COST –EFFECTIVENESS OF INTRODUCING BEDAQUILINE IN MDR-TB REGIMENS – A EXPLORATORY ANALYSIS

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INTRODUCTION

The landscape of drug development for treatment of tuberculosis (TB) has evolved dramatically over the last ten years. A series of Phase II and III trials of shortened treatment of drug-susceptible (DS) TB including repurposed drugs (e.g. fluoroquinolones) or new dosages of known drugs (e.g. rifamycins, rifapentine) are presently on-going, with earliest results expected in 2013/14. For the first time in nearly 50 years, two new molecular entities proposed for the treatment of multidrug-resistant (MDR) TB are currently making their way through the regulatory pathway in the European Union (EU) and the United States of America (US). These two novel drugs are presently in Phase IIb and III trials for the treatment of multidrug-resistant MDR-TB and dossiers have been submitted for registration by these regulatory authorities. Therefore, regulators in other countries will soon face the decision whether to approve these drugs for treatment of pulmonary MDR-TB. Additionally, other new compounds and novel combinations of drugs are being investigated for the treatment of drug-susceptible and/or MDR/XDR-TB. Treatment shortening regimens, as well as substitution compounds for existing regimens, are being investigated.

The World Health Organisation (WHO) Stop TB Department has recently set-up a process to guide development of policy guidance aiming at rational introduction and use of new TB drugs. WHO aims to pursue development of guidance based on all available data, including evidence on cost-effectiveness (CEA), on any new drugs and drug combinations. In December 2012, new data from a Phase IIb became available on a new product, Bedaquiline. WHO intends to convene an Expert Group to review the evidence about this drug and provide advice to WHO in early 2013. This meeting will focus on the role of Bedaquiline in the treatment of MDR-TB and whether current guidelines on the treatment of MDR-TB need to be updated or supplemented with provisional guidance. This short report was commissioned by the WHO to carry out a preliminary cost-effectiveness analysis of Bedaquiline based on the data from the Phase IIb trial and previous literature on the costs, and cost-effectiveness of the treatment of MDR-TB.

Although Bedaquiline is additional (rather than a substitute) to the WHO recommended MDR-TB drug regimen, and therefore will increase MDR-TB regimen costs, the Phase IIB trial has demonstrated improved efficacy - so any increased cost may be balanced out by its benefits, in terms of cost-effectiveness. Moreover, should Bedaquiline reduce treatment duration and the numbers of TB patients failing or defaulting, it may also reduce the cost of MDR-TB drugs and treatment overall. This report therefore aims to appraise the cost-effectiveness of adding Bedaquiline to existing WHO-recommended MDR-TB regimens, for various representative settings that allow for variation among countries in income level, the model of care used for MDR-TB treatment, and background patterns of drug resistance.

OBJECTIVES

The objective of this report is to inform the decision of the Expert group, through estimating the likely costs and effectiveness of Bedaquiline – and the pathways through which these may be incurred. The Cost-Effectiveness Analysis (CEA) is conducted from a TB programme perspective and focuses on the direct benefits to patients, rather than any indirect (and acquired) transmission benefits. It also excludes any broader economic benefits to patients. It is important to note from the start that this approach was taken purely for pragmatic (time constraint) reasons rather than scientific reasons. It is a *highly conservative* approach, as it is plausible that Bedaquiline may have additional benefits both to the wider health system, the economic conditions of patients and prevent the on-going transmission of TB.

Despite its limits however this approach can still inform decision makers – by highlighting where MDR-TB is highly likely to be cost-effective – particularly in the context of the general lack of any evidence base on the Cost-Effectiveness Analysis (CEA) of new MDR drugs at this current time.

TREATMENT STRATEGIES

The cost-effectiveness of two alternative MDR-TB treatment strategies is compared:

a. Current practice of MDR-TB treatment (hereafter referred to as the base case)
b. The addition of Bedaquiline to the base case (24 week regimen)

The analysis is conducted for 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 practices, and MDR-TB prevalence. A summary of the main characteristics of each base case can be found in Table 1 below for both the trial and the different country settings.

TABLE 1 - SUMMARY OF BASE CASE INTERVENTION[1]

	RUSSIA (TOMSK)	ESTONIA	THE PHILIPPINES	PERU	CHINA	NEPAL
REGIMEN	Individualised	Individualised	Individualised	Standardised	Standardised	Standardised
LOCATION FOR DOT	Hospital ward, health clinic	Hospital ward, health clinic	Clinic and patients home	Clinic	Hospital and clinic	Clinic
HOSPITALISATION DURING TREATMENT	Yes, lengthy (average 192 days)	Yes lengthy (average 239 days)	Limited (average 7 days)	None	Yes, around 60 days	None

METHODS

MODEL STRUCTURE

A decision analytic model is used to estimate the costs and benefits for a cohort of MDR-TB patients in a variety of different settings. The model divides treatment into four periods (0-6 months, 6-8 months, 8-18 months, 18-20 months cycles), and at the end of each time period MDR-TB patients either continue on treatment/cure, default, fail treatment, or die. In the early time periods (6/8 months) it is not possible to be cured – just to default, die or continue on treatment. MDR-TB patients who convert are allowed to fail thereafter. MDR-TB patients who fail treatment at the end of a completed cycle continue on one further cycle of MDR-TB retreatment – thereafter they become chronic cases. MDR-TB patients are followed in the model until they either cure or die.

