THE USE OF BEDAQUILINE IN THE TREATMENT OF MULTIDRUG RESISTANT TUBERCULOSIS

EXPERT GROUP MEETING REPORT

29-30 January 2013, Geneva

This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization. Mention of a drug does not imply endorsement of any specific commercial product.

Executive summary

Background

The emergence of drug-resistance is a major threat to global tuberculosis (TB) care and control. WHO estimates that around 310,000 multidrug-resistant tuberculosis (MDR-TB) cases (i.e. resistant to at least rifampicin and isoniazid) occurred among notified TB patients in 2011. Current treatment regimens for drug-resistant TB are far from satisfactory: overall duration is 20 months or more, and it requires the daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB. Among MDR-TB patients started on treatment globally in 2009, only 48% were treated successfully, as a result of high frequency of death (15%) and loss to follow-up (28%), commonly associated with adverse drug reactions, among other factors. In a subset of 200 (XDR-TB) patients in 14 countries, treatment success only reached 33% overall and 26% of patients died.

The landscape of TB drug development has evolved dramatically over the last ten years, and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB. WHO has convened an Expert Group on the 29th and 30th January 2013 to review the available evidence on the efficacy, safety and effectiveness of a new drug, bedaquiline, for the treatment of MDR-TB, and if appropriate, provide recommendations to WHO for interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment.

Summary of results

Available data arose from a series of studies and trials made public by the drug developer. Main findings on efficacy and safety originated from two Phase IIb trials: C208, a two-stage trial of which Stage 1 was an exploratory study, and Stage 2 was a multi-centre, stratified, randomised, double-blind placebo-controlled trial serving as a pivotal proof-of-efficacy study, and C209, a single-arm, open label trial.

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

Subjects aged 18 to 65 years with newly diagnosed MDR-TB were enrolled in the C208 Stage 2 efficacy trial from 15 sites in India, Russia, Latvia, Peru, Brazil, Thailand, the Philippines and South Africa; 160 subjects were randomized to receive bedaquiline or placebo on top of a standardised 5-drug MDR-TB background regimen (BR), that consisted of various combinations of fluoroquinolones, aminoglycosides, pyrazinamide, ethionamide, ethambutol, and/or cycloserine/terizidone. Bedaquiline was given at 400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks. After 24 weeks, subjects continued the BR of MDR-TB therapy until a total treatment duration of 96 weeks was achieved. The total study duration was 120 weeks (24+96).

The primary efficacy endpoint was *time to sputum culture conversion* in commercial liquid culture (MGIT™ 960 Mycobacterial Detection System, Becton Dickinson (BD) Diagnostic systems, USA) during the 24-week investigational treatment period (subjects who discontinued before week 24 were considered as not having culture converted). The analysis was conducted on a "modified" intention to treat population (mITT) of 132 subjects (66 in each of the bedaquiline and placebo groups)[1].

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[1] Subjects who had drug-sensitive TB, XDR- or unconfirmed MDR-TB (based on susceptibility tests taken prior to randomization), or had missing or negative baseline cultures, or who were positive at baseline, but had no post-baseline culture results, were excluded from the ITT

The median time to culture conversion was 83 days (95%CI: 56, 97) in the bedaquiline group vs. 125 days (95%CI: 98, 168) in the placebo group. Using Cox proportional hazards model (adjusted for lung cavitation and pooled centre) there was a higher chance of faster culture conversion in the bedaquiline vs. placebo arm (HR=2.44 [1.57, 3.80], p<0.0001). The proportion of subjects with culture conversion at Week 24 *(secondary efficacy endpoint)* was 78.8% in the bedaquiline group vs. 57.6% in the placebo group (p=0.008). The percentage of responders at Week 72 (i.e. the time point attained by all Stage 2 subjects at the interim analysis) was 71.2% in the bedaquiline group vs. 56.1% in the placebo group (p=0.069). Utilizing all available efficacy data up to end of study (Week 120), the percentage was 62.1% in the bedaquiline group vs. 43.9% in the placebo group (p=0.035). Efficacy was further evaluated using WHO-recommended treatment outcome definitions applied to Week 120 final data. The proportion of subjects defined as cured at 120 weeks was 57.6 % in the bedaquiline arm vs. 31.8 in the placebo arm (p=0.003).

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

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

Twelve deaths were reported from the C208 Stage 2 trial. Of these, 10/79 (12.7%) came from the bedaquiline group and 2/81 (2.5%) from the placebo group (p=0.017) (Intention to treat analysis) . In the bedaquiline group, 8 of the 10 deaths occurred in culture converters. TB was the cause of death in the two placebo-arm deaths and in 5 of the 10 bedaquiline-arm deaths (all occurred off bedaquiline treatment). There was no discernible pattern between death and culture conversion, relapse, microbiologic response, sensitivity to BR, HIV status, or severity of disease. Despite detailed descriptive line listings of all deaths the reason(s) for the imbalance were not clear.

Expert Group findings

The Expert Group concluded that the randomized, double-blind, design of the pivotal study was of high quality, although information on the desired sample size and on the actual randomization process was not available. The Expert Group was, however, concerned about the use of mITT (and subsequent assumptions made), as well as the representativeness of the study population and the fact that the BR used in various sites of the trial did not appear to be compliant with WHO recommendations. There was concern also on directness regarding the population of interest (e.g.: a greater proportion of HIV-co-infected TB cases occurred in the placebo arm; XDR patients were excluded). Lastly, there was concern on the generalizability of study findings to the general population and to all regions in the world. The

overall quality of evidence for efficacy was therefore graded as "Low", i.e. the Expert Group had low confidence in the estimate of effect (or efficacy) of bedaquiline.

The Expert Group expressed concern on the risk of QT prolongation and the additive effect of combination with other MDR-TB drugs reported to prolong QT. The Expert Group also expressed concerns regarding co-morbidities (notably HIV infection, liver diseases), and the effects of alcohol and substance abuse on the risk of severe adverse events. The evidence for safety as reflected by AEs was therefore graded as "Very Low".

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

Lastly, the Expert Group had concerns about the data on emergence of resistance, due to a high risk of bias, as data were not provided from paired samples from all subjects recruited and followed-up in the trial. The quality of evidence for acquisition of resistance to fluoroquinolones, aminoglycosides or capreomycin was therefore graded as "Very Low".

The cost-effectiveness analysis (CEA) model indicated that the addition of bedaquiline to WHO-recommended MDR-TB treatment was likely to be cost-effective in most environments. The Expert Group noted, however, that there might be some variations across settings based on data and assumptions used in the model that may not reflect the true-life situation. The Expert Group further noted that estimation of incremental cost-effectiveness could not be considered as a proxy for affordability or country willingness to pay.

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

Expert Group Recommendations

The Expert Group suggested that, as an interim recommendation, bedaquiline may be added to a WHO-recommended regimen in adult MDR-TB patients under the following conditions *(conditional recommendation, very low confidence in estimates of effect, i.e. very low quality of evidence)*:
- when an effective treatment regimen containing 4 second-line drugs from the different classes of drugs according to WHO-recommendations cannot be designed;
- when there is documented evidence of resistance to any fluoroquinolone in addition to MDR.

In addition, the Expert Group recommended that:
- a duly informed decision making-process by patients should be followed;
- bedaquiline be used with caution in persons living with HIV infection, as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol abuse, due to limited or no information;

- bedaquiline be used for a maximum duration of 6 months and at suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks);
- bedaquiline must not be added alone to a failing regimen;
- a duly informed decision making-process by patients should be followed;
- 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;[2]
- in the absence of a specific drug-susceptibility test, resistance to bedaquiline should be monitored through assessment of Minimum Inhibitory Concentrations (MICs)
- resistance to other anti-TB drugs should be monitored following WHO recommendations.

The Expert Group also recommended that interim recommendations be re-assessed in 2015, or earlier if substantial data become available increasing the knowledge on safety, toxicity and efficacy of the drug. In addition, the Expert Group identified a number of research topics to be addressed to inform future guidance on the use of bedaquiline.

