



Anti-Infective Drugs Advisory Committee Meeting

Briefing Document

TMC207 (bedaquiline) Treatment of Patients with MDR-TB

NDA 204-384

28 November 2012

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EXECUTIVE OVERVIEW

Janssen submitted a New Drug Application (NDA) for bedaquiline (NDA No. 204-384) to the Food and Drug Administration (FDA) with a request for an accelerated approval. The FDA has granted priority review for this application. Although the total number of newly infected people with tuberculosis (TB) is slowly decreasing worldwide¹, the increasing occurrence of more resistant strains makes TB control more complicated^{2,3}, and the need for novel compounds with good efficacy, safety and tolerability more urgent.

Globally, multidrug (MDR)-TB caused an estimated 150 000 deaths in 2008, 97 000 of which were co-infected with HIV². Tuberculosis is the leading cause of death among people with human immunodeficiency virus (HIV) infection^{4,5}. In the United States (US), the number of primary MDR-TB cases, i.e., MDR-TB cases in persons with no previous history of TB, steadily declined from 407 in 1993 to 115 in 2001. Since then, the total number of primary MDR-TB cases in the US has fluctuated from 88 to 132 cases, with 88 cases reported for 2010⁶.

Hence, although the incidence of TB and MDR-TB is limited in the US, sporadic outbreaks of this lethal airborne disease continue to occur in the US^{7,8}. To date there has not been an outbreak of extensively drug resistant (XDR)-TB (a virtually untreatable form of TB) in the US⁹, but the CDC reports that a total of 57 XDR-TB cases have been reported in the US between 1993 and 2012¹⁰. However, due to the global emergence of XDR-TB, global travel and the airborne transmission of this disease it seems prudent to prepare for the eventuality of an outbreak.

MDR-TB patients, have a lower cure rate and higher mortality rate than drug-susceptible (DS)-TB patients¹¹. The high mortality rate reflects poor diagnostic and limited treatment options for MDR-TB globally. For patients starting treatment for MDR-TB in 2007, countries reported deaths in 4%–45% (median: 11%)¹². Two independently conducted meta analyses from 2009, each including approximately 30 studies in MDR-TB, found death as a reported outcome in 11% of treated patients^{13,14}. An even more recent meta-analysis reflecting data from 9 143 individual patients reported a mortality rate of 15%¹³.

Therefore, after considerable internal consideration and discussion with the Division of Anti-Infective Drug Products, the Sponsor has decided to submit the NDA for bedaquiline for

accelerated approval based on interim Phase II data, which provide strong initial support of bedaquiline as an effective and well tolerated treatment for patients with MDR-TB.

The Sponsor acknowledges that a filing based on Phase II data is not without limitations and is, in part, hindered by a relatively small study population. The Sponsor has agreed to conduct a confirmatory Phase III study. Post launch, Janssen will deploy an appropriate and limited distribution of the product, apply rigorous pharmacovigilance and AE reporting, and will collaborate with public health authorities to ensure that bedaquiline will be used appropriately and safely. In brief, the Sponsor's actions will serve to ensure that bedaquiline is used appropriately and robustly monitored and in close collaboration with public health organizations.

To ensure that bedaquiline ultimately benefits the entire range of TB-infected populations, the Sponsor has established a collaboration with the Global Alliance for TB Drug Development (TB Alliance) to share expertise and resources in the development of bedaquiline. The Sponsor has granted a license to the TB Alliance for the worldwide development and commercialization of bedaquiline in the DS-TB population. Under the terms of the agreement, the Sponsor is responsible for the worldwide development of bedaquiline in the treatment of MDR-TB, while the TB Alliance is responsible for the worldwide development of bedaquiline for DS-TB. Therefore, the current new drug application submitted by the Sponsor is for MDR-TB and not for DS-TB.

As MDR-TB represents a small proportion of all TB patient populations in the US, the accelerated approval of bedaquiline is not being sought for commercial benefits. Because of the public health concerns, this special patient population should be allowed access to a new drug with a novel mechanism of action that likely will reduce the development of resistance to other anti-TB drugs in the background regimen and provide superior treatment outcomes versus the existing and antiquated regimen.

MDR-TB

While TB is a preventable and curable disease¹⁶, the 6-month treatment program which is required for DS-TB is long and burdensome¹⁷, and adherence is often challenging. Varying patient characteristics (physiological and behavioral), inappropriate treatment practices (incorrect dosing or treatment combinations), poor adherence to the long treatment regimen and to a lesser

extent, intrinsic bacterial characteristics of the disease (cavities harboring up to 10^8 organisms) have led to the development of MDR strains of TB^{16,18,19}.

MDR-TB is defined as an infection with a strain of *Mycobacterium tuberculosis* that is resistant to at least isoniazid and rifampin, the 2 most powerful first-line anti-TB drugs, and possibly to other drugs^{20,2}. MDR-TB is considered curable but cannot be adequately treated with the standard short-course therapy (SSCT) of 6 months^{21,22}. Unlike DS-TB, treatment of MDR-TB requires extensive chemotherapy (up to 2 years of treatment), use of less efficacious second-line drugs associated with greater side effects and requires extensive monitoring and is considerably more costly. National guidelines dictate utilization of a regimen consisting of 3 or 4 oral anti-TB drugs in combination with 1 injectable drug²³⁻²⁵.

As a further challenge to TB treatment programs, MDR-TB strains containing broader antibacterial resistance have emerged; pre-extensively drug-resistant (Pre-XDR)-TB and XDR-TB, are even more difficult to treat and have emerged as a public health threat²⁶. According to the 2010 World Health Organization (WHO) global report on surveillance and response, at least one case of XDR-TB has been confirmed in 58 countries².

TB and Bedaquiline

Bedaquiline has a novel mechanism of action (adenosine 5'-triphosphate [ATP] synthase inhibition), 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 *M. tuberculosis* and is equally active against DS, MDR_{H&R} (resistant to isoniazid and rifampin only), Pre-XDR, and XDR strains of *M. tuberculosis*^{27,28}. Due to its novel mode of action, bedaquiline defines a new class of anti-TB compounds. It is a diarylquinoline which, if approved, will be the first new anti-tuberculosis drug since 1998 (rifapentine received accelerated approval in the US on 22 June 1998). The distinct target and mode of action of bedaquiline minimizes the potential for cross-resistance with existing anti-TB drugs.

Special Considerations for this Advisory Committee

The Sponsor requested an accelerated approval for bedaquiline because of the expected benefit for individual patients and for the potential public health benefits gained from the addition of a

drug with a new mechanism of action to an antiquated and suboptimal MDR-TB treatment regimen.

In the following discussion, and in its presentation, the Sponsor will show evidence of a strong benefit as supported by the interim efficacy data. The Sponsor will also divulge, with complete transparency, potential safety signs that cannot be discounted but whose risk must be balanced in relation to the totality of data and in the view of the high unmet medical need.

When added to a background regimen for MDR-TB, bedaquiline improves treatment outcomes by approximately 20% while adding little to the constellation of adverse effects seen in MDR-TB (modest increase in QT and increase in hepatic transaminases). In the placebo-controlled **C208** trial, however, an imbalance of all-cause mortality has been observed with more deaths reported in the bedaquiline group (10/79 versus 2/81 in the placebo group in **C208 Stage 2**). Causes of death were varied and all but one occurred after the treatment period with bedaquiline.

You will also hear that clinical trials in this field are challenging: there is a limited clinical trial capacity in high burden countries, there are no validated surrogate endpoints and treatment duration is long (24 months). Accordingly, in the pivotal clinical trial the duration is a minimum of 30 months.

MICROBIOLOGY

Bedaquiline has potent in vitro activity against *M. tuberculosis* with a minimum inhibitory concentration (MIC) equal to or lower than that of approved anti-mycobacterial agents. The in vitro spectrum of bedaquiline is unique in its specificity to mycobacteria, including medically important species such as *M. leprae*, *M. ulcerans*, *M. avium complex*, *M. kansasii*, *M. fortuitum* and *M. abscessus*.

In isolates selected in vitro for elevated bedaquiline MICs (MICs up to 4µg/mL, fold increase up to 133 fold), mutations were found in *atpE*, the gene which encodes a protein of the F0 subunit of ATP synthase. This indicates that bedaquiline inhibits the proton pump of *M. tuberculosis* ATP synthase. Bedaquiline's distinct target suggests that cross-resistance with existing anti-TB drugs would be less likely to occur.

Bedaquiline has potent bactericidal activity in vitro and in vivo. Its bactericidal activity in a murine model of TB infection, matched or exceeded that of isoniazid or rifampin, the 2 most important first-line drugs to treat DS-TB.

A breakpoint analysis was performed based on (i) the susceptibility profile of preclinical and clinical isolates of *M. tuberculosis* including DS-, MDR-, pre-extensively drug resistant (Pre-XDR)- and XDR-TB to bedaquiline and (ii) microbiologic outcomes demonstrating favorable culture conversion rates of MDR-TB isolates from clinical trials with bedaquiline MIC ≤ 0.5 $\mu\text{g/mL}$ as determined by the agar method (and MIC ≤ 0.25 $\mu\text{g/mL}$ as determined by the REMA). The suggested MIC interpretive criteria are ≤ 0.5 $\mu\text{g/mL}$ for susceptible as determined by the agar method (and ≤ 0.25 $\mu\text{g/mL}$ for susceptible as determined by the REMA method). Because of the lack of clinical experience with isolates of *M. tuberculosis* with MICs > 0.5 $\mu\text{g/mL}$, a susceptible only breakpoint of ≤ 0.5 $\mu\text{g/mL}$ is proposed.

CLINICAL PHARMACOLOGY

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.

The recommended dose of bedaquiline for the treatment of pulmonary MDR-TB in adults is 400 mg q.d. for 2 weeks, followed by 200 mg t.i.w. with a total treatment duration of 24 weeks, taken with food and in combination with other anti-TB drugs.

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.

Based on in vitro data, bedaquiline does not significantly inhibit or induce CYP450 enzymes. In the Phase I drug-drug interaction trials, bedaquiline was coadministered with drugs from various classes, including CYP3A inducers and inhibitors. 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 may increase the systemic exposure to bedaquiline which could potentially increase the risk of adverse reactions (See Section [4.2](#)).

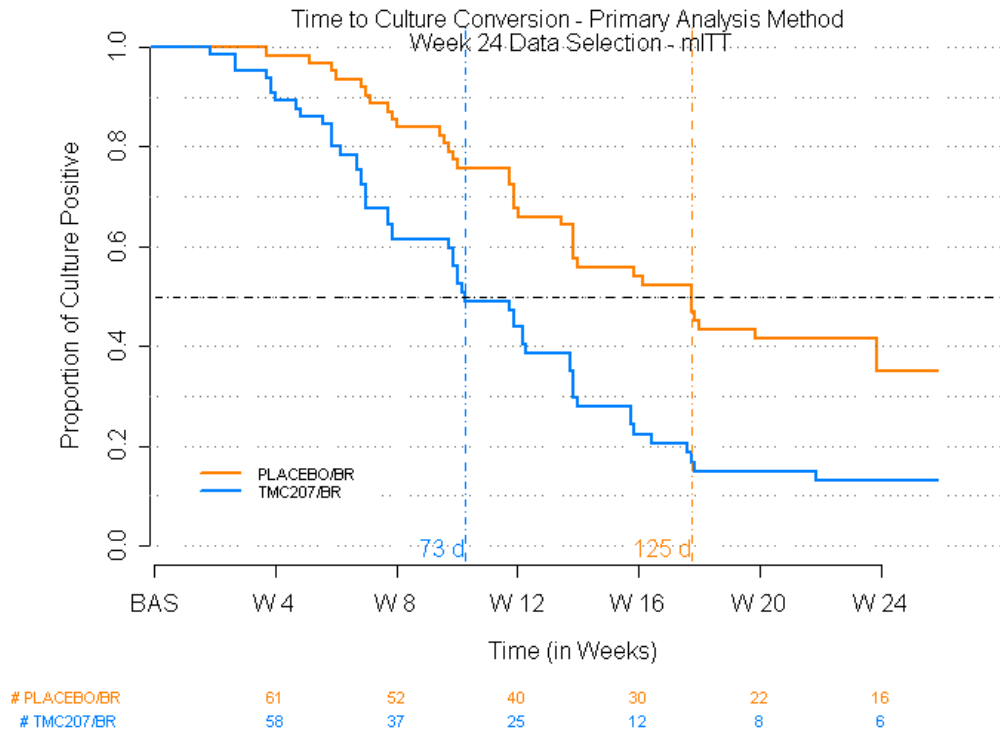
The results of the final population pharmacokinetic analysis showed that age, sex, body weight, and HIV co-infection did not influence the pharmacokinetics of bedaquiline. Black subjects had lower bedaquiline exposures than subjects from other race categories. However, this was not considered to be clinically relevant based on the similar clinical outcome in the subset of this subgroup who did not discontinue the trial prematurely by Week 24 in the Phase II studies.

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.

EVIDENCE OF CLINICAL EFFICACY

Three phase II trials have been conducted, one of them, **C208**, consisted of 2 independent stages. **C202** and **C208 Stage 1** have been completed at time of NDA while **C208 Stage 2** and **C209** are still ongoing. **C202** enrolled DS-TB subjects while the remaining two trials enrolled subjects with MDR-TB.

The primary efficacy results of the double blind Phase IIb pivotal trial (C208 Stage 2) demonstrate that the addition of bedaquiline to a 5-drug MDR-TB treatment regimen for 24 weeks resulted in significantly shorter time to culture conversion and a significantly higher proportion of culture conversion at 24 weeks ([Figure 1](#)). In addition, based on a second interim analyses when all patients had reached at least 72 week of follow up, this improved response appears durable.



#: number of subjects at risk (i.e., culture positive subjects ongoing in the trial at the corresponding time point)
 Note: The intersection of horizontal dotted line and each treatment arm represents the median time to sputum culture conversion.

Data on file, Janssen Research and Development

Figure 1: C208 Stage 2: Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (Interim Analysis / 24-Week Data Selection, Primary Missing = Failure Analysis Method) – mITT

Time to sputum culture conversion during the 24 week treatment with bedaquiline (or placebo) was the primary efficacy parameter in **C208 Stage 2**. A Cox proportional hazards model adjusting for lung cavitations and pooled center showed a statistically significant difference in time to culture conversion between the treatment groups ($p < 0.0001$) in favor of bedaquiline. Several pre-planned sensitivity analyses of the primary endpoint were also done and were supportive.