Broadly the parameterization of the model in terms of long-term outcomes post treatment follows past models of cost-effectiveness in order to allow for some comparability of results[1]. Probabilities of death of a chronic case and defaults are shown in Table 2, along with other key model parameters. These parameters were directly sourced from the previous studies of cost-effectiveness[2-4]. It should be noted however that the original data on which these were based is limited. Most were estimated from results reported in a paper by Goble et al[5] examining the long term outcomes of a cohort of 171 MDRTB patients in the US on treatment between 1973 and 1983. More recently a study by Chan et al[6] showed improved longer term outcomes – but study cohort was US based and has limited generalisability to other settings – given the probable dependence of outcomes on the availability and type of continuing MDR-TB treatment. An upper bound of 99% of long term death rates of defaults and chronic cases was therefore also applied in the uncertainty analysis.

It should also be noted that the model structure does not allow defaulters to return once they have left treatment. This structure has no effect in the primary estimates of cost-effectiveness however, as Bedaquiline is assumed to not impact on the default rate (despite the reduced default rate observed during the Phase II trial (see below)). Defaulters who leave have a 60% probability of death reflecting a possible future return to TB services. This probably of death is not impacted by prior MDR-TB treatment. This is a conservative assumption – in the absence of empirical evidence - as early conversion may increase the cure rate of defaulters.

TABLE 2 – MODEL PARAMETERS (EXCLUDING COSTS AND OUTCOMES)

	Parameters						
	Distribution	Tomsk	Estonia	Philippines	Peru	China	Nepal
Chronic death rate	Uniform	60%, 99%	60%, 99%	60%, 99%	60%, 99%	60%, 99%	60%, 99%
Default death rate	Uniform	60%, 99%	60%, 99%	60%, 99%	60%, 99%	60%, 99%	60%, 99%
Long term relapse rate	Normal	14% (4)	14% (4)	14% (4)	14% (4)	14% (4)	14% (4)
Long term relapse death rate	Uniform	100%	100%	100%	100%	100%	100%
DALYS per death averted	Normal	21.5 (3.3)	17.8 (3.3)	21.5 (3.3)	27.9 (3.3)	26.5 (3.3)	26.5 (3.3)

The metric used to describe cost effectiveness is the cost per DALY averted. Total costs and disability adjusted life years (DALYs) are measured for each alternative treatment strategy and compared. Conservatively DALYS averted are only gained from deaths averted. The DALYs used are the values in the original studies on the CEA of MDR-TB. Future versions of the model will also examine gains in terms of a reduction in morbidity; and update these values. This however is not anticipated to change results fundamentally. As above, this is a conservative approach – as the DALYs associated with TB are likely to have increased since the previous studies. The disability weights for TB have increased, as have the life expectancies in several countries studies. This means that DALYs averted by curing a case of TB have increased over time.

In order to be transparent about the potential cost-effectiveness of Bedaquiline, given the limitations of the evidence from Phase IIb trials – and the limited evidence on the relationship between time to culture conversion, sterilization and eventual cure - a phased approach is taken to the modeling.

The main estimate assumes no additional benefits (including cost savings) from a potential shortening of the MDR-TB treatment regimen. This first model simply takes into account the additional costs of Bedaquiline, and any extra monitoring and the potential from increased efficiency – as reported in the Phase IIb (C208) trial (hereafter referred to as the **Bedaquiline alternative**). It also includes any potential cost savings in terms of a reduction in costs associated with the retreatment of MDR-TB treatment failures.

A second more speculative model including potential costs and benefits from shortening the intensive phase of the MDR-TB regimen (hereafter referred to as **Bedaquiline (with shortening) alternative**) is then explored. 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. Bedaquiline (with shortening) models a reduction in treatment duration of 2 months to illustrate this potential.

The choice about the length of shortening was made by comparing the median time to culture conversion during the first 24 week period of the C208 (phase 2) trial between the placebo and Bedaquiline arms. The maximum possible shortening was taken in order to

best illustrate the potential impact on cost-effectiveness. However, C208 reports several possible results in relation to time to conversion. A 40 day reduction is presented in the primary analysis of efficacy performed when all subjects had completed their 24-week treatment with Bedaquiline or placebo (or had discontinued earlier) (i.e., with subjects who discontinued during the 24-week period being considered as not converted or their time to culture conversion assigned to the last MGIT culture result). In addition, two other estimates were made. The first, (no overruling for discontinuation) finds a difference of 27 days between the Bedaquiline and placebo arms, the other that assumes that missing subjects are treatment failures finds a slightly higher difference of 52 days. It should be noted that it may be possible to provide Bedaquiline for a longer period and shorten the overall MDR-TB regimen further, but this option is not explored here.