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

I. BACKGROUND:

The emergence of drug-resistance is a major threat to global tuberculosis (TB) care and control. WHO estimates that around 310,000 multidrug-resistant tuberculosis (MDR-TB) cases (i.e. resistant to at least rifampicin and isoniazid) occurred among notified TB patients in 2011. Of these, only 19% were reported to WHO, largely as a result of critical gaps in diagnostic and treatment capacity in most countries. Furthermore, 85 countries have now reported at least one case of extensively drug-resistant tuberculosis (XDR-TB), a form of TB which is resistant to at least four of the core anti-TB drugs, (rifampicin, isoniazid, fluoroquinolones and second-line injectable agents), and associated with high mortality, particularly among HIV-infected persons (Global TB Report 2012).

The global deployment of new, rapid diagnostics for drug resistance, such as the Xpert MTB/RIF assay, is increasing the demand for treatment of MDR-TB patients. Current treatment regimens for drug-resistant TB are far from satisfactory. Whereas most drug-susceptible TB patients can usually be treated successfully with a 6-month course of treatment, in most MDR-TB cases a treatment duration of 20 months or more is used, requiring the daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB. Among MDR-TB patients started on treatment globally in 2009, only 48% were treated successfully, as a result of high frequency of death (15%) and loss to follow-up (28%), commonly associated with adverse drug reactions, among other factors. In a subset of 200 (XDR-TB) patients in 14 countries, treatment success only reached 33% overall and 26% of cases died (Global TB Report 2012).

The landscape of TB drug development has evolved dramatically over the last ten years, and novel drugs are presently or soon entering Phase III trials for the treatment of MDR-TB. WHO has convened an Expert Group on the 29th and 30th January 2013 to review the available evidence on the efficacy, safety and effectiveness of a new drug, bedaquiline, for the treatment of MDR-TB, and to recommend whether WHO interim guidance on the use of this drug in treatment of MDR-TB is warranted. Dossiers are currently submitted to several national regulatory authorities and are being evaluated under procedures of "accelerated" or "conditional" approval based on early (Phase IIb) clinical data, and Member States have expressed the need for WHO to provide interim advice on the use of bedaquiline in MDR-TB treatment.

II. EVIDENCE SYNTHESIS

In order to facilitate rapid policy guidance on the use of new drugs or new drug regimens for the treatment of TB, WHO Stop TB Department has recently developed a systematic, structured, evidence-based process based on the principles of the WHO Guideline Review Committee. The first step involves a systematic review of available data, using standard methods appropriate for evaluation of drug safety and efficacy, including the review of pre-clinical and clinical data [3]. The second step involves the convening of an Expert Group to evaluate the potential and evidence for use of the new drug(s) or combination of drugs within current TB treatment guidelines, , and the subsequent development of policy recommendations if appropriate, so as to rationally introduce new drug(s) into national TB control programmes, and/or identify gaps to be addressed in future research. The third step involves preparation of WHO policy guidance on the use of these new drugs, presented to the WHO Strategic and Technical Advisory Group for TB (STAG-TB) for endorsement, and subsequent dissemination to Member States for implementation.

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[3] Information note to TB drug/regimen developers – available at : http://www.who.int/tb/new_drugs

This document presents the findings and recommendations from the Expert Group meeting on the use of bedaquiline, a novel drug proposed for the treatment of MDR-TB, convened by WHO in Geneva, Switzerland on 29-30th January 2013. The Expert Group (Annex 1) consisted of researchers, epidemiologists, end-users (clinicians and national TB programme representatives), community representatives and evidence synthesis experts. The Expert Group meeting followed a structured agenda (Annex 2) and was chaired by a clinical epidemiologist/ methodologist with expertise and extensive experience in evidence synthesis and guideline development.

1. Meeting objectives:

Aim: To evaluate the added benefit of bedaquiline for the treatment of MDR-TB, and if appropriate, provide recommendations to WHO for interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment.

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

All meeting documents are available at :
http://workspace.who.int/sites/stb/ExpertGroupMeetingBedaquiline/default.aspx

2. GRADE evaluation:

To comply with current standards for evidence assessment in formulation of policy recommendations, the GRADE system (www.gradeworkinggroup.org), adopted by WHO for all policy and guidelines development,[4] was used. The GRADE approach, assessing both the quality of evidence and strength of recommendations, aims to provide a comprehensive and transparent approach for developing policy guidance. The GRADE process assesses the impact of a particular intervention on patient-important outcomes and the 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

In the first stage, the Expert Group reviewed the evidence from all available studies on bedaquiline, including toxicity, dosing and pharmacokinetic studies, drug-drug interaction studies, early bactericidal activity studies, safety studies, and a pivotal Phase IIb clinical trial. Evaluation of the available evidence followed the GRADE system for grading quality of evidence and providing strength of recommendations, based on the formulation of an *a priori* agreed question (the PICO question) by the Expert Group:
"In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendations safely improve patient outcomes?"

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[4] World Health Organization. Handbook for Guideline Development, 2012. World Health Organization: Geneva.

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

- **P**opulation targeted by the action/intervention: MDR-TB patients, including newly diagnosed patients, patients treated empirically for MDR-TB, HIV-infected patients (+/- use of ARVs), and children;
- **I**ntervention: addition of bedaquiline to WHO-recommended background MDR-TB therapy during the first 6 months of treatment;
- **C**omparator: Addition of placebo to WHO-recommended MDR-TB treatment;
- **O**utcome: Efficacy (as demonstrated by culture conversion and final treatment outcomes based on WHO definitions), safety (toxicity, serious adverse events, mortality),

Determination of relative importance of patient outcomes:
A 3-step Delphi-like process was carried out with the Expert Group prior to the Expert Group Meeting to define the important patient outcomes for the GRADE evaluation of the addition of bedaquiline to MDRTB treatment:

1. Outcome identification
2. Outcome grouping
3. Outcome importance rating

12/16 experts contributed to the survey. Results are shown in **Figure 1.**
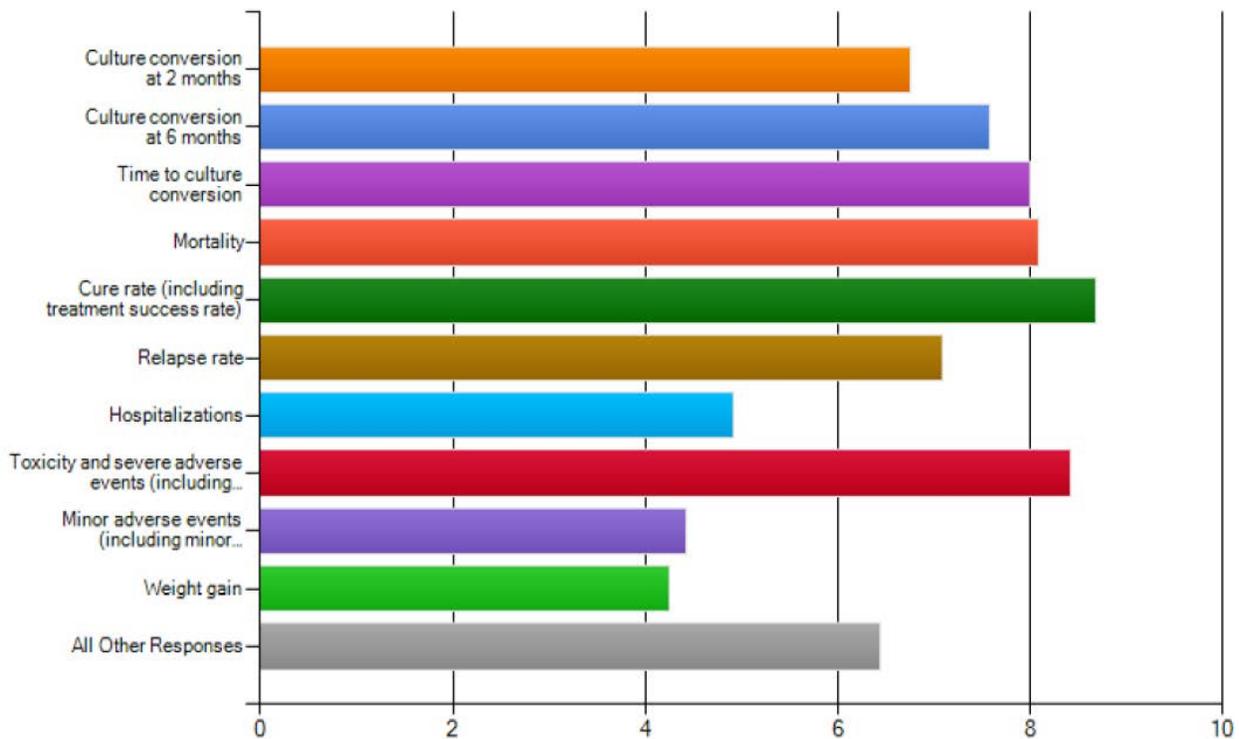
Fig 1: Determination of patients' important outcomes: identified outcomes and ratings

All experts gave responses for each outcome. Outcomes rated 7-9 were considered "critical" and therefore assigned the highest value for evaluation of the quality of evidence.