The efficacy results of **Stage 2** of trial **C208** were robust with consistently better microbiologic outcomes in the bedaquiline treatment group compared to the placebo treatment group.

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. In addition, a pre-planned sensitivity analysis of this secondary endpoint called "no overruling" was also statistically significant.

Microbiological response at Week 24 was durable in **C208 Stage 2**. 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 data up to efficacy cut-off date 10 May 2011, the percentage was 66.7% in the bedaquiline group and 47.0% in the placebo group ($p = 0.021$). Among the non-responders at that time point, more subjects in the placebo group than in the bedaquiline group failed to culture convert (22.7% versus 12.1%), experienced relapse (regardless of treatment status; 12.1% versus 7.6%) at time of their last assessment, or prematurely discontinued while culture converted (18.2% versus 13.6%). [Table 1](#) provides an overview of the proportion of conversions over time (missing = failure).

Table 1: C208 Stage 2: Proportion of Conversions (MGIT) Over Time (Missing = Failure) - mITT

Time Point ^a	TMC207/BR		Placebo/BR		TMC207/BR-Placebo/BR		
	N	n (%)	N	n (%)	% Difference (SE)	95% CI	p-Value
Week 24 Responder	66	52 (78.8)		38 (57.6)	21.2,	5.6, 36.8	0.008
Week 36 Responder	66	48 (72.7)	66	40 (60.6)	12.1	-4.0, 28.2	0.139
Week 48 Responder	66	49 (74.2)	66	42 (63.6)	10.6	-5.2, 26.4	0.187
Week 60 Responder	66	48 (72.7)	66	39 (59.1)	13.6	-2.5, 29.8	0.097
Week 72 Responder	66	47 (71.2)	66	37 (56.1)	15.2	-1.2, 31.5	0.069
All Available Data Responder	66	44 (66.7)		31 (47.0)	19.7	3.0, 36.4	0.021

N = number of subjects; n = number of subjects with observation

^a using the Week 36 data selection, Week 48 data selection, Week 60 data selection, and Week 72 data selection, respectively.

Data on file, Janssen Research and Development

Bedaquiline treatment also markedly decreased the risk of acquiring resistance to other background drugs, demonstrating another potential benefit of bedaquiline. In addition, in the

placebo-controlled **C208** trial an imbalance in resistance amplification was observed with fewer patients developing a pre-XDR or XDR TB profile in the bedaquiline group (1 versus 4 in stage 1, 0 versus 7 in Stage 2). The growing problem of resistance is among the key issues identified in the WHO Global Tuberculosis Report 2012²⁹.

Time to culture conversion during the 24-week treatment period with bedaquiline was also the primary efficacy outcome parameter for trial **C209**. Efficacy results in trial **C209** were generally consistent with those of **C208 Stage 2**. In **C209**, a somewhat shorter median time to culture conversion was observed after addition of bedaquiline for 24 weeks to an individually optimized background regimen (BR), compared to the bedaquiline arm in **C208 Stage 2**. This likely reflects that the majority of **C209** subjects in the ITT population (85.8%) were receiving anti-TB treatment during the Screening phase. Of note, **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.

Median time to sputum culture conversion (Mycobacteria Growth Indicator Tube [MGIT]) for subjects in the modified intent to treat (mITT) population was 57 days ([Figure 2](#)).

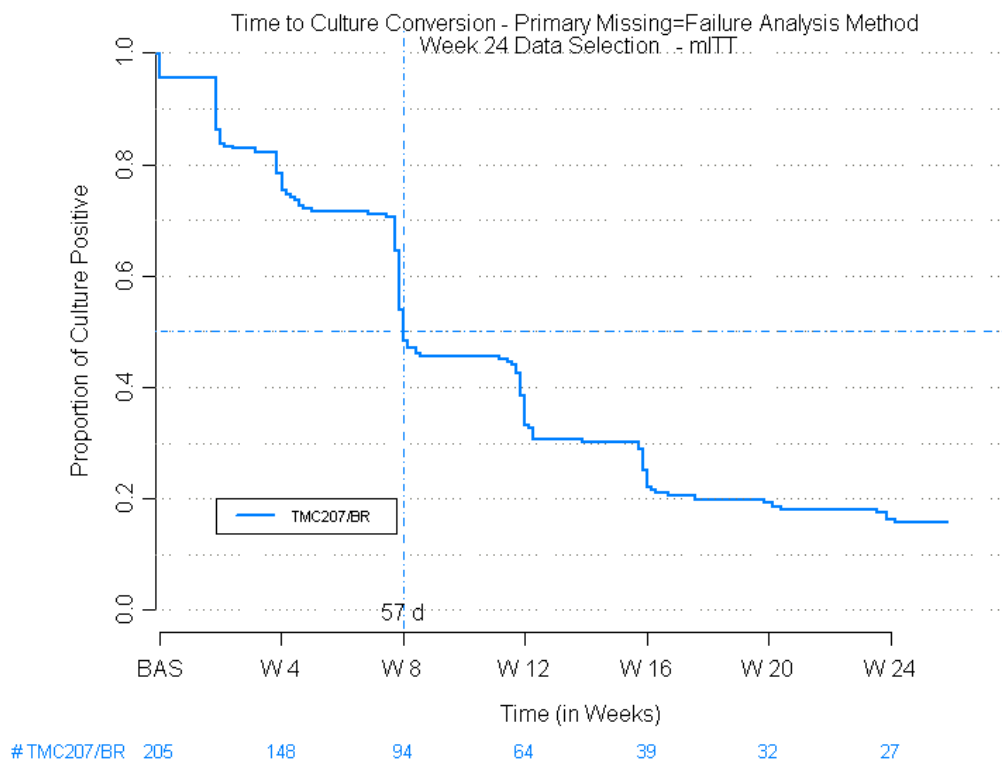


Figure 2: C209: Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (Interim Analysis / 24-Week Data Selection, Primary Missing = Failure Analysis Method) – mITT

Data on file, Janssen Research and Development

SUMMARY OF SAFETY RESULTS

The safety and tolerability of bedaquiline for the treatment of pulmonary MDR-TB in adult patients as part of combination therapy is characterized by the safety data from 14 trials: 11 completed Phase I trials in non-TB-infected subjects and 3 Phase II trials in TB-infected subjects (1 completed Phase IIa **C202** and 2 Phase IIb trials: **C208**, including the completed **Stage 1** and the ongoing **Stage 2** [1 subject still in rollover], and ongoing **C209**). **C208 Stage 1** and **Stage 2** are similar in design, with primary difference being the duration of treatment with bedaquiline/placebo was 8 weeks in **Stage 1** compared to 24 weeks in **Stage 2**. A pooling of the 2 Phase IIb trials (controlled data in **C208 stage 1** and **2**, and uncontrolled data in **C209**) was performed to increase the likelihood of detecting infrequent events due to the higher number of subjects per pooled treatment group and to increase the sample size for subgroup analyses. The Phase IIb pooled analysis consisted of 2 parts: pooling of the controlled data from **C208 Stage 1**

and **Stage 2**, and pooling of controlled + uncontrolled data from **C208 Stage 1**, **C208 Stage 2**, and **C209**. Safety information on mortality up to the cut-off date of 15 July 2012 for trials **C208 Stage 2** and **C209**, analyzed for and submitted in the Safety Update Report, is included in this Briefing Book to supplement the safety analysis.

During the Investigational Treatment phase of the pooled, controlled Phase IIb trials (**C208 Stage 1 and 2**), a higher incidence of serious adverse events (SAEs) was observed in the Any Bedaquiline group (this group included subjects randomized to receive bedaquiline for either 8 weeks (**C208 Stage 1**) or 24 weeks (**C208 Stage 2**) in combination with a background regimen for MDR-TB), with 7 (6.9%) subjects compared to 2 (1.9%) subjects in the Any Placebo group (this group included subjects from **C208 Stage 1 and 2** randomized to placebo). Despite this, the overall number of adverse events (AEs) leading to permanent discontinuation was low and balanced in both treatment arms. The incidence of grade 3 or 4 AEs was generally similar in the Any Bedaquiline and Any Placebo groups.

The pooled Phase IIb safety database was probed using standardized queries¹ for AEs of interest, which were identified due to their relevance in the target population or their potential importance based on nonclinical and clinical data on bedaquiline and included adverse events related to the liver, QT prolongation, pancreas, muscle and skin. 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 of which all but 2 resolved. A Hy's law analysis^{30,31} to identify cases of severe drug-induced liver toxicity revealed a single potential case of a patient who experienced concurrent >3 fold elevation of aspartate aminotransferase (AST) and >2 fold elevation in total bilirubin, but this case was confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background medications (including para-aminosalicylic acid and ethionamide). No differences were observed between the treatment groups for reported events related to any of the other AEs of interest.

¹ Standardized MedDRA Queries⁸³ (SMQs): Groupings of terms that relate to a defined medical condition or area of interest, intended to aid in case identification. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory, and other physiologic test data, etc., related to the medical condition or area of interest.

In the bedaquiline group in **C208 Stage 2**, a mean increase from reference in QTcF was observed from the first assessment after Day 1 (9.9 ms at Week 1). Mean increases from reference in QTcF grew gradually larger over the first 8 weeks of bedaquiline treatment and then remained more or less stable until Week 24. The largest mean increase in QTcF at a predose time point in the first 24 weeks was 15.7 ms in the bedaquiline group (at Week 18). In the placebo group, mean changes from reference were generally < 10 ms. The largest mean increase in QTcF at a predose time point in the first 24 weeks was 6.2 ms in the placebo group (at Week 18). After Week 24, QTcF increases in the bedaquiline group gradually became less pronounced.

In an additional safety finding in the **C209** trial, mean increases from reference in QTcF were larger in the subset of 17 subjects with concomitant clofazimine use (mean increase approximately 30 ms) than in subjects without concomitant clofazimine use. Other overall electrocardiogram (ECG) findings in the trial were consistent with the observations in the controlled trials, with mean increases in QTcF from the first assessment after Day 1 (9.3 ms at Week 2), and mean increases from reference of more than 10 ms observed from Week 8. After Week 24, QTcF increases were less pronounced. During the Investigational Treatment phase, QTcF values of more than 500 ms were observed in 1 subject (receiving concomitant clofazimine). One additional subject, also receiving clofazimine, experienced a QTcF >500 ms in the period after the Investigational Treatment phase.

A systematic and well-documented approach was used to identify adverse drug reactions (ADRs) for bedaquiline. These were identified from the pooled safety database of the **C208** trials, with additional review of safety data from Phase I and Phase IIa trials and the **C209** trial. In the **pooled C208 trials**, the most frequently reported ADRs (>20%) in the Any Bedaquiline group were nausea, arthralgia, headache, and vomiting. Additional ADRs identified were, in order of frequency: dizziness, transaminases increased, myalgia, diarrhea and ECG QT prolonged. ADRs of at least grade 3 were infrequent, and limited to reports of headache, arthralgia and increased transaminases occurring in at most 2 subjects (see [Table 2](#)).

Table 2: Pooled Controlled Phase IIb Trials: Adverse Drug Reactions of at Least Grade 3 During the Investigational Treatment Phase

SOC ADR (grouped term), n (%)	Investigational Treatment phase			
	TMC207		Placebo	
	24 Weeks N = 79	Any N = 102	24 Weeks N = 81	Any N = 105
<i>At least grade 3 ADR</i>	<i>5 (6.3)</i>	<i>5 (4.9)</i>	<i>0</i>	<i>0</i>
Nervous system disorders	1 (1.3)	1 (1.0)	0	0
Headache	1 (1.3)	1 (1.0)	0	0
Hepatobiliary disorders	2 (2.5)	2 (2.0)	0	0
Transaminases increased ^a	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	2 (2.5)	2 (2.0)	0	0
Arthralgia	2 (2.5)	2 (2.0)	0	0

N = number of ITT subjects with data, n = number of ITT subjects with this observation

^a Different AE preferred terms (i.e., transaminases increased, AST increased, ALT increased, hepatic enzyme increased, and hepatic function abnormal) do contribute to this ADR, while for the other ADRs the ADR is the preferred term.

Note: The determination of ADRs was not limited to one trial and consisted of several steps, including review of Pooled Phase I and Phase IIa safety databases.

Data on file, Janssen Research and Development

An important safety finding identified upon analysis of t **C208 Stage 2** was an imbalance in the number of deaths between the bedaquiline group and the placebo group reported during the trial or during the survival follow-up of subjects that had prematurely discontinued. Based on this information the Sponsor has chosen to proactively present the mortality information from the completed C208 Stage 2 trial based on the final Topline report, which was also presented in the Safety Update Report to the NDA. Overall, 10 of 79 subjects (12.7%) in the bedaquiline group died compared to 2 of 81 subjects (2.5%) in the placebo group. Only 1 death occurred during the Investigational Treatment phase with bedaquiline. Detailed analysis of length of follow up, baseline characteristics and risk factors for poor treatment outcome did not reveal relevant imbalances to explain the outcome observed. Similarly, no relationship between bedaquiline exposure (plasma concentration) and survival outcome was observed. None of subjects had a QTcF > 500 ms during the trial or a treatment-emergent increase in QTcF > 60 ms from baseline. The investigators considered the SAEs leading to death unrelated to TMC207/placebo in all cases except for 1 subject in the placebo group.