The Bedaquiline alternatives also assume no negative impact on adverse events – apart from the necessity to monitor potential QT prolongation. This assumption is made on the basis of the pooled analysis of the C208 trials that found that overall the frequency of adverse events leading to discontinuation of treatment was balanced between arms. However it should be noted that a higher incidence of serious adverse events was found in the Bedaquiline group (6.9%) compared to (1.9%) in the control group of the trials. This difference was probed and a higher incidence of hepatic disorders was found in the Bedaquiline group (8.8%) vs (1.9%) in the control group, due to the elevation of transaminases. Moreover, the analysis of adverse drug reactions in C208/ C209 found an increase in QT prolongation, and a higher incidence of headache and arthralgia.

PARAMETER SOURCES

Costs

Cost data for the base case in each country was sourced from published studies (Fitzpatrick 2012), with additional supplementary data provided by study authors. Cost data for China and Nepal was provided by the Stop TB department of the WHO.

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 (ECG) were added. The unit costs for the ECGs were sourced from WHO-Choice.

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 drugs costs were adjusted to take into account reductions in hospitalization and required length of

second-line parental 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.

All costs were considered to have uniform distributions. For the base case lower and upper bounds allowed were 10% higher and lower than the point estimates. For Bedaquiline, prices were allowed to vary between US$800-US$1000 and US$1000-US5000 for a complete regimen.

Base case outcomes

The outcomes for the Philippines, Estonia, Russia and Peru were taken from published studies (Tupasi 2006, Floyd 2012 and Suarez 2002). However, it should be noted that these studies report on different MDR-TB cohorts, in terms of previous treatment history. In Peru, outcomes are reported for a cohort of all chronic cases. Likewise the majority of cases in The Philippines study were chronic (77%). Tomsk (Russia) also reports on a mix of chronic, new and re-treatment cases, and Estonia on a cohort of new and retreatment only.

Orenstein (2009) finds no difference in treatment success in a pooled analysis comparing cohorts with less or more than 75% of previously treated cases – but does not specifically analyse how the proportion of chronic cases impacts treatment outcomes. Given the dearth of evidence in this area, we consider outcome estimates for the whole cohort as our 'likeliest' estimates of base case outcomes. However where data is reported by sub-categories of previous treatment history, differences in % of chronic, retreated and new cases are included in our probabilistic sensitivity analysis; using a triangular distribution.

No previous published cost-effectiveness studies were available for China and Nepal, therefore two systematic reviews of MDR-TB outcomes (Johnston 2009 and Orenstein 2009) were used to estimate outcomes[1]. Neither review found any studies from either Nepal or China. However Orenstein (2009) estimates means (and standard deviations) for standardized treatment and these (normal distributions) were used to estimate current outcomes for China and Nepal.

Where outcomes over time were not known (for the base case), deaths and defaults over time were estimated assuming they followed the same pattern as in Peru.

For Tomsk, Estonia and the Philippine MDR retreatment was assumed to have the same outcomes as the initial MDR-TB treatment. As Peru, China and Nepal all use standardized

[1] Future estimates will include the outcomes of on-going studies in both countries supported by the WHO

MDR-TB treatment, retreatment was assumed to have a higher cure rate – due to the assumed use of an individualized regimen.

TABLE 3 – BASE CASE INITIAL MDR TREATMENT AND MDR RETREATMENT OUTCOMES

	Initial MDR Treatment						MDR Retreatment					
	Tomsk	Estonia	Philippines	Peru	China	Nepal	Tomsk	Estonia	Philippines	Peru	China	Nepal
Cure/ Success	76%	61%	61%	49%	54%	54%	76%	61%	61%	62%	64%	64%
Failure	12%	9%	10%	28%	23%	23%	12%	9%	10%	16%	6%	6%
Default	8%	17%	14%	11%	12%	12%	8%	17%	14%	12%	12%	12%
Death	4%	13%	15%	12%	11%	11%	4%	13%	15%	10%	11%	11%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**93%**	**93%**

Bedaquiline outcomes

Bedaquiline outcomes were sourced from C208 trial data. The FDA submission for Bedaquiline reports on sputum culture conversion. However in order to apply the results to other settings where cohort outcomes are reported in terms of WHO defined outcomes, some adjustments needed to be made. Statisticians at Janssen supplied a summary of outcomes in terms of WHO guidelines (cure defined as 5 consecutive negative results) at three times points: 72 weeks, 78-82 weeks, and 120 weeks. For the six month and eight month periods in the model, outcomes (in terms of those continuing, death and defaults) were sourced from the FDA submission. The 78-82 outcomes were used for the 18 month time point (in addition a sensitivity analysis was conducted using the 72 week data). The 120 week data was used to estimate outcomes at 20 months.

TABLE 4 - TREATMENT OUTCOMES BEDAQUILINE CASE (CONVERTED DEFAULTERS CATEGORISED AS FAILURES 18/20 MONTHS)

	Bedaqualine				Placebo			
	6 months	8 months	18 month	20 months	6 months	8 months	18 month	20 months
Continue (6/8 months)/ Cure (18/20 months)	79%	73%	61%	58%	58%	61%	38%	32%
Failure	0%	0%	8%	8%	0%	0%	26%	30%
Default	20%	24%	26%	26%	42%	39%	35%	36%
Death	2%	3%	6%	9%	0%	0%	2%	2%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

It can be seen from the Table 4 above, that the placebo arm performs poorly compared to base case in all the countries being modeled. In part this may be due to the high number of defaulters associated with the heavier than normal treatment monitoring associated with

being enrolled in a trial. Some of these defaulters converted prior to default. If these are included in the cure rate then Table 5 shows the outcomes. Both arms of the trial perform better, but the difference between arms declines slightly.