Subsequently, the following outcomes were evaluated for the evidence profile:
1. *Cure by 120 weeks*
2. *Serious adverse events during investigational 24 weeks treatment phase*
3. *Mortality*
4. *Time to culture conversion over 24 weeks*
5. *Culture conversion at 24 weeks*
6. *Acquired resistance to second-line drugs (fluoroquinolones, amino-glycosides and capreomycin) at 72 weeks*

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

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
(Source: World Health Organization. Handbook for Guideline Development, 2012. World Health Organization: Geneva).

Quality	Definition	Implications
High	The guideline development group 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 guideline development group 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

Details of the GRADE assessment for bedaquiline are provided in section IV (Grade evidence profile).

2.2 Development of recommendation:

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

Details of the GRADE recommendation for use of bedaquiline are provided in section V.

3. Meeting procedural issues

3.1 Evidence retrieval and synthesis

An independent consultant was contracted to prepare a concise *summary report* of the publicly available evidence, that was circulated to the Expert Group for scrutiny before the meeting (see Annex 4). This report was based on detailed documents made publicly available by the manufacturer (also shared with the Expert group members). In addition, two technical resource consultants were requested to develop specific documents to assist the Expert Group in their evaluation of the product:

(1) an assessment of the validity of sputum culture conversion at 6 months and time to culture conversion as surrogate markers of MDR-TB treatment outcomes (Annex 5); and

(2) a cost-effectiveness analysis based on modeling (Annex 6).

The Expert Group members were familiar with the GRADE process and had completed an online course on GRADE prior to the meeting.

3.2 Management of declarations of interest

All Expert Group members submitted a completed Declaration of Interest (DOI) form. These were reviewed by the WHO Legal Department prior to the Expert Group meeting. A summary is attached in Annex 3. DOI statements were summarised by the secretariat (WHO-STB) of the Expert Group meeting at the start of the meeting. Technical resource consultants participated in the meeting to provide specific information on technical issues but were not involved in the preparation of the actual recommendations. Observers participated only at the request of the Chair and did not contribute to the preparation of the recommendations. All participants signed a confidentiality agreement and were reminded of the need for confidentiality until the full WHO process is concluded.

III. SUMMARY OF MAIN FINDINGS (see Annex 4)

The clinical development strategy followed by the sponsor (Janssen Pharmaceutical) is schematically presented below in **Figure 2**. A total of 265 subjects participated in **11 Phase I trials** with bedaquiline (208 subjects were enrolled in 8 single-dose trials evaluating bedaquiline doses up to 800 mg; and 57 subjects were enrolled in 3 multiple-dose trials evaluating bedaquiline doses up to 400 mg daily with a maximum treatment duration of 15 days). The Phase I trials provided a basic understanding of bedaquiline's pharmacokinetic characteristics, drug-drug interaction (DDI) potential, and short term safety/tolerability in healthy subjects and in a special population (moderately hepatic-impaired subjects, **trial C112**). A double-blind, single-dose trial (**TBC1003**) was conducted to evaluate the effect of a single supra-therapeutic (800 mg) dose of bedaquiline on the corrected QT interval (QTc).

A Phase IIa 7-day extended early bactericidal activity trial (**C202**) in 75 patients with drug susceptible TB (evaluating doses up to 400 mg bedaquiline daily) was conducted to evaluate the antimycobacterial activity of bedaquiline.

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

Fig 2: Development plan for bedaquiline and studies from which data were reviewed

★ February 2011: Clin EoPII Discussion
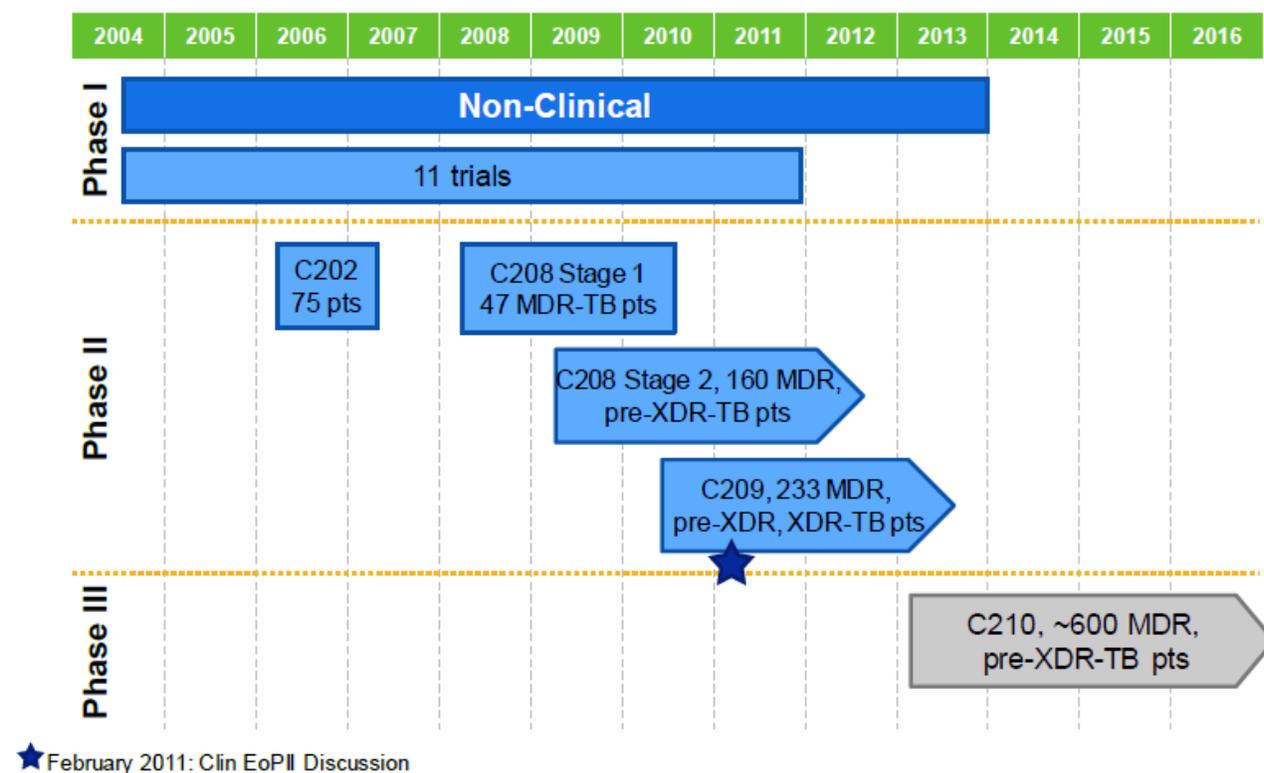
1. Evidence for the efficacy of bedaquiline in the treatment of MDR-TB

Evidence for efficacy derived from the **C208 Stage 2 trial**, in which subjects aged 18 to 65 years of age with newly diagnosed MDR-TB were enrolled from 15 sites in India, Russia, Latvia, Peru, Brazil, Thailand, the Philippines and South Africa. Subjects were randomised in a 1:1 ratio to receive either bedaquiline (BDQ) 400 mg, or placebo, daily for the first 2 weeks, followed by 200 mg BDQ, or placebo, three times per week for the remaining 22 weeks[5]. In both the bedaquiline and placebo arms, patients received a standardised 5-drug MDR-TB background medication regimen (BR) consisting of fluoroquinolones (mainly ofloxacin), aminoglycosides (mainly kanamycin), pyrazinamide, ethionamide, ethambutol, and

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

cycloserine/terizidone in various combinations. After 24 weeks, subjects continued the BR of MDR-TB therapy until a treatment duration of 96 weeks was achieved. Total study duration was 120 weeks (24+96). All subjects (modified intention to treat population – mITT – see below) presented in the data sets completed Week 72 (the pre-set study data cut-point), and also Week 120 (end of study).

