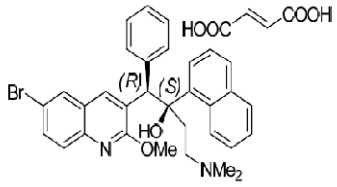
WHO/STB Expert Group Meeting

Geneva, 29-30 January 2013

The contribution of bedaquiline to the treatment of MDRTB

Synthesis of publicly available evidence



Prepared by Bernard Fourie, PhD

Commissioned by WHO Stop TB Department

21 January 2013

Key reference documents and sources of information

This summary has been condensed entirely from the following publicly available sources:

- Janssen Pharmaceutical Companies, 2012. TMC207 (bedaquiline) treatment of patients with MDR-TB (NDA 204-384). Briefing document to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012. **Briefing Document in the footnotes is referenced as BD [page number].**

- Slide set prepared by Janssen Research and Development and presented at the FDA Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012. **Slides quoted are referenced in footnotes as JRD [slide number].**

- FDA slide presentation by Dr Xianbi Li to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 entitled 'Efficacy evaluation of Bedaquiline (TMC207) in the treatment of MDR-TB.' **Slides quoted are referenced in footnotes as Li [slide number].**

- FDA slide presentation by Dr Ariel R Porcalla to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 entitled 'Review of Safety: Bedaquiline (TMC207) for the treatment of MDR-TB.' **Slides quoted are referenced in footnotes as Porcalla [slide number].**

- FDA slide presentation by Dr Dakshina M Chilukuri to the Anti-Infective Drugs Advisory Committee Meeting, 28 November 2012 entitled 'Review of Key Clinical Pharmacology Aspects of Bedaquiline.' **Slides quoted are referenced in footnotes as Chilukuri [slide number].**

All of the above are available at:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm

Table of Contents

List of abbreviations/terms

ADR	adverse drug reaction
AE	adverse event
ATP	adenosine 5'-triphosphate
AUC	area under the plasma concentration versus time curve
BR	background regimen
C0h	predose plasma concentration
CFU	colony forming unit
CI	confidence interval
CLcr	creatinine clearance
CL/F	estimate for apparent oral clearance
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CPK MB	creatine phosphokinase muscle-brain isoenzym
Css,av	average steady-state plasma concentration
CYP	cytochrome P450
DDI	drug-drug interaction
DOTS	directly observed therapy short-course
DS-TB	drug-susceptible TB
eEBA	extended early bactericidal activity
ECG	electrocardiogram
FDA	Food and Drug Administration
FQ	fluoroquinolone
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ITT	intent-to-treat
LFT	liver function test
LS	least square
M.	*Mycobacterium*
M2	*N*-monodesmethyl metabolite of TMC207
MBC	minimum bactericidal concentration
MDR	multi-drug resistant
MDR-TB	resistant to isoniazid (H) and rifampin (R) alone, excluding Pre-XDR- and XDR-TB
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
MGIT	Mycobacteria Growth Indicator Tube
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect level
NTP	National TB Program
OLSS	open-label safety study
PAS	para-aminosalicylic acid
PD	pharmacodynamic
PK	pharmacokinetic
Pre-XDR	pre-extensively drug resistant
PZA	pyrazinamide
q.d.	quaque die; once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia

SAE	serious adverse event
REMA	resazurin microtiter assay
RR	relative risk
SCC	sputum culture conversion
SLI	second line injectables
SSCC	serial sputum colony count
TB	tuberculosis
t.i.w.	3 times weekly
TMC	Tibotec Medicinal Compound
US	United States
Vc/F	apparent volume of distribution
WHO	World Health Organization
XDR	extensively drug resistant

Definition of Terms[1]

DS-TB: Drug-susceptible TB; defined as TB due to infection with a strain of *M. tuberculosis* that is susceptible to both isoniazid and rifampin, although it might be resistant to other anti-TB drugs (streptomycin mainly).

MDR-TB: Multi-drug resistant TB; defined as TB due to infection with a strain of *M. tuberculosis* that is resistant to both isoniazid and rifampin, the 2 most important first-line drugs to treat DS-TB. **Note:** Although the clinical definition of MDR-TB encompasses Pre- XDR-TB and XDR-TB, in this document MDR will be used to refer to MDR resistant to isoniazid and rifampin excluding Pre- XDR and XDR (e.g., in descriptions of trial populations or subgroups).

Pre-XDR-TB: Pre-extensively-drug resistant TB; defined as infection with MDR strains of M. tuberculosis that are resistant either to any fluoroquinolone (FQ) or at least one of the second-line injectable drugs (amikacin, kanamycin, capreomycin), but not to both.

XDR-TB: Extensively-drug resistant TB; defined as infection with MDR strains of M. tuberculosis that are resistant to at least one of the second-line injectable drugs (amikacin, kanamycin, capreomycin) and any FQ.

[1] All definitions follow the text as presented in the BD, as these definitions were applied as stated in the selection of participants into the various trials described in this document. Possible alternative definitions or terminologies that might be in use elsewhere have not been considered for the purpose of this summary.

Introduction to Bedaquiline (TMC207)

Pharmacological classification

INN: Bedaquiline (previously recognised as TMC207 or R207910)

Bedaquiline is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB).

Microbiology[2]

Bedaquiline (BDQ) has a novel mechanism of action. It binds to *Mycobacterium tuberculosis* ATP synthase, an enzyme that is essential for the generation of energy in *M. tuberculosis*. Inhibiting ATP synthesis results in bactericidal activity. The atpE gene product (subunit c, a proton pump) is the target of bedaquiline in mycobacteria. This distinct target and mode of action of bedaquiline minimizes the potential for cross-resistance with existing anti-TB drugs.

The MIC of bedaquiline against *M. tuberculosis* (both drug susceptible and resistant stains, including MDR-TB) and 21 other species is ≤0.063 μg/mL. In 3 more mycobacterial species the MIC is 0.12-0.50 μg/mL, and in a further 3 species a MIC of 4-8 μg/mL has been reported.[3] The drug is not active against non-mycobacteria. Bedaquiline has potent *in vitro* activity against both replicating and non-replicating bacilli, and significant bactericidal and sterilizing activity in the murine model of TB infection. It has been tested *in vitro* against multiple strains of *Mycobacterium tuberculosis* and is equally active against drug-sensitive (DS), drug resistant including MDR (resistant to isoniazid and rifampin), Pre-XDR (pre-extensively drug resistant), and XDR (extensively drug resistant) strains of *M. tuberculosis*.[4,5] In laboratory observations on (i) the susceptibility profile of preclinical and clinical isolates of *M. tuberculosis,* including drug-sensitive, drug resistant, MDR-, pre-extensively drug resistant (Pre-XDR)- and XDR-TB to bedaquiline, and (ii) microbiologic outcomes demonstrating favourable culture conversion rates of MDR-TB isolates from clinical trials with bedaquiline, the suggested MIC interpretive criteria for susceptible are MIC ≤ 0.5 μg/mL as determined by the agar method, and MIC ≤ 0.25 μg/mL as determined by the REMA method.[6,7]

Examining culture conversion rates by 24 weeks in the C208 and C209 clinical trials (introduced in later section on efficacy) in MDR-TB patients provide support for regarding a clinical isolate as susceptible to bedaquiline if growth is inhibited at a drug concentration of ≤ 0.5 μg/mL for *M. tuberculosis* (drug susceptibility breakpoint). Because of the lack of clinical experience with isolates of *M. tuberculosis* with MICs > 0.5 μg/mL, a susceptible only breakpoint of ≤ 0.5 μg/mL is proposed.

---

[2] BD Section 2.2 pp51-55

[3] Andries K, et al. Science 2005; 307:223

[4] Huitric E, et al. Antimicrob Agents Chemother 2007; 51: 4202- 4204.

[5] Lounis N, De Paepe , Van Baelen B, Andries K. A Phase II, open-label trial with TMC207 as part of a multi-drug resistant tuberculosis (MDR-TB) treatment regimen in subjects with sputum smear-positive pulmonary infection with MDR-TB. Clinical Microbiology Report, Janssen Research and Development, 8 May 2012.

[6] The Resazurin Microtiter Assay (REMA) in 7H9 broth medium has been shown to be accurate in detecting resistance to isoniazid, rifampin and second-line drugs in clinical isolates. This method has been conditionally endorsed by the WHO for DST of isoniazid and rifampin.

