Appendix 2: GRADE Evidence to Decision framework for clinical recommendations

An interactive version of this framework which includes subgroup information can be found at http://ietd.epistemonikos.org/#/frameworks/54992ce9352a502d58179c5c/question and at http://dbep.gradepro.org/profile/3879A46D-7E19-4EBA-9B96-BC2B3F996EB1

Appendix 2: GRADE Evidence to Decision framework

(Clinical recommendations – Population perspective)

1. Should bedaquiline be added to a background regimen of drugs recommended by WHO for patients with MDR-TB?

QUESTION

Question details

Patients: Multidrug-resistant tuberculosis (MDR-TB)
Option: Bedaquiline + background MDR-TB treatment
Comparison: Background MDR-TB treatment alone (regimen of drugs recommended by WHO)
Main outcomes: cured by end of study, serious adverse events, mortality, time to conversion, culture conversion at end of treatment and acquired resistance to other drugs.
Setting: Global, MDR-TB clinics
Perspective: Population
Conflicts of interest: the panel reported that all panellists declared either minor or no conflicts of interest

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 they require the daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible TB.
ASSESSMENT

Problem

Is the problem a priority?

Judgment

- Don’t know
- Varies
- No
- Probably No
- Probably Yes
- Yes

Research evidence

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].

Desirable effects

How substantial are the desirable anticipated effects?

Judgment

- Don’t know
- Varies
- Trivial
- Small
- Moderate
- Large
Research evidence

Summary of findings: Bedaquiline for multidrug-resistant tuberculosis (See an interactive version here) (Adapted from The Use of Bedaquiline in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance. Geneva: World Health Organization; 2013. [2])

Participants: Multidrug-resistant tuberculosis (MDR-TB)
Intervention: Bedaquiline + background MDR-TB treatment
Comparison: Background MDR-TB treatment alone (regimen of drugs recommended by WHO)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Plain language statements</th>
<th>Absolute Effect</th>
<th>Relative effect</th>
<th>Certainty of the evidence</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured by end of study</td>
<td>Bedaquiline may increase the number of patients cured.</td>
<td>32/100 vs 58/100</td>
<td>RR: 1.81 (1.29 to 2.48)</td>
<td>Based on data from 132 patients in 1 study</td>
<td>610 patients, 24 weeks</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>It is uncertain whether bedaquiline increases the number of patients who have adverse effects.</td>
<td>2/100 vs 7/100</td>
<td>RR: 3.6 (1.77 to 7.5)</td>
<td>Based on data from 132 patients in 1 study</td>
<td>610 patients, 24 weeks</td>
</tr>
<tr>
<td>Mortality</td>
<td>It is uncertain whether bedaquiline increases the number of patients who die.</td>
<td>1/100 vs 11/100</td>
<td>RR: 9.3 (1.2 to 75)</td>
<td>Based on data from 132 patients in 1 study</td>
<td>610 patients, 24 weeks</td>
</tr>
<tr>
<td>Time to conversion</td>
<td>Bedaquiline may decrease the time to conversion.</td>
<td>Median 62 days less (from 125 days without bedaquiline to 63 days with bedaquiline)</td>
<td>-</td>
<td>-</td>
<td>610 patients, 24 weeks</td>
</tr>
<tr>
<td>Culture conversion at end of treatment phase</td>
<td>Bedaquiline may increase the number of patients with a negative culture at the end of the treatment phase.</td>
<td>58/100 vs 79/100</td>
<td>RR: 1.37 (0.97 to 1.9)</td>
<td>Based on data from 132 patients in 1 study</td>
<td>610 patients, 24 weeks</td>
</tr>
<tr>
<td>Acquired resistance to other drugs</td>
<td>It is uncertain whether bedaquiline reduces the number of patients with acquired resistance to other drugs.</td>
<td>25/100 vs 19/100</td>
<td>RR: 0.83 (0.7 to 0.94)</td>
<td>Based on data from 132 patients in 1 study</td>
<td>610 patients, 24 weeks</td>
</tr>
</tbody>
</table>

Undesirable effects

How substantial are the undesirable anticipated effects?

Judgment

- Don’t know
- Varieties
- Large
- Moderate
- Small
- Trivial

Research evidence

See summary of findings table above
**Certainty of the evidence**

What is the overall certainty of the evidence of effects?

**Judgment**

<table>
<thead>
<tr>
<th>No included studies</th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
</table>

**Research evidence**

See summary of findings table above

**Values**

Is there important uncertainty about, or variability in, how much people value the main outcomes?