The ***primary efficacy endpoint for C208 Stage 2 was time to sputum culture conversion***[6] in commercial liquid culture (MGIT™ 960 Mycobacterial Detection System, Becton Dickinson (BD) Diagnostic systems, USA) during the 24-week investigational treatment period, evaluated after all subjects had completed the 24-week investigational treatment period, or discontinued earlier. In the primary efficacy analysis, subjects who discontinued before week 24 were considered as not having culture converted (censored at the last culture visit, i.e. missing = failure). Primary efficacy analysis was based on the mITT population, which excluded subjects who had drug-susceptible, XDR-TB or unconfirmed MDR-TB, based on susceptibility tests taken prior to randomization, or had missing or negative baseline cultures, or who were positive at baseline, but had no post-baseline culture results. The primary efficacy analysis was conducted on a mITT population of 132 subjects (66 in each of the BDQ and Placebo groups). The median time to culture conversion 83 days (95%CI: 56, 97) in the bedaquiline group compared to 125 days (95%CI: 98, 168) in the placebo group. Primary analysis at Week 24 using Cox proportional hazards model (adjusted for lung cavitation and pooled centre) showed a statistically significant difference in time to culture conversion between the two treatment groups in favour of bedaquiline: HR=2.44 [1.57, 3.80] (p<0.0001).

A work was commissioned by WHO/STB to the US Centres for Diseases Control to evaluate the directness of surrogate microbiological endpoints used in the Phase IIb trial, i.e. sputum culture conversion (SCC) by the end of the 6th month of treatment and time to culture conversion as proxy markers of treatment outcome in patients with MDR-TB. The report included a review of the medical literature and analyses from two observational studies: (1) the "Preserving Effective TB Treatment Study" (PETTS), a prospective cohort study of consecutive adults with locally confirmed, pulmonary MDR TB who started treatment with second-line drugs (SLDs) between 1/1/2005 and 12/31/2008 in 9 countries (nationwide in Estonia, Latvia, South Korea, and Taiwan; and subnational regions in Peru, the Philippines, Russia, South Africa, and Thailand), and (2) the DOTS-Plus Pilot Projects Case-based Study (CBS), a retrospective cohort study of adult patients with MDR TB starting treatment between 01/01/2000-12/31/2003 in 4 of the first 5 DOTS-plus projects approved by the Green Light Committee (GLC) at that time (nationwide in Latvia and subnational regions in the Philippines, Peru, and Russia). Overall, it was found that SCC at 6 months and time to culture conversion on solid media had statistically significant associations with end-of-treatment outcomes among MDR-TB patients. The risk difference of successful outcome in patients with SCC at 6 months compared to patients without SCC at 6 months was ≥29% in all studies. While specificity of SCC at 6 months in predicting treatment outcome varied widely (25%-88%), the Positive Predictive Value was ≥79% in all studies. In one study with available information, HIV infection and total duration of treatment had an impact on predictive values of SCC at 6 months.

Subsequently, the Expert Group agreed that time to culture conversion and culture conversion at 6 months could be considered as reliable surrogate markers of treatment outcome.

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

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

Efficacy was further evaluated using WHO-recommended treatment outcome definitions applied to Week 120 final data (**Table 2**). Cure was defined as "at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment - if only one positive culture is reported during that time, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart". In the bedaquiline arm, 38/66 (57.6%) subjects were categorized as cured while only 21/66 (31.8%) in the placebo arm (p=0.003).

Treatment Outcome	Bedaquiline/BR N = 66	Placebo/BR N = 66
Cure	38 (57.6)	21 (31.8)
Failure	5 (7.6)	20 (30.3)
Death	6 (9.1)	1 (1.5)
Transferred out/default*	17 (25.8)	24 (34.8)

(*: 3 TMC207/BR subjects and 1 Placebo/BR subject who died during survival follow-up after the 120 week endpoint are counted in this category)

Table 2: Treatment outcome at 120 weeks using WHO treatment outcome categories

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

The safety database covered non-clinical aspects (pharmacology and toxicology) during pre-clinical development, and human experience in Study C208 (pivotal RCT, double-blind, placebo controlled) and Study C209 (single arm, open label). The intention to treat (ITT) population in each of these studies was used for the description of safety.

Information was available from several studies:
- eight Phase I studies in 189 healthy subjects given bedaquiline alone;
- three individual studies of hepatic impairment (N=16), drug-drug interaction in HIV-infected subjects (N=16) or QTcF prolongation in 44 non-TB patients;
- a Phase IIa EBA study in 45 drug sensitive TB subjects, with 7-day monotherapy exposure to bedaquiline;
- a Phase IIb study (C208 Stage 1) in 23 MDR-TB subjects, with 8 week exposure to bedaquiline;
- two Phase IIb studies in 335 MDR-TB patients, comprising the C208 Stage 2 and C209 trials in which 312 subjects exposed for 24 weeks to bedaquiline were followed for adverse events (AEs).

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

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

Table 3. Adverse events of interest

Main safety concerns included cardio-toxicity (QT prolongation), hepatic toxicity, and deaths.

Cardiovascular toxicity (Trial C208: pooled experience Stage 1 and Stage 2)
Mean QTcF [7] increases were observed in both the pooled bedaquiline ("Any bedaquiline") and pooled placebo ("Any Placebo") groups, but they were more pronounced in the Any bedaquiline group. The largest mean increase in QTcF at a pre-dose time point in the Any bedaquiline group during the first 24 weeks was 15.4 ms (at Week 24). QTcF values above 450 ms and QTcF increases of 30 to 60 ms and > 60 ms were observed more frequently in the Any bedaquiline group than in the Any placebo group. There were no reports of Torsade de Pointes events, and no reported fatalities from sudden death. Bedaquiline, in multiple dosing, can prolong the QTc interval and the risk is highest during the treatment phase, but could extend beyond the treatment period. The use of BDQ with QT prolonging medications increases the risk of prolonged QT interval, i.e. QTcF prolongation from multiple QTcF prolonging drugs could be additive (viz. clofazimine).

Hepatic toxicity
During the Investigational phase of the pooled C208 trials, there was a higher incidence of events related to hepatic disorders in the Any bedaquiline group (9 subjects, 8.8%) compared to the Any Placebo group (2 subjects, 1.9 %). Increases in transaminases accounted for the majority of these reported events. Applying Hy's law, an analysis to identify cases of severe liver toxicity revealed 1 patient who experienced a concurrent >3 fold elevation of AST and >2 fold elevation in total bilirubin, but was confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background medications.

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[7] QTcF: QT interval corrected for heart rate according to the Fridericia method

Mortality

Twelve deaths were reported from **C208 Stage 2 (Figure 3)**. Of these, 10/79 (12.7%) came from the BDQ group and 2/81 (2.5%) from the placebo group (p=0.017). Of the 10 deaths in the bedaquiline group, 8 patients had culture conversion.