[7] World Health Organization. Noncommercial culture and drug-susceptibility testing. Policy statement. 2011. WHO/HTM/TB/2011.9

Clinical development of Bedaquiline

The clinical development strategy followed by Tibotec/Janssen Pharmaceutical to bring bedaquiline to the market is schematically presented below in **Figure 1**. A total of 265 subjects participated in **11 Phase I trials** with bedaquiline (208 subjects were enrolled in 8 single dose trials evaluating bedaquiline doses up to 800 mg; and 57 subjects were enrolled in 3 multiple dose trials evaluating bedaquiline doses up to 400 mg q.d. with a maximum treatment duration of 15 days). The Phase I trials have provided a basic understanding of bedaquiline's pharmacokinetic characteristics, DDI potential, and short term safety/tolerability in healthy subjects and in a special population (moderately hepatic-impaired subjects, **trial C112**).

A double-blind, single-dose trial (**TBC1003**) was conducted to evaluate the effect of a single supratherapeutic (800 mg) dose bedaquiline on the QT/QT interval corrected (QTc) interval. In addition, a Phase IIa 7-day extended early bactericidal activity (eEBA) trial (**C202**) in 75 patients with DS-TB (evaluating doses up to 400 mg bedaquiline q.d.) was conducted to evaluate clinical antimycobacterial activity of bedaquiline. The current development plan for bedaquiline reflects the understanding of both clinical and non-clinical studies with the compound, as well as an assessment of where this potential new drug can address the greatest medical need in treatment of TB.

The ongoing bedaquiline **Phase II program** currently encompasses 2 Phase IIb trials: **C208 (Stage 1 completed, Stage 2 ongoing)** and **C209 (ongoing)**.

On Dec. 28, 2012, the U.S. Food and Drug Administration approved **Sirturo (bedaquiline)** as part of combination therapy to treat adults with multi-drug resistant pulmonary tuberculosis (TB) when other alternatives are not available,[8] under the Subpart H accelerated approval mechanism.

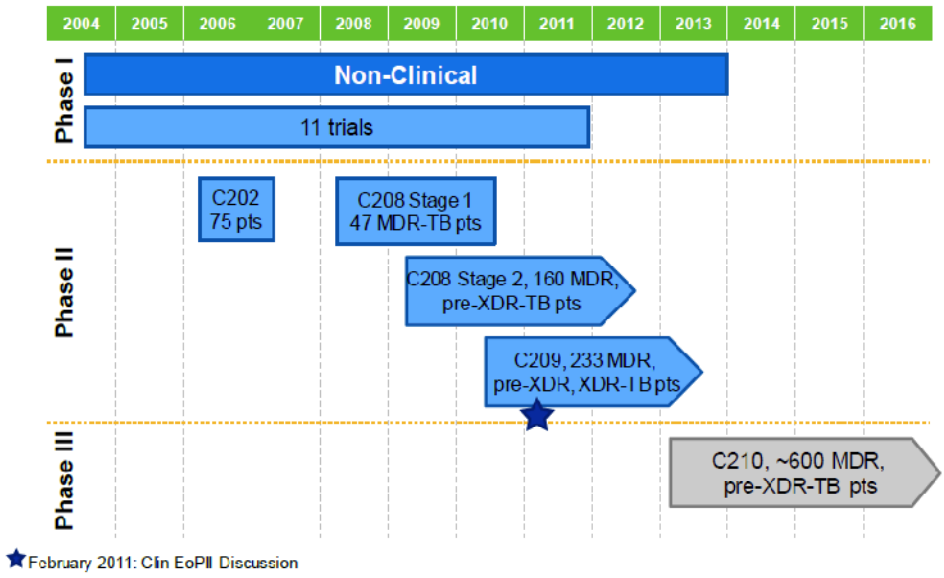


***Figure 1**. Bedaquiline clinical development pathway and timeline*

[8] FDA News Release 04 January 2013.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm

Clinical pharmacology

Pharmacokinetics data are available from 11 Phase I studies, including a single-dose & multiple-dose ranging study, a food-effect study, 5 drug-drug interaction studies, and an hepatic impairment study. A population pharmacokinetic analysis was also done.

Bedaquiline showed dose-proportional pharmacokinetics up to 700 mg after single-dose, and up to 400 mg q.d. upon repeated administration. Intake of bedaquiline with food increased the relative bioavailability by about 2-fold compared to fasted administration.[9]

Bedaquiline is primarily subjected to oxidative metabolism by CYP3A4 leading to the formation of N-monodesmethyl metabolite (M2). The M2 metabolite is not thought to contribute significantly to clinical efficacy given its lower exposure (23% to 31% compared to bedaquiline) in humans and a 3 - 6 fold lower antimycobacterial activity compared to the parent compound. However, bedaquiline is neither an inhibitor nor an inducer of major CYP enzymes.

Bedaquiline displayed a multi-phasic distribution and elimination profile with a long terminal elimination half-life ($t_{1/2,term}$) of about 5.5 months, reflecting the slow release of the compound from peripheral tissue compartments (**Figure 2**).

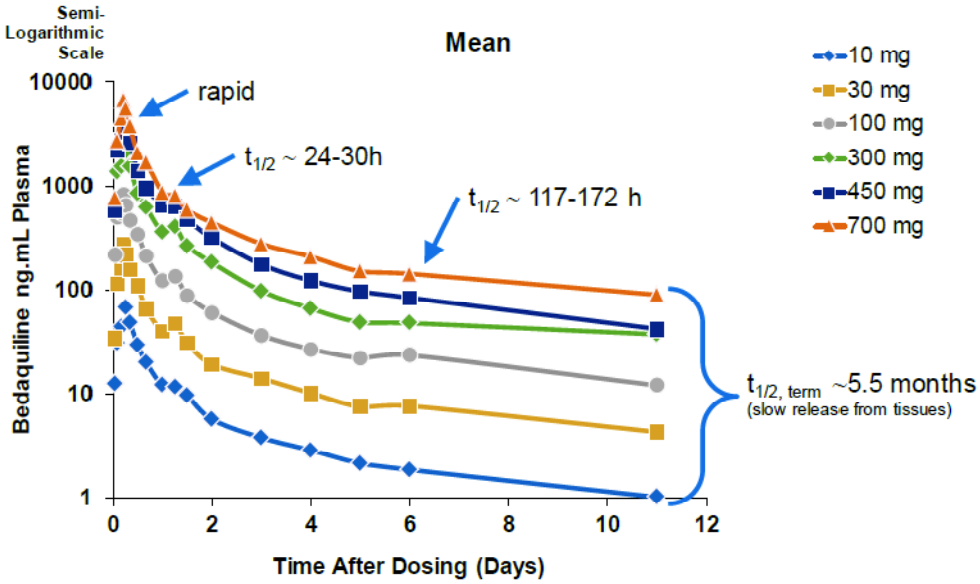


***Figure 2**. Multiphasic distribution/Elimination of bedaquiline*[10]

Impact of intrinsic factors

In the population PK analysis, black race subjects showed higher clearance rates (52%) than patients of other races (**Table 1**),[11] resulting in systemic exposure (AUC) in this race group to be 34% lower

[9] BD p71 Figure 18
[10] JRD Slide 31

than in patients of other race categories. The results of the final population pharmacokinetic analysis relative to conversion rates, however, showed that no dosage adjustment is needed based on race (**Table 2**).[12]

***Table 1**. Estimates of apparent oral clearance rates by race based on population PK analysis*

Parameters		N	Mean	SD
Apparent oral clearance (CL/F) (L/h)	Asian	99	2.73	0.84
	Black	149	5.28	2.39
	Caucasian/White	134	3.61	1.54
	Hispanic	41	3.7	0.88
	Other	57	3.84	2.15

***Table 2.** Week 24 culture conversion rates by race in Trail C208 Stage 2*

Race	Bedaquiline	Placebo
Asian	8/9 (88.9%)	5/6 (83.3%)
Black (South Africa)	17/24 (70.8%)	18/25 (72.0%)
Caucasian/White	4/6 (66.7%)	4/8 (50.0%)
Hispanic	4/6 (66.7%)	5/10 (50.3%)
Other	11/15 (73.3%)	6/17 (35.3%)

In the **Phase I drug-drug interaction (DDI) trials**, bedaquiline was coadministered with drugs from various classes, including CYP3A inducers and inhibitors. The outcomes of these studies are shown in **Tables 3-5** below.[13] Results show that co-administration of bedaquiline and drugs that induce CYP3A (e.g., rifampin) may decrease bedaquiline plasma concentrations and potentially reduce its therapeutic effect. Conversely, co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors (e.g. ketoconazole) may increase the systemic exposure to bedaquiline which could potentially increase the risk of adverse reactions. In co-administration with ketoconazole, a strong CYP3A inhibitor, the bedaquiline C_{max} and AUC increased by 9% and 22% respectively. M2 C_{max} and AUC showed no changes. Co-administering bedaquiline with certain anti-retrovirals in HIV-TB co-infected individuals, showed that single dose administration of BDQ with Kaletra® (lopinavir/ritonavir combination) at steady-state resulted in 22% increase in AUC, but no change in C_{max} of BDQ. A DDI trial with single dose BDQ + steady-state Nevirapine resulted in no significant change in C_{max} and AUC.