No clear relationship between mortality and bedaquiline in this trial has been identified given that the causes of death were varied (only death due to TB was reported more than once), and there was a wide range in time to death since last intake of bedaquiline (range 2-911 days in

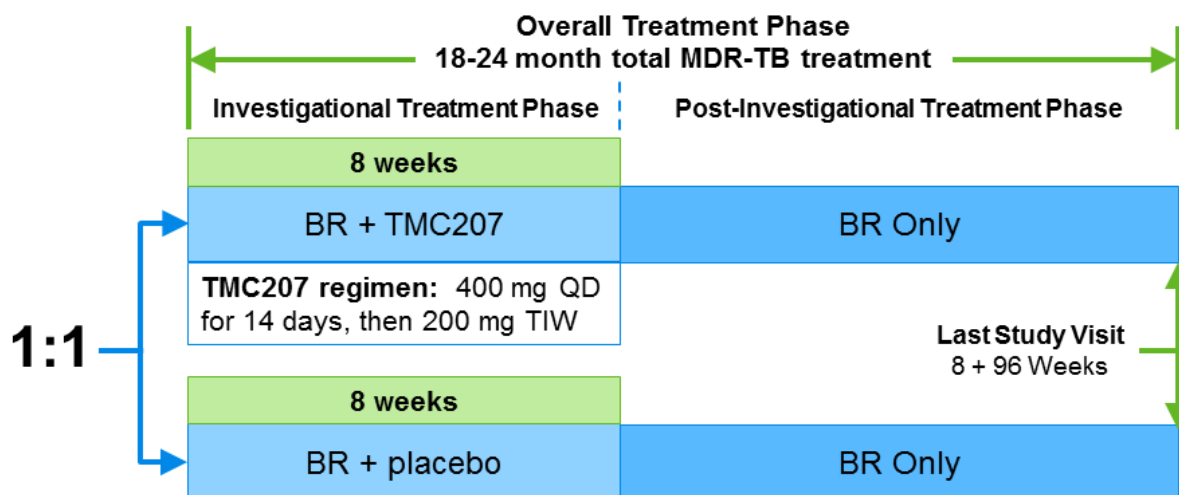
C208 Stage 2) and onset was generally late (median 313 days for deaths reported during the trial in **C208 Stage 2**). In general, the causes of death reported for the majority of the subjects are similar to the causes of death reported from a study from 1963 that utilized autopsies from 295 patients treated for pulmonary TB to ascertain probable causes of death in TB in the pre-and post antibiotic era in the US³².

Review of the safety databases for the Phase I and IIa trials did not reveal any additional safety findings.

BACKGROUND INFORMATION ON PHASE II PROGRAM

The Sponsor conducted two independent sequential stages in a placebo-controlled, double-blind, randomized Phase IIb trial (**C208**) in newly diagnosed MDR-TB subjects (including subjects infected with Pre-XDR strains):

- **C208 Stage 1** (exploratory) included 47 subjects of whom 23 subjects received bedaquiline and 24 subjects received placebo, both up to 8 weeks in combination with a standardized BR for MDR-TB ([Figure 3](#)). **C208 Stage 1** has been completed. See [Appendix 1](#) for a detailed flowchart of this trial.

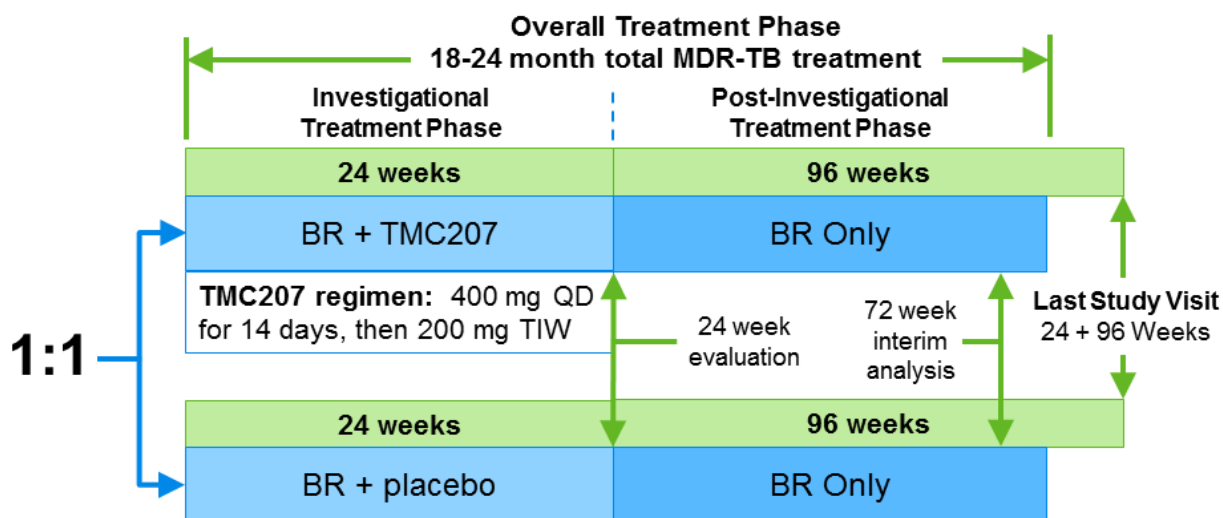


BR: background regimen; q.d.: once daily; t.i.w.: 3 times weekly

Figure 3: C208 Stage 1: Duration of Trial Periods and Relevant Time Points

Two analyses have been completed for **Stage 1**:

1. The primary analysis of **Stage 1** was performed when all **Stage 1** subjects had completed 8 weeks of double-blind treatment with bedaquiline or placebo (or had discontinued earlier).
 2. The final analysis of **Stage 1** was performed when all **Stage 1** subjects had completed the trial (or had discontinued earlier). This included an evaluation of the 96-week background treatment period. At time of final analysis, the Sponsor also conducted the analysis of the first 24 week data only to allow comparison with the primary efficacy results in **Stage 2**.
- **C208 Stage 2** (pivotal) included 160 subjects of whom 79 subjects received bedaquiline and 81 subjects received placebo up to 24 weeks in combination with a standardized BR for MDR-TB ([Figure 4](#)). The 24-week investigational treatment period with bedaquiline and the 96-week follow-up period of **C208 Stage 2** have been completed by all subjects, except for 1 subject in the rollover arm who is ongoing. In the interim analysis all subjects had reached at least the Week 72 visit of the trial or discontinued earlier. See [Appendix 1](#) for a detailed flowchart of this trial.



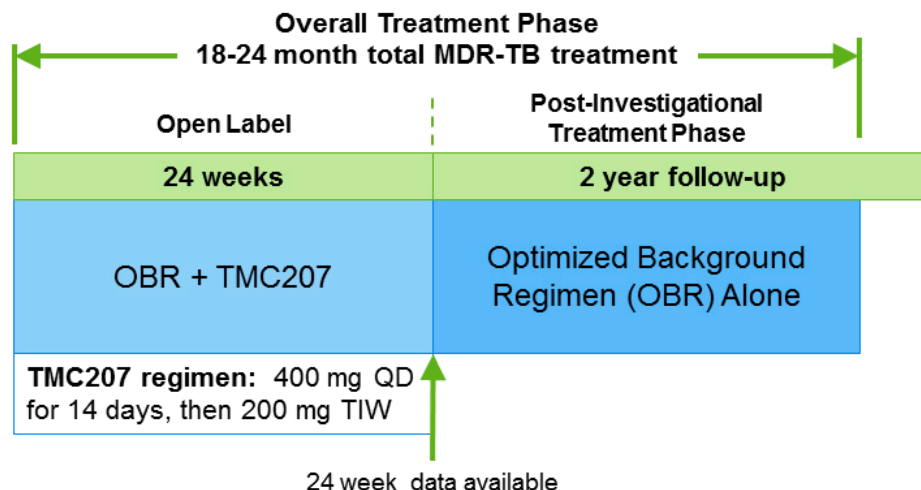
BR: background regimen; q.d.: once daily; t.i.w.: 3 times weekly

Figure 4: C208 Stage 2: Duration of Trial Periods and Relevant Time Points

Two analyses have been completed and one is ongoing for the **Stage 2** data:

1. The primary efficacy analysis of **Stage 2** was performed when all **Stage 2** subjects had completed 24 weeks of double-blind treatment with bedaquiline or placebo (or had discontinued earlier) and included data up to 12 July 2010.
2. The interim analysis of **Stage 2** was performed with an efficacy data cut-off date of 10 May 2011 for efficacy and 10 June 2011 for safety. At this cut-off date, all **Stage 2** subjects had completed the Week 72 visit or had discontinued. The interim analysis study report was submitted in the New Drug Application (NDA).
3. The final analysis Clinical Study Report is in preparation and was initiated when all subjects had completed or discontinued the trial, except for a single subject in the rollover arm whose status is ongoing. The cut-off date for the final analysis was 31 January 2012. The cut-off date for trial **C208 Stage 2** inclusion in the NDA submission was prior to this cut-off date (efficacy cut-off date 10 May 2011, safety cut-off date 10 June 2011). The interim Clinical Study Report for **C208 Stage 2** was thus included in the NDA submission package while the final analysis was not included. The final analysis clinical study report will be submitted to the FDA under the IND by mid November 2012.

Trial **C209** was a single-arm, open-label Phase IIb trial in 233 subjects with newly diagnosed or treatment-experienced MDR-TB infection who received bedaquiline up to 24 weeks in combination with an individualized BR for MDR-TB ([Figure 5](#)). Subjects with XDR-TB infection were allowed to enter the **C209** trial, provided they had at least 3 drugs in their anti-TB regimen to which their *M. tuberculosis* isolate was likely to be susceptible. The 24-week treatment period with TMC207 of the **C209** trial has been completed and the 96-week follow-up period of this trial is ongoing. See [Appendix 2](#) for a detailed flowchart of this trial.



q.d.: once daily; t.i.w.: 3 times weekly

Figure 5: C209: Duration of Trial Periods and Relevant Time Points

One analysis has been completed for **C209**:

1. The interim analysis was performed when all subjects had completed 24 weeks of treatment with bedaquiline or had discontinued earlier (cut-off date 29 March 2011). These results will be discussed in section 5.4 for efficacy and 6.3 for safety. Additional safety information on mortality, analyzed for the Safety Update Report with a cut-off date 15 July 2012, is included in this Briefing Book to supplement the safety analysis.

PLANNED PHASE III TRIAL C210

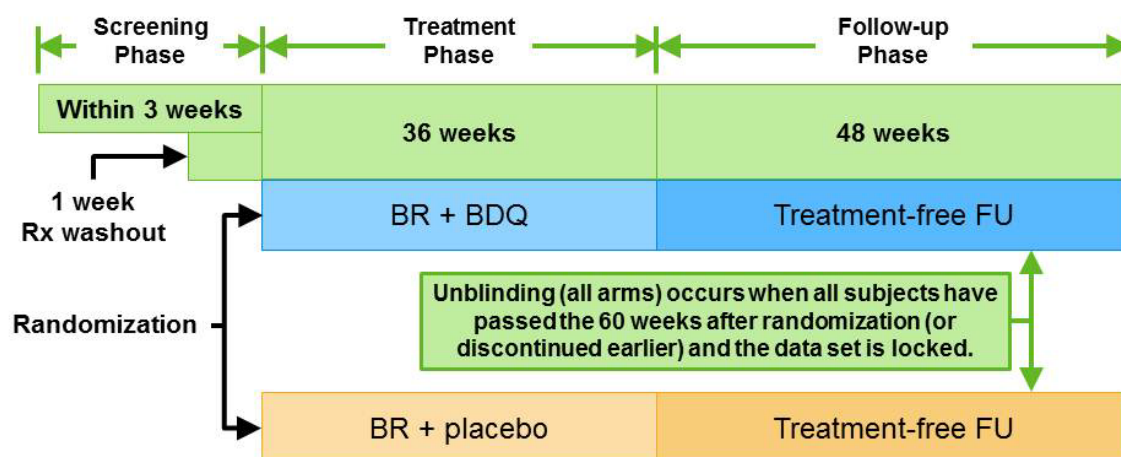
A Phase III confirmatory trial (**C210**) to support the traditional approval of bedaquiline will be initiated in 2013. **C210** will be a placebo-controlled, double blind, randomized trial in 600 MDR-TB patients to evaluate the efficacy and safety of a 9-month treatment with bedaquiline plus background regimen compared to the background regimen with placebo in subjects with sputum smear-positive pulmonary infection with MDR-TB or Pre-XDR-TB.

Trial **C210** is planned to be conducted in Brazil, Cambodia, China, Colombia, Estonia, Korea, Latvia, Mexico, Peru, the Philippines, Russia, South Africa, Taiwan, Thailand, Turkey, Ukraine, and Vietnam. This trial will utilize a BR similar to the BR that is currently being evaluated in several countries around the world, as part of the STREAM study³². This BR regimen was based on promising results from an observational study in Bangladesh⁵³. Levofloxacin will replace

gatifloxacin or moxifloxacin in the BR given the latter 2 drug's potential for QTc prolongation⁻³⁵. A target of approximately 600 subjects with sputum smear-positive pulmonary infection with MDR-TB or Pre-XDR-TB will receive a BR of MDR-TB therapy and are planned to be randomly assigned in a 1:1 ratio to one of 2 treatment arms (Arms A and B). The 2 randomized treatment arms shorten the overall treatment of MDR-TB compared to the WHO standard of care, by providing bedaquiline/placebo (Arm A/Arm B) with a 7-drug BR for 36 weeks. In this way, the study addresses one of the needs expressed by the TB community to explore regimens of shorter treatment duration and aims to provide confirmatory data that TMC207 added to a BR improves efficacy. Throughout the **C210** trial, an Independent Data Monitoring Committee will monitor safety and tolerability on a regular basis and make recommendations regarding the continuation, modification, or termination of the trial to the Sponsor.

The Sponsor submitted protocol TMC207-**C210** entitled “A Phase III Placebo-Controlled, Double-Blind, Randomized Trial to Evaluate the Efficacy and Safety of TMC207 in Subjects with Sputum Smear-Positive Pulmonary Infection with Multi-Drug Resistant Mycobacterium tuberculosis (MDR-TB)” to the FDA for review under a “Special Protocol Assessment” on 28 December 2011. A Special Protocol Assessment is an agreement between the Sponsor and the FDA indicating that the Sponsor’s proposed trial protocol, including clinical endpoints and statistical analyses, are acceptable to support regulatory approval of the treatment being evaluated. On 10 February 2012 the Sponsor received FDA’s Special Protocol Agreement.

A schematic overview of the study design is provided in [Figure 6](#).



BDQ: bedaquiline; BR: background regimen; FU: follow-up

Figure 6: Schematic Overview of the C210 Study Design

RISK MANAGEMENT CONSIDERATIONS

TB is a notifiable infectious disease in the US. A notifiable disease is one for which regular, frequent, and timely information regarding individual cases is considered necessary for the prevention and control of the disease³⁶. Through the existing global public health framework, the following data is routinely collected: diagnosis, duration of treatment, outcome: cure, failure or death (including cause of death).