TB was the cause of death in the two placebo-arm deaths and in 5 of the 10 bedaquiline-arm deaths (all occurred off bedaquiline treatment). There was no discernible pattern between death and conversion, relapse, microbiologic response, susceptibility to components of the BR, HIV status, or severity of disease. The reason for the imbalance in deaths was not clear. A detailed list of all deaths is provided in Annex 4 (Table 20).
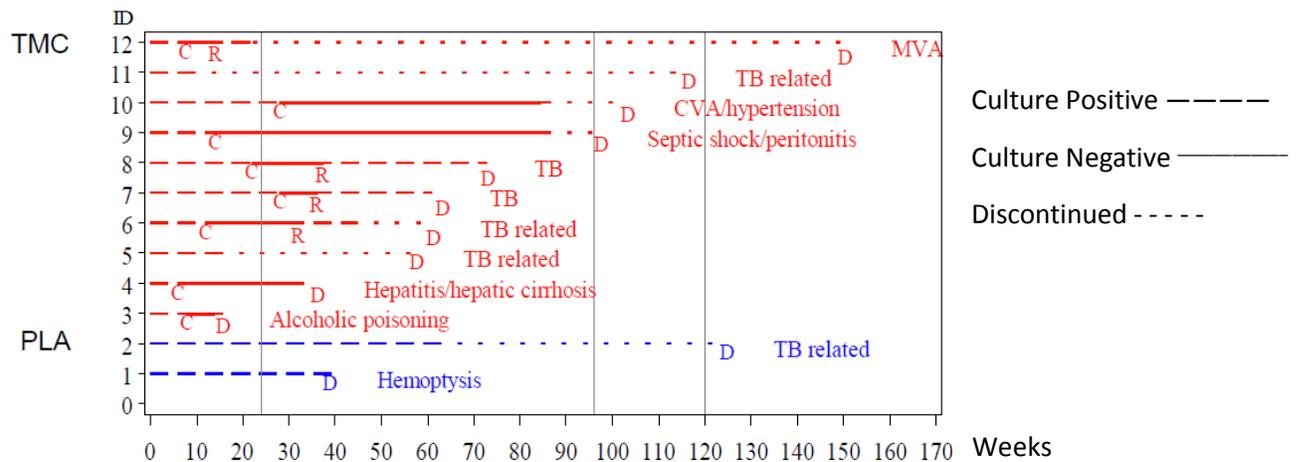
Figure 3. C208 Stage 2: Mortality by individual case: cause and time of occurrence
(C=Conversion; R=Relapse; D=Death; CVA=cardiovascular accident; MVA=motor vehicle accident)

In **Trial C209**, 16 deaths amongst 233 subjects (6.9%) were reported by the trial cut-off date (120 weeks). Of these, 12 deaths occurred during the trial: 3 during the expected bedaquiline treatment period, and 9 during the 96 week follow-up period. There were 4 deaths reported during follow-up for patients who discontinued prematurely (incomplete treatment). No recognizable association between predictive factors (HIV infection, susceptibility to BR drugs, cavitations) and death was observed. Eleven of the 16 deaths were reported as being related to TB disease (68.75%).

IV. GRADE EVIDENCE PROFILE

1. Grade evidence profile by set outcomes

The GRADE process was used to evaluate the quality of the evidence presented to the Expert Group to determine whether bedaquiline should be added to WHO recommended background MDR-TB regimen. For each identified critical endpoint, the quality of evidence was assessed based on the criteria of study limitations/risk of bias, inconsistency, indirectness, and imprecision. Full details are provided in Annex 4.

The GRADE evidence profile summary is presented in **Table 4.**

1.1 Outcome "Cured by end of study - 120 weeks"

132 subjects were included in an mITT analysis of cure at Week 120, using the WHO recommended treatment outcome definition. Cure was defined as "at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment, *OR* if only one positive culture is reported during that time, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart". Results indicated a statistically significant higher chance of cure in patients in the bedaquiline compared with patients in the placebo arm: in the former, 38/66 (57.6%) were categorized as cured while only 21/66 (31.8%) in the latter (RR: 1.81, 95%CI: 1.2 – 2.3, Fisher exact test p=0.005; Pearson's χ^2 test p=0.003).

- Design: The randomized, double-blind, design of the pivotal study was regarded as high quality, although information on the desired sample size and on the actual randomization process were not available. The Expert Group decided not to downgrade this domain.
- Risk of bias: The Expert Group was concerned about the use of mITT and assumptions made for ITT (there were about 20% patients "lost" from ITT to mITT population). However, in view of the need to consider only patients who fulfilled the criteria for inclusion (bacteriologically confirmed MDR-TB) the Expert Group considered that there was no additional serious risk of bias other than through indirectness/ imprecision (see below).
- Inconsistency: the Expert Group concluded that this was not to be considered serious, although there was only one pivotal study on efficacy, and inconsistency could therefore not be rated.
- Indirectness: There was concern about the representativeness of the population and the background regimen (BR) used: the observed BR used in various sites of the trial was not considered to be necessarily compliant with current WHO recommendations (particularly the study was designed and performed using the 2008 WHO guidelines, not the updated 2011 guidelines), and treatment outcomes in the population receiving placebo were relatively poor. In addition there was concern on directness regarding the population of interest (e.g. a much greater proportion of HIV-co-infected TB cases in the placebo vs. the bedaquiline arm; XDR-TB cases were excluded). Therefore, the Expert Group downgraded to "serious indirectness" for this outcome..
- Imprecision: the Expert Group concluded that analysis performed on small numbers caused significant imprecision and downgraded this domain;

Overall, the quality of evidence for "Cure by end of study – 120 weeks" was rated as "Low".

1.2 Outcome "Serious Adverse Events" (SAEs)

An adverse event was defined as "any undesirable experience associated with the use of a medical product in a patient". The event was considered serious when the patient outcome was death, life-threatening, lead to hospitalization, disability or permanent damage, or any important medical event.

207 subjects were included in an ITT analysis of safety based on the presence of a Serious Adverse Event defined as above, either on clinical or biological grounds. The risk of presenting an SAE in the bedaquiline vs. placebo arm was 3.6 (95% CI 0.77 - 16.95) higher than in the placebo arm, although not statistically significant.

The Expert Group expressed similar judgments as for the primary outcome of cure at 120 weeks on the criteria of study design, risk of bias and inconsistency. The Expert Group noted that the risk of adverse effects (e.g. prolonged QT) could be higher if moxifloxacin or clofazimine were used in the background

Table 4. The GRADE evidence profile summary

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

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline added to SLBR	SLBR alone	Relative (95%CI)	Absolute	Quality	Importance
Quality assessment							**No of patients**		**Effect**			
...												

Subjects Cured by end of study: 120 weeks (C208 Stage 2: mITT) [1, 2]

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline added to SLBR	SLBR alone	Relative (95%CI)	Absolute	Quality	Importance
1[3]	randomised trials	no serious risk of bias[4]	no serious inconsistency	serious[5]	serious[5]	none	38/66[1] (57.6%)	21/66[1] (31.8%)	RR 1.81 (1.26 to 2.31)[3,6]	26 more per 100 (from 8 more to 42 more)	⊕⊕OO LOW	CRITICAL

Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT) [7] (assessed through clinical and laboratory results)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline added to SLBR	SLBR alone	Relative (95%CI)	Absolute	Quality	Importance
2[8]	randomised trials	no serious risk of bias	no serious inconsistency	Serious[9]	very serious[5]	none	7/102[10] (6.9%)	2/105 (1.9%)	RR 3.6 (0.77 to 14.00)	5 more per 100 (from 0 to 25 more)	⊕OOO VERY LOW	CRITICAL

Mortality up to end of study at 120 weeks (C208 Stage 2: ITT) (deaths reported)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline added to SLBR	SLBR alone	Relative (95%CI)	Absolute	Quality	Importance
1[11]	randomised trials	no serious risk of bias	no serious inconsistency	serious[12]	very serious[3]	none	9/79[11] (12.7%)	1/81[11] (2.5%)	RR 9.23 (1.20 to 72.95)[13,14]	10 more per 100 (from 0 more to 53 more)	⊕OOO VERY LOW	CRITICAL

Time to conversion over 24 weeks (C208 Stage 2: mITT [1]) (measured with microbiological endpoints - MGIT960)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bedaquiline added to SLBR	SLBR alone	Relative (95%CI)	Absolute	Quality	Importance
1[15]	randomised trials	no serious risk of bias[4]	no serious inconsistency	serious[16]	serious[5]	none	n=66[1] median=83 days	n=66[1] median=125 days		median 42 days lower[17]	⊕⊕OO LOW	CRITICAL

Culture conversion at 24 weeks (C208 Stage 2: mITT [1]) (assessed with microbiological endpoint - MGIT960)

1[18]	randomised trials	no serious risk of bias[4]	no serious inconsistency	serious[16]	serious[5]	none	52/66[1] (78.8%)	38/66[1] (57.6%)	RR 1.37 (1.1 to 1.77)[19]	21 more per 100 (from 6 more to 44 more)	⊕⊕OO LOW	CRITICAL
Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT)[20] (assessed with: Microbiological endpoints)												
1[21]	randomised trials	Serious[22]	no serious inconsistency	serious[16]	very serious[5]	none	2/10[20] (20%)	14/27[20] (51.9%)	RR 0.39 (0.11 to 1.40)[23]	32 fewer per 100 (from 46 fewer to 21 more)	⊕OOO VERY LOW	CRITICAL
								7/27 (25.9%)[24]		6 fewer (22 fewer to 34 more)[24]		

[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 MDRH&R-TB or Pre-XDR-TB at baseline or for whom MGIT results were considered not evaluable.

