concern about the certainty of the evidence remains for both data sets.</td></tr>
<tr><td>VALUES</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?
● Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
○ No important uncertainty or variability</td><td>No evidence found.</td><td>Treatment success, serious adverse events and mortality were considered important to patients while time to conversion culture conversion and resistance were less so. 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.

Update: Treatment success (cured by the end of the study), serious adverse events, and mortality were considered critical outcomes to patients, while time to culture conversion and resistance were considered important, but not critical. It is the panels' view that although there is little variability in how much value people attach to avoiding death, there is uncertainty and, likely variability in how much people value the other outcomes. For patients with newly diagnosed MDR-TB, the treatment success is unlikely to outweigh the risk of taking a new drug with a potential increase in mortality, serious adverse effects, and very low certainty of the evidence. For patients with extensively drug-resistant tuberculosis (XDR) and limited, if any other options, the panel decided that the desirable effects probably outweigh the undesirable effects.</td></tr>
</table>

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	See evidence profile above	Evidence that emerged during meeting suggested that there might be a substantial mortality reduction based on the additional observational evidence. ***Update: The balance remains similar despite better data on mortality due to remaining concerns on safety and toxicity***
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	Cost data for the base case in each country were sourced from published studies [1], with additional supplementary data provided by study authors. For the primary estimates for the unit cost per patient treatment with bedaquiline, a regimen cost of US $900 (for Global Fund Eligible countries) and US $3000 (for all other countries) was used for a full course of bedaquiline based on estimates from Janssen. In addition the costs of four electro-cardiograms were added. To estimate the possible cost savings from a shortened course with bedaquiline, the costs of an intensive phase of six months were estimated. Eight month intensive phase drug costs were adjusted to take into account reductions in hospitalization and required length of second-line parenteral agents (injectable anti-tuberculosis drugs). Where hospitalization was not used extensively in the intensive phase of treatment (Peru and Nepal), a reduction was made in the cost of clinic visits. All other costs (programme management, testing costs etc.) were conservatively assumed to remain the same as the non-shortened bedaquiline regimen.	*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.)* ***Update: Although not specifically looked for, it was thought by the panel that no new cost effectiveness data was available. Presently bedaquiline is available under donation for Global Fund-eligible countries (for four years/30,000 courses), until April 2019, for use following WHO recommendations via the Global Drug Facility (GDF).***
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ● Very low ○ Low ○ Moderate ○ High ○ No included studies	Results were ambiguous in low-income settings, and highly dependent on the assumptions made about the generalizability of trial results to routine settings. The expert group noted that further analysis would be needed to test the robustness of the assumptions in various settings and to separately assess affordability [1].	

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● Varies ○ No included studies	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 expert group [2]. The model assumed that bedaquiline would be added to treatment for all patients starting MDR-TB treatment. 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.	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.) As the recommendation of the expert group 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. ***Update: judgment changed to varies given free provision of bedaquiline for some settings. Comments by panel, concern that on a global level cost-effectiveness is not changed.***
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● Varies ○ Don't know	No research evidence found	It is difficult to assess whether bedaquiline would have an impact on equity because of uncertainty about affordability and its effects. If it is effective and is not available to some people because it is not affordable or accessible, this would reduce equity. Lack of access to monitoring might also reduce equity. On the other, it is the panel's view that, to the extent that the desirable effects of bedaquiline outweigh the undesirable effects, ensuring that it is accessible. ***Update: The panel advises that the application of bedaquiline to XDR –TB patients could increase equity, although the situation may differ according to the setting.*** ***Affordability will be different for countries during the period of free access and may not be a concern.*** ***No clinical trial data in children or pregnant women.***
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No evidence found.	Some health care providers might be reluctant to treat patients with bedaquiline given the very low certainty of the evidence and possibly increased mortality and serious adverse effects. On the other hand, the panel decided that some health care providers might be reluctant not to treat patients with such a bad prognosis. ***Update: Increased use likely will affect this acceptability (higher). Judgement by panel members: Vietnam NTP no concerns about acceptability, pharmacovigiliance in place (42 patients). Belarus NTP - 228 patients on bedaquline. Providers must complete case forms. South Africa -health care workers are requesting use of bedaquiline.***
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No evidence found.	• Monitor resistance to bedaquiline through assessment of MIC in the absence of a specific bedaquiline DST assay • Clinical monitoring / Monitor resistance to other anti-TB drugs • Management of co-morbidities (cardiac diseases, etc.) • Concerns on scale-up due to costs and/or local regulatory constraints. Costs and local regulatory constraints might be barriers to scaling up the use of bedaquiline. The view of the panels is that clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place. **Update: monitoring in programs feasible based on NTP reports.** **Country experience (several) led to change in judgment.** **Not assured that it can be done in all settings (e.g. problem of active drug safety monitoring – needs to be emphasized).** **Feasibility only relates to bedaquiline added to existing regimen.** **21 countries are beginning bedaquiline treatment programs.** **Experience in countries with monitoring of side effects.** **1 for yes, 13 probably yes, 1 abstention.**