Until the results of the Phase III trial are available, the Sponsor is investigating the feasibility of a variety of measures to ensure an appropriate level of patient safety.

- Controlled access through public health authorities
- Patient registry
- Communication plan including a website with on-demand education materials

In addition,

- The Package Insert (PI) includes an identification of risks, with warnings and precautions regarding cardiovascular safety and QT prolongation, drug-drug interactions and use in HIV-coinfection; both ECG QT prolonged and transaminases increased are listed as ADRs.
- Phase III: Additional safety data will be collected during the planned Phase III controlled trial of 600 patients (300 exposed to bedaquiline), which will include frequent ECG monitoring, regular assessment of laboratory parameters including liver function tests and continued monitoring of the previously identified adverse events of interest. In addition, the protocol will standardize follow up of all subjects (including survival follow up in prematurely discontinued subjects who do not withdraw consent) for 2 years after the last intake of bedaquiline.

OVERALL BENEFITS/RISKS

Bedaquiline is the first drug to seek an indication specifically for MDR-TB in the US and the first drug with a new MOA for treating TB in over 40 years. It improves microbiological treatment outcomes and provides a new tool to reduce the emergence of background drug resistance.

The results of the initial clinical development program support the use of bedaquiline as part of combination therapy for the treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* in adults (≥ 18 years). This conclusion is drawn in the context of an accelerated approval filing, the traditional approval will be based on Phase III trial results (anticipated in 2017). It is also made with the knowledge of the planned risk minimization measures sought by the Sponsor that include setting up a controlled distribution of the drug through public health authorities in the US.

The addition of bedaquiline to a 5-drug MDR-TB treatment regimen for 24 weeks resulted in significantly shorter time to culture conversion ($p < 0.0001$) and a significantly higher proportion of subjects with culture conversion ($p = 0.008$) compared to placebo. At Week 24, the hazard ratio was 2.41 (95%CI [1.55-3.75]), and the percentage of subjects with culture conversion rates was 78.8% in the TMC207 group and 57.6% in the placebo group (based on the primary analysis method, i.e., missing = failure).

The results of a sensitivity analysis (no over ruling) of the primary endpoint was supportive and showed consistent improvement in time to culture conversion. The proportion of subjects with culture conversion at Week 24 was also numerically higher in the bedaquiline treatment arm and this treatment benefit was generally consistent within almost all subgroups, including both MDR-TB and Pre-XDR subgroups. Similarly, a clear treatment difference is observed in both the pyrazinamid susceptible and resistant subgroups. Strikingly, the subjects on placebo on each of aforementioned subgroups have response rates which are all inferior to the 24 week culture conversion rate observed in the bedaquiline subgroup. This underscores the magnitude of the relative effect of the addition of bedaquiline to a MDR regimen. In addition, the treatment effect appeared durable based on the interim analysis (M=F Week 24) when all subjects had completed Week 72 in the **C208 Stage 2** trial.

Although the overall safety profiles of bedaquiline and placebo are generally similar, there are 3 main safety findings associated with bedaquiline treatment. These include elevation of transaminases and QT prolongation, which can both be monitored in the clinical setting. In addition, there was an imbalance in the number of deaths between the bedaquiline group and the placebo group reported in Stage 2 of trial C208. No clear explanation to associate mortality and bedaquiline exposure in this trial has been identified. We observed that the causes of death were varied (only death due to TB was reported more than once), considered by the investigator as not related to bedaquiline, and displayed a wide range in time of death since last intake of bedaquiline/placebo, with 1 occurring during the treatment phase with bedaquiline. In general, the causes of death reported for the majority of the subjects are similar to the causes of death reported from a study from 1963 that utilized autopsies from 295 patients treated for pulmonary TB to ascertain probable causes of death in TB in the pre-and post antibiotic era in the US³².

The accelerated approval would provide the potential for a major public health improvement in the treatment of MDR-TB by providing broader and more rapid access to bedaquiline for patients suffering from MDR-TB. These patients could benefit from a new treatment option that decreases the time to culture conversion and increases the likelihood of culture conversion. The magnitude of change exceeded the 15 to 20% increase in the 2-month culture conversion rate of drug-susceptible TB that results from adding pyrazinamide to isoniazid and rifampin. Finally,

bedaquiline potentially represent a new powerful asset to control outbreaks of MDR-TB in the US.

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LIST OF ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AFB	acid fast bacilli
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine 5'-triphosphate
AUC	area under the plasma concentration versus time curve
BCOP	bovine corneal opacity-permeability
BMI	body mass index
BR	background regimen
BSA	bovine serum albumin
C _{0h}	predose plasma concentration
CAD	cationic amphiphilic drug
CFU	colony forming unit
CI	confidence interval
CLcr	creatinine clearance
CLSI	Clinical Laboratory Standards Institute
CL/F	estimate for apparent oral clearance
C _{max}	maximum plasma concentration
C _{min}	minimum plasma concentration
CPK MB	creatine phosphokinase muscle-brain isoenzym
CRF	case report form
CRP	c-reactive proteine
CSR	Clinical Study Report
C _{ss,av}	average steady-state plasma concentration
CU	compassionate use
CYP	cytochrome P450
DBP	diastolic blood pressure
DDI	drug-drug interaction
DOTS	directly observed therapy short-course
DSMB	Data and Safety Monitoring Board
DS-TB	drug-susceptible TB
EAP	Early Access Program
eEBA	extended early bactericidal activity
ECG	electrocardiogram
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FQ	fluoroquinolone
GGT	gamma-glutamyltransferase
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application

J	TMC207
LDH	lactate dehydrogenase
LLNA	local lymph node assay
LS	least square
<i>M.</i>	<i>Mycobacterium</i>
M2	<i>N</i> -monodesmethyl metabolite of TMC207
MBC	minimum bactericidal concentration
MDR	multi-drug resistant
MDR _{H&R} -TB	MDR-TB, i.e., resistant to isoniazid (H) and rifampin (R), excluding Pre-XDR- and XDR-TB
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
MGIT	Mycobacteria Growth Indicator Tube
MPS	mononuclear phagocytic system
NDA	New Drug Application
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
PI	Package Insert
PK	pharmacokinetic
Pre-XDR	pre-extensively drug resistant
PT	prothrombin time
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
RBC	red blood cell
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SBP	systolic blood pressure
SCS	Summary of Clinical Safety
SMQ	standardized MedDRA query
SLI	second line injectables
SSCC	serial sputum colony count
TB	tuberculosis
TB Alliance	Global Alliance for TB Drug Development
t.i.w.	3 times weekly
TMC	Tibotec Medicinal Compound
US	United States
Vc/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization
XDR	extensively drug resistant

Definition of Terms

DOTS	Directly observed therapy short-course, WHO-recommended treatment strategy for detection and treatment of TB. DOTS combines 5 elements: political commitment with increased and sustained financing; case detection through quality-assured bacteriology; standardized treatment with supervision and patient support; an effective drug supply and management system; and monitoring and evaluation system and impact measurement.
DS-TB	Drug-susceptible TB; defined as TB due to infection with a strain of <i>M. tuberculosis</i> 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 <i>M. tuberculosis</i> that is resistant to both isoniazid and rifampin, the 2 most important first-line drugs to treat DS-TB.
MDR _{H&R} -TB	Although the clinical definition of MDR-TB encompasses Pre-XDR-TB and XDR-TB, in this document MDR _{H&R} 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 <i>M. tuberculosis</i> 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 <i>M. tuberculosis</i> that are resistant to at least one of the second-line injectable drugs (amikacin, kanamycin, capreomycin) and any FQ.
<u>Trial C208:</u>	
Any TMC207 group (pooling C208 Stage 1 and 2)	Subjects from C208 Stage 1 and Stage 2 randomized to receive TMC207 for 8 or 24 weeks (400 mg q.d. for 2 weeks followed by 200 mg t.i.w.) in combination with multidrug MDR-TB treatment according to national guidelines
Any Placebo group (pooling C208 Stage 1 and 2)	Subjects from C208 Stage 1 and Stage 2 randomized to receive placebo for 8 or 24 weeks (q.d. for 2 weeks followed by t.i.w.) in combination with multidrug MDR-TB treatment according to national guidelines

INTRODUCTION

TB is a contagious bacterial infection caused by *M. tuberculosis* that commonly affects the lungs, but can also spread to other organs¹. The disease is transmitted by aerosols when people with pulmonary TB expel bacteria, e.g., by coughing¹⁶. About a third of the global population, i.e., more than 2 billion people, is infected with *M. tuberculosis*, of which the majority is latent but 10% will become sick with an active TB infection (including a positive chest X-ray)³⁷. TB is the leading cause of death among people with HIV infection^{37,5}. Patients who are HIV-seropositive and co-infected with TB are 20 to 40 times more likely to develop active TB compared to patients who are not co-infected with HIV living in the same country^{37,5}. It was estimated that a total of 8.8 million new TB cases occurred in 2010, including 1.1 million people co-infected with HIV, and that about 1.45 million people died due to TB, including approximately 350 000 people with HIV¹⁶.

The current treatment for DS-TB is effective and is generally well tolerated, when used as recommended by treatment guidelines. The WHO recommended treatment strategy for TB is the directly observed treatment, short-course (DOTS). DOTS combines 5 elements: political commitment; microscopy services; drug supplies; surveillance and monitoring systems; and use of highly efficacious regimens with direct observation of treatment³⁸. This standard WHO treatment regimen for DS-TB consists of a 2-month intensive phase during which 4 drugs are administered once daily (q.d.) or 3 times weekly (t.i.w.) (isoniazid, rifampin, pyrazinamide and ethambutol), with a 4-month continuation phase of 2 drugs (usually isoniazid and rifampin) to which the mycobacterium has been demonstrated to be sensitive^{39,40}. Streptomycin is also used as a first-line drug to treat DS-TB, usually for retreatment of newly diagnosed patients, who failed to complete the initial treatment course or are responding poorly to their first course of TB treatment. This 6-month treatment program for DS-TB is long and burdensome¹⁷, and adherence is often challenging. Poor adherence may lead to the development of MDR-TB strains and subsequent treatment failure (Figure 7). People can also be infected with MDR-TB by primary infection with resistant bacteria. MDR-TB is defined as infection with a strain of *M. tuberculosis* that is resistant to at least isoniazid and rifampin, 2 first-line anti-TB drugs, and possibly to other drugs^{20,2}.

MDR-TB has been reported in all regions of the world. The true burden of disease is likely underestimated due to limitations of surveillance data. According to the WHO report from the Global Project of Anti-Tuberculosis Drug Resistance Surveillance (issued in 2012)⁸², there are an estimated 310 000 cases of MDR-TB worldwide, of which only 60 000 cases are being treated. China and India carry nearly 50% of the global burden of incident MDR-TB cases in 2008, followed by the Russian Federation (9%). The number of new MDR-TB cases in the US was 1.1% of new TB cases; the number of new MDR-TB cases varied within Europe with the lowest number in Western Europe (up to 2.4% of new TB cases) and the highest number in Eastern Europe (up to 22.3% of new TB cases)². In Europe, the estimated number of MDR-TB cases (primary and acquired) in 2008 was 81 000^{2,41}. In the US, the number of primary MDR-TB cases, i.e., MDR-TB cases in persons with no previous history of TB, steadily declined from 407 in 1993 to 115 in 2001. Since then the total number of primary MDR-TB cases has fluctuated from 88 to 132 cases, with 88 cases reported for 2010⁶. Globally, MDR-TB caused an estimated 150 000 deaths in 2008, including patients with HIV co-infection (97 000 deaths excluding those with HIV)². Although the total number of newly infected people with TB is slowly decreasing¹⁶, the increasing occurrence of MDR-TB and HIV-TB co-infection (latent TB is more likely to become an active infection in subjects co-infected with HIV) are important drivers of the TB epidemic and make TB control more complicated^{42,3}.

MDR-TB strains with additional resistance have emerged; these strains, called Pre-XDR-TB and XDR-TB, are more difficult to treat and have emerged as a public health threat²⁶. According to the 2010 WHO global report on surveillance and response, at least one case of XDR-TB has been confirmed in 58 countries². Pre-XDR-TB is defined as having an infection with an MDR strain that is resistant either to any fluoroquinolone or at least one of the second-line injectable anti-TB drugs (amikacin, kanamycin, capreomycin), but not to both. XDR-TB is defined as having an infection with an MDR strain that is resistant to any fluoroquinolone and at least one of the second-line injectable anti-TB drugs^{2,43}. According to the 2010 WHO global report on surveillance and response, at least one case of XDR-TB has been confirmed in 58 countries².

The clinical definition of MDR-TB encompasses Pre-XDR- and XDR-TB. In this document MDR_{H&R}-TB will be used to refer to MDR-TB excluding Pre-XDR- and XDR-TB (e.g., in descriptions of trial populations or subgroups) (see [Figure 7](#)).