TABLE 5 - TREATMENT OUTCOMES BEDAQUILINE CASE (CONVERTED DEFAULTERS CATEGORISED AS CONTINUE/CURE 18/20 MONTHS)

	Bedaqualine				Placebo			
	6 months	8 months	18 month	20 months	6 months	8 months	18 month	20 months
Continue (6/8 months)/ Cure (18/20 months)	79%	74%	71%	68%	65%	70%	56%	50%
Failure	0%	0%	8%	8%	0%	0%	26%	30%
Default	20%	23%	15%	15%	35%	30%	17%	18%
Death	2%	3%	6%	9%	0%	0%	2%	2%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

Estimates of the potential incremental cure rate were made using a triangular distribution taking a mid-point between these two estimates above.

Applying these outcomes to the base case requires an assumption to be made on whether the trial results can be generalized to settings with different health systems, patient and base case characteristics. To reflect the uncertainty around generalisation – three alternative ways of estimating the incremental effect on the underlying base case performance were used to arrive at estimates of incremental cost-effectiveness. These are:

a) That Bedaquiline increases the underlying base case cure rate ***additively*** by the % difference in cure rate in the Bedaquiline and control arms. This implicitly assumes that Bedaquiline will always cure a set proportion of those treated in addition to the base case, independently of whether the base case is a standardized or individualized regimen.
b) That Bedaquiline increase the underlying base cure rate ***proportionally*** by the % difference in cure rate in the Bedaquiline and control arms. This implicitly limits the effect of Bedaquiline, to reflect possible health systems constraints. ie a low cure rate reflects a capacity constraint. However, when examining these results it should also be taken into account that lower base case effectiveness may be primarily driven by standardized treatment, rather than health systems constraints.
c) That there is a maximum ***limiting*** cure rate of 80% ever possible and Bedaquiline cannot improve cure beyond this.

It should be noted that in each scenario, the base case default rate is assumed to remain unaffected by Bedaquiline – and any increase in cure results in reductions of both the numbers of treatment failures and deaths. The plausibility of each of the above assumptions can be argued – however the intention of adopting this approach is to highlight to the WHO expert panel – the consequences of different views in this regard.

Finally, it is conceivable that Bedaquiline may have an impact on the proportions of those who do not cure, who either die, default or failure. In particular Bedaquiline was found to have a higher death rate and lower default rate in the C208 trial than the placebo arm. A further analysis is therefore also conducted to examine how a direct application of the trial results including an impact on death and default may impact cost-effectiveness (***additive/ C208 results)***. While the model is complex – as these rates are applied at different points in treatment – a simple illustration of this approach is shown in Table 6 below. This shows the simple additive approach and the additive/C208 approach for 20 month outcomes for Peru.

TABLE 6 - TREATMENT OUTCOMES APPLIED TO THE PERU BASE CASE (AT 20 MONTHS).

	Cure only			Cure/deaths/default		
	Base	**Bed**	**Bed S**	**Base**	**Bed**	**Bed S**
Cure	48%	70%	67%	48%	70%	67%
Failure	28%	13%	16%	28%	5%	9%
Default	12%	12%	11%	12%	5%	4%
Death	12%	5%	5%	12%	20%	20%
Total	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**

COST-EFFECTIVENESS ANALYSIS

The cost-effectiveness ratio is calculated for each strategy using each model. Where one strategy is more costly and more effective than the other, an **incremental cost-effectiveness ratio** (ICER) is calculated. In simple terms this informs decision makers on how much Bedaquiline buys them in US$ per DALY averted. For example an ICER of US$100 means that an extra DALY averted through Bedaquiline will cost US$100.

To establish cost-effectiveness, this ICER is compared against a willingness to pay (WTP) ratio. There is much academic debate around the appropriate levels of WTP for low and middle income countries. However, this study used one Gross National Income (GNI) per capita. This is the level recommended by the Commission on Macro-economics and Health and similar to the recommendation by WHO-CHOICE[7]. The GNI per capita for China is US$4920; Estonia, US$15260; Nepal, US$540; Peru, US$5150; Philippines, US$2210; and Russia, US$10730. Cost-effectiveness ratios are estimated using a 3% discount rate (rate used to value costs over time) - and all data are presented in US$ 2012.

SENSITIVITY ANALYSIS

To test the robustness of the cost-effective ratios to the structural assumptions made, a number of one and multi-way sensitivity analyses were conducted. Due to time constraints these were limited to:

a) The price of Bedaquiline
b) The assumption that one round of retreatment is provided
c) The extent of hospitalization averted

Other structural assumptions that may impact results are the assumptions made about long term outcomes and the levels of default and death at different periods during treatment. Due to time constraints, these results also do not currently include a probabilistic sensitivity analysis – which accounts for uncertainty in model parameterization (presenting upper and lower bounds for ICERS –rather than the point estimates below). All analyses were conducted using Treeage (Williamtown, USA) and Excel. No ethical approval was required for this analysis, as only secondary data was used.