Summary of judgements:

JUDGEMENT							
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Conclusions:

<table>
<tr><td>TYPE OF RECOMMENDATION</td><td>
<table>
<tr><td>Strong recommendation against the intervention
○</td><td>Conditional recommendation against the intervention
○</td><td>Conditional recommendation for either the intervention or the comparison
○</td><td>Conditional recommendation for the intervention
●</td><td>Strong recommendation for the intervention
○</td></tr>
</table>
</td></tr>
<tr><td>RECOMMENDATION</td><td>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):

Conditions (update in bold):
When a WHO-recommended shorter regimen is <u>not</u> used
• When an effective longer treatment regimen containing at least 4 recommended second line drugs in addition to pyrazinamide, according to WHO-recommendations cannot be designed
• When there is documented evidence of resistance to any fluoroquinolone or to a second line injectable agent in addition to MDR.
• A duly informed decision making-process by patients should be followed - this includes that the intervention be presented as an option and includes information about uncertainty about the effects. In some settings, informed consent is mandatory for MDR treatment and local practice should be observed. Local practice requiring written informed consent for MDR-TB treatment should be observed.
• Bedaquiline should be used with caution in persons living with HIV infection treated with ARVs that exhibit drug-drug interactions with bedaquiline (efavirenz) or prolong the QT interval (lopinavir/ritonavir) as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol use, due to limited or no information. Bedaquiline has been used in large cohorts of patients, experience is growing, drug monitoring is still required but concern is less due to the cohort data reviewed from South Africa.
• Bedaquiline should be used for 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) – Note: Bedaquiline has been used for longer than 6 months in research studies
• 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 (Note: pharmacovigilance changed to “active drug safety monitoring and management”)
• In the absence of a specific bedaquiline DST assay, 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.
• Programmes have used bedaquiline in adolescents.</td></tr>
<tr><td>JUSTIFICATION</td><td>Overall justification
The expert group judged that the impact on culture conversion was large enough to outweigh the harms for most patients, mortality data have changed</td></tr>
</table>

6. Summary of Evidence to Decision

The GRADE evidence profile and the evidence-to-decision framework are presented in **Tables 14** and **15** above**.** They present a summary of the evidence reviewed by the GDG, the assessment of desirable and undesirable effects of the intervention, and the judgement of the GDG on the balance of expected benefits to risks, as well as other considerations of importance for the implementation of the policy. Of note, given the absence of phase III trial data (higher quality) and the use of observational studies to inform the revision of the interim policy guidance on bedaquiline, the GDG panel opted for preserving the GRADE evidence profile and evidence to decision framework developed in the initial guidance in 2013 *(3)*. The panel did revise tables for specific outcomes that could be informed by newly available data, such as: cure at the end of treatment (20-24 months), SAEs, QTc prolongation, and mortality (**Table 14**). For these outcomes, estimates calculated using observational data captured in the present analysis, as well as the judgments and discussion of the panel were added to these tables. For the remaining outcomes (proportion of patients with culture conversion at 6 months, cure at 20 weeks), no new assessment was made.

6.1. Final grading of the evidence

Based on the careful review of evidence, members of the panel agreed on the use of observational data to make further inferences on the effectiveness and safety of bedaquiline. The panel emphasised that although observational studies can help answering questions about the benefits or intended effects of interventions, the methods used in these cohorts (selection of patients, collection and reporting of treatment outcomes) are liable to bias that cannot be fully controlled in the analysis. Therefore, the final grading of quality of evidence remains *very low* (See **section 5**).

6.2. Undesirable effects: balance between benefits and harms

The panel discussed the balance between benefits and harms. Experts agreed that current data suggest a reduction in mortality for patients using bedaquiline in combination with a WHO-recommended *longer* (or conventional) regimen. However, the panel emphasised the *very low certainty* in the evidence due to the variable quality of reporting treatment outcomes and safety events and important potential confounding factors. Specific harms (e.g. large number of SAE of respiratory origin unexplained) – not entirely explained by current observational data - continue to be observed, but these could also be attributed to other drugs administered in combination therapy or severity of disease, among other factors. Based on the programmatic observational data evaluated, the panel was confident to emphasise that mortality did not appear to be increased in patients receiving bedaquiline. Moreover, due to the apparent observed reduction in excess mortality compared with initial phase IIb trial data, the panel considered that the undesirable anticipated effects of bedaquiline were to be downgraded from '*large*' to '*moderate'*. The decision not to minimize this criterion further was due to the fact that current data still do not allow confident exclusion of the safety concerns raised by regulators. Additionally, although some GDG members emphasized that current data indicate that deaths in these cohorts were not attributed to bedaquiline use, the overall agreement in the panel was that there is still some residual uncertainty for mortality. The overall concern in the certainty of evidence remains, but the "pessimistic" view on the undesirable effects attributed to bedaquiline is moderated by data of equal certainty on effectiveness.

