Tuberculosis in South and Central Africa

Understanding epidemiology - Improving diagnosis and management

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Chapter 9

Bedaquiline for the treatment of drug-resistant tuberculosis

ABSTRACT

Bedaquiline is a much-needed novel drug which is highly effective against drug-resistant tuberculosis. While its clinical development has been laudably fast-tracked and the drug is now available for inclusion into treatment regimens when no suitable alternatives exist, clinical experience with bedaquiline is still limited. Phase III trial data and Phase IV studies are needed particularly to study different patient populations and to optimize treatment regimens. Drug resistance to bedaquiline needs to be monitored carefully, and full access to bedaquiline treatment where it is appropriate and needed must be promoted.
INTRODUCTION

Despite progresses in overall tuberculosis (TB) control over the past years, TB remains a global public health threat. Its control still poses a major challenge at international, national and community levels. Particularly, the treatment of drug-resistant TB is of ongoing concern, as access to diagnostic and treatment infrastructure (drug sensitivity testing, second- or third-line drugs and respective medical expertise) is still limited in many countries [1]. The latest WHO TB report estimated the incidence of all forms of TB to be 9.0 million cases in 2013; 1.5 million patients died from the disease, of which 360,000 individuals were HIV co-infected [2]. In 2013, multidrug-resistant TB (MDR-TB) was estimated to have newly developed in 480,000 cases; an estimated 210,000 (43.8%) died of MDR-TB [2]. In 2013, globally, about 3.5% of newly diagnosed TB cases and 20.5% of those previously treated for TB had MDRTB [2] and about 9.0% of MDR-TB cases in countries with representative surveillance data had extensively drug-resistant TB (XDR-TB) [2]. Of alarming concern, yet of very limited extent till date, is the emergence of patients with resistance beyond XDR-TB [3]; terms and definitions of totally drug-resistant TB and extremely drug-resistant TB should, however, be used with caution because of the poor reliability of current drug sensitivity testing for second- and third-line drugs.

Regimens for drug-resistant TB require long treatment periods with toxic drugs, implying high costs [4,5]; therefore, successful outcome depends on local infrastructure in order to support patients and on the resources available. The proportion of MDR-TB patients with a successful outcome varies substantially between countries, while averaging at about 48% globally [2]. In XDR-TB cases where TB is sustained by strains with further resistance, the favorable outcomes are as low as 19% [6,7].

For a long time, success in developing new antituberculous drugs was not tangible at all. Only recently, major advances in terms of repurposed drugs which were originally designed for combating diseases other than TB (e.g., linezolid [8–10]), developing alternative compounds within known antituberculous drug classes (e.g., rifapentin [11], gatifloxazin [12]), and, particularly, developing new classes of antituberculous drugs that successfully underwent clinical development were achieved. The first two of those new drugs were fast-tracked through Phase II clinical development over the past couple of years and registered very recently for the treatment of MDR-TB. Delamanid, a nitroimidazole (during initial development OPC-67683; now available as DeltybaTM), is one of them. Its development till date has been reviewed recently [13,14].

Bedaquiline, earlier dubbed as TMC207, R207910 and compound J and now being marketed under the brand name SirturoTM, obtained accelerated US FDA approval in December 2012. The European Commission approved bedaquiline in March 2014
following a favorable EMA opinion issued in December 2013. Bedaquiline was also registered in the Russian Federation in 2013 and approval was granted in South Korea in March 2014. Regulatory filings have been submitted in South Africa, China, India, Thailand, Vietnam and Colombia [15].

Several reviews on the development of bedaquiline for drug resistant TB have been published recently, covering many aspects regarding bedaquiline [16–19]. The aim of this review was to summarize the development of bedaquiline including the most recent clinical development data and experiences on compassionate use, and to discuss the perspectives and issues around further clinical trials, post-marketing evaluation of the drug and the global deployment of bedaquiline.

For this review, we searched PubMed using the search terms ‘bedaquiline’, ‘TMC207’, ‘diarylquinoline’, ‘R207910’ and ‘Sirturo’. Articles in English, French and Spanish were eligible. Original studies as well as literature reviews and case reports were included. There were no restrictions on study subjects; animal studies as well as studies with human participants were eligible. Also, the manufacturers’ websites, trial registration databases and references from related articles were reviewed.

**PRE-CLINICAL DEVELOPMENT**

Bedaquiline is a diarylquinoline that inhibits the mycobacterial ATP synthase by binding to the amino acid residue 61 at subunit c, initiating reduction of mycobacterial reproduction and mycobacterial death [20]. It is highly specific for mycobacteria. The 50% inhibitory concentration for mycobacterial ATP synthase is 20,000-times lower than that for human ATP synthase. The selectivity of bedaquiline might be caused by a different amino acid in the proximity of the binding side of subunit c (position 63 for mycobacteria: alanine and for humans: methionine) [21].

Several in vitro and animal studies in murine models showed that bedaquiline has strong activity against mycobacteria [22–27] (see TABLE 1 for a summary of pre-clinical studies). The bedaquiline effect during the first week of treatment is bacteriostatic, as mycobacteria reduce their ATP consumption and remodel the ATP production pathways following exposure; bactericidal killing commences after 5–7 days of treatment [20,25,28]. Dormant Mycobacterium tuberculosis bacilli require a 10-times lower ATP level than replicating bacilli, but are successfully killed by bedaquiline when ATP levels drop even further [20].

Bedaquiline monotherapy had a higher bactericidal activity than any other TB drug used as single drug; was more active than most of the two-drug combinations [22,23,26]; its effect was dose dependent [29,30] and it exhibited a higher activity than the combination of the first-line drugs rifampicin (RIF), isoniazid (INH) and
pyrazinamide (PZA) [25]. Addition of bedaquiline resulted in faster bactericidal clearance [25]. Bactericidal and sterilizing activity increased, especially if bedaquiline was combined with PZA; the addition of a third drug did not improve this activity [23,31,32]. Four months of treatment with a bedaquiline–PZA–RIF-containing regimen was as effective in preventing relapse as the standard 6-month treatment [31].

The slow elimination of bedaquiline and a terminal half-life of 50–60 h [30] suggested the potential of intermittent dosing for bedaquiline. Bedaquiline, given once weekly or five-times a week, yielded the same bactericidal activity, provided the weekly bedaquiline dose was equal. Once weekly dosing of bedaquiline–rifapentine–PZA had a very high bactericidal activity and was superior to five-times a week RIF–INH–PZA [27].

Bedaquiline is as active against drug-susceptible TB as against drug-resistant TB. In murine studies, the oral combination of bedaquiline–moxifloxacin–PZA shortened the treatment duration for MDR-TB by 6 months [33]. The combination sutezolid (PNU)–bedaquiline was the drug combination with the best bactericidal activity in XDR-TB [29]. Due to its effect on dormant bacilli, bedaquiline also showed good activity in latent (MDR-)TB with the combination bedaquiline–PA-824–PNU resulting in the highest activity [26]. Therefore, bedaquiline may reduce the treatment duration for latent TB by drug-resistant M. tuberculosis to 3–4 months [34]. At this point, bedaquiline has only been registered for use in drug-resistant TB, but other applications are being investigated. However, the significant reduction of bedaquiline concentration when co-medicated with rifampicin (and other rifamycins such as rifapentin) limits its possible applicability and development as a potential first-line combination drug for drug-sensitive TB [35,36].

Naturally occurring bedaquiline resistance is thought to be low. The mutation rate in mycobacteria exposed to bedaquiline decreases with increasing bedaquiline concentration; at a concentration of 3.0 mg/l (100 x MIC), no mutations were seen [37]. Initially, bedaquiline resistance was found to be caused by polymorphisms within the atpE gene (A63P and I66M), which encodes for subunit c of ATP synthase [38,39]. A more recent and larger study showed that only 28% of the bedaquiline-resistant M. tuberculosis bacilli had mutations at the atpE gene, which occurred at five different points: three known point mutations for bedaquiline resistance (A28V, A63P, I66M) and two new mutations (A28P and G61A) [37]. The resistant mutants did not show any reduction in fitness [37].