No clinically relevant DDIs were observed with a range of commonly used drugs for MDR-TB, including pyrazinamide, ethambutol, kanamycin, ofloxacin, cycloserine. However, co-administration with rifampin (used in the treatment of DS-TB and non-rifampin resistant TB), a strong CYP inducer, resulted in the bedaquiline C_{max} and AUC being decreased by 43% and 52%, respectively. The M2 C_{max} and AUC increased by 31% and 21%, respectively.

[11] BD p78; Chilukuri Slide 7
[12] Chilukuri Slide 8
[13] BD pp74-77 for discussion

Table 3. *Drug interactions: Plasma pharmacokinetic parameters for TMC207 in the presence of co-administered drugs*[14]

Coadministered Drug Dose/Schedule (Trial)	TMC207 Dose/Schedule Analyte	N	PK Effect[a]	Mean Ratio (90% CI) of TMC207 Pharmacokinetic Parameters With/Without Coadministered Drug No Effect = 1		
				C_{max}	AUC	C_{min}
Anti-Tuberculosis Drugs						
Rifampin[b] 600 mg q.d. 7 days	**TMC207** 300 mg single dose	16	↓	0.57 (0.48 - 0.67)	0.48 (0.43 - 0.54)	-
Isoniazid and pyrazinamide 300/2000 mg q.d. 5 days	**TMC207** 400 mg q.d. 15 days	22	↔	0.94 (0.89 - 1.00)	0.87 (0.84 - 0.91)	0.92 (0.88 - 0.96)
Other Drugs						
Ketoconazole 400 mg q.d. 3 days	**TMC207** 400 mg q.d. 14 days	15	↑	1.09 (0.98 - 1.21)	1.22 (1.12 - 1.32)	1.33 (1.24 - 1.43)
Lopinavir/ Ritonavir 400/100 mg q.d. 24 days	**TMC207** 400 mg single dose	13	↑	0.99 (0.88 - 1.12)	1.22 (1.11 - 1.34)	-
Nevirapine 200 mg b.i.d. 4 weeks	**TMC207** 400 mg single dose	16	↔	0.80 (0.62 - 1.04)	1.03 (0.87 - 1.22)	-

N = maximum number of subjects with data; - = no information available.
[a] Pharmacokinetic effect according to change in mean ratio for AUC.
[b] Only trial in which TMC207 was administered under fasted conditions.

[14] BD Table 15 p73

***Table 4**. Drug interactions: Plasma pharmacokinetic parameters for co-administered drugs in the presence of TMC207*[15]

Coadministered Drug Dose/Schedule Analyte (Trial)	TMC207 Dose/Schedule	N	PK Effect [a]	Mean Ratio (90% CI) of Coadministered Drug Pharmacokinetic Parameters With/Without TMC207 No Effect = 1		
				C_{max}	AUC	C_{min}
Anti-Tuberculosis Drugs						
Rifampin [b] 600 mg q.d. 7 days	300 mg single dose	16	↓	0.73 (0.65 - 0.81)	0.57 (0.53 - 0.62)	-
Isoniazid 300 mg q.d. 5 days	400 mg q.d. 15 days	22	↔	1.20 (1.09 - 1.33)	1.07 (1.02 - 1.11)	1.20 [c] (1.08 - 1.32)
Pyrazinamide 2000 mg q.d. 5 days	400 mg q.d. 15 days	22	↔	1.10 (1.07 - 1.14)	1.08 (1.06 - 1.11)	1.18 (1.12 - 1.25)
Other Drugs						
Ketoconazole 400 mg q.d. 3 days	400 mg q.d. 14 days	15	↔	0.93 (0.87 - 0.98)	0.89 (0.84 - 0.94)	0.55 (0.44 - 0.70)
Lopinavir 400 mg q.d. 24 days	400 mg single dose	13	↓	-	-	0.79 [c] (0.72 - 0.87)
Ritonavir 100 mg q.d. 24 days		13	↓	-	-	0.86 [c] (0.78 - 0.94)[f]
Nevirapine 200 mg b.i.d. 4 weeks	400 mg single dose	16	↔	-	-	0.99 [c] (0.91 - 1.08)

N = maximum number of subjects with data; - = no information available.
[a] Pharmacokinetic effect according to change in mean ratio for AUC.
[b] Only trial in which TMC207 was administered under fasted conditions.
[c] C_{0h} value.

[15] BD Table 16 p74

***Table 5**. Drug interactions: Plasma pharmacokinetic parameters for background regimen anti-TB drugs in the presence of TMC207*[16]

Coadministered Drug Dose/Schedule Analyte (Trial)	TMC207 Dose/Schedule	N	PK Effect [a]	Mean Ratio (90% CI) of Background Regimen Anti-TB Drug Pharmacokinetic Parameters With/Without TMC207 No Effect = 1		
				C_{max}	AUC	C_{min}
Anti-Tuberculosis Drugs						
Pyrazinamide Dose normalized to 1500 mg q.d. (**C208, Stage 1**)	400 mg q.d. 2 Weeks	20	↑	0.99 (0.87 - 1.13)	1.10 (0.92 - 1.32)	1.03 (0.75 - 1.42)
Ethambutol dose normalized to 1200 mg. q.d. (**C208, Stage 1**)	400 mg q.d. 2 Weeks	13	↑	1.02 (0.77 - 1.34)	1.16 (0.95 - 1.42)	1.23 (0.85 - 1.78)
Kanamycin dose normalized to 1000 mg q.d. (**C208, Stage 1**)	400 mg q.d. 2 Weeks	16	↑ [b]	1.32 1.03 - 1.71	1.51 (1.15 - 1.98)	-
Ofloxacin Dose normalized to 600 mg q.d. (**C208, Stage 1**)	400 mg q.d. 2 Weeks	21	↔	0.96 (0.81 - 1.15)	1.00 (0.84 - 1.19)	-
Cycloserine/ Terizidone Dose normalized to 750 mg q.d. (cycloserine and terizidone combined) (**C208, Stage 1**)	400 mg q.d. 2 Weeks	8	↔	-	-	1.15 [c] (0.78 - 1.68)

N=maximum number of subjects with data; - = no information available.

[a] Pharmacokinetic effect is driven by AUC where available.

[b] Increase is probably an artifact of the difference in renal clearance between the TMC207 and placebo treatment groups.

[c] $C_{ss,avg}$ value.

[16] BD Table 17 p77

Early Bactericidal Activity

In a **Phase IIa (C202)**, proof-of-principle, open-label, randomized trial in treatment-naïve subjects with sputum smear-positive pulmonary DS-TB, the early bactericidal activity of 3 different doses of bedaquiline were compared to standard doses of rifampin or isoniazid. Short-term safety, tolerability, and the PK of bedaquiline were also evaluated. This study formed the basis for the dose indication and schedule for bedaquiline in MDR-TB, as used in the **pivotal C208 Phase IIb** study.

The primary endpoint used to assess the activity of the drugs was the degree of reduction in the sputum viable colony forming unit (CFU) count over a 7-day period (i.e., extended early bactericidal activity, or eEBA). Bedaquiline was dosed at 25 mg, 100 mg, or 400 mg q.d., rifampin was dosed at 600 mg q.d., and isoniazid at 300 mg q.d.; all were administered as monotherapy for 7 days. Thereafter, subjects in all treatment groups received standard anti-TB therapy according to national TB treatment guidelines. The 400-mg q.d. dose regimen of bedaquiline was the highest multiple dose regimen evaluated in earlier Phase I trials with bedaquiline.