**Judgment**

<table>
<thead>
<tr>
<th>Important uncertainty or variability</th>
<th>Possibly important uncertainty or variability</th>
<th>Probably no important uncertainty or variability</th>
<th>No important uncertainty or variability</th>
</tr>
</thead>
</table>

**Research evidence**

No evidence found.

**Additional considerations**

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.
**Balance of effects**

*Does the balance between desirable and undesirable effects favour the option or the comparison?*

<table>
<thead>
<tr>
<th>Judgment</th>
<th>Don’t know</th>
<th>Varies</th>
<th>Favours the comparison</th>
<th>Probably favours the comparison</th>
<th>Does not favour either the option or the comparison</th>
<th>Probably favours the option</th>
<th>Favours the option</th>
</tr>
</thead>
</table>

**Research evidence**

See summary of findings table above

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**Resources required**

*How large are the resource requirements (costs)?*

<table>
<thead>
<tr>
<th>Judgment</th>
<th>Don’t know</th>
<th>Varies</th>
<th>Large costs</th>
<th>Moderate costs</th>
<th>Negligible costs or savings</th>
<th>Moderate savings</th>
<th>Large savings</th>
</tr>
</thead>
</table>

**Research evidence**

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.
**Certainty of evidence of required resources**

What is the certainty of the evidence of resource requirements (costs)?

<table>
<thead>
<tr>
<th>Judgment</th>
<th>No included studies</th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
</table>

**Research evidence**

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].

**Cost-effectiveness**

Does the cost-effectiveness of the option favour the option or the comparison?

<table>
<thead>
<tr>
<th>Judgment</th>
<th>Don’t know</th>
<th>Varies</th>
<th>Favours the comparison</th>
<th>Probably favours the comparison</th>
<th>Does not favour either the option or the comparison</th>
<th>Probably favours the option</th>
<th>Favours the option</th>
</tr>
</thead>
</table>

**Research evidence**

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.

**Additional considerations**

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.

**Equity**

**What would be the impact on health equity?**

**Judgment**

<table>
<thead>
<tr>
<th>Don't know</th>
<th>Varies</th>
<th>Reduced</th>
<th>Probably reduced</th>
<th>Probably no impact</th>
<th>Probably increased</th>
<th>Increased</th>
</tr>
</thead>
</table>

**Research evidence**

No evidence found.

**Additional considerations**

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 to XDR patients could increase equity.

**Acceptability**

**Is the option acceptable to key stakeholders?**

**Judgment**

<table>
<thead>
<tr>
<th>Don’t know</th>
<th>Varies</th>
<th>No</th>
<th>Probably No</th>
<th>Probably Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

**Research evidence**

No evidence found.

**Additional considerations**

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.
**Feasibility**

Is the option feasible to implement?

**Judgment**

<table>
<thead>
<tr>
<th></th>
<th>Don't know</th>
<th>Varies</th>
<th>No</th>
<th>Probably No</th>
<th>Probably Yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

**Research evidence**

No evidence found.

**Additional considerations**

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.

**CONCLUSIONS**

**Type of recommendation**

<table>
<thead>
<tr>
<th>Strong recommendation against the option</th>
<th>Conditional recommendation against the option</th>
<th>Conditional recommendation for either the option or the comparison</th>
<th>Conditional recommendation for the option</th>
<th>Strong recommendation for the option</th>
</tr>
</thead>
</table>

**Recommendation**

The panel suggests adding bedaquiline to a WHO recommended regimen in MDR-TB adult patients under the following conditions (conditional recommendation, very low certainty of the evidence):

- An effective treatment regimen containing four recommended second line drugs in addition to pyrazinamide, according to WHO-recommendations, cannot be designed
- There is documented evidence of resistance to any fluoroquinolone in addition to MDR

In addition:

- 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 use, due to limited or no information.
- Bedaquiline should be used for a maximum duration of six months with suggested doses (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.
- In the absence of a specific bedaquiline DST assay, resistance to bedaquiline should be monitored through assessment of Minimum Inhibitory Concentrations (MICs).

**Justification**

Given the important potential harms and the uncertainty about both the benefits and the harms of bedaquiline, the panel concluded that most patients would choose not to take bedaquiline. However, for patients with extensively drug-resistant (XDR) TB and limited, if any other options, the panel concluded that most patients would choose to take bedaquiline.

The recommendation is a conditional recommendation that should only be implemented for a very specific subpopulation under very specific circumstances. The recommendation is also provisional, as the panel decided to revise it in 2015 or earlier, if new data become available regarding the safety and effectiveness of bedaquiline (from post marketing studies and on-going trials and studies).
Detailed justification

Desirable effects: More patients were successfully treated (cured by the end of the study) with bedaquiline compared to without (26 more per 100; 95% CI 8 to 42 more).