For a more comprehensive summary and in-depth information on the pre-clinical development, we would like to refer to two other reviews written by Matteelli et al. [40] and Chan et al. [41].
### Table 1 Bedaquiline pre-clinical studies – activity against DS/DR-TB in *vitro* and in animal models.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Short title</th>
<th>Type of study</th>
<th>Aim/Drug regimens</th>
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<tbody>
<tr>
<td><strong>DS-TB</strong></td>
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<tr>
<td>Koul et al. (2007)</td>
<td>Delayed bactericidal response of <em>Mycobacterium tuberculosis</em> to bedaquiline involves remodelling of bacterial metabolism</td>
<td><strong>In vitro</strong></td>
<td>Individual cells of <em>M. tuberculosis</em> in microfluidic devices</td>
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<td>Andries et al. (2010)</td>
<td>Bacterial potencies of new regimens are not predictive of their sterilizing potencies in a murine model of tuberculosis</td>
<td><strong>Murine model</strong></td>
<td>4-week-old female Swiss mice inoculated iv - treatment 2 weeks post infection</td>
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<tr>
<td>Ibrahim et al. (2007)</td>
<td>Synergistic activity of R207910 combined with pyrazinamide against murine tuberculosis</td>
<td><strong>Murine model</strong></td>
<td>4-week-old female Swiss mice inoculated iv - treatment 2 weeks post infection</td>
</tr>
<tr>
<td>Lounis et al. (2006)</td>
<td>Combinations of R207910 with drugs used to treat multidrug-resistant tuberculosis have the potential to shorten treatment duration</td>
<td><strong>Murine model</strong></td>
<td>4-week-old female Swiss mice iv inoculated - treatment 2 weeks post infection</td>
</tr>
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<td>Lounis et al. (2008)</td>
<td>Impact of the interaction of R207910 with rifampin on the treatment of tuberculosis studied in the mouse model</td>
<td><strong>Murine model</strong></td>
<td>4-week-old female Swiss mice iv inoculated - treatment 2 weeks post infection</td>
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<tr>
<td>Dhillon et al. (2010)</td>
<td>Bactericidal activity of diarylquinoline TMC207 against <em>Mycobacterium tuberculosis</em> outside and within cells</td>
<td><strong>In vitro</strong></td>
<td>Liquid culture medium, mouse peritoneal macrophages, J774 macrophage-like cell line</td>
</tr>
<tr>
<td>Ibrahim et al. (2009)</td>
<td>Sterilizing Activity of R207910 (TMC207)-containing Regimens in the Murine Model of Tuberculosis</td>
<td><strong>Murine model</strong></td>
<td>4-week-old female Swiss mice iv inoculated - treatment 18 days post infection</td>
</tr>
<tr>
<td>Tasneen et al. (2011)</td>
<td>Sterilizing Activity of Novel TMC207- and PA-824-Containing Regimens in a Murine Model of Tuberculosis</td>
<td><strong>Murine model</strong></td>
<td>5-week-old female BALB/c mouse aerosol infected - treatment 2 weeks post infection</td>
</tr>
</tbody>
</table>
Conclusions

- Bacterial killing is associated with depletion of cellular ATP by >10x
- Due to remodelling of ATP consuming and ATP producing pathways ATP levels for bacterial viability maintain for several days and prevents killing
- Dormant M. tuberculosis bacilli are viable with 10x lower ATP levels, further ATP depletion kills
- TMC207 has strongest bactericidal activity
- Best combination TMC207-PZA-MXF containing regimens: lung culture conversion within 4 weeks
- RFT had strongest sterilizing activity
- Best combination TMC207-PZA-RFT containing regimens: lower relapse rates after 3/12 than standard treatment
- TMC207 was the most active monotherapy and as active as the standard regimen
- PZA increases the activity of TMC207
- 3-drug combinations were not more active than TMC207 plus PZA

- All TMC207-containing combinations were significantly more active
- TMC207 alone was more active than standard regimen (RIF-INH-PZA)
- TMC207 combined with 2nd line drug was more active than AMK-ETH-MXF-PZA and culture negativity was reached in almost every case

- TMC207 added to RIF-INH-PZA increased the speed of bactericidal clearance and culture negativity
- The minimal bactericidal dose of TMC207 was 12.5 mg/kg (when added to RIF-INH-PZA)
- The bactericidal effect of TMC207 during the 1st week of treatment was modest but accelerated in the 2nd week
- Bactericidal effect of INH during the 1st week of treatment was limited
- Extra-cellular: bacteriostatic phase first 7-14 days followed by a bactericidal phase, which was dose related
- Intra-cellular: no bacteriostatic phase, bactericidal killing accelerated after 5-7 days

- 4 months of TMC207-PZA-RIF-containing regimen showed the same relapse rate as the 6-month standard regimen
- TMC207 and PZA increase each others activity
- Best sterilizing activity in regimens containing TMC207-PZA-RIF

- CFZ is the best third drug combined with TMC207-PZA at 1 month of treatment
- PA-824 seems to have an antagonistic effect on TMC207
- TMC207-PZA plus either RPT or MXF was the most effective combination at 2 months of treatment
- RPT (in addition to TMC207-PZA) had a better sterilizing effect (not significant)
Table 1 Bedaquiline pre-clinical studies – activity against DS/DR-TB in vitro and in animal models.

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<tr>
<td>Reddy et al. (2010)</td>
<td>In Vitro Interactions between New Antitubercular Drug Candidates SQ109 and TMC207</td>
<td>In vitro</td>
<td>Evaluate the efficacy of monotherapy TMC207 or SQ109 compared to the efficacy of various 2- or 3-drug regimens containing TMC207, SQ109, RIF</td>
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<tr>
<td>Veziris et al. (2011)</td>
<td>A once-weekly R207910-containing regimen exceeds activity of the standard daily regimen in murine tuberculosis</td>
<td>Murine model</td>
<td>Evaluate the efficacy of: 1. TMC207 5x, 2x, 1 x/week or 1x every 2 weeks 2. 1x/week monotherapy compared to the efficacy of various 2- or 3-drug regimens containing TMC207, RPT, INH, MXF, PZA</td>
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<tr>
<td>Huitric et al. (2007)</td>
<td>In Vitro Antimycobacterial Spectrum of a Diarylquinoline ATP Synthase Inhibitor</td>
<td>In vitro</td>
<td>Evaluate the efficacy of different doses TMC207 in the range of 0.002 to 0.256 μg/ml</td>
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<td>Shang et al. (2011)</td>
<td>Activities of TMC207, Rifampin, and pyrazinamide against Mycobacterium tuberculosis Infection in Guinea Pigs</td>
<td>Animal model</td>
<td>Evaluate the efficacy of TMC-RIF-PZA vs standard therapy with RIF-INH-PZA</td>
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<td>Williams et al. (2012)</td>
<td>Sterilizing Activities of Novel Combinations Lacking First- and Second-Line Drugs in a Murine Model of Tuberculosis</td>
<td>Murine model</td>
<td>Evaluate the efficacy of various 3- &amp; 4- drug regimen containing TMC207, PNU, PA-824, CFZ</td>
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<td><strong>MDR / XDR TB</strong></td>
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<tr>
<td>Lanoix et al. (2014)</td>
<td>Novel Regimens Identified in Mice for Treatment of Latent Tuberculosis Infection in Contacts of Patients with multidrug-Resistant Tuberculosis</td>
<td>Murine model</td>
<td>Evaluate the efficacy of INH, RIF, LFX, MXF, TMC207, Pa and PNU as monotherapy and in various 2- or 3-drug combinations to treat MDR-latent TB.</td>
</tr>
<tr>
<td>Wallis et al. (2012)</td>
<td>Rapid Evaluation in Whole Blood Culture of Regimens for XDR-TB Containing PNU-100480 (Sutezolid), TMC207, PA-824, SQ109, and Pyrazinamide</td>
<td>In vitro</td>
<td>Examine the bactericidal activities of PNU-100480, TMC207, PA-824 and SQ109, singly and in various combinations</td>
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Bedaquiline pre-clinical studies – activity against DS/DR-TB