In subjects with DS-TB, a significant decrease in log10 CFU counts compared to baseline was observed with bedaquiline 400 mg, which was apparent from Day 4 onwards. The lower bedaquiline doses (25 mg and 100 mg) did not show relevant changes during the 7 days of treatment. Changes in $\log_{10}$ sputum CFU counts from baseline over time with 95% CI are shown in **Figure 3** below. There seemed to be a delay in onset of bactericidal activity for subjects receiving bedaquiline 400 mg g.d. treatment (from Day 4 onwards) compared to subjects receiving rifampin or isoniazid (from Day 1 onwards). On Day 7, mean change from baseline in $\log_{10}$ sputum CFU counts was smaller for the bedaquiline 400 mg group compared to the rifampin and isoniazid groups. Note that Day 8 $\log_{10}$ sputum CFU counts are affected by standard TB treatment, which was initiated on Day 8.[17]

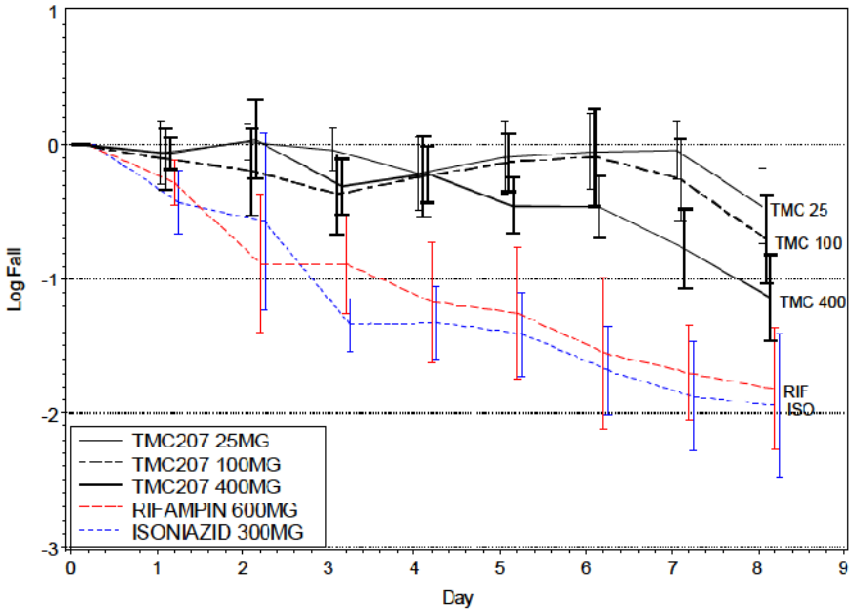


***Figure 3**. Changes in $\log_{10}$ sputum CFU counts from Phase IIa EBA study (C202)*

[17] Rustomjee R. et al. Antimicrob. Agents Chemother. 2008;52(8):2831-2835

Evidence for the efficacy of Bedaquiline in the treatment of MDR-TB

Data from two **Phase IIb studies** are available for review of efficacy: **Study C208,** consisting of two stages, of which **Stage 1** was an exploratory study an **Stage 2** was a multi-centre, stratified, randomised, double-blind placebo-controlled trail, serving as a pivotal proof-of-efficacy study. **Study C209** is a single-arm, open label trial.

Study C208 Stage 2

For study **C208 Stage 2**, subjects aged 18 to 65 years of age with newly diagnosed MDRTB were randomised in a 1:1 ratio to receive bedaquiline (BDQ) 400 mg, or placebo, daily for the first 2 weeks, followed by 200 mg BDQ, or placebo, three times per week for the remaining 22 weeks.[18] In both the BDQ and placebo arms, patients received a standardised 5-drug MDR-TB background medication regimen (BR) consisting of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone.

The most frequently used anti-TB drugs in the baseline BR (i.e., within the first 2 weeks of investigational treatment) for subjects in the ITT population of **Stage 2** were fluoroquinolones (99.4%; mainly ofloxacin: 74.4%), aminoglycosides (95.6%; mainly kanamycin: 62.5%), pyrazinamide (93.1%), ethionamide (84.4%), and ethambutol (65.0%). No clinically significant differences between the treatment groups in the use of these drugs were noted. Other baseline BR drugs (including cycloserine and terizidone) were taken by < 30.0% of ITT subjects.[19]

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

Efficacy analysis

The **primary efficacy endpoint for C208 Stage 2 was time to sputum culture conversion** in MGIT during the 24-week investigational treatment period, this was evaluated after all subjects had completed the 24-week investigational treatment period, or discontinued earlier. In the primary efficacy analysis, subjects who discontinued before week 24 were considered as not having culture converted (censored at the last culture visit, i.e. missing = failure).

Primary efficacy analysis is based on the mITT population, which excludes subjects who had DS-TB, XDR-TB or unconfirmed MDR-TB based on susceptibility tests taken prior to randomization, or had missing or negative baseline cultures, or who were positive at baseline, but had no post baseline culture results. (**Table 6**)

[18] This dose regimen was selected based on non-clinical safety and microbiology data as well as safety and pharmacokinetic results from several Phase I clinical trials with bedaquiline and early bactericidal activity results from the earlier Phase IIa trial C202.
[19] BD p104

***Table 6**. Disposition of subjects in C208 Stage 2*[20]

	Bedaquiline	Placebo
Randomised	80	81
Treated (ITT)	79	81
mITT	66	66
Excluded from mITT	13	15
(MGIT results did not allow for primary efficacy analysis)	(6)	(3)
(DS or XDR-TB or MDR-TB status could not be confirmed)	(7)	(12)

Overall, 282 subjects were enrolled from 15 sites in the six regions (Asia, Eastern Europe, 3 sites in South Africa, and South America) each site with 2 to 58 subjects. Of these, 161 were randomized. After exclusions because MGIT results did not allow for primary efficacy evaluation or the patient's DS or XDR-TB or MDR-TB status could not be confirmed, the primary efficacy analysis was conducted on a mITT population of 132 subjects (66 in each of the BDQ and Placebo groups).[21] Of these, 82% and 86% (or 57 and 54 subjects) in each group had culture data available for the Week 24 primary efficacy analysis and 74% and 67% respectively in each group for Week 72 analysis.

Treatment compliance was reported to be very high (>85% subjects with a 95% or higher compliance). Baseline variables, such as age, gender, race, weight, lung cavitation were balanced between the two groups. There were 5 HIV positives in the BDQ group vs 14 in the Placebo group (7.6% vs 21.2%; p=0.045 Fischer's Exact[22]). This imbalance has not affected culture conversion rates, as can been seen from the relevant subgroup analyses (presented in Table 12 on page 19).

Results: Primary Endpoint C208 Stage 2[23]

As can be seen in **Figure 4**, the median time to culture conversion was 83 days in the bedaquiline group and 125 days in the placebo group. A Week 24 updated primary analysis, using Cox proportional hazards model adjusting for lung cavitations and pooled centre showed a statistically significant difference (p<0.0001) in time to culture conversion between the treatment groups in favour of bedaquiline over the first 24 weeks of treatment (**Table 7**). For Week 72 mITT population (**Figure 5**), the median time to culture conversion was 87 days in the bedaquiline arm vs 345 days in the placebo arm. The difference is statistically significant (p=0.029). **Figure 5** also shows the durability of the Week 24 culture conversion rate over time. Whilst conversions were gradually continuing to be recorded over the rest of the treatment period in the placebo arm, the proportion of patients who culture converted almost all did so within the first 24 weeks, and maintained their status over the rest of the treatment period.

***Table 7**: Week 24 results from the Cox proportional hazards model (mITT population)*[24]

	Relative Risk [95% CI]	P-value
Week 24 Primary – time to SCC*	2.44 [1.57, 3.80]	<0.0001
Week 72 Primary – time to SCC	1.65 [1.05, 2.59]	0.0290

* FDA's analysis: 2.15 [1.39, 3.31] p-value 0.0005

[20] Li Slide 19
[21] In their analysis, FDA included one more culture positive subject from the ITT population in the mITT population for BDQ (N=67, therefore). Where relevant in this summary, a footnote is provided.
[22] BF calculation by Proportion Test (Statistix 7)
[23] BD Figures 23 and 24 pp108-109
[24] Lin Slides 25 and 27