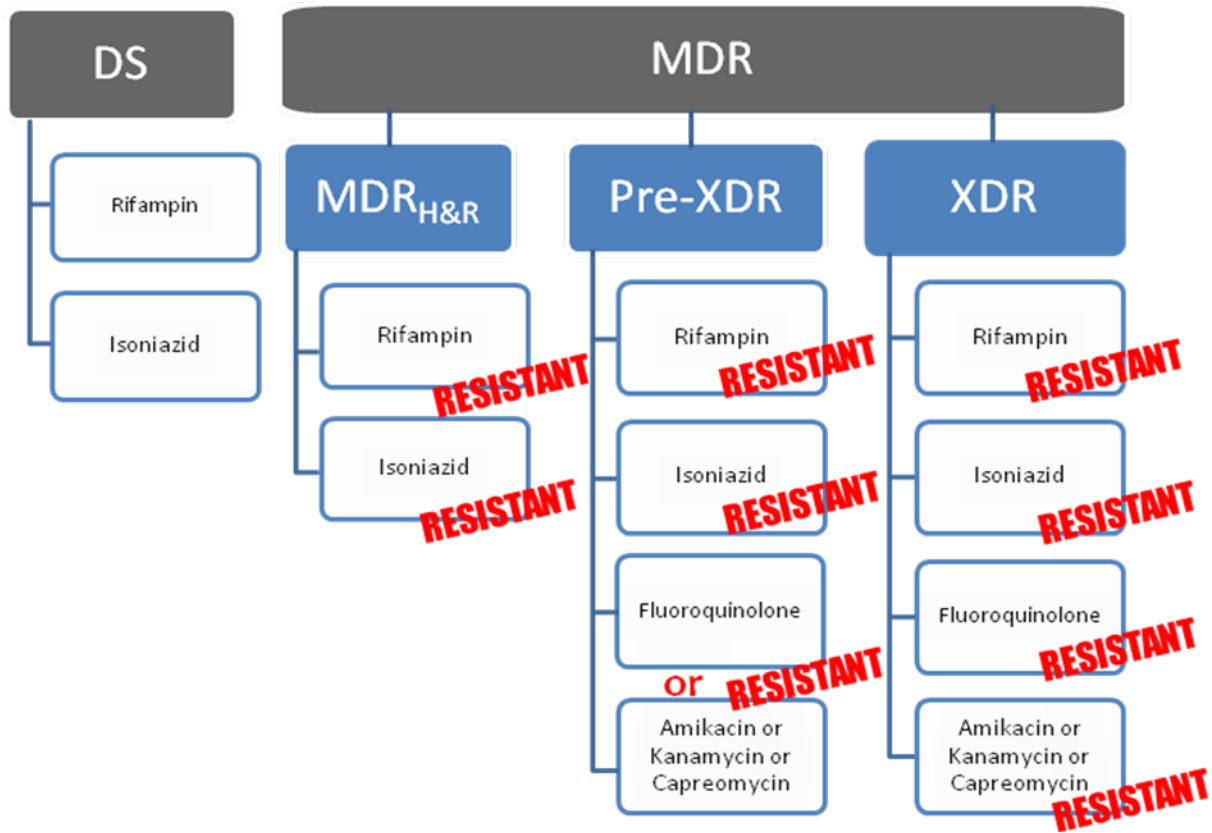


Figure 7: Classification of TB and Clinical Definition of MDR-TB, Including MDR_{H&R}-TB, Pre-XDR-TB, and XDR-TB

MDR-TB cannot be treated with the standard 6-month treatment with first-line anti-TB drugs. MDR-TB-infected patients are currently treated with at least 5 anti-TB drugs for an extended period of time, lasting up to 2 years. These second-line drugs are less effective and the regimen is more toxic than isoniazid- and rifampin-based regimens which are used to treat DS-TB^{44,2,45}. Current treatment guidelines⁴⁶ suggest that treatment regimens for MDR-TB should always include an injectable agent (an aminoglycoside or capreomycin) and pyrazinamide for the first 6 months and a fluoroquinolone throughout treatment, whenever the strain is susceptible. Other drugs used to treat MDR-TB include ethionamide, para-aminosalicylic acid, and cycloserine/terizidone. In addition, surgical resection of cavitary lung lesions, which is rarely needed for subjects with DS-TB due to the availability of effective treatment, may be required in patients with MDR-TB due to treatment failure, symptomatic complications, and sequelae of the disease^{47,48,49}.

The first available anti-TB drug was streptomycin, which was developed in the 1940s. However, it appeared that streptomycin monotherapy could not cure the disease. After the discovery of isoniazid, both TB drugs were used in combination and this reduced the emergence of drug-resistant strains. In the 1970s, pyrazinamide and rifampin became available and from the late 1970s onwards, durable cure rates of DS-TB, based on 2 years follow-up, exceeded 95%⁵⁰. The incidence of TB then began to decrease substantially in developing countries and no new anti-TB drugs were developed for decades. Ethambutol was discovered in 1960, and is an important antibacterial drug which is commonly administered together with rifampin to protect rifampin against resistance⁵¹. Rifapentine (Priftin®), a close analogue of rifampin with a longer half-life, is the most recent TB drug approved by the FDA. Rifapentine received accelerated approval in the US on 22 June 1998 and traditional approval on 1 June 2009 for the treatment of pulmonary tuberculosis caused by *M. tuberculosis* in combination with one or more anti-TB drugs.

MDR-TB patients, have a lower cure rate and higher mortality rate than drug-susceptible (DS)-TB patients¹¹. The high mortality rate reflects poor diagnostic and limited treatment options for MDR-TB globally. For patients starting treatment for MDR-TB in 2007, countries reported deaths in 4%–45% (median: 11%)¹². Two independently conducted meta analyses from 2009, each including approximately 30 studies in MDR-TB, found death as a reported outcome in 11% of treated patients^{13,14}. An even more recent meta-analysis reflecting data from 9 143 individual patients reported a mortality rate of 15%¹³. A systemic review of treatment outcome among patients with MDR-TB, including studies performed between 1973 and 2006, showed that the cure rate of MDR-TB with treatment in the most optimal public health program circumstances was 69% (95% CI: 64%-73%)⁵². Recently, promising results have been published based on a 12-year observational study in Bangladesh in which different regimens were examined and refined over time³⁴. In this study with 427 MDR-TB patients, the most effective treatment regimen consisted of a minimum of 9 months of treatment with gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the treatment period, supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of a minimum of the first 4 months of treatment. This treatment (tested in 206 patients) resulted in favorable outcome of 87.9% (95% CI: 83%-92%) with no relapse cases during a 2-year follow-up period. However, some caveats should be made about this high success rate: Most patients were resistant to

isoniazid and rifampin only (i.e., most patients had MDR_{H&R}-TB), no patients were co-infected with HIV, and there was a lack of a broad spectrum of racial and ethnic groups.

Treatment outcomes are typically less favorable in patients with Pre-XDR- and XDR-TB compared to patients with MDR_{H&R}-TB. A study that investigated treatment outcomes and survival in 1407 patients with MDR-TB strains showed that treatment success, defined as cure or treatment completion, ranged from 36% (57 out of 159 patients) to 47% (55 out of 117 patients) in patients with Pre-XDR-TB and was 29% (22 out of 75 patients) in patients with XDR-TB³⁴. In addition, 11 to 20% of patients with Pre-XDR-TB and 27% of patients with XDR-TB died. The results of a meta-analysis of 13 studies with a total of 560 patients with XDR-TB reported that 44% (95% CI: 33%-55%) of the patients experienced favorable outcomes, defined as either cure or treatment completion, and 21% (95% CI: 14%-27%) died⁵⁴. The observations over 13 years in a TB referral hospital in China showed that of 48 patients with XDR-TB, only 29% had treatment success; i.e., 10% of the subjects were cured and 19% had completed treatment⁵⁵. Furthermore, there are several factors that are generally associated with poorer treatment outcome of patients with MDR-TB, such as prior treatment, the degree of resistance to anti-TB drugs including baseline resistance to pyrazinamide, the number of susceptible (“active”) drugs in the regimen, and the degree of pulmonary cavitation^{52,54}.

A novel compound with a new mode of action likely resulting in no to minimal cross-resistance, highly effective against MDR-TB and with a good safety and tolerability profile, would be an important contribution for the treatment of MDR-TB. The increasing incidences of Pre-XDR- and XDR-TB cases make the need for new TB drugs even more urgent⁴³.

1 PRODUCT DEVELOPMENT RATIONALE

1.1 PHARMACOLOGIC CLASS AND TARGETED INDICATION

Bedaquiline is a diarylquinoline and a novel anti-mycobacterial agent²⁹. During early development, bedaquiline was referred to as R207910 or JNJ-16175328-AAA (free base form), or R403323 or JNJ-16175328-AEP (fumarate salt). The international nonproprietary name (INN) and the United States adopted name (USAN) are both bedaquiline, and the USAN modified is bedaquiline fumarate. This document will describe the product as bedaquiline in text, however, tables and figures may use TMC207 or the abbreviation BDQ.

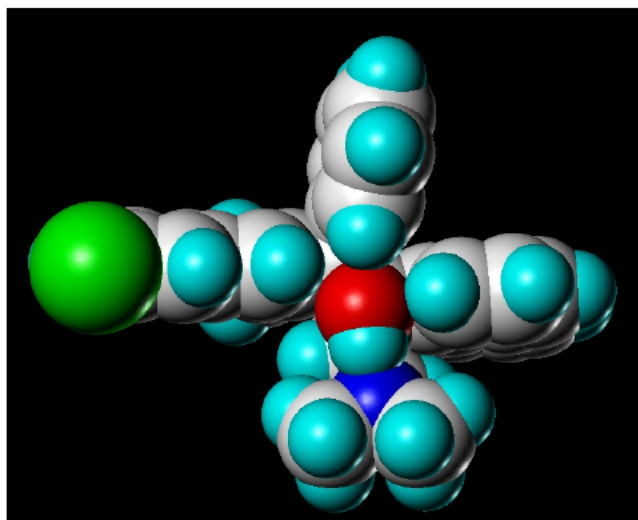
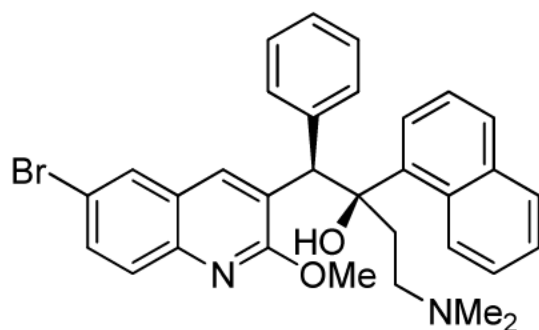


Figure 8 Chemical Structure of Bedaquiline (TMC207)

Bedaquiline has been developed as part of an oral combination therapy for MDR-TB. Bedaquiline has a unique mechanism of action involving specific inhibition of mycobacterial ATP synthase, an enzyme that is essential for the generation of energy in mycobacteria. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating (dormant) tubercle bacilli⁵⁷.

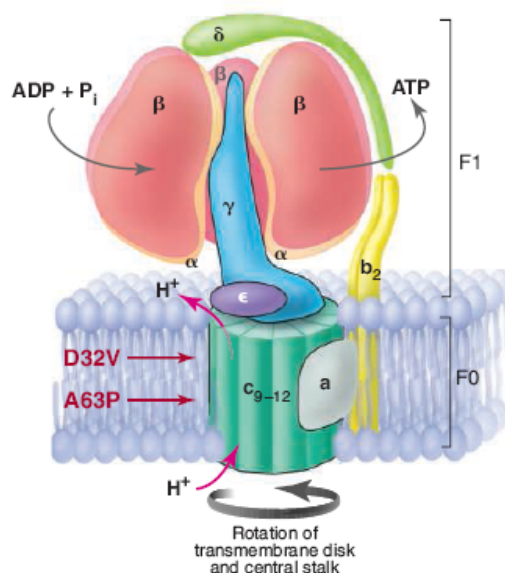


Figure 9: ATP Synthase

Model of the mycobacterial ATP synthase showing the position of some mutations that confer resistance to bedaquiline. ATP synthase has two major structural domains, F₀ and F₁ that act as a biological rotary motor. F₁ is composed of nine subunits and is located in the cytoplasm, where it generates ATP. F₀ spans the cytoplasmic membrane and contains 13 to 15 subunits (a, b₂, c₉₋₁₂). Rotation of the transmembrane ring (c-subunit, in green) and the central stalk is driven by the proton-motive force. (from: Science, 2005, 307, 214).

Due to its novel mode of action, bedaquiline defines a new class of anti-TB compounds; currently, no other drugs belonging to the same pharmacological class as bedaquiline are available. The distinct target of bedaquiline minimizes the potential for cross-resistance with existing anti-TB drugs.

Bedaquiline has potent in vitro activity against a broad range of mycobacterial species. It has been tested in vitro against multiple clinical isolates of *M. tuberculosis* and is active against DS, MDR_{H&R}, Pre-XDR, and XDR strains of *M. tuberculosis*²⁷. In vitro and in vivo studies showed that bedaquiline was primarily subjected to oxidative metabolism leading mainly to the formation of the M2. This metabolite was found to be active against *M. tuberculosis*, although it is 3 to 6 times less potent than bedaquiline itself. In a mouse model of TB infection, the addition of bedaquiline increased the bactericidal and sterilizing (prevention of relapses) potency of both first-line and second-line regimens, resulting in shorter minimal treatment durations.

The Sponsor has established a collaboration with the Global Alliance for TB Drug Development (TB Alliance) to share expertise and resources in the development of bedaquiline. The Sponsor has granted the TB Alliance a license for the worldwide development of bedaquiline for DS-TB.

Under the terms of the agreement, the Sponsor is responsible for the worldwide development of bedaquiline in the treatment of MDR-TB, while the TB Alliance is responsible for the worldwide development of bedaquiline for DS-TB. Therefore, the current application submitted by the Sponsor is for MDR-TB and not for DS-TB.

The key data for the current application are from the placebo-controlled trial **C208** which consisted of 2 consecutive, independent stages, an exploratory **Stage 1** and a proof-of-efficacy **Stage 2**, in newly diagnosed* sputum smear-positive subjects with pulmonary MDR-TB. Both **Stage 1** and **Stage 2** included subjects infected with Pre-XDR-TB. **Stage 2** of the **C208** trial provide the pivotal data, because this stage has been performed with the proposed 24-week therapeutic regimen of bedaquiline.

In the application submitted by the Sponsor, bedaquiline is proposed for the treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* in adults (≥ 18 years), as part of combination therapy. It is recommended that bedaquiline is administered by DOT. The prescribing physician should refer to the prescribing information of bedaquiline and national TB treatment guidelines for direction on selection and duration of use of companion drugs. To minimize the risk of development of resistance to the drug, bedaquiline should only be used in combination with at least 3 drugs to which the patient's isolate has been shown to be susceptible in vitro. If in vitro testing results are unavailable, treatment may be initiated with bedaquiline in combination with at least 4 other drugs to which the patient's isolate is likely to be susceptible, based on historical data of resistance testing results and previous TB treatment exposure. The total duration of treatment with bedaquiline is 24 weeks. Throughout treatment with, and following the last intake of bedaquiline, patients should continue to take their companion drugs in accordance with national TB treatment guidelines and local MDR-TB treatment practice.

An orphan-drug designation was granted for the use of bedaquiline in the treatment of TB by both the FDA (10 January 2005) and the European Commission (26 August 2005).

* Newly diagnosed was defined as subjects with MDR-TB who had never been treated for TB before or with only first-line anti-TB drugs

1.2 CLINICAL DEVELOPMENT PROGRAM

First-in-human dosing with bedaquiline occurred in February 2004. 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 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 nonclinical 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). [Figure 10](#) below provides a schematic overview of the trial design and treatment period in the Phase IIb trials.