6.3. Balance of desirable and undesirable effects

The panel agreed that the balance between desirable and undesirable effects *probably favours* the use of bedaquiline. The evidence that emerged during the meetings suggested that there might be a substantial mortality reduction influencing the panel decision and attenuating the previously raised concerns about an excess mortality related to bedaquiline use.

6.4. Patients' values and preferences

In the 2013 guidance, experts indicated that there was important uncertainty or variability in how much people value the main outcomes. However, GDG members considered that in the absence of new data on the potential variability for new outcomes, patients' values and preferences should remain the same (*important uncertainty or variability*).

6.5. Cost-effectiveness

The panel did not address the issue on resource requirements (costs) for implementation of bedaquiline as no new cost-effectiveness data were available. For the 2013 evaluation, experts at the time indicated that in terms of cost-effectives, the use of bedaquiline would *probably favours the intervention*. However, this judgement changed to "*varies*" during the 2016 GDG assessment, given the provision of bedaquiline for some settings under variable schemes[14]. However, the panel concluded that cost-effectiveness at a global level is not changed.

6.6. Equity

GDG members agreed that equity would vary. This was primarily as a result of affordability aspects for some countries. National TB Programme managers acting as GDG members indicated that acceptability is likely to increase as bedaquiline is rolled-out in various settings. Although affordability might be an issue for some countries, this was not deemed a concern given the current free availability of the drug for Global Fund-eligible countries. Members of the panel agreed that for some patient groups, for instant, XDR-TB cases, with the limited treatment options, the use of bedaquiline would *probably increase* equity. Despite this, the panel sustained that the overall judgement should remain as "*varies*" as equity will not be increased in all settings.

6.7. Acceptability

Members of the panel agreed that the use of bedaquiline is "*probably*" accepted by stakeholders.

6.8. Feasibility

Members of the panel agreed that the use (roll-out) of bedaquiline is feasible to implement (*probably yes*).

[14] Bedaquiline is currently available for Global Fund-eligible countries through the United States Agency for International Development (USAID) supported Bedaquiline Donation Program, provided that WHO recommendations are followed. Through this programme, USAID seeks to provide the drug free of charge for 30,000 MDR-TB patients from low- and middle-income countries during a four year period (concluding in 2019).

7. Guideline Development Group Recommendation

The GDG agreed, after deliberating on findings of the systematic review, that benefits outweighed harms overall. The GDG decided that, despite fewer concerns due to a reduced risk of excess mortality, the ***conditional recommendation, as established in 2013, should remain valid*** *(2)*. The justification of the GDG panel to not change the strength of the recommendation was due to the very low quality of evidence, leaving uncertainty about the actual estimates of effect.

Therefore, in response to the PICO question: "*In MDR-TB patients, does the addition of bedaquiline to WHO-recommended second-line drug therapy safely improve patient outcome, as reflected by sputum culture conversion at the end of 6 months, cure at the end of treatment, and patient survival?*" and based on the available evidence, the GDG continues to recommend that ***bedaquiline may be added to a WHO-recommended longer 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*):

- The population to whom this recommendation applies is adult MDR-TB patients not eligible for the newly WHO-recommended shorter regimen. These may include patients with additional resistance or intolerance to fluoroquinolones or second line injectable drugs, those with extended pulmonary lesions, advanced disease and others deemed at higher baseline risk for poor outcomes, as well as patients with XDR-TB.
- Bedaquiline can be used when an effective WHO-recommended longer regimen (~20-month total treatment duration) containing at least four second-line drugs in addition to pyrazinamide cannot be designed.
- Bedaquiline must *not* be added alone to a failing regimen.
- Healthcare authorities should set up an informed decision-making process that enables patients to make a duly informed decision regarding the use of bedaquiline.
- Though long-term data on drug-drug interactions (DDI) between bedaquiline and ARVs are limited, bedaquiline has been used in large cohorts of patients with HIV co-infection who are receiving ARVs (e.g. South Africa), including nevirapine-, lopinavir/ritonavir- and rilpivirine or raltegravir-based regimens. Caution should be used with ARVs that exhibit drug-drug interactions with bedaquiline (efavirenz) or prolong the QT interval (lopinavir/ritonavir). As bedaquiline is a substrate of liver P450 metabolizing enzymes (cytochrome P450 enzyme 3A, or CYP3A), co-administration of bedaquiline with ARVs (or any other drugs) that induce or inhibit that enzyme may increase its toxicity or reduce its efficacy, so careful monitoring is recommended *(19, 20)*.
- Bedaquiline shall be used for a duration of 6 months and at suggested dosing (400 mg daily for the first two weeks, followed by 200 mg three times per week for the remaining 22 weeks), preferably at the start of a *longer* regimen, which usually is given for at least 20 months *(2)*. There is limited evidence, so far, to warrant its use beyond 6 months.
- The GDG noted that in some instances, bedaquiline has been used in adolescents. However, data are insufficient to make any recommendation.
- Settings introducing bedaquiline for MDR-TB treatment require active TB drug safety monitoring and management (aDSM) *(21)*.

- Clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place. Baseline testing and monitoring for QT prolongation and for dysrhythmias are imperative.
- In the absence of a specific drug-susceptibility test (DST) assay specific for bedaquiline, resistance should be monitored through assessment of minimum inhibitory concentrations (MICs) of bedaquiline.
- Resistance to other anti-TB drugs should be monitored in accordance to WHO recommendations.

It is important to note that, although the GDG was convened to review the 2013 initial interim guidance on the basis of newly available data, the recommendation set in the initial interim guidance remains unchanged. This is justified on the grounds that the level of evidence arising from observational studies was not sufficiently strong to extend the use of bedaquiline to all MDR-TB patients, and in view of the recent WHO recommendation for the use of a shorter regimen, to keep it to the sub-set of patients not eligible for the shorter regimen (i.e. MDR-TB with additional resistance or intolerance to fluoroquinolones and second-line injectable drugs) *(22)*.

7.1. Implementation considerations

As bedaquiline is to be administered in combination with a WHO-recommended *longer* regimen (~20-month total treatment duration), it is necessary that implementers follow the specific considerations for the introduction of the drug:

- TB stakeholders, namely national and local authorities must ensure that an informed decision-making process be established;
- It is required that healthcare facilities have the respective equipment for baseline testing and monitoring for QT prolongation as well as monitoring of other toxicities (e.g. liver function tests).
- The GDG noted that programmes reported use of bedaquiline in adolescents.

7.2. Monitoring and Evaluation

- Spontaneous reporting of adverse drug reactions should be reinforced at country level and aDSM should be established or reinforced among patients treated with bedaquiline.
- Resistance to bedaquiline should be monitored.
- Resistance to other anti-TB drugs should be monitored following WHO recommendations.

7.3. Research gaps

The GDG identified further research gaps, including:

- Drug-drug interactions, including with other existing and newly developed TB drugs and ARVs. Also, further research in HIV co-infected patients is required to determine whether dose adjustments are needed;
- Assessment of overlapping toxicities (cardiac risk) when bedaquiline is prescribed with other drugs known to prolong the QT interval (delamanid, fluoroquinolones, clofazimine);
- Safety and efficacy studies in specific populations (children and adolescents, people living with HIV, people who use alcohol and drugs, elderly, pregnant women, people with extrapulmonary TB, persons with diabetes);
- Pharmacokinetics, safety and efficacy studies in specific sub-populations (i.e. children under 6 years of age, paediatric cases with HIV co-infection – especially those on ART in order to confirm DDI and adjust accordingly); once daily dosing; adjustment of doses, applying optimal designs in clinical dose finding studies (e.g. dose-response models);
- The duration of bedaquiline treatment (i.e. opportunity and safety of extending use beyond six months);
- Substitution of a second-line injectable agent by bedaquiline within MDR-TB regimens;
- Appropriate child-friendly formulations of medicines (i.e. age-adapted dosage forms and taste-masking);
- Further research on the cardiotoxicity of bedaquiline, and its effect on QT prolongation, and the clinical significance of it, is also encouraged, especially when bedaquiline is administered in conjunction with other QT prolonging drugs; and
- Development of accurate and reproducible DST methods for bedaquiline and other second-line drugs.