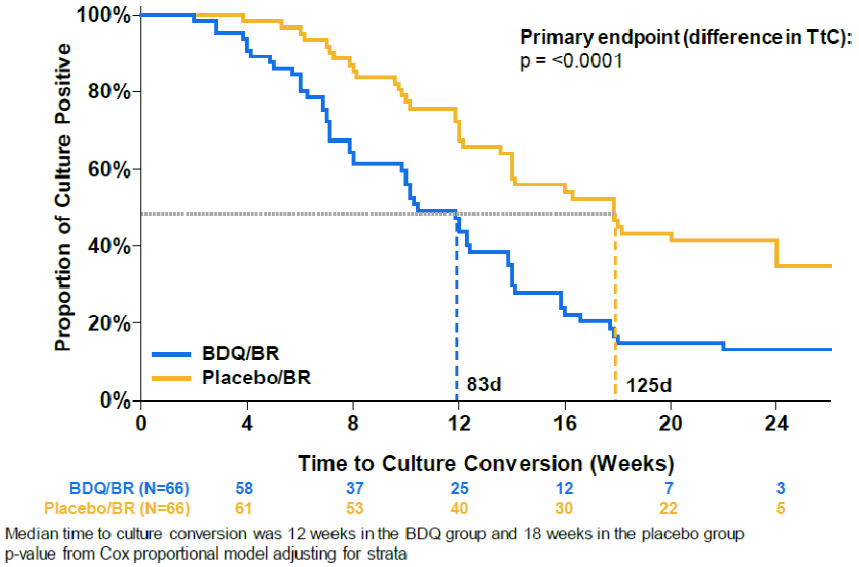


***Figure 4**. Week 24 time-to-culture-conversion (mITT)*

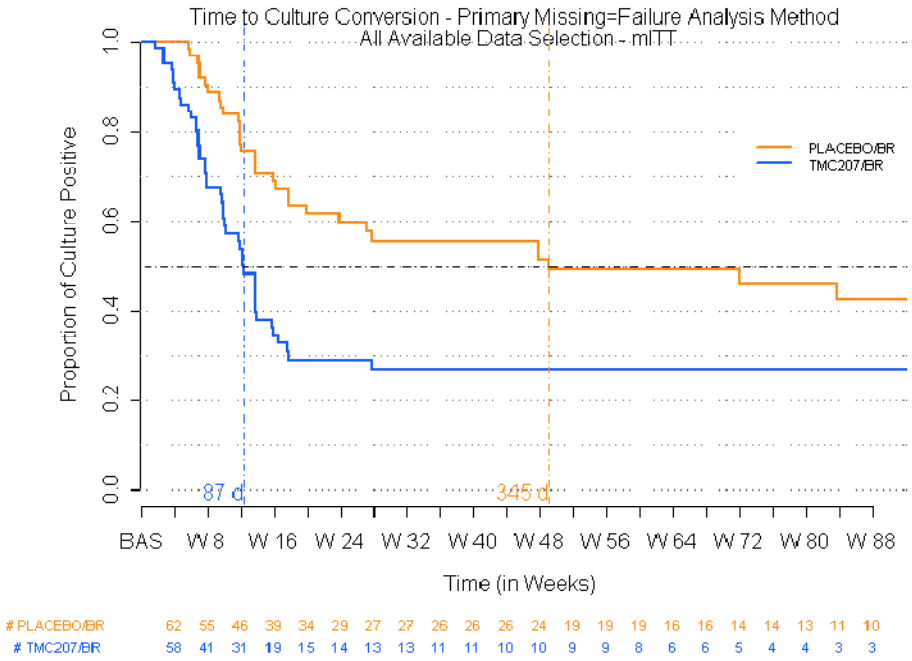


***Figure 5**. Week 72 time-to-culture-conversion (mITT)*[25]

[25] JRD Slide ST-122

Secondary endpoint: Proportion culture converted C208 stage 2[26]

The proportion of subjects with culture conversion at Week 24 (i.e., 24-week responders [missing = failure]) was: 78.8% in the bedaquiline group and 57.6% in the placebo group. The difference in proportion of responders was statistically significant (p = 0.008) based on a logistic regression model with only treatment as covariate.

Analyses similar to those for Week 24 were conducted at Week 72 and Week 120 (**Table 7**). The percentage of responders (missing = failure) at Week 72 (i.e., the time point attained by all Stage 2 subjects at the interim analysis who were ongoing in the trial) was 71.2% in the bedaquiline group and 56.1% in the placebo group (p= 0.069). Utilizing all available efficacy data up to end of study (Week 120), the percentage was 62.1% in the bedaquiline group and 43.9% in the placebo group (p= 0.035). **Table 8** provides an overview of the proportion of conversions over time (missing = failure).

By week 120, reported relapse cases[27] numbered 6/66 (9.1%) in the bedaquiline arm, and 10/66 (15.2%) in the placebo arm ([95% CI -0.17, 0.051];p=0.425).[28] The difference is not statistically significant. Calculated as a proportion of responders plus responders in the discontinued group, relapses amounted to 6/52 (11.5%) and 10/41 (24.4%) in the two arms respectively. This difference also is not statistically significant ([95% CI -0.28, 0.026];p=0.165).

Table 8: *Week 24, Week 72 and Week 120 (end of study) culture conversion proportions (mITT)*[29]

Time-point	Bedaquiline	Placebo	Diff [95% CI] P-value
Week 24*	52/66 (79%)	38/66 (58%)	21.2% [5.6%, 36.8%] 0.008
Week 72	47/66 (71%)	37/66 (56%)	15.2% [-1.2%, 31.5%] 0.069
Week 120	41/66 (62%)	29/66 (44%)	18.2% [1.3%, 35.1%] 0.035

* FDA Week 24 analysis: 52/67 (78%) vs 38/66 (58%), 20% [4.5%, 35.6%] 0.014

Subgroup analyses

Week 24 culture conversion rates were analysed by subgroup for a number of covariates, including baseline TB type, race, geographical region, and HIV-status. In general, culture conversion rates in subgroups showed that responder rates using the missing = failure response definition in the bedaquiline group were higher than or similar to those in the placebo group at Week 24, except for the pooled center 'South Africa-2' for which responder rates were lower in the bedaquiline group (9 of 13 subjects, 69.2%) compared to the placebo group (11 of 13 subjects, 84.6%).

[26] BD Table 28 p112
[27] JRD Slide EF-1
[28] BF calculation – Proportion test (Statistix 7)
[29] JRD Slide EF-142

Culture conversion rates for subgroups[30] at Week 24 show a clear treatment difference in both MDR-TB and Pre-XDR subgroups. Addition of bedaquiline to the background regimen of Pre-XDR TB patients resulted in 82.1% conversions vs 62.2% in the background regimen group only, and in XDR-TB patients 73.3% and 33.3 % respectively).

A clear treatment difference is observed between the treatment arms in both the PZA susceptible and resistant subgroups, as is evident from **Tables 9 and 10**. By both Week 24 and Week 72, the subjects on placebo have response rates which are inferior to the response rates observed in the bedaquiline subgroup. This underscores the potential effect of BDQ in a MDR-TB patient population where susceptibility to pyrazinamide as a companion drug is likely resistant (or unknown).

Table 9. *C208 Stage 2: Pyrazinamide susceptibility at baseline (MGIT960)*

Parameter	Bedaquiline/BR		Placebo/BR	
	N	24-week Responder (Missing=Failure) n (%)	N	24-week Responder (Missing=Failure) n (%)
Resistant	38	28 (73.7)	33	16 (48.5)*
Susceptible	18	16 (88.9)	25	16 (64.0)

* Fischer's Exact p <0.05 (BDQ vs Placebo)

Table 10. *C208 Stage 2: Culture Conversion Rates 72-Week Data Selection (Missing=Failure) by pyrazinamide subgroup (mITT)*

Parameter	Bedaquiline/BR		Placebo/BR	
	N (Baseline)	Culture conversion Wk 72 n (%)	N (Baseline)	Culture conversion Wk 72 n (%)
Resistant	38	27 (71.1)	33	14 (42.4)*
Susceptible	18	13 (72.2)	25	19 (76.0)

* Fischer's Exact p <0.02 (BDQ vs Placebo)

For subgroups by pooled centre, lower responder rates were observed in the 3 South African pooled centres compared to the South American site for subjects in the bedaquiline group. The number of subjects in pooled centres Asia and Eastern Europe was below 10 in both treatment arms and therefore no conclusions could be drawn from these results (**Table 11**).

An analysis by region was performed because population pharmacokinetic results showed lower exposure of bedaquiline in Black subjects compared to the other races in C208 Stage 2; the majority of subjects enrolled in South Africa designated themselves as Black (about 2/3) or of mixed or coloured (about 1/3) race.[31]

There were more discontinuations (mITT) in the region South Africa compared to the other regions, which might have affected conversion rates at week 24 (**Table 12**).