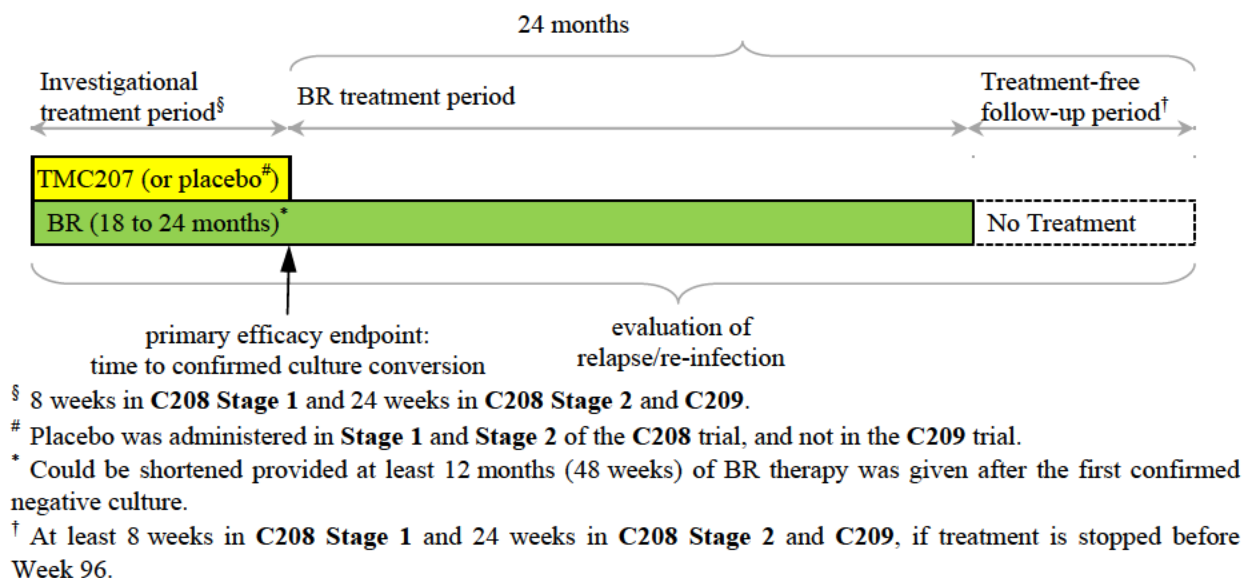


Figure 10: Overview of Trial Design and Treatment Periods in Phase IIb Trials

1.2.1 Trial TMC207-C208

Trial C208 is a Phase IIb, randomized, placebo-controlled, double-blind, multicenter trial in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection. The trial was designed to evaluate the antibacterial activity, safety, and tolerability of bedaquiline or placebo when added to a preferred BR of MDR-TB therapy. Additionally, the pharmacokinetics (PK) of bedaquiline and M2 in plasma and sputum, PK/PD relationships for activity and tolerability/safety, and drug-drug interactions between bedaquiline and anti-TB drugs in the BR are assessed.

This trial was conducted in 2 independent consecutive stages, a concluded exploratory stage (Stage 1) and an ongoing proof-of-efficacy stage (Stage 2). Stage 1 and Stage 2 of the C208 trial can conceptually be considered as 2 separate trials, because Stage 2 was only initiated after the primary Week 8 analysis of Stage 1. Subjects of Stage 1 were not allowed to participate in Stage 2, and analyses of both stages were done independently. The results of Stage 2 of the C208 trial provide the pivotal data as this stage was performed with the proposed 24-week therapeutic regimen of bedaquiline.

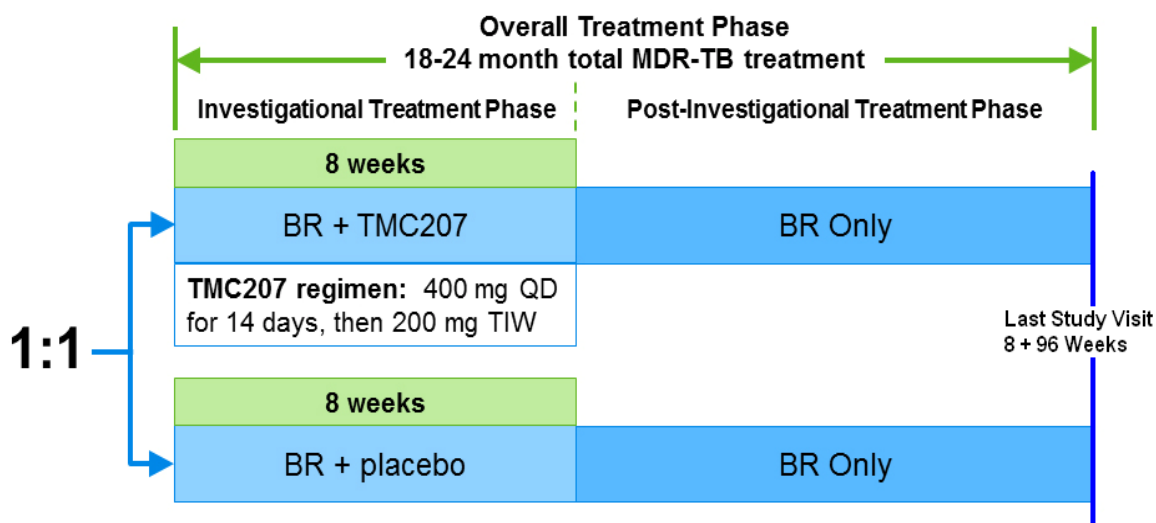
Subjects with newly diagnosed pulmonary MDR-TB infection (defined as subjects with MDR-TB who had never been treated for TB before or with only first-line anti-TB drugs) who were sputum smear-positive (i.e., ≥ 1 + smear-positive for acid fast bacilli [AFB]) and infected

with strains with confirmed resistance to at least both rifampin and isoniazid were eligible for the **C208** trial (**Stage 1** and **Stage 2**). Subjects found to have XDR-TB were to be discontinued from the trial.

Subjects were randomized to receive treatment with either bedaquiline or placebo for 8 (**Stage 1**) or 24 weeks (**Stage 2**) in combination with a preferred 5-drug BR of MDR-TB medication consisting of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone. Treatment throughout the trial was administered using DOT. Bedaquiline or placebo was dosed as 400 mg q.d. for the first 2 weeks and as 200 mg t.i.w. for the following 6 or 22 weeks. 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 Phase IIa trial **C202**. Randomization was stratified by trial site and lung cavitation (i.e., no cavitation, cavitation in one lung, or cavitation in both lungs, with cavitation defined as the presence of at least one cavity ≥ 2 cm). After 8 weeks (Stage 1) or 24 weeks (Stage 2), subjects continued the BR of MDR-TB therapy until a total treatment duration of 72 to 96 weeks was achieved. This period could be shortened provided that at least 48 weeks of treatment had been given after documentation of sputum culture conversion from positive to negative. Subjects were to be followed for 96 weeks after the last dose of bedaquiline or placebo (comprising the BR treatment period and a treatment-free follow-up period).

Stage 1

In **Stage 1** of trial **C208** (which is completed), subjects received investigational treatment for 8 weeks ([Figure 11](#)). In this stage, 47 subjects (all from South Africa), including 6 subjects with Pre-XDR-TB strains, were randomized and treated; 23 subjects received bedaquiline and 24 subjects received placebo up to 8 weeks (in combination with a standardized BR for MDR-TB). Recruitment for **Stage 1** of the trial was completed in December 2007, and the results supported the start of **Stage 2** of the trial. Bedaquiline (or placebo) was dosed as 400 mg q.d. for the first 2 weeks and as 200 mg t.i.w. for the following 6 weeks in **Stage 1**.



BR = background regimen

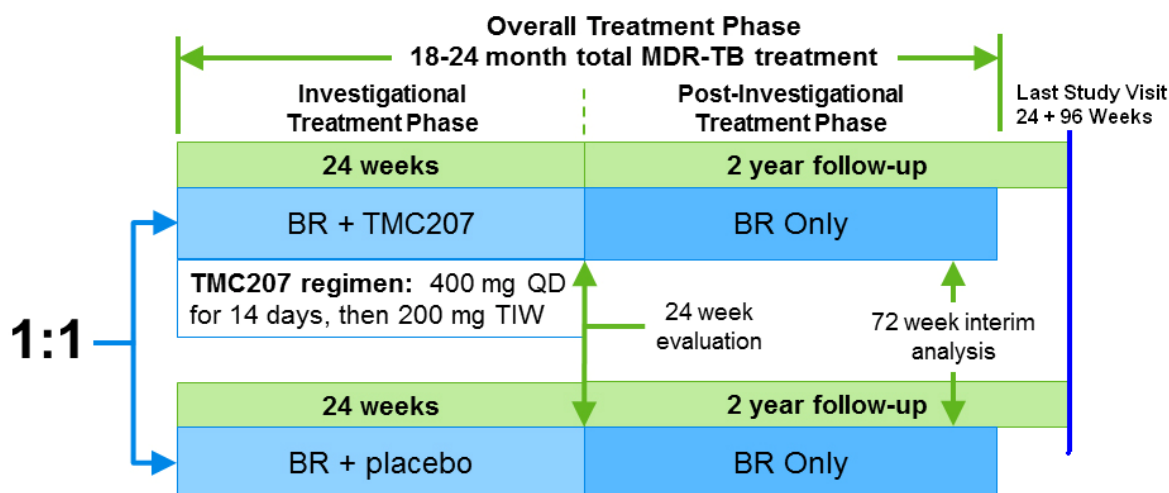
Figure 11: C208 Stage 1: Duration of Trial Periods and Relevant Time Points

Stage 2

Stage 2 of the trial **C208** is a proof-of-efficacy stage in which subjects with newly diagnosed pulmonary MDR-TB were randomized to receive 24 weeks of investigational treatment (bedaquiline or placebo in combination with a preferred BR of MDR-TB treatment)(Figure 12). Recruitment for **Stage 2** was completed Q3 2009, and included other countries beyond South Africa, i.e., India, Russia, Latvia, Peru, Brazil, Thailand, and the Philippines. In **Stage 2**, 160 subjects were randomized and treated, including 28 subjects with Pre-XDR-TB strains; 79 subjects received bedaquiline and 81 subjects received placebo up to 24 weeks (in combination with a standardized BR for MDR-TB).

Upon availability of the **Stage 1** results, a rollover arm was added to **Stage 2** per protocol amendment to offer open-label treatment with bedaquiline to those subjects from **Stage 2** who received placebo and were not adequately responding to their BR regimen after 24 weeks of double-blind treatment (including subjects who developed XDR-TB during investigational treatment). **Stage 2** subjects who were found to have XDR-TB at baseline (for whom susceptibility results to second-line drugs only became available after randomization) were also given the option to immediately receive open-label treatment with bedaquiline in the rollover arm. Of note, only 1 subject in C208 Stage 2 rolled over to this rollover arm.

The investigational treatment period and treatment-free follow-up period in **Stage 2** of trial **C208** has been completed by all subjects, except for 1 subject in the rollover arm whose status is ongoing. However, at the time of the cut-off date for the NDA application all subjects in **Stage 2** had reached at least the Week 72 visit or had discontinued earlier.



BR = background regimen

Figure 12: C208 Stage 2: Duration of Trial Periods and Relevant Time Points

The primary efficacy endpoint for **C208** was time to sputum culture conversion in MGIT during the 8-week (**Stage 1**) or 24-week (**Stage 2**) investigational treatment period, this was evaluated after all subjects had completed the 8-week or 24-week investigational treatment period or discontinued earlier.

1.2.2 Trial TMC207-C209

The other Phase IIb trial in the bedaquiline program with MDR-TB subjects is the single-arm, open-label trial **C209**, which provides supportive data (Figure 13). The **C209** trial was performed in 233 subjects with either newly diagnosed or treatment-experienced MDR-TB, including Pre-XDR-TB (44 subjects) and XDR-TB (37 subjects), to further assess the safety and efficacy of bedaquiline when added to an individually optimized MDR-TB treatment regimen according to national and international guidelines, and to collect data in non-newly diagnosed MDR-TB subjects. HIV-infected subjects (with CD4+ count ≥ 250 cells/ μ L at screening) were allowed to enter the trial.

In contrast to the **C208** trial, subjects with XDR-TB infection were allowed to enter the **C209**

trial, provided they had at least 3 drugs in their anti-TB regimen to which their *M. tuberculosis* isolate was likely to be susceptible. All subjects received bedaquiline. Bedaquiline was administered as 400 mg q.d. for the first 2 weeks and 200 mg t.i.w. for the following 22 weeks, as was done in **Stage 2** of the **C208** trial. After 24 weeks, subjects continued to receive their BR under the care of their physician and in accordance with national TB program (NTP) treatment guidelines (usually for a total of 72 to 96 weeks or a minimum of 48 weeks after sputum conversion in most national and international treatment guidelines). All subjects are to be followed up for a total of 96 weeks after their last intake of bedaquiline, comprising the BR treatment period and a subsequent treatment-free follow-up period of at least 24 weeks (6 months), to allow for evaluation of relapse/re-infection.

Trial **C209** is ongoing, but all subjects have completed at least the Week 24 visit of the trial or discontinued earlier, which allowed analysis of the primary efficacy endpoint, i.e., time to culture conversion in MGIT during the 24-week investigational treatment period (similar to the **C208** trial).