SUMMARY OF RESULTS

When assessing the results of this study, it is important that readers note that, while the conservative approach described above is highly robust when it finds Bedaquiline to be cost-effective, it does not establish the converse. Any situation where Bedaquiline is not found to be cost-effective using these methods – does not mean Bedaquiline is not cost-effective. It should rather be seen as an area that requires further modeling/data in order to establish cost-effectiveness (or not). Moreover the absolute values in terms of ICERs may substantially under-represent the true cost-effectiveness of Bedaquiline.

Tables 7-9 below summarise the findings for the six countries using different assumptions about the application of the trial results. Thereafter further tables outlining the findings of the sensitivity analysis are presented. On the basis of these, the following section briefly summarises the main study results and interpretation.

A. Bedaquiline is highly likely to be cost-effective in most environments – for a wide range of assumptions about the translation of trial results to current practice.
B. In some environments it 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)[2]. This cost reduction will be strongest in environments which have high MDR-TB treatment costs.
C. The incremental effectiveness of Bedaquiline does not vary substantially by setting – unless the base case has high cure rates (Russia).
D. 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.
E. The impact of Bedaquiline on costs will depend on price and the cost savings from retreatment. This latter 'savings' effect will benefit countries either with higher retreatment costs or high current levels of treatment failures.
F. The cost-effectiveness of Bedaquiline is ambiguous in low income countries like Nepal, with much lower willingness to pay thresholds. Further work is required in low income settings to fully take into account transmission and patient cost consequences.
G. The possible effect of treatment shortening does not substantially impact the above conclusions or results – although in some cases costs may be reduced. DALYs averted (excluding transmission consequences) may also be reduced -

[2] The conclusion is also substantiated by the first attempt at the model – which only allowed Bedaquiline to impact failure rather than default rates. This found higher cost savings than the final results below. The results below – which allow for Bedaquiline to reduce deaths result in higher levels of effectiveness.

depending on the extent to which shortening reduces defaults compared to the slightly lower cure rates.

H. High end prices reduce cost-effectiveness. However, in no setting do they bring the ICER above the WTP threshold. In the case of Russia however they can make the difference between Bedaquiline as a potentially cost-saving to a cost-effective intervention and the base case scenario.

I. Removing the option of retreatment for MDR-TB can improve cost-effectiveness – as more of those who otherwise die will be cured.

J. No hospitalization has an impact on cost-effectiveness - but does not change the central findings on cost-effectiveness above. In countries with higher hospitalization costs, less cost savings are made.

TABLE 7 – UNIT COSTS PER PATIENT TREATED: BASE, BEDAQUILINE AND SHORTENED BEDAQUILINE (US$2012)

	Base Case						Bedaqualine no- shortening						Bedaqualine shortening					
	Tomsk	**Estonia**	**Philippines**	**Peru**	**China**	**Nepal**	**Tomsk**	**Estonia**	**Philippines**	**Peru**	**China**	**Nepal**	**Tomsk**	**Estonia**	**Philippines**	**Peru**	**China**	**Nepal**
Drugs	4542	2711	1959	592	1994	1737	5442	3611	2859	1492	2894	2637	4966	3318	2641	1411	2673	2441
Hospital stays	7295	6527	131	301	434	0	7295	6527	131	301	434	0	5472	4895	98	225	326	0
Clinic visits	230	1292	142	716	119	36	230	1292	142	716	119	36	230	1292	142	663	119	32
Laboratory tests/ X-rays/ ECGs	478	453	258	145	673	46	497	491	259	164	689	46	497	491	259	164	689	46
Other	4268	1532	1670	1036	5411	476	4268	1532	1670	1036	5411	476	4268	1532	1670	1036	5411	476
Total	**16879**	**12529**	**4161**	**2790**	**8632**	**2294**	**17798**	**13468**	**5061**	**3709**	**9548**	**3194**	**15492**	**11542**	**4811**	**3500**	**9218**	**2995**

*Other category includes items such as programme management, treatment of adverse events, food supplements etc.

TABLE 8 – COST-EFFECTIVENESS (US$2012)

Peru	**Moderate costs/low cure**	Decision rule = recommend if ICER < US$ 5,150					
	Strategy	**Cost per MDR-TB patient starting treatment US($)**	**Incremental cost compared to base case (US$)**	**DALYs averted per MDR-TB patient starting treatment**	**Incremental DALYs averted compared to base case**	**Incremental cost-effectiveness**	**Cost-effectiveness**
Additive	Base Case	3211.77		17.31			185.54
	Bed Case	3872.55	660.78	19.82	2.51	263.26	195.4
	Bed S Case	3794.29	582.52	19.71	2.4	242.72	192.51
Proportional	Base Case	3211.77		17.31			185.54
	Bed Case	4060.68	848.91	18.53	1.22	695.83	219.2
	Bed S Case	3954.24	742.47	18.5	1.19	623.92	213.79
Limited	Base Case	3211.77		17.31			185.54
	Bed Case	3872.55	660.78	19.82	2.51	263.26	195.4
	Bed S Case	3794.29	582.52	19.71	2.4	242.72	192.51
All C208 (including death /default)	Base Case	3211.77		17.31			185.54
	Bed Case	3660.7	448.93	18.11	0.8	561.16	202.15
	Bed S Case	3634.24	422.47	17.91	0.6	704.12	202.87

Comments/ observations

a) Bedaquiline clearly below the WTP threshold, hence highly likely to be cost-effective
b) Incremental costs lower than Bedaquiline price due to reduction in retreatment from improved cure rate
c) Proportional application of the trial results substantially reduces cost-effectiveness, but not above the WTP threshold
d) Bedaquiline shortened case is less effective (lower cure outweighs lower default) – but it should be noted that this result may be reversed if transmission and patient costs were taken into account
e) Limited results same as additive results due to low base cure rate – so the limit becomes irrelevant
F) Where C208 increased death and default rate modeled less DALYs averted – but reduction in deaths also results in less treatment and re-treatment costs.