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Conclusions

- TMC207 and SQ109 work synergistically; - improved each other MIC, rate of killing and the postantibiotic effect with 4 h
- TMC207 and RIF work additive or indifferent but did not improve each others MIC - RIF reduces AUC for TMC207
- RIF does not have any effect on the combination of SQ109 and TMC207
- SQ109-RIF was most effective combination, closely followed by SQ109-TMC207
- TMC207 given 1x or 5x a week gave a similar bactericidal activity when the weekly dose was similar
- TMC207 monotherapy had the highest bactericidal effect
- Adding RPT-INH or MXF to TMC207 did not increase the activity
- Once weekly TMC207-RPT-PZA had a very high bactericidal activity (better than 5x/week RIF-INH-PZA)

- MIC mycobacterial ATP synthase 0.032 μg/ml
- XDR-TB was as susceptible as MDR-TB and DS-TB
- TMC207 had a binding pocket around amino acid residue 61 on subunit c

- TMC207-RIF-PZA rapidly reduced lung bacterial load to undetectable (within 8 weeks) but had no effect in the draining lymph nodes
- After ±11 months 3/13 guinea pigs treated with TMC207-RIF-PZA showed signs of relapse vs 6/15 guinea pigs treated with RIF-INH-PZA (not significantly different)
- TMC207-PNU-CFZ was the most effective three-drug-combination in reducing bactericidal activity
- All regimens containing TMC207-PNU were more effective in reducing bactericidal activity and had lower relapse rates

- TMC207-PA-824-PNU was most effective
- No 2-drug combination was more effective than TMC207 monotherapy

- Most active monotherapy: PNU
- Most active combination: PNU-TMC207
- Activity of TMC207 and SQ109 increased with increasing dose
- PA-824 – TMC207 showed antagonism
Table 1 Bedaquiline pre-clinical studies – activity against DS/DR-TB in vitro and in animal models. (continued)

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<td>Veziris et al. (2011)</td>
<td>Sterilizing activity of second-line regimens containing TMC207 in a murine model of tuberculosis</td>
<td>Murine model 4-week-old female Swiss mice iv inoculated - treatment 19 days post infection</td>
<td>Evaluate sterilizing efficacy &amp; optimal duration of MDR treatment of TMC207, RIF, PZA, AMK, ETH and MXF in 3-, 4- or 5-drug combinations ± 2, 4, 7 or 10 months of a 2- or 3-drug combination with TMC207, RIF, ETH and MXF.</td>
</tr>
<tr>
<td>Zhang et al. (2011)</td>
<td>Short-Course Chemotherapy with TMC207 and Rifapentine in a Murine Model of Latent Tuberculosis Infection</td>
<td>Murine model 5-week-old female BALB/c mice aerosol infected after aerosol-immunization with BCG – treatment 5 weeks post-infection</td>
<td>Compare 5x a week dosing of INH, RIF, RPT, TMC207 and PZA singly and in various 2- or 3-drug regimens vs 1x/week INH-RPT.</td>
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<tr>
<td>Pharmacokinetics and pharmacodynamics</td>
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<tr>
<td>Rouan et al. (2012)</td>
<td>Pharmacokinetics and pharmacodynamics of TMC207 and Its N-Desmethyl Metabolite in a Murine Model of Tuberculosis</td>
<td>Murine model 4-week-old male and female Swiss mice, female mice iv inoculated - treatment day after infection.</td>
<td>4 weeks TMC207 ranging 6.25-50 mg/kg vs N-Desmethyl TMC207 ranging 8-64 mg/kg</td>
</tr>
<tr>
<td>Haagsma et al. (2009)</td>
<td>Selectivity of TMC207 towards Mycobacterial ATP Synthase Compared with that towards the Eukaryotic Homologue</td>
<td>In vitro Isolated mitochondria from human ovarian cancer cells line; inverted membrane vesicles of M. smegmatis</td>
<td>Monitor the effect of TMC207 on ATP synthesis</td>
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<td>Bedaquiline resistance</td>
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<tr>
<td>Huitric et al. (2007)</td>
<td>Rates and Mechanisms of Resistance Development in Mycobacterium tuberculosis to a Novel Diarylquinoline ATP Synthase Inhibitor</td>
<td>Murine model 4-week-old male and female Swiss mice, female mice iv inoculated - treatment day after infection.</td>
<td>Characterize the development of resistance to TMC207 in vitro in M. tuberculosis with regards to mutation rates (MR), mechanisms of resistance and potential impacts on bacterial fitness</td>
</tr>
<tr>
<td>Petrella et al. (2006)</td>
<td>Genetec Basis for Natural and Acquired Resistance to the Diarylquinoline R207910 in Mycobacteria</td>
<td>Murine model 4-week-old female Swiss mice, female mice iv inoculated - treatment day after infection.</td>
<td>Investigate atpE from new M. tuberculosis in vitro mutants resistant to TMC207</td>
</tr>
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</table>

AMK: Amikacin; AUC: Area under the curve; CFU: Colony forming units; CFZ: Clofazimine; DR: Drug resistant; DS: Drug sensitive; DS-TB: Drug sensitive TB; ETH: Ethionamide; GI: Growth index; INH: Isoniazid; LFX: Levofloxacin; MDR-TB: Multidrug-resistant TB; MGIT: Mycobacteria growth indicator tube; MIC: Minimum inhibitory concentration; MR: Mutation rates; MXF: Moxifloxacin; OADC: Oleic acid, albumin, dextrose, and catalase; PK-PD: Pharmacokinetic and pharmacodynamic; PNU: Sutezolid; PZA: Pyrazinamide; RIF: Rifampicin; RFT: Rifapentine; RPT: Rifapentine; RLU: Relative light units; XDR-TB: Extensively drug-resistant TB.
Conclusions

- Regimens containing MXF-PZA for the treatment of MDR-TB results in a stable cure after 12 months
- An oral combination of TMC207-MXF-PZA could shorten the treatment duration with 6 months to gain the same relapse rate

- TMC207 has a sterilizing activity as strong as RIF alone and INH+RIF
- Daily RPT +/- INH had the best sterilizing activity
- Addition of TMC207 to RPT did not improve the sterilizing activity of RPT
- TMC207 may reduce the duration of treatment for drug resistant-latent TB to 3-4 months

- The bactericidal activity of TMC207 is concentration dependent
- PK-PD profile supports intermittent administration of TMC207
- TMC207 is rapidly absorbed and slowly metabolised after oral administration
- Both are slowly eliminated with terminal half-life of 50-60 hours

- MIC human ATP synthase : MIC mycobacterium ATP synthase = 200 μM : 0.01 μM
- Human mitochondria have a methionine at position 63 of subunit c, this might cause a reduced binding of TMC207

- At MR at 0.3mg/L: 4.7×10⁻⁷ - 8.9×10⁻⁹ mutations/cell division; MR at 0.9 mg/L: 3.9×10⁻⁸ - 2.4×10⁻⁹ mutations/cell division; no mutations observed at 3.0 mg/L
- Level of resistance: 0.12-3.84 (median 0.48) mg/L = 4-128x the MIC
- MR at 0.3 mg/L is similar to MR of RIF and INH
- In 53/97 mutants atpE gene was sequenced; 15/53 had 5 different point mutations; 38/53 had no atpE mutations
- The mutants did not show a reduction in fitness

- Two of the seven mutants had a mutation at A63P
- Five of the seven had a mutation at I66M

- Conclusion: this may affect the interaction between TMC207 and subunit c of ATP synthase

Ref.