[30] BD Table 29 p116
[31] BD Table 30 p117

***Table 11**. C208 Stage 2: Culture Conversion Rates at Week 24 by region and trial discontinuation before Week 24 (mITT)*

Culture Conversion Rates	C208 Stage 2			
	TMC207/BR		Placebo/BR	
	N	24-week responder (missing = failure) n (%)	N	24-week responder (missing = failure) n (%)
by Region				
Asia	8	8 (100)	4	4 (100)
China	-	NA	-	NA
Eastern Europe	6	3 (50.0)	7	3 (42.9)
South Africa	37	27 (73.0)	42	24 (57.1)
South America	15	14 (93.3)	13	7 (53.8)
by Region, Excluding Subjects who Discontinued the Trial Before Week 24				
Asia	8	8 (100)	4	4 (100)
China	-	-	-	-
Eastern Europe	4	3 (75.0)	7	3 (42.9)
South Africa	31	27 (87.1)	34	24 (70.6)
South America	15	14 (93.3)	9	7 (77.8)

N = number of subjects in subgroup; n = number of subjects with this observation; NA = not applicable
Data on file, Janssen Research and Development

The inclusion of sites in the study from regions with high-prevalence of TB-HIV co-infection allowed for subgroup analysis by HIV status as recorded at baseline. Conversion rates at Week 24 in the BDQ group was similar for HIV positive and HIV negative subjects. However, in the placebo group, more conversions were seen in HIV positive subjects than in HIV negative (**Table 12**).

***Table 12**. C208 stage 2: Conversion by HIV at Week 24*

HIV	Bedaquiline	Placebo
Positive	4/5 (80%)	11/14 (79%)
Negative	48/61 (79%)	27/52 (52%)*

* Fischer's exact p = 0.003 (BDQ vs Placebo)

Twelve deaths were reported from **C208 Stage 2 (Figure 6)**. Of these 10/79 (12.7%) came from the BDQ group and 2/81 (2.5%) from the placebo group (also see section on Safety aspects). In the BDQ group, 4 of the 10 were culture converters at week 24.

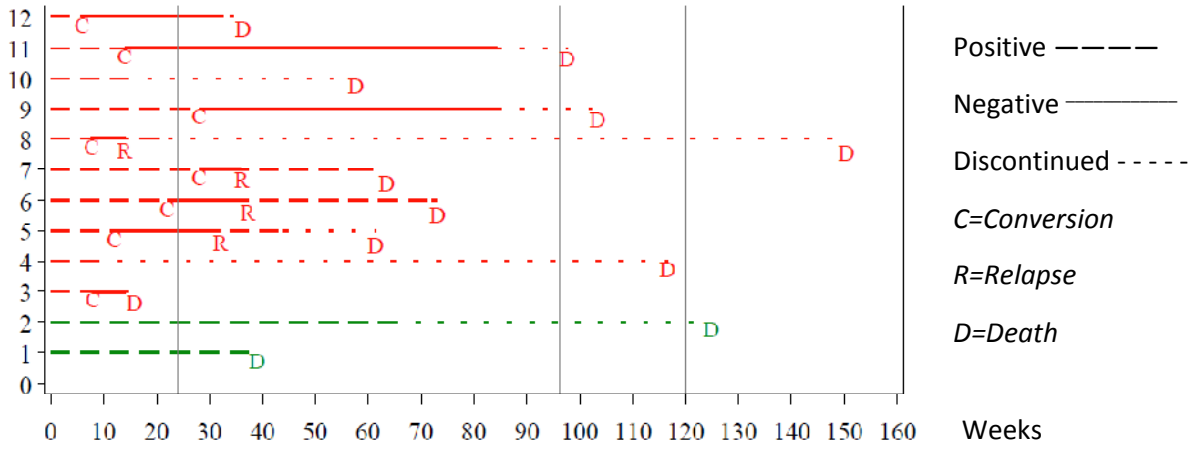


***Figure 6**. C208 Stage 2: Mortality by individual case*[32]

[32] Porcalla Slide 57

Supporting evidence from other studies

Study C208 Stage 1

This study followed the same design as in Stage 2, but the investigational treatment phase was 8 weeks (study duration: 8+96=104 weeks). The primary endpoint was time to SCC during this treatment period. There was no requirement of 25 days apart for two negative culture results.

A total of 47 subjects were randomized, 23 in the Bedaquiline group and 24 in the placebo groups, and of these 21 and 23, respectively, were included in the mITT analyses. Week 8 analysis results show that conversion was faster in the Bedaquiline group (median 72 days) than in the placebo group (126 days).

The results of a Cox proportional hazards model with lung cavitation and pooled centre as covariates showed a statistically significant difference in time to sputum conversion between the treatment groups (p = 0.0022) in favour of the bedaquiline group (hazard ratio [95% CI]: 3.14 [1.51; 6.53]),[33] and a pronounced treatment effect (RR 11.77 [95% CI 2.26 – 61.23] p-value 0.0034).[34]

***Table 13**. C208 Stage 1: Culture conversion rates*[35]

Week	Bedaquiline N=21	Placebo N=23	Diff (95% CI); p-value
8	10 (47.6%)	2 (8.7%)	38.9% [12.3%, 63.1%]; p= 0.004
24	17 (81.0%)	15 (65.2%)	14.8% [-11.9%, 41.9%]; p= 0.29
104 (Final)	11 (52.4%)	11 (47.8%)	4.6% [-25.5%, 34.1%]; p= 0.76

Study C209

Design was a single-arm open-label study in subjects with confirmed pulmonary MDR-TB, including subjects with XDR-TB. The same treatment and same regions as in Stage 2 were retained.

Time to culture conversion during the 24-week treatment period with bedaquiline was also the primary efficacy outcome parameter for trial C209. C209 differs from C208 Stage 2 in that subjects were included who were either newly or non-newly diagnosed with MDR-TB, whereas in C208 previous use of second-line drugs was an exclusion criterion. A total of 233 were treated (37 XDR-TB), 205 were included in mITT population, and all subjects had completed week 24 visit or had discontinued.

The median time to sputum culture conversion (SCC) in the mITT population was 57 days [95% CI 56-83],[36] with 80% of subjects in the mITT population achieving culture conversion at the end of Week 24 [95% CI 73%, 85%].[37] The somewhat shorter median time to culture conversion relative to C208

[33] BD Figure 21 p94
[34] Li Slide 42
[35] Li Slide 44
[36] BD Figure 29 p128
[37] BD Table 38 p130

Stage 2 (83 days) likely reflects the fact that the majority of C209 subjects in the ITT population (85.8%) were receiving anti-TB treatment during the pre-trial screening phase.

Conclusions on efficacy

Study C208 (Stages 1 and 2) demonstrated statistically significant treatment effects of Bedaquiline in the primary endpoints (time to SCC) and culture conversion rates at corresponding time points (week 8 or 24) in both Stages 1 and 2. Results from Study C209 were supportive. In study C208 Stage 2, culture conversions were durable over the remainder of the study period, resulting in a statistically significant difference between the two treatment arms, with the bedaquiline arm showing more conversions overall.

Safety profile of Bedaquiline in the treatment of MDR-TB

Background

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

Non-clinical safety

Toxicology studies after repeated dosing of bedaquiline have been conducted with durations of up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs. Key observations were:

Cardiac safety in vivo (dog study, 6 months): QT prolongation of 12%-16% at 2 months of exposure to 40 mg/kg/day, which was above the maximum tolerated dose. No prolongation after dose reduction to 20 mg/kg/day, and also no prolongation at 140 mg/kg twice weekly for 6 months. Cardiac troponin/CPK was increased at all dose strengths. No ECG changes or cardiac lesions were seen with lower doses (6 month dog at 10 mg/kg/day, and 9 month dog at 18 mg/kg/day). In dogs, at the NOAEL[38] of the QT prolongation, the exposures were approximately 8- and 9-fold higher than the clinical exposures for bedaquiline and M2, respectively. The QT prolongation was regarded as a finding with clinically relevant implication.

Hepatic safety: Centrilobular hypertrophy was seen in mice, rats, dogs. Severity was dose-related, and effects partially reversible. Liver function test (LFT) changes were also observed, associated with transaminase increases but no bilirubin changes or cholestasis.

Phospholipidosis: Observed in all preclinical species and consisted of the accumulation of pigment-laden and/or foamy macrophages or (micro)vacuolization in various tissues, mostly in lymphoid tissue (lymph nodes and spleen), lungs, liver, stomach, skeletal muscle, pancreas and/or uterus. Phospholipidosis was seen in rats (minimal) at exposures similar to the clinical exposure for bedaquiline and M2 (the main metabolite of Bedaquiline). In dogs, phospholipidosis was seen at 3- and 6 fold higher exposures compared to those in humans for bedaquiline and M2, respectively.