Russia	**High cost/ high cure**	Decision rule = recommend if ICER < US$ 10,730					
	Strategy	**Cost per MDR-TB patient starting treatment US($)**	**Incremental cost compared to base case (US$)**	**DALYs averted per MDR-TB patient starting treatment**	**Incremental DALYs averted compared to base case**	**Incremental cost-effectiveness**	**Cost-effectiveness**
Additive	Base Case	18290.81		16.42			1113.77
	Bed Case	19616.35	1325.54	17.36	0.94	1410.15	1129.75
	Bed S Case	17415.35	-875.46	17.42	1	Cost saving	999.75
Proportional	Base Case	18290.81		16.42			1113.77
	Bed Case	19616.35	1325.54	17.36	0.94	1410.15	1129.75
	Bed S Case	17415.35	-875.46	17.42	1	Cost saving	999.75
Limited	Base Case	18290.81		16.42			1113.77
	Bed Case	21009.54	2718.73	16.66	0.24	11328.04	1261.25
	Bed S Case	18961.9	671.09	16.7	0.28	2396.75	1135.29
All C208 (including death /default)	Base Case	18290.81		16.42			1113.77
	Bed Case	19543.99	1253.18	16.18	-0.52	Dominated	1207.67
	Bed S Case	17391.97	-898.84	16.24	-0.18		1070.96

Comments/ observations

a) Assuming either an additive or proportional increase in cure rates, Bedaquiline is highly cost-effective. If treatment shortening is possible may be cost saving (i.e. the savings from reductions in re-treatment and reduced hospitalization outweigh the increased regimen cost).

b) If cure rate limited to 80% - then given the high base case cure rate – Bedaquiline has a modest effect and may not be cost-effective.

c) If Bedaquiline adversely impacts death rate then may be more costly and less effective than base case (dominated by the base case) – as current high cure rates (and failures going onto retreatment) would be reduced to levels below the current situation.

Philippines	**Moderate cost/moderate cure**	Decision rule = recommend if ICER < US$ 2,210					
	Strategy	**Cost per MDR-TB patient starting treatment US($)**	**Incremental cost compared to base case (US$)**	**DALYs averted per MDR-TB patient starting treatment**	**Incremental DALYs averted compared to base case**	**Incremental cost-effectiveness**	**Cost-effectiveness**
Additive	Base Case	4022.76		13.25			303.51
	Bed Case	4915.71	892.95	16.12	2.87	311.132	304.89
	Bed S Case	4873.83	851.07	16.03	2.78	306.140	304.06
Proportional	Base Case	4022.76		13.25			303.51
	Bed Case	4999.43	976.67	15	1.75	558.097	333.2
	Bed S Case	4947.06	924.3	14.94	1.69	546.923	331.05
Limited	Base Case	4022.76		13.25			303.51
	Bed Case	4944.73	921.97	15.74	2.49	370.269	314.25
	Bed S Case	4797.12	774.36	15.78	2.53	306.071	304.03
All C208 (including death /default)	Base Case	4022.76		13.25			303.51
	Bed Case	4773.06	750.3	13.3	0.05	15006.000	358.76
	Bed S Case	4617.89	595.13	13.4	0.15	3967.533	344.54

Comments/ observations

a) Bedaquiline likely to be cost –effective independent of assumptions about the application of trial cure rate.
b) A shortened regimen reduces costs and effectiveness slightly (to note excludes transmission and patient benefits)
c) Moderate base cure rate results in reasonably comparable impact whichever assumption about incremental cure rate is applied.
d) If all trial results (including death and default are applied) then Bedaquline may not be cost-effective.

China	High cost/low cure	Decision rule = recommend if ICER < US$ 4,940					
	Strategy	Cost per MDR-TB patient starting treatment US($)	Incremental cost compared to base case (US$)	DALYs averted per MDR-TB patient starting treatment	Incremental DALYs averted compared to base case	Incremental cost-effectiveness	Cost-effectiveness
Additive	Base Case	9693.64		17.02			569.49
	Bed Case	11945.86	2252.22	19.4	2.38	946.311	615.67
	Bed S Case	12049.01	2355.37	19.3	2.28	1033.057	624.26
Proportional	Base Case	9693.64		17.02			569.49
	Bed Case	12447.88	2754.24	18.31	1.29	2135.070	679.93
	Bed S Case	12481.4	2787.76	18.26	1.24	2248.194	683.52
Limited	Base Case	9693.64		17.02			569.49
	Bed Case	11945.86	2252.22	19.4	2.38	946.311	615.67
	Bed S Case	12049.01	2355.37	19.3	2.28	1033.057	615.86
All C208 (including death /default)	Base Case	9693.64		17.02			569.49
	Bed Case	11228.46	1534.82	17.64	0.62	2475.516	636.42
	Bed S Case	11499.95	1806.31	17.47	0.45	4014.022	658.42