[2] Cure defined as 5 consecutive negative cultures during 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 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 FDA Anti-Infective Drugs Advisory Committee Meeting, DC, 28 November 2012 (referred to as "JRD"), JRD Slide 71.

[9] Risk of side-effects (e.g. prolonged QT) could be higher if clofazimine were used; concern about follow-up being short in spite of the long half-life of BDQ.

[10] See JRD Slide 63.

[11] see BD Table 45, Appendix 4; Analysis on ITT population, C208 Stage 2 trial only (n=79 in bedaquiline arm, 81 in placebo arm); Mortality amongst all subjects exposed to BDQ in the C208 Phase 2 study, irrespective of when deaths occurred (i.e. including deaths post-120 weeks), count 10 deaths in the BDQ and 2 deaths in the Placebo group. Counting deaths strictly at the 120 weeks cut-point reveal 9 in the BDQ and 1 in the placebo group.

[12] Concern that if, in HIV patients, ARV treatment was given, there might have been drug-drug interactions affecting SAE and mortality.

[13] Fisher Exact p=0.017; Pearson p=0.014.

[14] The imbalance in deaths is unclear; clinical factors (such as HIV-status or severity of disease) and clinical outcome (disease improved or not) do not seem associated with higher/lower risk for death.

[15] see BD Figure 22.

[16] Concern re. extrapolating to general population; background treatment regimen was considered sub-optimal and not in line with WHO recommended regimens (PZA plus 4 active second-line drugs)

[17] Cox proportional hazards model: HR 2.44 [95%CI 1.57, 3.80] p<0.0001 (BD p106).

[18] see JRD slide EF-142.

[19] Fisher Exact p=0.015; Pearson p=0.009.

[20] Analysis on paired samples, mITT population (n=10 in bedaquiline arm, 27 in placebo arm).

[21] see JRD Slide 52;

[22] Selected and differential ascertainment of acquired resistance to bedaquiline. Last available positive culture interrogated against baseline for all patients would have been useful; acquired resistance to bedaquiline as seen in non-responders in the bedaquiline arm (using the indicative breakpoint for susceptibility) should also be stated.

[23] Fisher Exact p=0.14; Pearson p=0.08.

[24] The expert panel 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

regimen, given that use of these drugs is also reported to prolong QT. The Expert Group also expressed concerns regarding co-morbidities (HIV infection, liver diseases), and the effects of alcohol and substance abuse on the risk of SAE. Therefore, indirectness was qualified as serious and imprecision downgraded to "very serious". The overall quality of evidence for safety (SAEs) was therefore downgraded to "Very Low".

1.3 Outcome "Mortality"

160 subjects were included in an ITT analysis of mortality. Results indicated a statistically significant higher risk of death in the bedaquiline arm than in the placebo arm (RR: 9.23, 95%CI: 1.20 – 72.9, Fisher exact test p=0.017; Pearson's χ^2 test p=0.014).

The Expert Group noted that there was high imprecision with regard to deaths reported in the studies. No clear pattern could be observed, and reason(s) for the imbalance were unclear. Time of death with reference to drug intake was highly variable, but the majority of deaths occurred after the end of study treatment (24 weeks). There were concerns that 8 deaths arose among patients who had achieved culture conversion. In addition, there was concern that in HIV-infected patients, concomitant ARV treatment might result in drug-drug interactions affecting SAE and mortality. The overall quality of evidence for mortality was therefore graded as "Very Low".

1.4 Outcome "time to culture conversion at 24 weeks"

132 subjects were included in an mITT analysis of time to culture conversion. Median time to culture conversion was 83 days (95%CI: 56, 97) in the bedaquiline arm vs. 125 days (95%CI: 98, 168) in the placebo arm (Cox proportional Hazard ratio: HR: 2.44, 95%CI: 1.57 – 3.80, p<0.0001).

The Expert Group agreed that time to culture conversion and culture conversion at 6 months could be considered as reliable surrogate markers of treatment outcome. There was concern, however, on the generalisability of study findings to the general population and to all regions of the world. The Expert Group noted that data on the background regimens used in both the bedaquiline and placebo arms were not available and might not have been in compliance with WHO recommendations. For these reasons, indirectness was considered to be serious and downgraded by one point. Quality of evidence for this outcome was therefore graded as "Low".

1.5 Outcome "culture conversion at 24 weeks"

132 subjects were included in an mITT analysis of culture conversion at 24 weeks: 52/66 (78.8%) converted in the bedaquiline arm while 38/66 (57.6%) converted in the placebo arm (RR: 1.3, 95%CI: 1.1 – 1.7, Fisher exact test p=0.01).

Similarly as for "time to culture conversion", the Expert Group was concerned on the generalizability of study findings to the general population and to all regions of the world. The group noted that data on the background regimens used in both the bedaquiline and placebo arms were not available and might not have been in compliance with WHO recommendations. For these reasons, indirectness was considered to be serious and downgraded by one point. Quality of evidence for this outcome was graded as "Low".

1.6. Outcome "Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks"

Analysis was carried out in the mITT population (n=132). However, paired samples wereanalysed in only 37 patients considered to have failed treatment Of these, 2 out of 10 (20%) developed resistance to any of the above drugs in the bedaquiline compared to 14 out of 27 (51.9%) in the placebo arm (RR: 0.39, 95%CI: 0.11 – 1.40).

As data were not provided from paired samples from all subjects recruited and followed-up in the trial, the Expert Group was concerned about a high risk of bias and limited representativeness. It was not clear how these paired samples were selected and no data were available on drug resistance patterns for the vast majority of patients. The Expert Group also had concerns about the appropriateness of the analysis done, as the last positive culture should have been used in all patients to compare resistance patterns relative to the baseline (rather than the cultures from only failure cases, as reported in the study).

The Expert Group assumed that the true baseline risk for developing resistance would be substantially lower if all samples had been tested. Assuming a true baseline risk of 50% of the actual baseline risk reported, the estimate of effect would be lower, resulting in fewer events (acquisition of resistance) per 100 patients (see detail in Table 4). As a result, the "risk of bias" was graded as serious, imprecision as "very serious" and the overall quality of evidence for this outcome was graded "Very Low".

2. Cost effectiveness:

A cost-effectiveness analysis (CEA) was conducted to model the incremental cost-effectiveness of adding bedaquiline to existing WHO-recommended MDR-TB regimens. This CEA was undertaken for various settings toallow for variation among countries in income level, the model of care used for MDR-TB treatment, and background patterns of drug resistance (see Annex 6). It was also conducted from a TB programme perspective and focused on the direct benefits to patients, but did not assess any indirect (and acquired) transmission benefits. It excluded any broader economic benefits to patients or society.[8] Despite its limits, this approach was considered appropriate to inform decision makers, given the need of looking at incremental costs and effectiveness relative to current MDR-TB treatment, and given the context of the general lack of any evidence-base on the CEA of new MDR drugs at this current time.

Incremental cost-effectiveness was evaluated by comparing the current practice of MDR-TB treatment (i.e. base case) and the addition of bedaquiline to the base case (24 week regimen). The analysis was conducted with data provided by WHO from six countries (Russia, Estonia, Philippines, Peru, Nepal and China). These countries were primarily selected due to availability of cost data, but were also assessed to obtain a range of different income levels, current treatment practices and outcomes, and MDR-TB prevalence. The model was built in 2 phases:

> (1) A first simple model looking at the additional costs of bedaquiline, including any extra monitoring and the potential for increased efficiency – as reported in the Phase IIb (C208) trial. It also included any potential cost savings in terms of a reduction in costs associated with the retreatment of MDR-TB treatment failures.