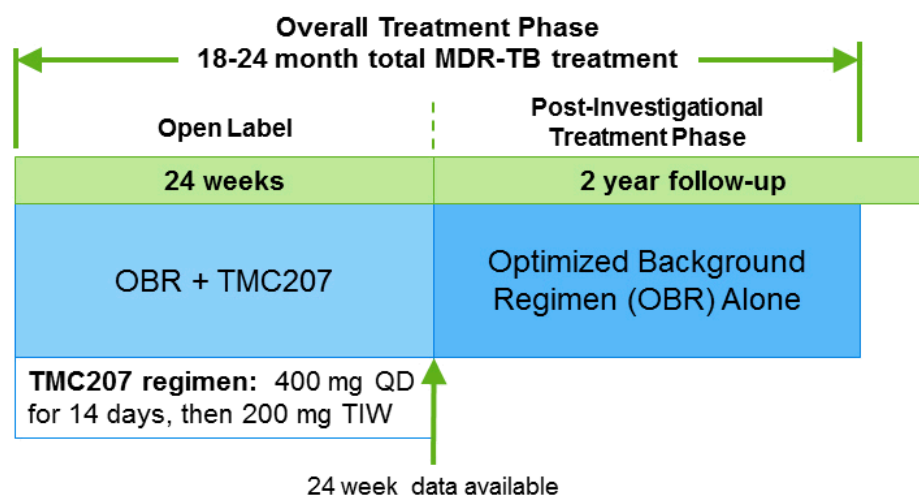


Figure 13: C209: Duration of Trial Periods and Relevant Time Points

2 MICROBIOLOGY

Bedaquiline is a diarylquinoline with broad antimycobacterial activity, but has much higher MICs for non-mycobacteria. It binds to *M. tuberculosis* ATP synthase, thereby inhibiting ATP synthesis and resulting in bactericidal activity. Bactericidal activity of bedaquiline was

confirmed in a mouse model of TB infection, and matched or exceeded that of isoniazid and rifampin, the 2 most important first-line drugs to treat DS-TB. The addition of bedaquiline to regimens to treat DS- and MDR-TB increased both bactericidal and sterilizing activities of these combinations in this model.

A breakpoint analysis was performed based on (i) the susceptibility profile of preclinical and clinical isolates of *M. tuberculosis* including DS-, MDR-, pre-extensively drug resistant (Pre-XDR)- and XDR-TB to bedaquiline and (ii) microbiologic outcomes demonstrating favorable culture conversion rates of MDR-TB isolates from clinical trials with bedaquiline MIC ≤ 0.5 $\mu\text{g/mL}$ as determined by the agar method (and MIC ≤ 0.25 $\mu\text{g/mL}$ as determined by the REMA). The suggested MIC interpretive criteria are ≤ 0.5 $\mu\text{g/mL}$ for susceptible as determined by the agar method (and ≤ 0.25 $\mu\text{g/mL}$ for susceptible as determined by the REMA method). Because of the lack of clinical experience with isolates of *M. tuberculosis* with MICs > 0.5 $\mu\text{g/mL}$, a susceptible only breakpoint of ≤ 0.5 $\mu\text{g/mL}$ is proposed.

2.1 SUSCEPTIBILITY TEST METHODS

The 7H11 agar dilution method was proposed as the primary susceptibility test method for bedaquiline. This method is derived from the agar proportion method developed by the Clinical Laboratory Standards Institute (CLSI) and approved by the WHO. The rationale for the agar proportion method is that for most TB drugs, when 1% or more of drug resistant mycobacteria are present in a given population of *M. tuberculosis* exposed to a concentration called the “critical concentration”, therapeutic success is unlikely. Therefore, the *M. tuberculosis* isolate would be considered resistant to the drug. Currently the agar proportion and the liquid MGIT960 methods are the primary methodologies for drug susceptibility testing (DST) for approved anti-TB drugs. As no critical concentration is available for bedaquiline, the agar proportion method was modified to define the minimum inhibitory concentration (MIC) defined as the lowest concentration of bedaquiline that prevents growth of *M. tuberculosis* by 99% in vitro.

A rapid methodology utilizing liquid culture-based rapid method system, for identifying resistance to first and second line TB drugs has been recognized to improve the diagnosis of patients with MDR-TB. The Resazurin Microtiter Assay (REMA) in 7H9 broth has been shown to be accurate in detecting resistance to isoniazid, rifampin and second-line drugs in clinical isolates. Furthermore, this method has been endorsed by the WHO for DST of isoniazid and

rifampin⁵⁸. The REMA method is based on the oxido-reduction of resazurin, an indicator added to a 7H9 broth liquid culture medium after *M. tuberculosis* has been exposed in vitro to various concentrations of test TB drug for 7 to 10 days. Mycobacterial growth is detected by a change in color from blue to pink, which is directly proportional to the number and metabolic activity of viable mycobacteria in the medium. For validation of bedaquiline MIC by the agar and 7H9 broth with resazurin (REMA) methods, quality control was performed by testing the *M. tuberculosis* H37Rv strain (ATCC-American Type Culture Collection- number 27294), a susceptible strain to bedaquiline. The bedaquiline MIC distribution supports the quality control parameters shown in Table 3.

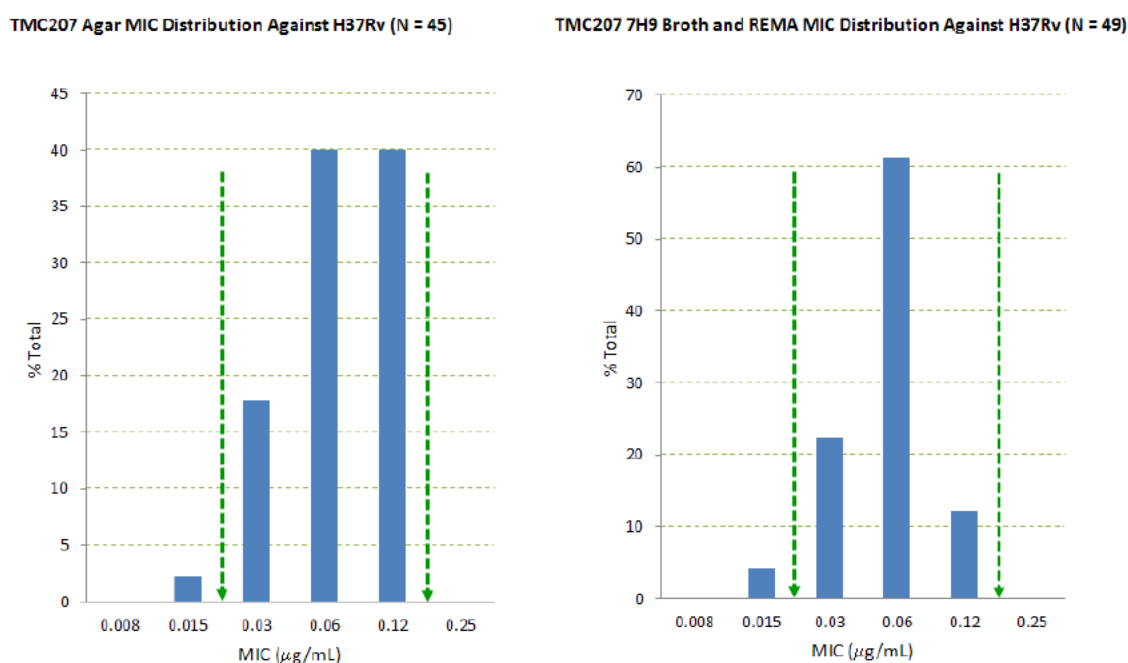


Figure 14: Agar and 7H9 Broth and REMA MIC Distribution Against H37Rv

Table 3: Acceptable Quality Control Ranges for TMC207

QC Organism	Recommended TMC207 MIC (µg/mL)	
	7H11 Agar	REMA (7H9 broth)
<i>M. tuberculosis</i> H37Rv	0.03 – 0.12	0.03 – 0.12

Both methods -7H11 agar and REMA were used for bedaquiline susceptibility testing of *M. tuberculosis* isolates in nonclinical studies as well as in the central laboratory for the susceptibility testing isolates from bedaquiline clinical trials. Because limited data were

generated using the REMA method, only results for the 7H11 agar method are discussed in detail in this Briefing Book.

2.2 IN VITRO ANTIMYCOBACTERIAL ACTIVITY

2.2.1 In Vitro Susceptibility

The in vitro susceptibility of 109 *M. tuberculosis* isolates to bedaquiline was determined on both 7H11 and 7H10 agar media^{29,27}. Data summarized in [Table 4](#) are compilations of data from Andries et al. (2005)²⁹ and Huitric et al. (2007)²⁷, as well as an internal source. MIC ranges were ≤ 0.008 $\mu\text{g/mL}$ to 0.12 $\mu\text{g/mL}$ regardless of *M. tuberculosis* resistance subtype (i.e., DS-TB, MDR-TB, etc.). The MIC to inhibit the growth of 50% and 90% of isolates (MIC₅₀ and MIC₉₀) of bedaquiline were 0.03 and 0.06 $\mu\text{g/mL}$, respectively, for both DS-TB and MDR-TB isolates. Bedaquiline demonstrated similar in vitro efficacy against *M. tuberculosis* clinical isolates resistant to other anti-TB drugs (isoniazid, rifampin, streptomycin, ethambutol, pyrazinamide, or fluoroquinolones)⁵⁹.

Table 4: In Vitro Activity of TMC207 Against *M. tuberculosis* Preclinical Isolates

Organism	MTB Resistance Subtype	N	TMC207 MIC ($\mu\text{g/mL}$)			
			MIC Range	MIC ₅₀	MIC ₉₀	MIC ₉₅
<i>M. tuberculosis</i>	All	109	≤ 0.008 - 0.12	0.03	0.06	0.06
	DS-TB	65	≤ 0.008 - 0.12	0.03	0.06	0.06
	MDR-TB	44	≤ 0.008 - 0.12	0.03	0.06	0.06

N = number of isolates

Data from clinical isolates are summarized in [Table 5](#) and were collected from the **C208**, **C209** and pooled **C208/C209** trials. The MIC₉₀ and MIC₉₅ of bedaquiline by the agar method (7H11) for pooled *M. tuberculosis* from **C208/C209** trials (321 isolates) was 0.12 $\mu\text{g/mL}$ for all *M. tuberculosis* resistance subtypes (MDR_{H&R}-TB, Pre-XDR-TB and XDR-TB).

Table 5: In Vitro Activity of TMC207 Against Baseline *M. tuberculosis* Clinical Isolates From mITT Subjects (Agar Method)

Clinical Trial	MTB Resistance Subtype	N	TMC207 Agar MIC (µg/mL)			
			MIC Range	MIC ₅₀	MIC ₉₀	MIC ₉₅
C208	All Isolates	155	≤ 0.008 - > 1	0.06	0.12	0.25
	MDR _{H&R} -TB	113	≤ 0.008 - > 1	0.06	0.12	0.25
	Pre-XDR-TB	32	0.015 - 0.25	0.06	0.12	0.12
	Unknown	10	≤ 0.008 - 0.06	0.06	NA ^a	NA ^a
C209	All Isolates	166	≤ 0.008 - > 1	0.06	0.12	0.12
	MDR _{H&R} -TB	88	≤ 0.008 - 0.5	0.06	0.12	0.12
	Pre-XDR-TB	44	0.015 - > 1	0.06	0.12	0.12
	XDR-TB	34	0.015 - 0.5	0.06	0.12	0.12
C208 and C209	All Isolates	321	≤ 0.008 - > 1	0.12	0.12	0.12
	MDR _{H&R} -TB	201	≤ 0.008 - > 1	0.06	0.12	0.12
	Pre-XDR-TB	76	0.015 - > 1	0.06	0.12	0.12
	XDR-TB	34	0.015 - 0.5	0.06	0.12	0.12
	Unknown	10	≤ 0.008 - 0.06	0.06	NA ^a	NA ^a

^a Number of isolates is too small (< 30) to draw a MIC₉₀ or MIC₉₅

Bedaquiline MICs were generally < 0.1 µg/mL for other mycobacterial species, including species naturally resistant to many other anti-TB agents and involved in opportunistic infections, such as *M. avium complex*, *M. abscessus*, *M. fortuitum*, and *M. marinum*. In comparison to *M. tuberculosis*, higher MICs were found for one isolate each of *M. abscessus* (0.25 µg/mL) and *M. ulcerans* (0.50 µg/mL) (Table 6). *M. xenopi*, *M. novocastrense* and *M. shimoidei* had significantly higher MICs (4 to 8 µg/mL) and are considered to be naturally resistant to bedaquiline. Their genomes were shown to have a polymorphism in the *atpE* gene²⁷.

Table 6: In Vitro Activity of TMC207 Against Other Mycobacterial Species

Mycobacterial Organism	N	TMC207 MIC (µg/mL)	
		MIC Range	Median
<i>M. bovis</i>	1	-	0.003
<i>M. kansasii</i>	1	-	0.003
<i>M. marinum</i>	1	-	0.003
<i>M. smegmatis</i>	7	0.003 - 0.010	0.007
<i>M. avium/M. intracellulare</i> (MAC)	7	0.007 - 0.010	0.010
<i>M. fortuitum</i>	5	0.007 - 0.010	0.010
<i>M. abscessus</i>	1	-	0.250
<i>M. ulcerans</i>	1	-	0.500

N = number of strains

Source: data published by Andries et al., Science 2005²⁹

The activity of bedaquiline appeared to be specific for *Mycobacterium* species. Bedaquiline had much higher MICs for non-mycobacteria (Table 7).