Comments/ observations

a) Bedaquiline likely to be cost-effective independent of method used to apply cure rate.
b) As with Peru, death and default rate adjustments do not substantially impact cost –effectiveness or effectiveness due to high base line cure rate. As they also result in lower costs – overall cost-effectiveness is not substantially different than estimates made without death or default adjustments.
c) Bedaquiline shortened in some cases is less cost-effective than the longer regimen – due to the trade-off between a reduction in the underlying default and death rates.

Estonia

Decision rule = recommend if ICER < US$ 15,260

	Strategy	Cost per MDR-TB patient starting treatment US($)	Incremental cost compared to base case (US$)	DALYs averted per MDR-TB patient starting treatment	Incremental DALYs averted compared to base case	Incremental cost-effectiveness	Cost-effectiveness
Additive	Base Case	12519.34		10.97			1141.53
	Bed Case	15133.47	2614.13	13.32	2.35	1112.396	1135.91
	Bed S Case	13841.99	1322.65	13.26	2.29	577.576	1043.67
Proportional	Base Case	12519.34		10.97			1141.53
	Bed Case	15439.57	2920.23	12.4	1.43	2042.119	1244.72
	Bed S Case	14117.39	1598.05	12.37	1.4	1141.464	1141.1
Limited	Base Case	12519.34		10.97			1141.53
	Bed Case	15239.56	2720.22	13	2.03	1340.010	1171.88
	Bed S Case	13632.88	1113.54	13.06	2.09	532.794	1043.96
All C208 (including death /default)	Base Case	12519.34		10.97			1141.53
	Bed Case	14931.31	2411.97	10.97	0	Dominated	1360.96
	Bed S Case	13293.94	774.6	11.07	0.1	7746.000	1200.87

Comments/ observations

a) Bedaquiline likely to be highly cost-effective
b) However, if the impact of default and death is also taken into account then the base case may be more cost-effective.
c) Due to the relatively high base case default rate – a shortening of the MDR regimen improves cost–effectiveness as reduces defaults.
d) Costs are lower for the shortened regimen due to the prevention of retreatment and less hospitalisation

Nepal	**Low cost/low cure**	Decision rule = recommend if ICER < US$ 540					
	Strategy	**Cost per MDR-TB patient starting treatment US($)**	**Incremental cost compared to base case (US$)**	**DALYs averted per MDR-TB patient starting treatment**	**Incremental DALYs averted compared to base case**	**Incremental cost-effectiveness**	**Cost-effectiveness**
Additive	Base Case	2577.06		17.02			151.4
	Bed Case	3268.6	691.54	19.4	2.38	290.56	168.46
	Bed S Case	3189.96	612.9	19.3	2.28	268.82	165.27
Proportional	Base Case	2577.06		17.02			151.4
	Bed Case	3401.02	823.96	18.31	1.29	638.73	185.77
	Bed S Case	3304.94	727.88	18.26	1.24	587.00	180.99
Limited	Base Case	2577.06		17.02			151.4
	Bed Case	3189.96	612.9	19.3	2.28	268.82	165.27
	Bed S Case	2980.9	403.84	17.75	0.73	553.21	167.93
All C208 (including death /default)	Base Case	2577.06		17.02			151.4
	Bed Case	3076.67	499.61	17.64	0.62	805.82	174.38
	Bed S Case	3044.07	467.01	17.47	0.45	1037.80	174.28

Comments/ observations

a) Bedaquiline cannot be established as cost-effective. Whether the ICER is below or above the WTP threshold is dependent on the assumptions made about the application of cure rate.
b) If however it is possible to reproduce trial results in an additive way – then Bedaqualine is highly likely to be cost-effective.
c) If proportionally applied, cure rate has substantially less impact than if additively applied. Limiting the cure rate has little impact as low base cure rate

TABLE 9 – SENSITIVITY ANALYSES

Peru				Decision rule = recommend if ICER < US$ 5,150			
	Strategy	**Cost per MDR-TB patient starting treatment US($)**	**Incremental cost compared to base case (US$)**	**DALYs averted per MDR-TB patient starting treatment**	**Incremental DALYs averted compared to base case**	**Incremental cost-effectiveness**	**Cost-effectiveness**
Increased price	Base Case	3211.77		17.31			186.81
	Bed Case	3972.55	760.78	19.82	2.51	303.10	200.44
	Bed S Case	3894.29	682.52	19.71	2.4	284.38	197.58
No retreatment	Base Case	2469.15		12.28			201.06
	Bed Case	3537.81	1068.66	17.55	5.27	202.78	201.56
	Bed S Case	3364.83	895.68	16.8	4.52	198.16	200.28
No hospitalisation	Base Case	3105.43		17.31			179.4
	Bed Case	3774.74	669.31	19.82	2.51	266.66	190.46
	Bed S Case	3753.91	648.48	19.71	2.4	270.20	190.46