Undesirable effects: There were more deaths (10 more per 100; 95% CI 0 to 53 more) and more serious adverse events (5 more; 95% CI 0 to 25 more) with bedaquiline compared to without.

Certainty of the evidence: There was very low certainty of the evidence for mortality and serious adverse events, and low certainty of the evidence for successful treatment (cure by the end of the study) due to imprecision (a small sample size and few events), risk of bias (inappropriate exclusion of 19 randomized patients), and use of a surrogate outcome (culture conversion).

Values: 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.

Balance of effects: For patients with newly diagnosed MDR-TB, the increase in treatment success (cure by the end of the study) 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 (XDR) tuberculosis and limited, if any other options, the desirable effects probably outweigh the undesirable effects.

Subgroup considerations

Bedaquiline is only suggested for patients with extensively drug-resistant (XDR) TB under the specified conditions.

Implementation considerations

- A process to ensure informed decision-making by patients should be established.
- Equipment for baseline testing and monitoring for QT prolongation and development of arrhythmia should be available.
- Monitoring of cardiac and liver disease should be available.

Monitoring and evaluation

- Spontaneous reporting of adverse drug reactions should be reinforced at country level and active pharmacovigilance should be established among patient groups treated with the drug.
• Resistance to bedaquiline should be monitored.
• Resistance to other anti-TB drugs should be monitored following WHO recommendations.

Research priorities
• 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
• Impact on mortality (including cause of death)
• Acquisition of resistance to bedaquiline and to other TB drugs
• Duration and dosing of treatment
• Patients' values
• Further research on the validity of culture conversion as a surrogate marker of treatment outcome
**EVIDENCE PROFILE**

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


<table>
<thead>
<tr>
<th>Evidence assessment</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty (quality) of the evidence</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of studies</td>
<td>Design</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
</tr>
<tr>
<td>Subjects Cured by end of study: Follow up 120 weeks (C208 Stage 2: mITT)</td>
<td>1</td>
<td>randomized trials</td>
<td>Not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Serious Adverse Events during investigational 24 week treatment phase (C208 Stages 1 and 2: ITT)</td>
<td>2</td>
<td>randomized trials</td>
<td>Not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Mortality up to end of study at 120 weeks (C208 Stage 2: ITT)</td>
<td>1</td>
<td>randomized trials</td>
<td>Not serious</td>
<td>not serious</td>
</tr>
<tr>
<td>Time to conversion over 24 weeks (C208 Stage 2: mITT)</td>
<td>1</td>
<td>randomized trials</td>
<td>Not serious</td>
<td>not serious</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1</th>
<th>randomized trials</th>
<th>Not serious</th>
<th>Not serious</th>
<th>Not serious</th>
<th>Not serious</th>
<th>very serious</th>
<th>very serious</th>
<th>none</th>
<th>none</th>
<th>n=66</th>
<th>n=66</th>
<th>median=83 days</th>
<th>median=125 days</th>
<th>median 42 days lower</th>
<th>LOW</th>
<th>LOW</th>
<th>CRITICAL</th>
</tr>
</thead>
</table>

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

<table>
<thead>
<tr>
<th>1</th>
<th>randomized trials</th>
<th>Not serious</th>
<th>Not serious</th>
<th>Not serious</th>
<th>Not serious</th>
<th>very serious</th>
<th>very serious</th>
<th>none</th>
<th>none</th>
<th>n=66</th>
<th>n=66</th>
<th>median=83 days</th>
<th>median=125 days</th>
<th>median 42 days lower</th>
<th>LOW</th>
<th>LOW</th>
<th>CRITICAL</th>
</tr>
</thead>
</table>

Acquired resistance to fluoroquinolones, aminoglycosides or capreomycin at 72 weeks (C208 Stage 2: mITT) [assessed with: Microbiological endpoints]

<table>
<thead>
<tr>
<th>1</th>
<th>randomized trials</th>
<th>Serious</th>
<th>Not serious</th>
<th>Not serious</th>
<th>Not serious</th>
<th>very serious</th>
<th>very serious</th>
<th>none</th>
<th>none</th>
<th>n=66</th>
<th>n=66</th>
<th>median=83 days</th>
<th>median=125 days</th>
<th>median 42 days lower</th>
<th>LOW</th>
<th>LOW</th>
<th>CRITICAL</th>
</tr>
</thead>
</table>

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. Raw data is used for the mortality at 120 weeks in BDQ and placebo groups (reference document numbers have been corrected here).

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

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)

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

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

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.

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

REFERENCES