In addition to changes related to phospholipidosis, other main organs affected by repeated administration of bedaquiline (in one or more species) were skeletal muscle, heart, stomach, and pancreas.

[38] NOAEL: No observed adverse effect level

Data base for human safety experience with Bedaquiline

Information is available from a large pool of observations made from:

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

Because Study **C208 Stage 2** was double blind, placebo-controlled, it offers the opportunity to objectively compare AEs of interest, as identified from the above studies (and from non-clinical observations), between bedaquiline and placebo exposures.[39] From these observations, safety concerns signalled included QTcF prolongation and cardiac events, hepatic events, and deaths. These are considered individually below.

Adverse events of interest

Similar number of patients in the bedaquiline group and placebo group reported adverse drug reactions (ADRs) related to skeletal muscle, the pancreas, and the stomach. Safety signals related to these organs of interest appear to be similar in the bedaquiline and placebo groups (**Table 14**).[40]

Table 14*. Adverse effects of interest*

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

[39] BD Table 43 p154 for full list of AEs reported in at least 10% of subjects in any treatment group
[40] Porcalla Slides 12 and 13

Prolongation of the QTcF interval

***Table 15**. Summary of cardiovascular safety experience with BDQ*

Study	Subjects (N)	BDQ dose	Findings
Phase I Thorough QT Trial[41]	44	800 mg (single dose)	• Mean change QTcF from baseline (placebo corrected): < 10 ms[42] • QTcF interval > 500 ms: None • Discontinuations: None • Conclusion: Negative, comply ICH E14
Drug-drug interaction trial with ketoconazole[43]	15	BDQ 400 mg qd 14 days; ketoconazole 400 mg qd 3 days	• Subjects receiving both drugs – 3/16 increased QTcF at day 3 – BDQ C_{max} increased 9%, AUC 22%
Trial C208 Stage 1[44]	23	400 mg qd for 2 weeks, then 200 mg t.i.w for 6 weeks	• Vital Signs: No change • Postbaseline increase of > 60 ms: 2/23 • Postbaseline increase of >500 ms: None • QTcF increases of 30 - 60 ms: More frequent in bedaquiline > placebo in the 8 week treatment period • Torsade de Pointes: None • ECG monitoring: – Onset BDQ QTc prolongation from WK 2 onwards, persisting beyond 8 wk BDQ Rx period; – Mean increases of > 10 ms from baseline occurred WK6
Trial C208 Stage 2[45] (double blind RCT with BDQ compared to placebo in 1:1 ratio, all receiving background regimen of 5 other anti-TB drugs)	79	400 mg q.d. for 2 weeks, then 200 mg t.i.w. for 22 weeks	• More BDQ patients had QTcF values 450-480 ms (26.6% vs 8.6%) • More BDQ patients developed a > 60 ms increase from reference values group (9.1% vs 2.5%) • Investigator-reported Events – 3 patients with QTcF prolongation events and 1 patient with syncope in BDQ arm, none reported in placebo arm • None developed Torsade de Pointes
Trial C209[46] (single arm, open label)	233	400 mg qd 2 weeks, then 200 mg twice weekly for 22 weeks	• Mean QTcF values increased by WK 2 • Increases from reference of > 10 ms observed from Week 8 onwards • The largest mean change from reference was 14.2 ms at week 24 • Investigator-reported Events – Torsade des Pointes: None – One SAE: Grade 3 prolongation of the QT interval leading to discontinuation of BDQ – AE of ECG QT prolongation: 6 pats – Syncope: 1 patient

[41] BD Section 6.1 p148
[42] Mean difference: 5.19 ms, 90% confidence interval [CI]: [1.46, 8.92] – Refer BD p150
[43] BD Table 15 p73 and text p75
[44] BD Section 6.2 p152
[45] BD Section 6.2.4 p163 and Figure 33 p165
[46] BD Section 6.3.4 p175 and Figure 35 p176

Specific cardiovascular adverse events reported from studies **C208** and **C209**, and summarised in **Table 15**, are described below.

Trial C208: Cardiovascular safety (pooled experience Stage 1 and Stage 2)[47]

During the Investigational Treatment phase, mean QTcF increases were observed in both the pooled bedaquiline (Any bedaquiline) and pooled placebo (Any Placebo) groups but they were more pronounced in the Any bedaquiline group, with mean increases in the Any bedaquiline group observed from the first assessment after Day 1 onwards. The largest mean increase in QTcF at a predose time point in the Any bedaquiline group during the first 24 weeks was 15.4 ms (at Week 24). In the Any bedaquiline group, the mean changes from reference in QTcF were comparable between the 5 h post-dose assessments (i.e., bedaquiline T_{max}) and the respective pre-dose assessments. After the end of the bedaquiline dosing period, QTcF increases in the Any bedaquiline group gradually became less pronounced (**Figure 7**). In 1 subject of the Any bedaquiline group, QTcF values of more than 500 ms were observed. QTcF values above 450 ms and QTcF increases of 30 to 60 ms and > 60 ms were observed more frequently in the Any bedaquiline group than in the Any placebo group (**Table 16**).

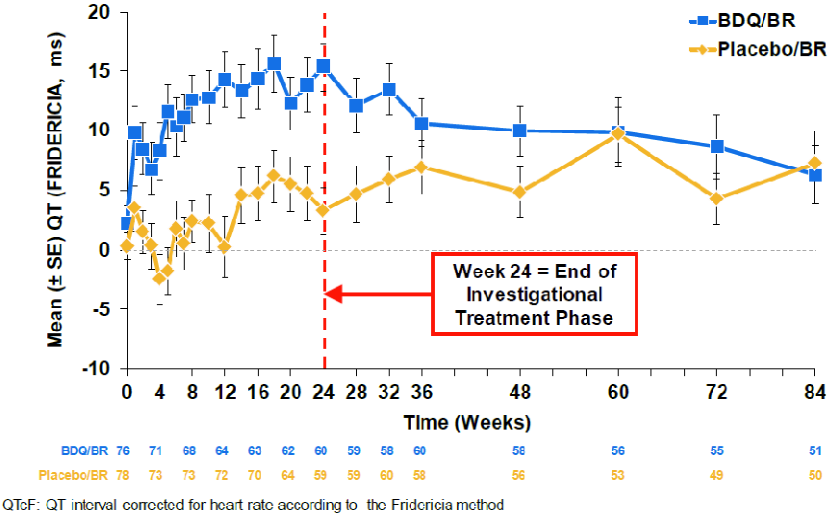


Figure 7*. Trial C208: QTcF changes from reference (ITT population)*

Table 16*. QT prolongation: Treatment-emergent worst QTcF*

ECG parameter, abnormality	Investigational treatment phase: Pooled controlled trials	
	BDQ (Any) N (%)	Placebo (Any) N (%)
QTcF calc (ms)	102	105
– 450 ms - ≤480 ms	23 (22.5)	7 (6.7)
– 480 ms - ≤500 ms	3 (2.9)	1 (1.0)
– More than 500 ms	1 (1.0)	0
QTcF calc (ms)	99	101
– Increase by 30-60 ms	52 (52.5)	33 (32.7)
– Increase by >60 ms	10 (10.1)	4 (4.0)

N = number of ITT subjects with data; QTcF: QT interval corrected for heart rate to the Fridericia method

[47] BD p169 and JRD Slides 68 and 69

Trial C209: Cardiovascular safety and concomitant use of Clofazimine

In a subgroup analysis of the C209 trial, mean increases from reference in QTcF were larger in subjects with concomitant clofazimine use than in subjects without concomitant clofazimine use (**Table 17**).[48] Mean increases in QTcF at Week 24 were larger in the 17 subjects who were using clofazimine at Week 24 (mean change from reference at 0 h of 31.94 ms) than in subjects who were not using clofazimine at Week 24 (mean change from reference at 0 h of 12.28 ms).

Table 17*. ECG effects of concomitant use of Bedaquiline and Clofazimine*

Changes from reference for QTcF in subgroups by concomitant use clofazimine by Wk 24		
QTcF (calculated, ms) at time-point 0 hr, Week 24	Clofazimine use at 24 weeks	
	No	Yes
N*	177	17
Mean	12.3	31.9
SE	1.23	5.74
SD	16.35	23.64
Median	13.0	27.0
Min	-34.0	6.0
Max	67.0	82.0

*Number of subjects who had an ECG assessment at Day -1 (reference) and Week 24, and did not use clofazimine at Week 24.