[33]
[34]
[30]
[21]
[37]
[38]
A range of Phase I trials has been conducted; details of those trials listed in the clinical trials registry ClinicalTrials.gov are presented in TABLE 2. However, only part of the resulting data has been published in peer-reviewed journals [35,36,42,43]. Summarized pharmacokinetic and early safety data have been presented at conference meetings and in the prescribing information for Sirturo [44]. Key findings from Phase I trials were linear pharmacokinetics, a positive food effect with a twofold increase of bedaquiline exposure, a reduction of bedaquiline exposure by 50% when rifampicin is co-administered (CYP3A4 induction), an increase in bedaquiline exposure by 22% when lopinavir/ritonavir is co-administered, a long terminal elimination half-life and no effect of nevirapine on bedaquiline exposure [45]. A summary of pharmacokinetic properties is well presented by Chahine et al. [18].

Phase II clinical trials are summarized in TABLE 3. Early bactericidal activity studies of bedaquiline were conducted in patients with treatment-naïve, smear-positive, drug-susceptible pulmonary TB. These studies showed significant bactericidal activity (with delayed onset) similar to rifampicin and isoniazid [46], increased activity of bedaquiline by PZA [47], a linear trend for dosing of bedaquiline suggesting that the highest dose compatible with safety being taken forward [48] and good safety profiles [46–48].

A first Phase II efficacy trial in patients with MDR-TB was conducted in two stages. In Stage I, 47 patients were randomly assigned to either placebo (n = 24) or bedaquiline (n = 23) 400 mg daily for 2 weeks, followed by 200 mg three-times a week for 6 weeks, that is, 8 weeks in total; the study medication was added to a five-drug background MDR-TB regimen. Eight-week outcomes were reported by Diacon et al. in 2009 [49]; the 6-month outcomes were published later by the same authors [50]. In the bedaquiline group, a significantly higher proportion of culture conversion compared to placebo (48 vs 9%; hazard ratio 11.8; 95% CI: 2.3–61.3; p = 0.003) was observed at the end of the 8-week administration period [49]; the time to 50% culture conversion was 78 days in the bedaquiline group and 129 days in the placebo group [50]. In subgroup analyses, the time-dependent bactericidal activity of bedaquiline (by accelerating the bactericidal activity of the background regimen) was confirmed for the time after the first and up to the fourth week [49]. In the bedaquiline group, fewer patients acquired resistance to companion drugs possibly reflecting a protective effect of bedaquiline against the acquisition of additional resistance and XDR-TB in patients with MDR-TB [50].

In Stage II, 160 patients with newly diagnosed, smear-positive MDR-TB were randomly assigned to 24 weeks placebo or 24 weeks bedaquiline (400 mg once daily for 2 weeks, followed by 200 mg three-times per week for 22 weeks) in addition to a
background regimen standardized as far as possible. The results were recently published by Diacon et al. [51]; in the intervention arm, culture conversion at week 24 was 79% compared to 58% (bedaquiline group: hazard ratio 2.44; 95% CI: 1.57–3.80; p < 0.001) and was sustained at week 120 (62 vs 44%; p = 0.04), thus translating into cure rates at 120 weeks of 58 versus 32% (p = 0.003) according to the WHO outcome definition [51]. The median time to culture conversion was reduced from 125 to 83 days [51]. Again, adding bedaquiline to the background regimen reduced the risk of acquisition of further drug resistance to the background drugs [51].

In both Phase II trials, an increase in the mean corrected QT interval was observed in the intervention arms. In the 8-week bedaquiline trial, the intergroup difference ranged from 1.0 to 10.8 ms (p > 0.05) at 8 weeks [49]; in the 24-week bedaquiline trial, the mean change from baseline in the QTcF was an increase of 15.4 ms in the intervention group (3.3 ms in the placebo group, p < 0.001) [51]. After cessation of study drug intake, the QTcF gradually decreased and was similar to the placebo group at study week 60 [51].

The overall side effect profiles in both Phase II trials were similar in the two treatment groups; only nausea occurred in a higher proportion of patients in the bedaquiline group during and after 8 weeks of bedaquiline administration [49,50]. Common adverse effects reported during the Phase II trials were nausea, hearing impairment, arthralgia, hemoptysis, hyperuricemia, pain in the extremities, rash and chest pain [49–51]. Laboratory safety assessments did not differ between the study groups [49].