Reference list

1. Global tuberculosis report 2016 (WHO/HTM/TB/2016.13): Geneva: World Health Organisation; 2016.
2. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: Expert group meeting report. Available from: http://www.who.int/tb/challenges/mdr/Report_EGM_BDQ_2013.pdf [Accessed: 15 November 2016]. Geneva: World Health Organisation; 2013.
3. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance (WHO/HTM/TB/2013.6). Available from: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf [Accessed: 23 January 2017].
4. WHO handbook for guideline development. Available from: http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf?ua=1 [Accessed: 24 January 2017]. Geneva: World Health Organisation; 2014.
5. Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug-and extensively drug-resistant tuberculosis. European Respiratory Journal. 2015:ERJ-00724-2015.
6. Guglielmetti L, Le Dû D, Jachym M, Henry B, Martin D, Caumes E, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clinical Infectious Diseases. 2015;60(2):188-94.
7. Ndjeka N, Conradie F, Schnippel K, Hughes J, Bantubani N, Ferreira H, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. The International Journal of Tuberculosis and Lung Disease. 2015;19(8):979-85.
8. Ministry of Health of Republic of Armenia and Medecins Sans Frontières (MSF). Interim data from compassionate use and expanded access programmes in Armenia [Unpublished dataset]. 2016.
9. Ministry of Health Labour and Social Affairs of Georgia and Medecins Sans Frontières (MSF). Interim data from compassionate use and expanded access programmes in Georgia [Unpublished dataset]. 2016.
10. Department of Health of South Africa. Data source: South African Electronic Drug-Resistant Tuberculosis Register (EDRWeb) [Unpublished dataset]. 2016.
11. Guidance for Industry, Pulmonary Tuberculosis: Developing Drugs for Treatment (Draft guidance): United States Food and Drug Administration; 2013.
12. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (WHO/HTM/TB/2014.11). Available from: http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf [Accessed: 15 November 2016]. Geneva: World Health Organisation; 2014.
13. Cegielski JP, Dalton T, Yagui M, Wattanaamornkiet W, Volchenkov GV, Via LE, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. Clin Infect Dis. 2014;59(8):1049-63.
14. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.
15. Ho AH, Dion P, Ng C, Karmakar M. Understanding immortal time bias in observational cohort studies. Anaesthesia. 2013;68(2):126-30.
16. Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiology and drug safety. 2007;16(3):241-9.
17. Janssen Pharmaceutical Companies. Anti-Infective Drugs Advisory Committee Meeting Briefing Document: TMC207 (bedaquiline), Treatment of Patients with MDR-TB. NDA 204-384. 28 November 2012. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf.
18. 2012 Meeting Materials, Antimicrobial Drugs Advisory Committee (formerly known as the Anti-Infective Drugs Advisory Committee). Slide presentations by Janssen R&D; Slide presentations

by US-FDA. Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm: United States Food and Drug Administration; 2012.

19. Svensson Elin M, Dooley Kelly E, Aweeka Francesca, Jeong-Gun Park, Mats K, editors. Population pharmacokinetics of bedaquiline (TMC207) and its M2 and M3 metabolites with efavirenz demonstrate reduced exposure. [Paper presented at: 5th International Workshop on Clinical Pharmacology of TB Drugs] Available from: http://regist2.virology-education.com/2012/5tbpk/docs/13_Svensson.pdf2012.
20. Van Heeswijk R, Dannemann B, Hoetelmans R. Bedaquiline: a review of human pharmacokinetics and drug–drug interactions. Journal of Antimicrobial Chemotherapy. 2014:dku171.
21. Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation (WHO/HTM/TB/2015.28). Available from: http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf?ua=1 [Accessed: 27 October 2016]. Geneva: World Health Organisation; 2015.
22. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva: World Health Organisation. 2016.

Annexes

Annex 1: Meeting agenda

Agenda for the Guideline Development Group convened to review WHO policy guidance on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis, 28 - 29 June 2016

Day 1		
		Welcome and Introduction
09:00 – 09:10	Message from the Director	Mario Raviglione
09:10 – 09:40	Objectives of the meeting Presentation of participants & DOI	Christian Lienhardt
		Session 1: Background and procedures
09:40 – 10:00	WHO requirements for evidence-based guidelines & the GRADE approach for WHO guidelines	Holger Schünemann
10:00 – 10:20	Synopsis of the revised MDR-TB treatment guidelines	Dennis Falzon / Ernesto Jaramillo
10:20 – 10:45	Synopsis of Interim policy guidance on Bedaquiline	Christian Lienhardt
Coffee break		
		Session 2: Effectiveness aspects
11:00 – 11:30	Review of effectiveness data	Lawrence Mbuagbaw
11:30 – 12:30	Discussion	All
Lunch break		
		Session 3: Safety and mortality aspects
13:30 – 14:00	Review of safety data	Lawrence Mbuagbaw
14:00 – 15:30	Discussion	All
Coffee break		
16:00 – 16:20	Establishing DST protocols for bedaquiline	Christopher Gilpin
16:20 – 16:40	Discussion	All
16:40 – 17:45	Establish draft recommendations for the use of bedaquiline based on quality of the evidence, balance between desirable and undesirable effects, resources, feasibility, values and preferences	All
17:45 – 18:00	Re-cap and key points	Holger Schünemann
Day 2		
		Session 4: Updating interim recommendations for use of bedaquiline
09:00 – 09:15	Re-cap and key points	Holger Schünemann
09:15 – 10:30	Establish draft recommendations based on quality of the evidence, balance between desirable and undesirable effects, resources, feasibility, values and preferences	All
Coffee break		
10:45 – 12:05	Mortality data from South Africa Programmatic Study	Norbert Ndjeka
12:05 – 12:45	Final recommendations. Next steps, implementation and conclusion on interim guidance review process	Holger Schünemann
Lunch break		