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[8] This purely pragmatic approach, warranted by time constraints, is *conservative*, as it is plausible that bedaquiline may have additional benefits to the wider health system, the economic conditions of patients and the prevention of on-going transmission of TB, that were not considered in the model.

(2) A second more speculative model included potential costs and benefits from shortening the intensive phase of the MDR-TB regimen by 2 months, based on the reduction of the median time to culture conversion during the first 24 week period of the C208 (phase 2) trial. While there is currently no trial evidence available on the optimal length of a bedaquiline regimen, the earlier median time to conversion suggests that this may be feasible in the future. Both these models assumed no negative impact on adverse events – apart from the necessity to monitor potential QT prolongation.

For the primary estimates of 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 price estimates provided by the drug producer. To reflect the uncertainty around generalization, three alternative ways of estimating the incremental effect on the underlying base case performance were used to arrive at estimates of incremental cost-effectiveness, namely:

a) an "additive" effect of bedaquiline, that increases the underlying base case cure rate *additively* by the % difference in cure rate in the bedaquiline vs. control arms.
b) A "proportional" effect whereby bedaquiline increases the underlying base cure rate *proportionally* by the % difference in cure rate in the bedaquiline vs. control arms.
c) A "maximum limiting" effect, whereby bedaquiline could not improve cure beyond a maximum limit of 80%.

The CEA suggested that:

- Adding bedaquiline to existing WHO-recommended MDR-TB regimens is likely to be cost-effective in most environments, for a wide range of assumptions about the translation of trial results to current practice. The incremental effectiveness of bedaquiline does not vary substantially by setting.
- In some environments, the addition of bedaquiline may be cost-saving – depending on the extent to which increases in cure rate reduce the levels of MDR-TB retreatment (i.e. impacts failures as compared to deaths)[9]. This cost reduction will be strongest in environments which have high MDR-TB treatment costs.
- Applying the full trial results (including the possible effect on deaths and defaults) - compared to cure rate alone can substantially impact both effectiveness and cost-effectiveness. In all settings it substantially reduces the DALYs averted.
- The impact on costs of adding bedaquiline to MDR-TB regimens will depend on price and the cost savings from retreatment. This latter 'savings' effect will benefit countries with higher retreatment costs or with high current levels of treatment failures.
- The cost-effectiveness of adding bedaquiline to MDR-TB regimens is ambiguous in low income countries like Nepal, with much lower willingness to pay thresholds.
- The possible effect of treatment shortening does not appear to substantially impact the above conclusions or results – although in some cases costs may be reduced. DALYs averted (excluding transmission consequences) may also be reduced - depending on the extent to which shortening reduces defaults compared to the slightly lower cure rates.

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[9] The conclusion is also substantiated by the first attempt at the model – which only allowed bedaquiline to impact failure rather than default rates.

3. Summary of Evidence to Recommendation

The GRADE Evidence to Recommendation summary is presented in **Table 5** *(pp 24-27).*

3.1 Final grading of quality of evidence

FINAL GRADING OF OVERALL QUALITY OF EVIDENCE: VERY LOW

Overall, the Expert Group had a low level of confidence in using the available data for global decision making, given that the available evidence was very limited. There were concerns about imprecision and indirectness due to the small sample size, the use of mITT (vs. ITT) analysis, and relatively poor outcomes of the background MDR-TB treatment regimens used in the trial.

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

The Expert Group also concluded that recommendations could only be made on the use of bedaquiline in addition to current WHO-recommended regimens, and not on the use of bedaquiline as a substitute for any of the currently recommended second-line drugs.

3.2 Balance between benefits and harms

All critical outcomes were assessed for balance between benefit and harms (see **Table 5**). In summary, an overall judgment was needed between a 23% increase in success (low confidence) against a 5% increase in SAEs (very low confidence) and 10% increase in deaths (very low confidence).

There was modest agreement that the quality of evidence for benefits was "low" due to imprecision and indirectness, and high agreement that the quality of evidence for harms was "low" or "very low" due to imprecision, indirectness and risk of bias.

Experts Group members considered a "modest to large benefit" for outcomes 1 (cure by 120 weeks), 4 (time to culture conversion over 24 weeks), 5 (culture conversion at 24 weeks), and 6 (acquired resistance to second-line drugs at 72 weeks), but "modest to large harms" for outcome 2 (serious adverse events during investigational 24 weeks treatment phase) and 3 (mortality). The Expert Group expressed particular concern about mortality risk, but with a high degree of uncertainty about the evidence. The need for caution in prescribing bedaquiline was stressed, as well as the importance of clear and understandable communication with patients at the time of drug prescription. Mention was made of the need to support this by informed consent, leaving it up to the end-users to make it written or not.

Concerns were raised on the interpretation of the "overall" harms-benefits balance for MDR-TB patients as a whole, as MDR-TB populations include very heterogeneous categories based on DST patterns, which represent highly variable prognosis and feasibility for designing effective regimens. For example, patients with XDR-TB or more severe drug resistance profiles have very limited options for

treatment, and some Expert Group members felt that both patient and provider perspectives on the risk vs. benefit from a bedaquiline-containing regimen in these groups of patients may be different to those with MDR-TB without additional resistance.

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

3.3 Patients' values and preferences

The Expert Group felt that there were potentially large variations in patient values and preferences for each outcome. Most members felt that patients would place high value on survival but that it was less clear that patients would value culture conversion in the same way. Expert Group members expressed the view that patient acceptance of bedaquiline would depend on the severity of their disease and the likelihood of designing an effective background regimen - e.g. XDR-TB patient groups might be more likely to accept the risk of taking a new drug with increased risk of death than patients with newly diagnosed MDR-TB without additional drug resistance.

3.4 Resources

The Expert Group had difficulty reaching consensus on the resource requirements of the proposed recommendation. While the cost-effectiveness modeling suggested that the addition of bedaquiline to WHO-recommended MDR-TB regimens would be cost-effective in most settings. However, there were some concerns from several Expert group members about the limits in the model assumptions (e.g. no accounting for the difference in serious adverse events, no accounting for effect on transmission, uncertainty about inclusion of deaths in the model, etc ….) and the model representativeness for different settings. The Expert Group noted that the relative cost-effectiveness does not necessarily translate into affordability or country readiness to pay, given a potential high relative cost of adding bedaquiline. Resource implications related to training of health care staff, and establishing active pharmacovigilance systems were not explicitly discussed due to time constraints. The Expert Group nevertheless concluded that the resource implications of introducing bedaquiline in addition to MDR-TB treatment would probably involve "small cost relative to net benefits".

3.5 Equity

The Expert Group felt that the effects of introduction of bedaquiline in MDR-TB treatment regimens on equity was difficult to assess for several reasons: these include uncertainty on affordability and country willingness to pay, as well as the difference in opinion on the balance of benefit and harms discussed above.

Table 5. *The GRADE Evidence to Recommendation*

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

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

DOMAIN	JUDGEMENT	DETAILS OF JUDGEMENT	EVIDENCE/EXPLANATION
QUALITY — **What is the overall confidence in effect estimates?** Is there high or moderate quality evidence? The higher the quality of evidence, the more likely is a strong recommendation	☐ High ☐ Moderate ☐ Low ☒ Very low	*Critical Outcomes:* — columns: High / Moderate / Low / Very low 1 Cure by 120 weeks. — ☐ ☐ ☒ ☐ 2. ADR (clinical and biological SAEs). — ☐ ☐ ☐ ☒ 3. Mortality — ☐ ☐ ☐ ☒ 4. Time to culture conversion…. — ☐ ☐ ☒ ☐ 5. Culture conversion at 24 weeks — ☐ ☐ ☒ ☐ 6. Acquired resistance to FQ, AG and CP — ☐ ☐ ☐ ☒ columns: Agree / Somewhat agree / Uncertain / Somewhat disagree / Disagree High confidence in the typical values — ☐ ☒ ☐ ☐ ☐	*All critical outcomes measured* *There were concerns about imprecision (due to small sample size and few events), and indirectness (due to (1) background MDRTB 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 MDRTB from mITT analysis).*
BENEFITS & HARMS — **What is the balance between benefits and risks/ burden?** Are you confident that the benefits outweigh the harms and burden or vice versa? The larger the difference between the benefits and harms, the more likely is a strong recommendation. The smaller the net benefit or net harm and the lower the certainty for that net effect, the more likely is a conditional/weak recommendation.	☐ Benefits outweigh harms/ burden ☒ Benefits slightly outweigh harms/ burden ☐ Benefits and harms/ burden are balanced ☐ Harms/ burden slightly outweigh benefits ☐ Harms/ burden outweigh benefits	*Critical Outcomes:* — columns: Large/Modest benefit / Small benefit / No effect / Small harm/ burden / Modest/Large harm/ burden 1. Cure by 120 weeks. — ☒ ☐ ☐ ☐ ☐ 2. ADR/SAE. — ☐ ☐ ☐ ☐ ☒ mod 3. mortality…. — ☐ ☐ ☐ ☐ ☒ large 4. time to conversio…. — ☒large ☐ ☐ ☐ ☐ 5. culture conversi…… — ☒large ☐ ☐ ☐ ☐ 6. resistance…… — ☒large ☐ ☐ ☐ ☐ *The issue is to balance a 23% increase in success (low confidence) vs. 5% increase in SAEs (very low confidence) and 10% increase in deaths (very low confidence)*	See evidence profile *QoE for benefits: Low due to imprecision and indirectness* *QoE for harms: Low or very low (resistance to BDQ) 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)*