While the superior efficacy of regimens including bedaquiline compared to a ‘standard’ treatment was strong and beyond doubt, safety issues arose. With bedaquiline as an (arylamino) quinoline, safety concerns during the early clinical development focused on QTc time prolongation; particularly in view of potential co-medication also prolonging QTc time, such as fluoroquinolones, other novel and potential partner drugs, such as delamanid, or potentially necessary co-medication unrelated to TB, such as the aminoquinoline derivate mefloquine for malaria treatment or prophylaxis [52], possibly aggravating the QT interval prolongation through potentiating effects. While adverse event assessment during those clinical trials did not reveal safety concerns decelerating the clinical development progress, a puzzling question arose when comparing mortality in the intervention versus placebo group of this trial. An overall number of 10 (13%) deaths in the intervention group and 2 (2%) in the control arm called for detailed investigation on the causes of deaths. All but one death in the bedaquiline group occurred after termination of the study drug administration (median time after the receipt of last study medication 49.1 weeks, range 12.3–130.1) and none of the deaths was related to bedaquiline [51]. Most of the deaths were either directly related to TB (n = 5) or clearly related to other
Table 2 Phase 1 TMC207 trials registered on ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Trial registration No.</th>
<th>Short study title</th>
<th>Study design</th>
<th>Study completion date</th>
<th>Primary objectives</th>
<th>Further objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svensson et al. (2014)</td>
<td>NCT00828529</td>
<td>TMC207 Interaction Study With Lopinavir/Ritonavir in Healthy Adults</td>
<td>Open-label randomized pharmacokinetic study</td>
<td>May 2009</td>
<td>Effect of daily lopinavir/ritonavir on TMC207</td>
<td>Effect of TMC207 on lopinavir and ritonavir; safety and tolerability of co-administration</td>
</tr>
<tr>
<td>Svensson et al. (2014)</td>
<td>NCT00910806</td>
<td>TMC207-Nevirapine Interaction Study in Anti-retroviral Naïve HIV-1 Infected Adults</td>
<td>Open-label, non-randomized pharmacokinetic study</td>
<td>June 2010</td>
<td>Effect of daily nevirapine on the pharmacokinetics of TMC207</td>
<td>Effect of TMC207 on plasma concentrations of nevirapine; safety and tolerability of co-administration of TMC207 and nevirapine</td>
</tr>
<tr>
<td>Dooley et al. (2012)</td>
<td>NCT00992069</td>
<td>Safety, Tolerability, and Effect of TMC207 and Efavirenz in Healthy Adult</td>
<td>Open-label safety study</td>
<td>December 2010</td>
<td>Pharmacokinetics</td>
<td>Safety</td>
</tr>
<tr>
<td>NCT01012284</td>
<td>TMC207 in Healthy Adults and Patients With Moderately Impaired Hepatic Function</td>
<td>Open-label, non-randomized pharmacokinetic study</td>
<td>January 2011</td>
<td>Pharmacokinetics</td>
<td>Safety and tolerability</td>
<td></td>
</tr>
<tr>
<td>NCT01291563</td>
<td>Effect of TMC207 on the QT/QTc Interval in Healthy Adults</td>
<td>Double-blind randomized safety and efficacy trial</td>
<td>April 2011</td>
<td>QT and QTc evaluation</td>
<td>Further ECG evaluation; pharmacokinetics; safety and tolerability</td>
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<tr>
<td>NCT00946842</td>
<td>Oral Bioavailability of TMC207 in Healthy Adults under Fed and Fastened Conditions</td>
<td>Open-label randomized bioavailability study</td>
<td>March 2012</td>
<td>Bioavailability of TMC207 phase II clinical trial tablet formulation and of a newly developed tablet formulation</td>
<td>Pharmacokinetics; effect of food on bioavailability; effect of particle size of active ingredient (TMC207) on bioavailability; evaluation of short-term safety and tolerability TMC207</td>
<td></td>
</tr>
<tr>
<td>NCT01341184</td>
<td>TMC207 +/- Rifabutin/Rifampin in Healthy Adults</td>
<td>Open-label randomized pharmacokinetic study</td>
<td>May 2012</td>
<td>Pharmacokinetics; safety and tolerability</td>
<td>Cell-associated levels of TMC207 and M2 in peripheral blood mononuclear cells</td>
<td></td>
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<tr>
<td>Intervention</td>
<td>Sample size</td>
<td>Findings and conclusions</td>
<td>Ref.</td>
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<tr>
<td>- TMC207 (400mg) (twice single dose 4 weeks apart)</td>
<td>n=16</td>
<td>Lopinavir/ritonavir decreased TMC207 and M2# clearances to 35% and 58%, respectively. Almost 3-fold (TMC207) and 2-fold (M2) increases in exposures with Lopinavir/ritonavir are expected, dose adjustments are suggested for evaluation. Predicted elevation of TMC207 and M2 levels with Lopinavir/ritonavir co-administration may be a safety concern, monitoring recommended.</td>
<td>[43,91]</td>
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<tr>
<td>- Lopinavir/ritonavir at 400/100 mg twice daily was started 10 days before TMC207</td>
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<tr>
<td>- TMC207 (two 400mg doses)</td>
<td>n=16</td>
<td>No significant effects of nevirapine on TMC207 pharmacokinetics were identified. Modelling results suggest that TMC207 can be co-administered with nevirapine without dose adjustments. No dosage adjustment of bedaquiline required.</td>
<td>[43,92]</td>
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<tr>
<td>- Nevirapine (200mg once daily for 2 weeks, followed by 200mg twice daily) started at least 4 weeks prior to second BDQ dose</td>
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<tr>
<td>- TMC207 (400mg)</td>
<td>n=37</td>
<td>TMC207 was well tolerated alone and with steady-state efavirenz. Effect of efavirenz on TMC207 concentrations is unlikely to be clinically significant.</td>
<td>[42,93]</td>
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<tr>
<td>- Efavirenz (600mg nightly)</td>
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<tr>
<td>- TMC207 (400mg)</td>
<td>n=16</td>
<td>AUC672h of TMC207 is 20% lower in patients with moderate hepatic impairment. No TMC207 dose adjustment needed in patients with moderate hepatic impairment.</td>
<td>[94]</td>
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<tr>
<td>- TMC207 (800mg)</td>
<td>n=88</td>
<td>No data available.</td>
<td>[95]</td>
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<tr>
<td>- Moxifloxacin (400mg)</td>
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<td></td>
<td></td>
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<tr>
<td>- Placebo</td>
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<tr>
<td>- TMC207 tablet (100mg)</td>
<td>n=28</td>
<td>No data available.</td>
<td>[96]</td>
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<tr>
<td>- TMC207 fine particle size tablet (100mg)</td>
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<tr>
<td>- TMC207 coarse particle size tablet (100mg)</td>
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<tr>
<td>- TMC207 (400mg)</td>
<td>n=33</td>
<td>Rifampin reduced AUC of TMC207 by 52%. Combination of rifamycins and TMC207 should be avoided.</td>
<td>[97]</td>
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<tr>
<td>- Rifabutin (300mg)</td>
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<tr>
<td>- Rifampin (600mg)</td>
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</tbody>
</table>
concomitant conditions or acute events (alcohol [n = 2], cerebrovascular accident, peritonitis with sepsis, motor vehicle accident). None of those individuals had a significant QTc time prolongation recorded at any time of the observation period. On this background, chance was discussed as a possibility, as well as a remarkable ‘under-mortality’ in the control group [51].

On the grounds of those efficacy trials, and in view of the urgent need for novel drugs, bedaquiline was fast-tracked into compassionate use and then registration and marketing in 2013 and 2014, on the condition that a Phase III trial would be accomplished in due course.

THE NEED FOR PHASE III TRIALS & THE CHALLENGE IN STUDY DESIGN

With the extraordinary fast-tracking from Phase II studies into registration and marketing, albeit with restrictions (the FDA registration carries a ‘black box’ warning) [53] and confining the use to drug-resistant TB where alternative regimens alone are no alternative, there is a need to still accomplish a Phase III trial and well-conducted and comprehensive Phase IV studies are of utmost importance.

In a rapidly changing ‘treatment landscape’ for drug-resistant TB and being faced with complex multiple-drug background regimens as a ‘gold standard’ comparator arm, defining optimal duration of treatment, clinical endpoints and outcome definitions for a Phase III study design with the goal to provide unquestionable efficacy data in good quality and within a reasonable time frame constitutes a formidable challenge. With the forthcoming addition of bedaquiline arms to the STREAM trial

### Table 2 Phase 1 TMC207 trials registered on ClinicalTrials.gov (continued)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Trial registration No.</th>
<th>Short study title</th>
<th>Study design</th>
<th>Primary objectives</th>
<th>Further objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svensson et al. (2014) NCT02216331</td>
<td>TMC207 Interaction with Rifapentine or Rifampicin in Healthy Adults</td>
<td>Open-label, randomized pharmacokinetic study</td>
<td>May 2010</td>
<td>Pharmacokinetics</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>NCT01803373</td>
<td>Bioavailability of Two Pediatric Formulations of TMC207 in Healthy Adults</td>
<td>Open-label, randomized bioavailability study</td>
<td>August 2013</td>
<td>Pharmacokinetics</td>
<td>Effect of food; taste; safety</td>
</tr>
</tbody>
</table>

# M2 = TMC207 metabolite N-monodesmethyl metabolite

AUC: Area under the curve.
[54], a workable solution to this problem seems to be found. While STREAM I [54] compares the standard WHO MDR-TB regimen with a modified 9-month Bangladesh regimen [55], STREAM II will compare 6- and 9-month bedaquiline-containing regimens against WHO and Bangladesh regimens [56]. That notwithstanding, further studies are needed to explore potentially even shorter, highly efficacious regimens including combination of bedaquiline and delamanid, as well as combinations of other advanced novel compounds such as PA-824. Indications beyond treatment-naive MDR-TB need to be evaluated, such as incorporation of bedaquiline in shortened primary or salvage regimens for drug-resistant TB or incorporation of bedaquiline into treatment regimens for drug-susceptible or latent TB. The RESIST-TB Clinical Trial Progress Report [56] provides an overview of trials which have at the time of writing just started to recruit or which are in advanced stages of planning.