Notes—. The above describes the initial agenda for Guideline Development Group (GDG) meeting convened on 28 - 29 June 2016, but does not outline the modifications to the schedule throughout the course of the meeting and subsequent webinars and other consultations with members of the GDG panel during September 2016 and January 2017.

Annex 2: List of participants

Experts involved in the Guideline Development Group convened to review WHO policy guidance on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis, 28 - 29 June 2016

Guidance Development Group (GDG) members

Professor Holger Schünemann (Chairman; methodologist)
Departments of Clinical Epidemiology & Biostatistics and of Medicine
McMaster University
Ontario
Canada

Dr Martien Borgdorff (Epidemiologist)
Director
Centers for Disease Control and Prevention (CDC), Western Branch
Kisumu
Kenya

Dr Grania Brigden (Clinician, civil society)
TB and AMR Advisor
Médecins sans Frontières, Access Campaign
Geneva
Switzerland

Ms Lucy Chesire (Patient representative)
Executive Director
Tuberculosis Consortium
Nairobi
Kenya

Dr Daniela Cirillo (Laboratory)
Head
Emerging Bacterial Pathogens Unit
Fondazione Centro San Raffaele
San Raffaele
Italy

Dr Gerry Davies (Infectious disease pharmacology)
Reader in Infection pharmacology
Institutes of Global Health & Transnational Medicine
University of Liverpool
Liverpool
United Kingdom

Dr Poonam Dhavan (PMDT, TB care, end-user)
Migration Health Programme Coordinator
International Organization for Migration
Geneva
Switzerland

Professor Peter Donald (Paediatrics)
Emeritus professor
Department of paediatrics and child health
Tygerberg Hospital and the University of Stellenbosch
Stellenbosch
South Africa

Professor Christopher Kuaban (Clinician, MDR-TB expert)
Dean
Faculty of Health Sciences
University of Bamenda
Bamenda
Cameroon

Dr Miranda Langendam (Methodologist)
Academic Medical Center
Netherlands Epidemiology Society Amsterdam
Netherlands

Professor Mauricio Lima-Barreto (Trialist, **p**ublic health specialist)
Senior Researcher
Fundação Oswaldo Cruz- FIOCRUZ
Bahia
Brazil

Dr Anna Mandalakas (Paediatrician; end-user)
Associate Professor
Baylor College of Medicine
Texas
United States

Dr Beatrice Mutayoba (National TB programme, end-user)
Program Manager
National Tuberculosis Programme Manager
Ministry of Health
Dar es Salaam
Tanzania

Dr Payam Nahid (Clinician, trialist)
Professor of Medicine
University of California
San Francisco
United States

Dr Viet Nhung Nguyen (National programme, end-user)
National Tuberculosis Programme Manager and Director of National Lung Hospital
Hanoi
Viet Nam

Dr Rohit Sarin (National programme, end-user)
Director
National Institute of Tuberculosis & Respiratory Diseases (NITRD)
New Delhi
India

Dr Alena Skrahina(National TB programme, end-user)
Scientific Director
Republican Research and Practical Centre for Pulmonology and Tuberculosis
Minsk
Belarus

Dr Carlos Torres-Duque (Clinician, end-user)
Director
Tuberculosis Department
Latin American Thoracic Association
Bogotá
Colombia

Dr Carrie Tudor (TB infection control, nursing)
Tuberculosis Project Director
International Council of Nurses
Durban
South Africa

Technical Resource Persons

Dr Lawrence Mbuagbaw
Assistant Professor
McMaster University
Hamilton
Canada

Professor Anneke Hesseling *(via WebEx)*
Director
Desmond Tutu TB Centre Department of Paediatrics and Child Health
Faculty of Health Sciences
Tygerberg
South Africa

Ms Erica Lessem
Director
TB/HIV Project
Treatment Action Group
New York, NY
United States

Dr Norbert Ndjeka
Director
Drug-Resistant TB, TB & HIV
National Department of Health
Pretoria
South Africa

Ms Kate Schnippel Bistline
Senior Epidemiologist
Right to Care
School of Family Medicine and Public Health
University of Cape Town
Cape Town
South Africa

Dr Fraser Wares
Senior Consultant
KNCV Tuberculosis Foundation
Koninklijke Nederlandse Chemische Vereniging (KNCV)
The Hague
Netherlands