Russia

Decision rule = recommend if ICER < US$ 10,730

	Strategy	Cost per MDR-TB patient starting treatment US($)	Incremental cost compared to base case (US$)	DALYs averted per MDR-TB patient starting treatment	Incremental DALYs averted compared to base case	Incremental cost-effectiveness	Cost-effectiveness
Increased price	Base Case	18290.81		16.42			1113.77
	Bed Case	21616.35	3325.54	17.36	0.94	3537.81	1244.94
	Bed S Case	19415.35	1124.54	17.42	1	1124.54	1114.56
No retreatment	Base Case	16313.45		14.4			1132.49
	Bed Case	19616.35	3302.9	17.36	2.96	1115.84	1129.75
	Bed S Case	17415.35	1101.9	17.42	3.02	364.87	999.75
No hospitalisation	Base Case	11045.16		16.42			672.56
	Bed Case	12320.48	1275.32	17.36	0.94	1356.72	709.57
	Bed S Case	11899.15	853.99	17.42	1	853.99	683.08

Philippines

Decision rule = recommend if ICER < US$ 2,210

	Strategy	Cost per MDR-TB patient starting treatment US($)	Incremental cost compared to base case (US$)	DALYs averted per MDR-TB patient starting treatment	Incremental DALYs averted compared to base case	Incremental cost-effectiveness	Cost-effectiveness
Increased price	Base Case	4022.76		13.25			303.51
	Bed Case	5015.71	992.95	16.12	2.87	345.976	311.09
	Bed S Case	4973.83	951.07	16.03	2.78	342.112	310.29
No retreatment	Base Case	3623.99		11.9			304.64
	Bed Case	4669.49	1045.5	15.33	3.43	304.810	304.53
	Bed S Case	4867.38	1243.39	15.96	4.06	306.254	305.01
No hospitalisation	Base Case	3841.61		13.25			289.84
	Bed Case	4723.17	881.56	16.12	2.87	307.164	292.95
	Bed S Case	4711.4	869.79	16.03	2.78	312.874	293.92

China

Decision rule = recommend if ICER < US$ 4,940

	Strategy	Cost per MDR-TB patient starting treatment US($)	Incremental cost compared to base case (US$)	DALYs averted per MDR-TB patient starting treatment	Incremental DALYs averted compared to base case	Incremental cost-effectiveness	Cost-effectiveness
Increased price	Base Case	9693.64		17.02			569.49
	Bed Case	13945.86	4252.22	19.4	2.38	1786.647	718.75
	Bed S Case	14049.01	4355.37	19.3	2.28	1910.250	727.88
No retreatment	Base Case	7779.09		12.96			600.31
	Bed Case	11268.43	3489.34	17.97	5.01	696.475	627.23
	Bed S Case	11036.99	3257.9	17.15	4.19	777.542	643.43
No hospitalisation	Base Case	9181.21		17.02			539.39
	Bed Case	11470.04	2288.83	19.4	2.38	961.693	591.15
	Bed S Case	11663.95	2482.74	19.3	2.28	1088.921	604.31

Estonia

Decision rule = recommend if ICER < US$ 15,260

	Strategy	Cost per MDR-TB patient starting treatment US($)	Incremental cost compared to base case (US$)	DALYs averted per MDR-TB patient starting treatment	Incremental DALYs averted compared to base case	Incremental cost-effectiveness	Cost-effectiveness
Increased price	Base Case	12519.34		10.97			1141.53
	Bed Case	17133.47	4614.13	13.32	2.35	1963.460	1286.03
	Bed S Case	15841.99	3322.65	13.26	2.29	1450.939	1194.47
No retreatment	Base Case	11448.63		9.96			1149.67
	Bed Case	15131.99	3683.36	13.32	3.36	1096.238	1135.92
	Bed S Case	13378.67	1930.04	12.83	2.87	672.488	1043.08
No hospitalisation	Base Case	6008.83		10.97			547.89
	Bed Case	8452.71	2443.88	13.32	2.35	1039.949	634.46
	Bed S Case	8704.98	2696.15	13.26	2.29	1177.358	656.35

Nepal	**Low cost/low cure**		Decision rule = recommend if ICER < US$ 540				
	Strategy	**Cost per MDR-TB patient starting treatment US($)**	**Incremental cost compared to base case (US$)**	**DALYs averted per MDR-TB patient starting treatment**	**Incremental DALYs averted compared to base case**	**Incremental cost-effectiveness**	**Cost-effectiveness**
Increased price	Base Case	2577.06		17.02			151.4
	Bed Case	3368.6	791.54	19.4	2.38	332.58	1292.2
	Bed S Case	3289.96	712.9	19.3	2.28	312.68	1154.79
No retreatment	Base Case	2068.24		12.96			159.61
	Bed Case	3088.57	1020.33	17.97	5.01	203.66	171.92
	Bed S Case	2921.01	852.77	17.15	4.19	203.53	170.29
No hospitalisation	Base Case	2577.06		17.02			151.4
	Bed Case	3268.6	691.54	19.4	2.38	290.56	168.46
	Bed S Case	3189.96	612.9	19.3	2.28	268.82	165.27

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