THE NEED FOR EVIDENCE-BASED USAGE OF BEDAQUILINE IN CHILDREN

The burden of drug-resistant TB in children is on the rise, along with the global emergence of MDR-TB and XDR-TB; and children are as likely to be affected by drug-resistant TB as adults [57,58]. Improved pediatric specimen collection and molecular diagnostic methods are supporting to better delineate the still under-recognized burden of drug-resistant TB in children. However, still only few children with drug-resistant TB are diagnosed and appropriately treated [59]. Most current guidelines provide recommended dosages for second-line drugs [60], but evidence-based data on pharmacokinetic and pharmacodynamic characteristics of these drugs in chil-

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Sample size</th>
<th>Findings and conclusions</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>- TMC207 tablet (100mg)</td>
<td>n=36</td>
<td>No data available.</td>
<td>[98]</td>
</tr>
<tr>
<td>- TMC207 dispersible tablet (5 x 20 mg)</td>
<td>n=36</td>
<td>No data available.</td>
<td>[35, 99]</td>
</tr>
<tr>
<td>- TMC207 granules (equivalent to 100mg)</td>
<td>n=32</td>
<td>No data available.</td>
<td>[35, 99]</td>
</tr>
<tr>
<td>- TMC207 (400mg)</td>
<td>n=32</td>
<td>No data available.</td>
<td>[35, 99]</td>
</tr>
<tr>
<td>- Rifapentine (600mg)</td>
<td>n=32</td>
<td>No data available.</td>
<td>[35, 99]</td>
</tr>
<tr>
<td>- Rifampicin (600mg)</td>
<td>n=32</td>
<td>No data available.</td>
<td>[35, 99]</td>
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<tr>
<td>Study (year) trial registry no.</td>
<td>Short study title</td>
<td>Study design, sites and completion date</td>
<td>Primary objectives</td>
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<tr>
<td><strong>Early bactericidal activity studies</strong></td>
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<tr>
<td>Rustomjee et al. (2008) NCT00523926</td>
<td>Early Bactericidal Activity and Pharmacokinetics of TMC207 for pulmonary DS-TB</td>
<td>Open-label randomized two-centre study</td>
<td>Effects of 3 doses of TMC207 administered over a 7 day period on <em>M. tuberculosis</em> in sputum</td>
</tr>
<tr>
<td>Diacon et al. (2012) NCT01215851</td>
<td>Early Bactericidal Activity in pulmonary DS-TB with PA-824 – TMC207 – Pyrazinamide - Moxifloxacine</td>
<td>Double-blind randomized study</td>
<td>Early bactericidal activity rate of change in log colony forming units in sputum (day 14)</td>
</tr>
<tr>
<td>Diacon et al. (2013) NCT01215110</td>
<td>Dose-ranging Early Bactericidal Activity of TMC207 in pulmonary DS-TB</td>
<td>Double-blind randomized study</td>
<td>Early bactericidal activity measured as rate of change in log colony forming units in sputum (day 14)</td>
</tr>
<tr>
<td>NCT01691534</td>
<td>Early Bactericidal Activity in Pulmonary DS-TB With Clofazimine -TMC207-PA-824- Pyrazinamide</td>
<td>Single-blind randomized Study</td>
<td>Extended early bactericidal activity as the rate of change in log colony forming units (day 14)</td>
</tr>
<tr>
<td><strong>Efficacy and safety studies</strong></td>
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<tr>
<td><strong>Stage 1</strong></td>
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<tr>
<td>Diacon et al. (2009)</td>
<td>Anti-bacterial Activity, Safety, and Tolerability of TMC207 in Patients With Pulmonary New MDR-TB</td>
<td>Multicentre double-blind randomized placebo-controlled trial</td>
<td>Sputum culture conversion</td>
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<tr>
<td>Diacon et al. (2012)</td>
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<tr>
<td>Intervention</td>
<td>Sample size</td>
<td>Main findings and conclusions</td>
<td>Ref.</td>
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</tbody>
</table>
| - TMC207 (25mg) | n=75 (TMC207=45) | • Significant bactericidal activity of TMC207 from day 4 onward was similar to rifampicin and isoniazid  
• Pharmacokinetics of TMC207 were linear across dose range  
• Good tolerability | [46,100] |
| - TMC207 (100mg)  
- TMC207 (400mg)  
- Rifampicin (600mg)  
- Isoniazid (300mg) | n=85 (TMC207=45) | • 14 day early bactericidal activity of PA-824-moxifloxacin-pyrazinamide was significantly higher than that of TMC207, TMC207-PZA, TMC207-PA-824  
• Pyrazinamide appears to increase activity of TMC207 | [47,101] |
| - TMC207  
- TMC207 + pyrazinamide  
- TMC + PA-824  
- PA-824 + PZA  
- PA-824 + moxifloxacin + pyrazinamide  
- Rifafour (RHZE) | n=68 (TMC207=60) | • Significant linear trend for dose of TMC207 (p=0.001)  
• Activity of 400mg TMC207 was greater than that of 100mg (p = 0.014)  
• Suggestion that the highest dose compatible with safety should be taken forward to longer-term clinical studies  
• No data available. | [48,102], [103] |
| - TMC207 (100mg - 700mg)  
- Rifafour (RHZE) | Estimated enrolment n=105 |  |  |
| - TMC207  
- PA-824  
- Pyrazinamide  
- Clofazimine  
- Rifafour (RHZE) |  |  |  |
| - TMC207 (8 weeks)  
- Placebo  
- Background regimen | n=47 (TMC207=23) | • TMC207 significantly reduced time to sputum culture conversion at 8 weeks (hazard ratio 11.8, p = 0.0003)  
• TMC207 increased the proportion of patients with sputum culture conversion at 8 weeks (48% vs. 9%)  
• TMC207 significantly reduced time to sputum culture conversion at 24 weeks (hazard ratio 2.25, p = 0.031)  
• Acquired resistance to companion drugs was reduced with TMC207 (4.8% vs 21.7%, p = 0.18) | [49,50] |
children are very limited or not available [59]. Previous studies have shown age-related changes in drug clearance, resulting in higher elimination of antituberculous agents in children and lower serum drug levels [61–64]. Therefore, pediatric studies on the pharmacokinetics and safety of existing and new antituberculous drugs as well as the development of child-friendly drug formulations are considered as research priorities [59].

Till date, no studies have been conducted to evaluate the safety, efficacy or pharmacokinetics of bedaquiline within the pediatric population [44]. Current CDC guidelines discuss the use of bedaquiline in children on a case-by-case basis when an effective treatment regimen cannot otherwise be provided [65]. Withholding or

<table>
<thead>
<tr>
<th>Study (year) trial registry no.</th>
<th>Short study title</th>
<th>Study design, sites and completion date</th>
<th>Primary objectives</th>
<th>Secondary objectives</th>
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<tr>
<td><strong>Stage 2</strong></td>
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<tr>
<td>Diacon et al. (2014)</td>
<td></td>
<td>Multicentre double-blind placebo-controlled trial</td>
<td>Time to Sputum Culture Conversion at Week 24 and 72</td>
<td>Safety and tolerability; rates of culture conversion after 24 weeks and 120 weeks</td>
</tr>
<tr>
<td>NCT00449644</td>
<td></td>
<td>Brazil, India, Latvia, Peru, Philippines, Russian Federation, South Africa, Thailand January 2012</td>
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<tr>
<td>NCT0061462</td>
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<td>NCT00614627</td>
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<td>NCT00910871</td>
<td>Safety, tolerability, and efficacy of TMC207 in individualized MDR-TB regimens in pulmonary MDR-TB and XDR-TB</td>
<td>Open-label single arm study</td>
<td>Median Time to Sputum Culture Conversion (24 weeks)</td>
<td>Rate of Participants With Sputum Culture Conversion (24 weeks); pharmacokinetics; safety</td>
</tr>
<tr>
<td>NCT00980811</td>
<td></td>
<td>33 sites (Asia, South Africa, Eastern Europe, South America) January 2013</td>
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<tr>
<td>NCT02193776</td>
<td>Efficacy, Safety and Tolerability of TMC207, Moxifloxacin, PA-824 and Pyrazinamide in Patients With Pulmonary DS- or MDR-TB</td>
<td>Open-label randomized study</td>
<td>Bactericidal activity by change in time to sputum culture conversion days 0-56</td>
<td>Detailed early and late bactericidal activity, pharmacokinetics</td>
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<td></td>
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<td>South Africa, Tanzania, Uganda</td>
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off-label use of bedaquiline in children may continue until data from a recently initiated pediatric bedaquiline development program will be approved.