Observers

Dr Draurio Barreira
Technical Manager
International drug purchase facility
UNITAID
Geneva
Switzerland

Dr Francesca Conradie
Clinical Research Advisor
Clinical HIV Research Unit
Wits Health Consortium
Department of Medicine
University of Witwatersrand
Johannesburg
South Africa

Professor Keertan Dheda
Director
Lung Infection and Immunity Unit University of Cape Town
Cape Town
South Africa

Dr Jan Gheuens
Deputy Director
TB Drugs
Bill & Melinda Gates Foundation
Washington
United States

Dr Ya-Diul Mukadi
Senior TB Technical Advisor
Infectious Disease Division
Global Health Bureau
USA Agency for International Development (USAID)
Washington D.C.
United States

Dr Mohammed Yassin
The Global Fund to Fight AIDS, Tuberculosis and Malaria
Geneva
Switzerland

WHO Regional Advisors

Dr Martin van den Boom
Technical Officer
Joint Tuberculosis, HIV/AIDS & Hepatitis Programme
rGLC/ TBTEAM focal point
WHO Regional Office for Europe (EURO)

Dr Partha Pratim Mandal
Medical Officer, Tuberculosis
Department of Communicable Diseases
WHO Regional Office for South-East Asia (SEARO)

WHO/HQ

Dr Mario Raviglione, GTB Director
Dr Christian Lienhardt*, GTB/RTE
Ms Lice González-Angulo*, GTB/RTE
Dr Dennis Falzon*, GTB/LDR
Dr Giulliano Gargioni, GTB/TSC
Dr Christopher Gilpin, GTB/LDR
Dr Malgorzata Grzemska, GTB/TSC
Dr Ernesto Jaramillo*, GTB/LDR
Dr Alexei Korobitsyn, GTB/LDR
Dr Linh Nhat Nguyen, GTB/TSC
Dr Karin Weyer*, GTB/LDR
Dr Matteo Zignol*, GTB/TME
Dr Rajiv Bahl, HQ/MRD

Note—.* Members of the WHO Guidelines Steering Group.

Annex 3: Declaration of interests and resolution

Summary of interests declared by participant to the Guideline Development Group meeting to review the WHO policy guidance on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

No interests declared	
Holger Schünemann (Chairman)	Mauricio Lima-Barreto
Martien Borgdoff	Anna Mandalakas
Lucy Chesire	Beatrice Mutayoba
Poonam Dhavan	Viet Nhung Nguyen
Christopher Kuaban	Rohit Sarin
Miranda Langendam	

Interests declared, but deemed <u>not conflicting</u>	
Peter Donald	(6c) Any person or entity paid or contributed towards travel costs in connection with this WHO meeting – Attending a post-graduate educational course at Borstel (Germany) as a speaker and participant in June 2016. Airfare is paid by Forschungszentrum Borstel. <u>*Conflict of interest management:*</u> *No competing interests.*
Payam Nahid	(2a) Research support – Federal contract to support clinical trial units in San Francisco and Hanoi, Viet Nam. <u>*Conflict of interest management:*</u> *No competing interests.*
Carlos Torres D.	(1b) […] received a one-time fee ($2500) from Janssen Pharmaceuticals to present the WHO interim policy on the use of bedaquiline at the Latin American Forum on drug-resistant TB, Lima, Peru, 2013. <u>*Conflict of interest management:*</u> *No competing interests.*
Carrie Tudor	(1a, 1b) The International Council of Nurses receives funding from Eli Lilly Foundation (~ $3,000,000 over 5 years). (2a, 2b) Research support for dissertation research (K-RITH) on TB and post-doc research support (Fogarty/NIH). <u>*Conflict of interest management:*</u> The ICN TB Project is supported by a United Way Worldwide grant made possible by the Lilly Foundation on behalf of the Lilly MDR-TB Partnership. *No competing interests.*