VALUES AND PREFERENCES	**What are the patient's values and preferences?** Are the assumed or identified relative values similar across the target population? The greater the similarity in values and preferences, the more likely is a strong recommendation.	☐ Similar values ☐ Some variation ☒ Large variation	<table><tr><td></td><td>*Agree*</td><td>*Somewhat agree*</td><td>*Uncertain*</td><td>*Somewhat disagree*</td><td>*Disagree*</td></tr><tr><td>Values and preferences likely similar</td><td>☐</td><td>☐</td><td>☐</td><td>☒</td><td>☐</td></tr></table>	*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 MDRTB population – e.g. pre-XDR or XDR patient groups 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 MDRTB. There is minimal variation for death, larger variation for other outcomes*
RESOURCES	**Is the incremental cost (or resource use) small relative to the benefits? Are the resources worth the expected net benefit from following the recommendation?** The lower the cost of an intervention compared to the alternative, and other costs related to the decision – that is, the fewer resources consumed – the more likely is a strong recommendation in favour of that intervention.	☐ Cost is very small relative to the net benefits ☒ Cost is small relative to the net benefits ☐ Cost is borderline relative to the net benefits ☐ Cost is high relative to the net benefits ☐ Cost is very high relative to the net benefits	*No accounting of serious adverse events*	*There are variations of cost effectiveness across settings based on data and assumptions used in the model – that may not reflect real life situations. In addition, there were a series of limitations in the model being used for analysis of cost-effectiveness (e.g.. no accounting of serious adverse events, no accounting for effect on transmission, etc ….)*
EQUITY	**What would be the impact on health inequities?**	☐ High ☐ Moderate ☐ Low ☐ Very low ☒ Uncertain		*Will the intervention reduce inequities? Difficult to assess because of uncertainty on affordability*

Recommendation						
In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendations safely improve patient outcomes?						
Overall balance of consequences	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	The balance between desirable and undesirable consequences is too uncertain*	The balance of desirable and undesirable consequences indicates they are very similar*	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
	☐	☐	☐	☐	☒	☐
	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	No recommendation		We suggest using the option	We recommend the option
	☐	☐			☒	☐
Panel decisions	There was no consensus among the panel as per the "balance of harms and benefits", hence a vote: 10 experts evaluated that the benefits did outweigh the harms, 4 experts evaluated that the harms did outweigh the benefits and 2 (including chair) abstained					
Recommendation	**The Expert Group Panel suggests that bedaquiline may be added to a WHO recommended regimen in MDR-TB adult patients under the following conditions (conditional recommendation, very low confidence in estimates of effect)**					
Remarks and justifications	Conditions: • When an effective treatment regimen containing 4 recommended second line drugs from the different classes of drugs according to to WHO-recommendations cannot be designed • When there is documented evidence of resistance to any fluoroquinolone in addition to MDR • A duly informed decision making-process by patients should be followed; • Bedaquiline should be used with caution in persons living with HIV infection, as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol abuse, due to limited or no information. • Bedaquiline should be used for a maximum duration of 6 months and at suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks) • 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;[10] • 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.					
Explanation	The expert group judged that the impact on culture conversion was large enough to outweigh the harms for most patients					

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

Implementation and feasibility	- Monitor resistance to bedaquiline through assessment of MIC in the absence of a specific bedaquiline DST assay - Monitor resistance to other anti-TB drugs - Management of co-morbidities (cardiac diseases, etc.) - Clinical monitoring - Concerns on scale-up due to costs and/or local regulatory constraints
Research gaps	- Phase 3 clinical trial(s) of safety and efficacy of bedaquiline, with particular attention to mortality (including causes of death), in the treatment of MDRTB should be accelerated - Development of a reliable test for bedaquiline resistance - Pharmacokinetics, safety and efficacy studies in specific populations (paediatrics, HIV patients, alcohol and drug users, elderly, pregnant women, extrapulmonary TB, persons with diabetes - Safety studies, including type; frequency and severity of adverse events (short term and long term) - Drug-drug interactions, including with other existing and newly developed TB drugs and ARVs - Mortality (including cause of death) - Acquisition of resistance to bedaquiline and to other TB drugs - Duration and dosing of treatment - Patient acceptability - Further research on the validity of culture conversion as a surrogate marker of treatment outcome
Revision planned	- By 2015 or earlier if substantial data become available increasing the knowledge on safety, toxicity and efficacy (e.g. post marketing studies, on-going trials and studies)

* In this situation no recommendation could be reasonable

V. Expert Group Recommendation

In response to the PICO question: "***In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendations safely improve patient outcomes?***" the Expert Group formulated the following recommendation based on the available evidence:

Recommendation:

The Expert Group 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 effects)*:
- when an effective treatment regimen containing 4 second-line drugs from the different classes of drugs according to WHO-recommendations cannot be designed;
- when there is documented evidence of resistance to any fluoroquinolone in addition to MDR.

In addition, the Expert Group recommends that:
- a duly informed decision making-process by patients should be followed;
- bedaquiline be used with caution in persons living with HIV infection, as well as in patients with co-morbidities (such as diabetes) or persons with drug or alcohol abuse, due to limited or no information;
- bedaquiline be used for a maximum duration of 6 months and at suggested dosing (400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks):
- bedaquiline must not be added alone to a failing regimen;
- a duly informed decision making-process by patients should be followed;
- 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;[11]
- in the absence of a specific drug-susceptibility test, resistance to bedaquiline should be monitored through assessment of Minimum Inhibitory Concentrations (MICs);
- resistance to other anti-TB drugs should be monitored following WHO recommendations.

The Expert Group also recommended that this interim recommendation be re-assessed in 2015, or earlier if substantial data become available increasing the knowledge on safety, toxicity and efficacy of the drug.

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

VI. RESEARCH GAPS

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

- Development of a reliable drug susceptibility test for bedaquiline resistance;
- Pharmacokinetics, safety and efficacy studies in specific populations (infants and children, HIV patients – especially those on ART, alcohol and drug users, elderly persons, pregnant or nursing women, persons with extrapulmonary TB, persons with diabetes;
- Safety studies, including type; frequency and severity of adverse events (short term and long term), and mortality (including cause of death);
- Drug-drug interactions, including with other existing and newly developed TB drugs and ARVs;
- Acquisition of resistance to bedaquiline and to other TB drugs;
- Duration and dosing of treatment;
- Patient acceptability.

ANNEXES

Annex 1.   List of participants

Annex 2.   Agenda of the meeting

Annex 3.   Declaration of interests and resolution

Annex 4.   The contribution of bedaquiline to the treatment of MDR-TB – synthesis of
                publicly available evidence (Bernard Fourie, South Africa)

Annex 5.   Evaluation of sputum culture conversion as a surrogate marker of MDRTB
                treatment outcome (Ekaterina Kurbatova et al, CDC, Atlanta, GA, USA)

Annex 6.   Cost-effectiveness of introducing bedaquiline in MDR-TB regimens – an
                exploratory analysis (Anna Vassall, LSHTM, London, UK)