In 2013, Janssen Pharmaceuticals started a pediatric bedaquiline program with the development of two pediatric formulations, a dispersible tablet and a granule formulation of bedaquiline. A Phase I open-label, randomized study assessed the relative bioavailability of a single dose of the two pediatric bedaquiline formulations in comparison to a tablet formulation and in relation to food in healthy adults. The study enrolled 36 participants and was completed in the Netherlands in August 2013. Results on pharmacokinetic parameters, safety, effect of food on bioavailability and taste are not yet available.
The first study of bedaquiline in children is planned in collaboration with International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) with the start of recruitment being scheduled for early 2015. The study will be a Phase I/II open-label, single-arm study to evaluate the pharmacokinetics, safety, tolerability and antimycobacterial activity of bedaquiline in combination with optimized background regimen treatment of HIV-uninfected and HIV-infected children and adolescents with MDR-TB disease [66]. An adult tablet formulation of bedaquiline will be studied in adolescents and older children first; thereafter, younger children as well as toddlers and infants will be recruited to receive a pediatric formulation of bedaquiline which will be selected based on results from the completed bioavailability study in adults.

RATIONAL USE OF BEDAQUILINE, ACCESS & THE NEED FOR MONITORING

Following FDA approval, the WHO Interim Policy Guidance on Bedaquiline specifies that bedaquiline may be used as part of a MDR-TB treatment regimen when an effective MDR-TB regimen cannot otherwise be provided, and provided the following five conditions are met [67]: effective treatment and monitoring using sound protocols by relevant national authorities; proper patient inclusion with special caution if used in elderly or HIV-infected patients (use in pregnant women and children is not advised); patients need to be aware of the potential benefits and harms of the new drug and give documented informed consent; adherence to WHO treatment recommendations for MDR-TB, especially the inclusion of four effective second-line drugs, and active pharmacovigilance measures must be in place to ensure early detection of adverse events.

The recommended dosage for bedaquiline is 400 mg once daily for 2 weeks, followed by 200 mg three-times a week for 22 weeks, taken orally with food in order to maximize absorption [44]. Bedaquiline should never be used as a single drug and should be used only in combination with at least three other drugs (i.e., for a four-drug regimen) to which the patient’s MDR-TB isolate has been shown to be susceptible in vitro. As bedaquiline has a particularly long terminal half-life (4–5 months), it should be discontinued 4–5 months prior to scheduled treatment termination to avoid bedaquiline being the sole effective circulating TB drug [68]. Sputum culture monitoring is recommended monthly during the treatment course, even after conversion to negative result [68]. All patients receiving bedaquiline need to be monitored for elevation of transaminases and QTc prolongation prior to treatment initiation and monthly thereafter or if symptomatic [68]. Specific caution should
be warranted when bedaquiline is co-administered with drugs associated with QTc prolongation, such as moxifloxacin or clofazimine, a fact that also hampers the prospects for exploring combinations of both novel drugs delamanid and bedaquiline in combination regimens [14]. Also, co-administration with drugs that induce (e.g., rifamycins) [35,36] or inhibit (e.g., ketoconazole or lopinavir/ritonavir) CYP3A4 should be avoided where possible, as serum drug levels of bedaquiline can be either decreased (potentially leading to development of resistance) or increased (leading to an increased risk of development of adverse events).

In a symposium organized by the European Respiratory Society (ERS), supranational agencies such as WHO and The European & Developing Countries Clinical Trials Partnership (EDCTP) came together with industry and key TB stakeholders to discuss and agree on the common principles of rational introduction and responsible use of new TB tools [69]. The Policy Implementation Package for New TB Drug Introduction, published by WHO in 2014, addresses the challenges in preparing and enabling safe and effective uptake of new drugs or regimens under programmatic conditions and aims at supporting countries in preparing for introduction of new TB drugs [70]. For the individual case and clinical decision on how to design a regimen including a new drug, a team-based decision by experts appears sensible and could follow the model of the ERS-WHO Electronic Consilium, launched in 2012, with the overarching aim to provide scientifically sound and evidence-based advice to national consilia and individual clinicians [71,72].

In many countries, bedaquiline is not registered yet. However, several countries have set up programs allowing distribution of bedaquiline within the pre-approval period through ‘compassionate use’ or ‘expanded access’. These programs are conceived for patients whose treatment alternatives have been exhausted and for whom the access to the investigational new drug is essential in a timely manner [73]. At the same time, ‘compassionate use’ refers to individual physicians applying directly to the manufacturer and being responsible for acting within the national regulations, while the manufacturers provide administration guidelines but do not monitor treatment outcomes. ‘Expanded access programs’ refer to clinical trial-like set-ups by the manufacturer into which patients meeting specific criteria can be enrolled and within which follow-up will take place [73]. As for TB there has not been a need for such compassionate use/early access programs until recently. RESIST-TB and the Critical Path to TB Drug Regimens’ Access and Appropriate Use Working Group developed specific concepts and principles for pre-approval TB drug distribution programs and the following goals were formulated: to protect patients, to minimize the risk of treatment failure and emergence of resistance, to exercise fairness and to comply with regulatory guidance [73]. An exemplary model for a compassionate use/early access program combined with enhancement of capacity for future research
on drug-resistant TB has been reported from South Africa [74]. This far-sighted approach clearly acknowledges the persistent need for further new effective, safe and evidence-based treatment regimens even beyond the availability of and access to bedaquiline. Unfortunately, many countries with high MDR-TB burden still lack adequate infrastructure for diagnosing MDR-TB and perform drug sensitivity testing and optimal MDR-TB management – all prerequisites before introducing new TB drugs, irrespective of their pre-approval or post-approval status. For the majority of low and middle-income countries, bedaquiline can only be procured through the Global Drug Facility [75]. There is no special funding; bedaquiline is supposed to be financed through national TB programs. Although the cost–effectiveness model of WHO (estimating the unit cost per patient treatment with bedaquiline at US$ 900 and US$ 3000 for global fund eligible countries and all other countries, respectively) indicated that adding bedaquiline to WHO-recommended MDR-TB treatment was likely to be cost-effective in most environments [76,77], incremental cost–effectiveness should not be taken as a proxy for affordability or a country’s willingness to pay [77].

EXPERIENCES FROM COMPASSIONATE USE/EARLY ACCESS OF BEDAQUILINE

First experiences from compassionate use of bedaquiline were recently published and provide first data on the use of bedaquiline beyond clinical trial settings.

The first cases with compassionate use of bedaquiline for XDR-TB were published in the European Respiratory Journal in January 2014. Tiberi et al. reported on two HIV-negative patients from Italy with pre-XDR-TB and XDR-TB, who had limited treatment options and suffered from different adverse events [78]. Both patients received bedaquiline for 24 weeks, in addition to a background regimen including clofazimine and achieved culture conversion after around 2 months without any additional adverse events or QT interval prolongation. A case report on bedaquiline use for primary pulmonary and pericardial XDR-TB in a patient in the UK was reported by van Halsema et al. [79]. Bedaquiline was started at week 14 when full drug sensitivity testing became available and was given for 24 weeks. No specific adverse events were attributed to bedaquiline and the patient remained culture negative at the end of her planned 2-year treatment regimen.

Danckers et al. reported on the first XDR-TB patient treated with bedaquiline in the USA. After lobectomy for severe disease and around 90 months of multi-second-line drug treatment, the patient experienced severe drug reactions, especially to linezolid, which needed to be discontinued prematurely. At this time, bedaquiline
was started and administered for 24 weeks in parallel to six further second-line tu-
berculostatics. The authors report that bedaquiline was well tolerated and that the
patient had a favorable outcome 10 months after the completion of treatment [80].