Summary of interests declared by participant to the Guideline Development Group meeting to review the WHO policy guidance on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interests declared, but deemed insignificant	
Grania Brigden	MSF received a donation of 400 treatments of Delamanid (programmatic use) from Otsuka in Feb 2016. This was a one off donation and is not expected to be repeated with MSF now procuring delamanid directly from the GDF. *Conflict of interest management:* The MSF Access Campaign — for whom Dr Brigden worked — did not directly receive the donation, but a different department within MSF. The *WHO Guidelines Steering Group* and the *WHO Compliance, Risk Management and Ethics* resolved that interests declared were deemed "not significant", and therefore Dr Brigden was granted membership within the Guideline Development Group convened to review the WHO policy guidance on the use of bedaquiline in the treatment of MDR-TB.
Daniela Cirillo	(1b) Participation in expert writing group […] establishing recommendations on the use of delamanid and bedaquiline in Italy. €1000 sponsored by pharmaceutical company. (2a) Her laboratory was involved in the standardization of the agar and microtitre-based DST for bedaquiline in 2014. €1000 sponsored by Janssen Italy. *Conflict of interest management: Recommendations were in line with the WHO policy. The focus was not only on the selection of cases, but on who should be prescribing the drugs, where the DST was going to be performed and on data collection.* The *WHO Guidelines Steering Group* and the *WHO Compliance, Risk Management and Ethics* resolved that interests declared were deemed "not significant", and therefore Dr Cirillo was granted membership within the Guideline Development Group convened to review the WHO policy guidance on the use of bedaquiline in the treatment of MDR-TB.
Gerry Davies	(6e) Academic co-ordinator of the PreDiCT-TB consortium (PDP funded by the European Union Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations). *Conflict of interest management:* Financial resources are provided entirely by the European Union. No direct or indirect funding of academic research by industry. The *WHO Guidelines Steering Group* and the *WHO Compliance, Risk Management and Ethics* resolved that interests declared were deemed "not significant", and therefore Dr Davies was granted membership within the Guideline Development Group convened to review the WHO policy guidance on the use of bedaquiline in the treatment of MDR-TB.
Alena Skrahina	(5b) […] held a position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work. Participation in the development of "Rapid Clinical Advice – The use of delamanid and bedaquiline for children with drug-resistant tuberculosis". Document publically made available on 20 May 2016 via the TB Online Weekly Newsletter. *Conflict of interest management:* The *WHO Guidelines Steering Group* and the *WHO Compliance, Risk Management and Ethics* resolved that there were competing interests for development of any WHO guideline recommendations (present and future) on the use of bedaquiline and delamanid in children. However, as the Guideline Development Group was convened primarily to review the 2013 WHO policy guidance on the use of bedaquiline in the treatment of MDR-TB in adults, interests disclosed by Dr Skrahina were deemed not significant, and therefore Dr Skrahina was granted membership as a full member of the GDG.

Summary of interests declared by participant to the Guideline Development Group meeting to review the WHO policy guidance on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interests declared and judged <u>significant</u>	
Anneke Hesseling	(2a) Research support. NIH (DAIDS) would fund a multi-site phase I/II trial of bedaquiline in HIV infected and uninfected children with MDR-TB, through the IMPAACT network (P1108). (2a) PI of two phase II, open-label, multiple-dose trials funded by Otsuka pharmaceuticals (Study 242-12-232 and Study 242-12-233). <u>*Conflict of interest management:*</u> The *WHO Guidelines Steering Group* and the *WHO Compliance, Risk Management and Ethics* judged that interest declared by Prof Hesseling were significantly conflicting. Prof Hesseling participated as a *Technical Resource Person*, contributing to the overall discussion, but abstaining from the deliberations made by the Guideline Development Group panel.
Erica Lessem	(2a) Stop TB Partnership – Non-commercial support to track investments in TB R&D ($46,000) in 2015. (2a) Bill & Melinda Gates Foundation – Non-commercial support to advocate for increased funding for TB R&D, research and access to evidence-based interventions ($2,937,759) from January 2014 to March 2017 (2a) US Department of Veterans Affairs (on behalf od US CDC TB Trials Consortium) – Non-commercial support to manage the Community Research Advisors Group ($75,000), fiscal year 2015. (2a) TB Alliance – Non-commercial support for work to tract resources invested in TB R&D and primarily paediatric TB R&D. (2a) Janssen Pharmaceutical / Tibotec Therapeutics – General support to Treatment Action Group's Hepatitis C/HIV Programme (not for her work or the TB/HIV Project) Various funds (Total $108,000) from 2010 to 2015. <u>*Conflict of interest management:*</u> The *WHO Guidelines Steering Group* and the *WHO Compliance, Risk Management and Ethics* judged that interest declared by Ms Lessen were significantly conflicting. Ms Lessem participated as a *Technical Resource Person*, contributing to the overall discussion, but abstaining from the deliberations made by the Guideline Development Group panel.
Fraser Wares	(1a) Employment – Technical input into the development of the WHO's interim policy guidance on bedaquiline in 2013 and provisional technical assistance to India in the development of their bedaquiline implementation plan. (6b) KNCV role in the USAID bedaquiline donation programme through Challenge-TB. <u>*Conflict of interest management:*</u> The *WHO Guidelines Steering Group* and the *WHO Compliance, Risk Management and Ethics* judged that interest declared by Dr Wares were significantly conflicting. Dr Wares participated as a *Technical Resource Person*, contributing to the overall discussion, but abstaining from the deliberations made by the Guideline Development Group panel.