Conclusions on QTcF prolongation

- Based on data from a Phase 1 study and Phase 2 trials, bedaquiline can prolong the QTcF interval.
- There were no reports of Torsade de Pointes events, and also no fatalities from sudden death.
- Bedaquiline, in multiple dosing, can prolong the QTc interval and that the risk is highest during the treatment phase, but could extend beyond the treatment period. The use of BDQ with QT prolonging medications increases the risk of prolonged QT interval, i.e. QTcF prolongation from multiple QTcF prolonging drugs could be additive (viz. clofazimine).

Hepatic events

During the Investigational phase of the pooled C208 trials, there was a higher incidence of events related to hepatic disorders in the Any bedaquiline group (9 subjects, 8.8%) compared to the Any Placebo group (2 subjects, 1.9 %). Increases in transaminases accounted for the majority of these reported events.

Applying Hy's law, an analysis to identify cases of severe liver toxicity revealed 1 case of a patient who experienced concurrent >3 fold elevation of AST and >2 fold elevation in total bilirubin, but was confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background

[48] BD p151 and Table 50 pp177-178

medications. Investigator-reported events for the C208 Stage 2 results revealed consistently higher AE rates in the bedaquiline group (**Table 18**).[49]

***Table 18**. Investigator-reported hepatic events*

Investigator reported events	Bedaquiline 24 weeks (N=79)	Placebo 24 weeks (N=81)
Liver related signs/symptoms	8 (10%)	3 (3.7%)
Hepatic disorders	10 (12.5%)	5 (6.7%)
Possible hepatic related disorders	10 (12.5%)	5 (6.7%)
Hepatitis (non-infectious)	2 (2.5%)	1 (1.23%)
Hepatic failure, fibrosis, cirrhosis, liver damage related conditions	1 (1.25%)	0

Mortality

***Table 19**. Summary of deaths by treatment group*

Study	Type of study	Bedaquiline	Placebo
Phase 1 Deaths		0	0
Phase 2			
Study C202* Deaths	Randomised, open-label, dose ranging, EBA study	N=45 2 (4.4%)	N=30 0
Trial C208 Stage 1 Deaths	Randomised, placebo-controlled, 8 week exposure	N=23 2 (8.7%)	N=24 2 (8.3%
Trial C208 Stage 2 Deaths**	Randomised, placebo-controlled, 24 week exposure	N=79 10 (12.7%)	N=81 2 (2.5%)
Trial C209 Deaths	Open label, uncontrolled, 24 week exposure	N=233 16 (6.9%)	n/a

* Reference drugs: INH+RMP, not placebo

** Relative Risk 5.1 (p=0.017)

***Of the 10 deaths in the bedaquiline group in Trial C208 Stage 2* (Figure 9[50] and Table 20[51])**

- 8 patients converted
- The 2 patients who did not convert died from a TB- related cause
- Of the 8 who converted:
    - 4 relapsed
        - 3 died from TB-related causes (1 from hemoptysis)
        - 1 discontinued and died from MVA
    - 4 did not relapse but died from non-TB related causes (as shown in **Figure 8**)

The 2 deaths in the placebo group did not convert and died from TB-related causes.

[49] Porcalla Slide 41
[50] BD pp151-161, including Tables 44 and 45
[51] BD pp206-217

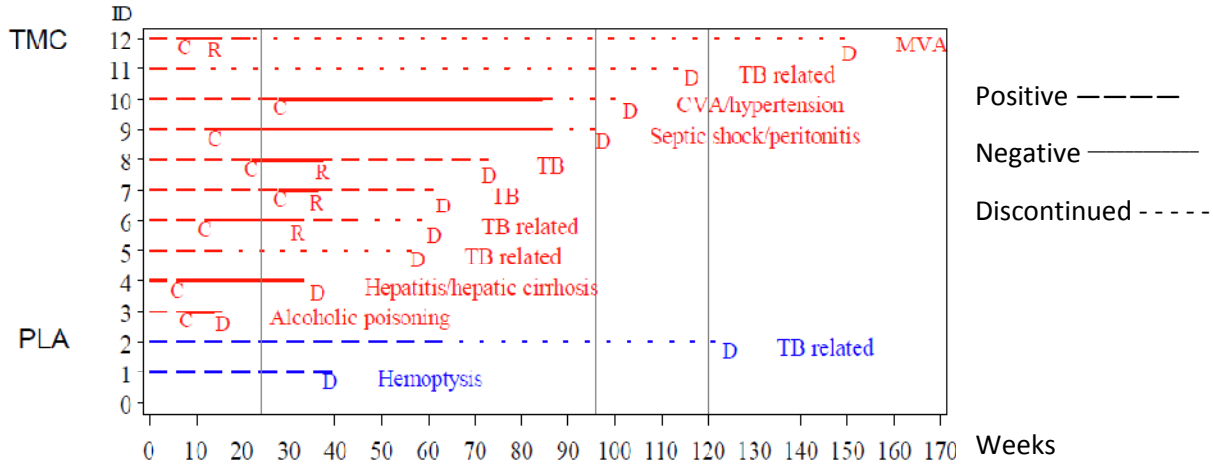


***Figure 8**. C208 Stage 2: Mortality by individual case*[52]
(C=Conversion; R=Relapse; D=Death; CVA=cardiovascular accident; MVA=motor vehicle accident)

Table 20. C208 Stage 2: Causes of death

Subject	Treatment arm	Category	Cause of death
Deaths while followed during trial			
208-4041	BDQ	Non-responder; converted; discontinued	Alcohol poisoning
208-4153	BDQ	Non-responder; relapse	TB-related illness
208-4224	BDQ	Non-responder; relapse	TB-related illness
208-5069	BDQ	Non-responder; converted; discontinued	Cirrhosis, hepatitis, anaemia
208-4399	BDQ	Responder; converted	Cerebrovascular accident
208-5067	BDQ	Responder; converted	Peritonitis and septic shock
208-4120	Placebo	Non-responder; failure to convert	Haemoptesis (TB)
Deaths during long-term survival follow-up of prematurely withdrawn subjects			
208-4127	BDQ	Non-responder; failure to convert	TB-related illness
208-4145	BDQ	Non-responder; relapse	TB-related illness
208-4378	BDQ	Non-responder; relapse	Motor vehicle accident
208-4464	BDQ	Non-responder; failure to convert	TB-related illness
208-4155	Placebo	Non-responder; failure to convert	TB-related illness

A significant imbalance in fatalities was noted in Trial **C208 Stage 2**, with a higher number of deaths in the bedaquiline group (10 vs 2 in the placebo group; RR=5.1; p=0.017[53]). TB was the cause of death in both placebo deaths and in 5 of the 10 bedaquiline deaths (all occurred off bedaquiline treatment). Of the 10 deaths in the bedaquiline group, 8 patients converted. There is no discernible pattern between death and conversion, relapse, microbiologic response, sensitivity to BR, HIV status, severity of disease, and the type of TB isolate. The reason for the imbalance in deaths is not clear.

In **Trial C209**, 16 deaths amongst 233 subjects (6.9%) were reported by the trial cut-off date (120 weeks). Of these, 12 deaths occurred during the trial: 3 during the expected bedaquiline treatment

[52] After Porcalla, Slide 57
[53] Porcalla slide 56

period, and 9 during the 96 week follow-up period. There were 4 deaths reported during follow-up for patients who discontinued prematurely (incomplete treatment).[54] No recognizable association between predictive factors (HIV infection, susceptibility to BR, cavitations) and death was observed. Eleven of the 16 deaths were caused by TB-related diseases (68.75%).

Overall conclusions on safety

- Bedaquiline causes QTcF interval prolongation. The risk of QT interval prolongation, when bedaquiline is given with other QT prolonging medications, is additive.
- Bedaquiline can cause hepatotoxicity. Conditions and medications associated with hepatotoxicity could pose additional hepatotoxic risks.
- A significantly greater number of deaths occurred in the bedaquiline group than in the placebo group. Reasons are unclear from the current safety data.
- The most frequently reported ADRs in the bedaquiline group (from both controlled and uncontrolled trials) were nausea, arthralgia, headache, and vomiting. Additional ADRs identified were, in order of frequency: dizziness, transaminases increased, myalgia, diarrhoea and ECG QT prolonged. ADRs of at least grade 3 were infrequent.[55]

[54] BD pp171-174, including Tables 47-49
[55] BD Table 51 p184