Experience with five patients (one HIV-infected) from India was published by
Udwadia et al. [81]; all patients received bedaquiline for MDR-TB or XDR-TB after fail-
ing second-line drug regimens of between 4 and 40 months duration. Bedaquiline
was added onto an individualized optimal background regimen for 24 weeks. Beda-
quiline was well tolerated; despite clofazimine and moxifloxacin co-administration
in five and two patients, respectively, no QTc prolongation was observed. Sputum
conversions occurred after around 3 months and were sustained after stopping
bedaquiline.

Data from a retrospective French cohort study report on the outcomes at 6
months of bedaquiline treatment in 35 patients (all HIV-negative, but half of them
hepatitis C positive) with drug-resistant TB (19 patients with XDR-TB) [82]. Most pa-
tients had a history of previous TB treatment and 49% had already been treated with
second-line drugs. Background regimens included clofazimine in five patients, and
89% patients received at least a fluoroquinolone or a second-line injectable drug. At
6 months of bedaquiline treatment, culture conversion was achieved with a median
time of 85 days (range 8–235 days) in 28 of 29 (97%) patients with culture-positive
pulmonary TB at bedaquiline initiation. Fluoroquinolone-containing regimens were
significantly associated with culture and sputum-smear conversion after 3 months.
Longer time to culture conversion was associated with the presence of lung cavi-
tations and with hepatitis C infection. At 6 months of bedaquiline treatment, only
one patient remained culture positive; in this case, culture conversion was finally
achieved after 235 days of bedaquiline treatment. One-fifth of patients showed a
‡60 ms increase in QT interval. The increase was greater, although not statistically
significantly so, in patients receiving a fluoroquinolone or clofazimine containing
background regimen; three (9%) had a QTcB value >500 ms without a significant as-
sociation to fluoroquinolone or clofazimine. However, persistent QTcB prolongation
led to premature bedaquiline discontinuation in 2 (6%) patients. One patient died
due to a bedaquiline-unrelated malignancy. Long-term efficacy and safety outcomes
of this cohort are not available yet.

Of concern is a case report by Somoskovi et al. describing acquired drug resis-
tance to bedaquiline in a patient with MDRTB [83]. The patient received bedaqui-
line for 6 months, culture converted during this time and continued second-line
therapy for another 12 months. Five months later, the patient was re-admitted with
acid-fast bacilli in his sputum. Antituberculous treatment was re-initiated without
bedaquiline, as the manufacturer rejected a request for repeated administration of
bedaquiline. Surprisingly, the drug susceptibility results from re-admission showed
new clofazimine resistance, although the patient had never received clofazimine. Molecular studies on the isolates revealed a mutation in the Rv0678 gene, which has previously been shown to be responsible for in vitro cross-resistance between clofazimine and bedaquiline by resulting in overexpression of the efflux pump mmpL5 gene [84]. Data on acquired resistance to bedaquiline in vivo were further published by Andries et al. [85]. Paired clinical isolates with increased minimal inhibitory concentrations for bedaquiline from patients participating in a clinical trial completed in January 2013 [86] were studied for the mechanism of resistance to bedaquiline and cross-resistance to clofazimine, which was found to be due to mutations in Rv0678, a transcriptional repressor of the genes encoding the MmpS5–MmpL5 efflux pump. These findings suggest that bedaquiline and clofazimine will not protect each other against the emergence of resistance.

In summary, experience on 45 patients receiving bedaquiline for compassionate use due to limited other effective or tolerable treatment options has been published; for the first time, these reports include data on patients with drug-resistant extrapulmonary TB, on patients who had already received various TB drugs before and on those who were on bedaquiline treatment for up to 235 days. Overall, a high efficacy was observed and no new safety concerns arose. Although it is too early to draw conclusions from these experiences, available data on compassionate use is reassuring with regard to further use of bedaquiline within the approved indications and as well for patients with XDR-TB or with co-morbidities.

SUMMARY & AUTHOR’S EXPERT COMMENTARY ON THE CURRENT STATUS OF THE FIELD

Bedaquiline is a much-needed novel drug which is highly effective against drug-resistant TB. While its clinical development has been laudably fast-tracked to a stage that it is now available for inclusion into treatment regimens when no alternatives exist, clinical experience with bedaquiline is still at an early stage. The excitement about bedaquiline’s success must not derogate the need for extended Phase III and Phase IV studies, which are either in advanced stage of planning or underway. Access to bedaquiline is still limited for many patients by infrastructural or regulatory obstacles, or by restrictions due to insufficient data as in the case of children.
FIVE-YEAR VIEW

Within 5 years, a wealth of crucial additional clinical data addressing yet unanswered questions on safety, efficacy, optimal duration of treatment and compatibility with other novel TB drugs will have been obtained. As well, information on bedaquiline’s value as part of shortened regimens for drug-sensitive TB may be at hand, raising the question on whether to safeguard novel drugs for drug-resistant TB treatment only or not. Tools for comprehensive international pharmacovigilance will be set up, and tools to better monitor drug resistance to bedaquiline will have been developed.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

MP Grobusch served as South African PI on the TMC207-C208 and C209 trials and is a member of the Bedaquiline Advisory Board to Janssen Pharmaceuticals. S Bélard is a participant in the Charité Clinical Scientist Program funded by the Charité-Universitätsmedizin Berlin and the Berlin Institute of Health. S Janssen is partially funded through a Marie Curie People grant. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

KEY ISSUES

• Bedaquiline belongs to a new class of antituberculous drugs (diarylquinolines) and has received fast-track approval for the treatment of multidrug-resistant tuberculosis (MDR-TB) by the US FDA in 2012.
• Bedaquiline inhibits the mycobacterial ATP synthase; its activity against drug-sensitive and drug-resistant TB has been demonstrated in pre-clinical studies.
• Eleven Phase I trials provided understanding on pharmacokinetic characteristics, drug–drug interactions (with antiretrovirals, rifamycins and fluoroquinolones) and safety.
• Four Phase II trials evaluating early bactericidal activity in drug-sensitive pulmonary TB patients showed significant bactericidal activity from day 4 onward and a significant linear trend for dose.
• Bedaquiline added for 8 weeks to a background regimen for the treatment of pulmonary MDR-TB significantly reduced the time to sputum culture conversion,
increased the proportion of patients with sputum culture conversion at 8 weeks (48 vs 9%) and reduced the risk for acquired resistance to companion drugs.

- Bedaquiline added for 24 weeks to a background regimen for the treatment of pulmonary MDR-TB reduced the time to culture conversion from 125 to 83 days and increased the rate of culture conversion at 24 weeks (79 vs 58%) and 120 weeks (62 vs 44%).

- In the Phase II Stage II trial, mortality was higher in the bedaquiline arm with none of the deaths having been related to bedaquiline.

- Despite FDA approval, Phase III trials are needed to expand our knowledge on the efficacy and safety of bedaquiline with particular attention to mortality.

- Following FDA approval, the WHO Interim Policy Guidance on Bedaquiline specifies that bedaquiline may be used as part of an MDR-TB treatment regimen when an effective MDR-TB regimen cannot otherwise be provided.

- Bedaquiline has been made available through regulated compassionate use/early access programs, and the first reports confirm high efficacy of bedaquiline for drug-resistance TB.
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**Long-term outcomes of the Diacon et al. NEJM 2009 trial showing that bedaquiline significantly reduced the time to sputum culture conversion at 24 weeks (hazard ratio 2.25, p = 0.031) and reduced the risk for acquired resistance to companion drugs.


**Second RCT of bedaquiline given for 24 weeks along with a background regimen for MDR-TB; bedaquiline reduced the time to culture conversion from 125 to 83 days (p < 0.001) and increased the rate of culture conversion at 24 weeks (79 vs 58%, p = 0.008) and 120 weeks (62 vs 44%, p = 0.04). Cure rates at 120 weeks were 58% in the TMC207 group and 32% in the placebo group (p = 0.003). Ten deaths occurred in the bedaquiline group and two in the placebo group, with no causal pattern evident.


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