Table 7: In Vitro Activity of TMC207 Against Non-Mycobacterial Isolates

Non-Mycobacterial Organisms	N	TMC207 MIC (µg/mL)	
		MIC Range	Median
<i>Corynebacterium jeikeium</i>	1	-	4
<i>Corynebacterium urealyticum</i>	1	-	4
<i>Helicobacter pylori</i>	20	2 - > 4	4
<i>Nocardia asteroides</i>	1	-	> 16
<i>Nocardia farcinica</i>	1	-	> 16
<i>Escherichia coli</i>	1	-	> 32
<i>Haemophilus influenzae</i>	1	-	> 32
<i>Streptococcus pneumoniae</i>	10	16 - > 32	> 32
<i>Staphylococcus aureus</i>	1	-	> 32

N = number of strains

Source: data published by Andries et al., Science 2005²⁹

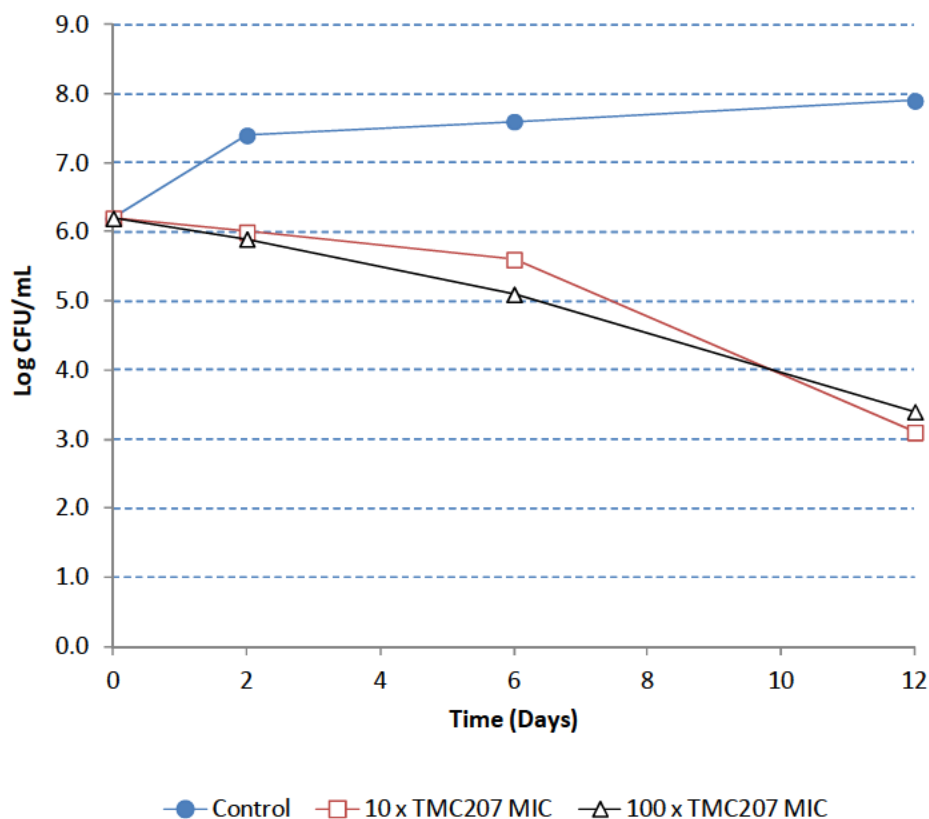
The MIC of M2, the main metabolite of bedaquiline for *M. tuberculosis* H37Rv, was 0.1 µg/mL on both 7H11 agar and 7H9 broth media or 3 to 6 times higher than the parent compound bedaquiline. The MIC of M3, another metabolite, was 6 µg/mL on both 7H11 agar and 7H9 broth media or 100 times higher than the parent compound bedaquiline.

The effect of protein binding on bedaquiline in vitro activity was assessed against *M. tuberculosis* H37Rv strain in 7H9 broth in the presence or absence of 5% bovine serum albumin (BSA). The MIC of bedaquiline was also assessed in the LJ medium (i.e., an egg and glycerol-based medium rich in ovalbumin). In non-supplemented 7H9 broth, bedaquiline MIC was 0.05 µg/mL. In the presence of 5% BSA, the MIC increased 18-fold to 0.9 µg/mL. In the LJ medium, the average MIC of bedaquiline against the *M. tuberculosis* H37Rv strain tested 3 times was increased over 400-fold (14.33 µg/mL) in comparison to 7H11 agar (0.03 µg/mL). These data suggest that serum albumin may impact MIC testing of bedaquiline. The data also suggest that the activity of bedaquiline could be compromised in an environment with a high protein concentration. However, such impact was not seen on antibacterial effectiveness in an in vivo model of TB infection.

2.2.2 Bactericidal Activity

Bactericidal activity is considered an important attribute in treating life-threatening infections such as TB. In several studies, bedaquiline was shown to be bactericidal for *M. tuberculosis*.

The bactericidal activity of bedaquiline was evaluated using the CLSI methodology⁵⁹ of minimum bactericidal concentration (MBC) against *M. tuberculosis* H37Rv. The MIC of bedaquiline against the *M. tuberculosis* H37Rv strain in 7H9 broth medium was 0.05 µg/mL and the MBC was 0.40 µg/mL. A time-kill experiment was conducted in broth under appropriate culture conditions for the test isolate H37Rv, at bedaquiline concentrations 10x and 100x the MIC. Exposure of *M. tuberculosis* in log-phase growth to concentrations of bedaquiline at 10x MIC resulted in a reduction in bacterial load of 3 log units after 12 days. The killing effect was not further increased by using a higher concentration of the compound (100x MIC), suggesting time-dependent rather than concentration-dependent killing during the first 12 days of exposure (Figure 15). Bedaquiline was also shown to be bactericidal against dormant bacilli⁵⁷.



Source: Andries et al., Science 2005²⁹

Figure 15: In Vitro Bactericidal Activity of TMC207 Against *M. tuberculosis* H37Rv

2.3 INTRACELLULAR ANTIMICROBIAL ACTIVITY ASSESSMENT

One mechanism that *M. tuberculosis* uses to evade the immune system is to reside within host cells or within the phagolysosome⁶⁰. The intracellular activity of bedaquiline was tested in primary mouse peritoneal macrophages and in the J774 macrophage-like cell line. Bacteriostatic concentrations were 0.22 $\mu\text{g/mL}$ for extra-cellular cultures, 0.17 $\mu\text{g/mL}$ for mouse peritoneal macrophages, and 0.06 $\mu\text{g/mL}$ for the J774 cells macrophage cell line, while high concentrations of bedaquiline resulted in bacterial killing⁶¹.

2.4 MECHANISM OF ACTION

Bedaquiline is the first diarylquinoline reported to exhibit anti-TB activity. Thus, the mechanism of action of bedaquiline could not be inferred from an existing drug class of compounds and experiments were conducted in order to elucidate its mechanism of action. Mutants of

M. tuberculosis and *M. smegmatis* with high bedaquiline MICs were selected in vitro. Whole genome sequencing of these mutants as well as the parental strains revealed point mutations in *atpE*, a gene encoding the subunit c of ATP synthase, an enzyme that is essential for the generation of energy in *M. tuberculosis*. Complementation studies verified that the mutant *atpE* gene was responsible for the elevated bedaquiline MICs, implying that the *atpE* gene product (subunit c, a proton pump) is the target of bedaquiline in mycobacteria. Bedaquiline strongly inhibited ATP synthase activity in *M. smegmatis* membrane vesicles with 50% inhibition (IC₅₀) achieved at 0.0014 - 0.0056 µg/mL, and binding studies using compound-linked affinity chromatography and BIAcore confirmed binding of bedaquiline to subunit c of the ATP synthase. Taken together, these findings support the notion that bedaquiline inhibits the proton pump of *M. tuberculosis* ATP synthase.

ATP synthase is also present in mitochondria of eucaryotes. In order to assess the selectivity of bedaquiline towards mycobacterial ATP synthesis, ATP synthesis inhibition was studied in mitochondria from a human cancer cell line, and compared to ATP synthesis inhibition in reversed membrane vesicles of *M. smegmatis*. The sensitivity of mycobacterial ATP synthase to bedaquiline was higher (IC₅₀ 0.01 µM) in comparison to that of human mitochondria (IC₅₀ > 100 µM), resulting in a Selectivity Index of > 10 000. These results suggest that bedaquiline is specific for mycobacterial ATP synthase and may not elicit target-based toxicity in mammalian cells⁶².

2.5 MECHANISMS OF RESISTANCE

2.5.1 Resistance Selection in Vitro

Since bedaquiline is the first drug in its class, a mechanism of resistance could not be inferred from an existing anti-TB drug. Therefore, studies were conducted to characterize the potential mechanisms that may mediate resistance to bedaquiline. The mechanism of action studies identified *atpE* mutations as a one of the mechanisms of resistance to bedaquiline. In these studies, the bedaquiline spontaneous resistant proportions were 5×10^{-7} and 2×10^{-8} at 4x the MIC, and 5×10^{-8} and 1×10^{-8} at 8x the MIC, for *M. tuberculosis* and *M. smegmatis*, respectively. In the case of *M. tuberculosis*, these proportions were comparable to those of rifampin-resistant mutants (1×10^{-7} to 10^{-8}). The susceptibility of the parental *M. tuberculosis*

strain and the bedaquiline-selected resistant mutant to other anti-TB agents remained unchanged²⁹.

A second study used the Luria-Delbrück fluctuation assay⁶³ to select independent, spontaneous bedaquiline-resistant mutants and to estimate the mutation rates²⁷. Bedaquiline-resistant isolates were selected at the rates of 4.7×10^{-7} to 8.9×10^{-9} mutations per cell division at 10x MIC, and 3.9×10^{-8} to 2.4×10^{-9} mutations per cell division at 30x MIC. The bedaquiline MICs of the mutants ranged from 0.12 µg/mL to 3.84 µg/mL, representing 4- to 128-fold increases in the MICs. No resistant mutants were obtained at 3 µg/mL (100x the MIC). Fifty-three mutant isolates selected at 10x and 30x bedaquiline MIC were characterized at the molecular level by sequencing the *atpE* gene (Table 8). In 15 isolates, 5 different point mutations in *atpE* resulting in 5 different amino acid substitutions were identified and the MIC fold increases ranged from 16 to 128. In 38 isolates with MIC fold increases ranging from 4 to 32, no *atpE* mutations were found and sequencing of the whole genome from 3 such isolates revealed no mutations, indicating the existence of other alternative resistance mechanisms yet to be elucidated⁶⁴. Additional studies including the effect of efflux pump inhibitors on the in vitro activity of bedaquiline are planned.

Table 8: Resistance Mutations in the *atpE* Gene and TMC207 MIC Levels

Strain (MIC, µg/mL)	Selection Concentration (multiple of MIC)	No. of Mutants Sequenced (total no. obtained)	<i>atpE</i> , F0 operon, or ATP synthase operon mutation	No. of Independent Mutants Characterized	MIC Range of the Mutants (µg/mL)
MDR Parent Strains					
1 (0.03)	10	6 (12)	Glu ⁶¹ →Asp (GAG-GAC)	1	0.48
			WT <i>atpE</i>	5	0.12-0.48
2 (0.06)	30	2 (2)	Ala ⁶³ →Pro (GCA-CCA)	2	1.92-3.84
	10	3 (5)	Asp ²⁸ →Val (GAC-GTC)	1	0.48
			Glu ⁶¹ →Asp (GAG-GAC)	1	0.24
			WT <i>atpE</i>	1	0.12
3 (0.06)	10	6 (12)			
			WT <i>atpE</i>	2	0.9
			WT <i>atpE</i> and F0 operon	1	0.9
	30	5 (11)	WT <i>atpE</i> and ATP synthase	3	0.9
			WT <i>atpE</i>	3	0.48-0.9
			WT <i>atpE</i> and F0 operon	2	0.9
5 (0.03)	10	3 (7)	WT <i>atpE</i>	2	0.12-0.24
			WT <i>atpE</i> and F0 operon	1	0.24
	30	2 (2)	Ala ⁶³ →Pro (GCA-CCA)	1	0.9
			Ile ⁶⁶ →Met (ATC-ATG)	1	0.48
DS Parent Strains					
4 (0.06)	10	7 (12)	Asp ²⁸ →Pro (GAC-GGC)	1	0.3
			Glu ⁶¹ →Asp (GAG-GAC)	1	0.96
			WT <i>atpE</i>	3	0.12-0.24
			WT <i>atpE</i> and F0 operon	2	0.3-0.48
	30	1 (1)	Glu ⁶¹ →Asp (GAG-GAC)	1	0.48
6 (0.12)	10	5 (10)	WT <i>atpE</i>	5	0.24-0.96
	30	5 (5)	Glu ⁶¹ →Asp (GAG-GAC)	1	0.48
			Ala ⁶³ →Pro (GCA-CCA)	1	0.9
			WT <i>atpE</i>	3	0.12-0.24
7 (0.06)	10	3 (10)	WT <i>atpE</i>	1	0.48
			WT <i>atpE</i> and F0 operon	2	0.48
	30	5 (5)	Ala ⁶³ →Pro (GCA-CCA)	3	3.84
			WT <i>atpE</i>	2	0.24-0.48

WT = wild-type

2.5.2 Resistance Development on Therapy - TMC207 Clinical Trial Isolates

Clinical isolates from trials **C208 Stage 1**, **C208 Stage 2** and **C209** were examined for the development of increased MICs to bedaquiline. Overall, 13 of 28 bedaquiline -treated subjects with paired MIC data (baseline and post-baseline) had at least a 4-fold increase in bedaquiline MIC from baseline as assessed by the 7H11 agar test method. Compared to subjects with Pre-XDR-TB or XDR-TB profiles at baseline, fewer results were available from subjects with MDR_{H&R}-TB who achieved culture-negativity more rapidly and submitted a larger proportion of

sputum samples that did not grow in cultures for resistance testing. An overview of the relevant individual data for the 13 pairs of isolates is provided in [Table 9](#).

Out of these 13 pairs, 3 were found to be genetically different between baseline and post-baseline. Nine of the remaining 10 bedaquiline -treated subjects failed to convert or relapsed. One of the 10 post-baseline isolates with ≥ 4 -fold MIC increase as assessed by the 7H11 agar method was an MDR-TB, but his ≥ 4 -fold MIC increase was not confirmed when tested by the REMA method. ATP synthase sequencing was performed to determine potential polymorphisms in the *atp* operon, which is comprised of *atpB*, *atpE*, *atpF*, *atpH*, *atpA*, *atpG*, *atpD*, and *atpC* and their inter-genic areas. Polymorphisms in the coding sequence of the whole *atp* operon of the strains before and after treatment were identified in none of these 10 subjects' isolates.

Table 9: Summary of Subjects' Isolates With at Least 4-Fold Increase in TMC207 MIC and *atp* Operon Sequencing Results (Clinical Trials C208 Stage 1, C208 Stage 2 and C209, mITT Subjects)

Subject CRF ID	Outcome (No Overruling ^a – All Available Data) ^b	MIC (REMA) µg/mL			MIC (Agar) µg/mL			Extent of Resistanc e at BL	<i>atp</i> Operon Variance in Coding Regions Between Strains (BL vs Post-BL)
		BL	Post-BL	F	BL	Post-BL	F		
C208 (Stage 1)									
208-3004	relapse	0.0313	0.0156 (W8)	0.5x	0.06	0.24 (W8)	<u>4x</u>	MDR _{H&R}	no coding variation
C208 (Stage 2)									
208-4465	failure to convert	0.0156	0.25 (W24)	<u>16x</u>	0.06	0.24 (W24)	<u>4x</u>	Pre-XDR	no coding variation
C209									
209-0269	failure to convert	0.062 5	0.25 (W24)	<u>4x</u>	0.06	0.48 (W24)	<u>8x</u>	Pre-XDR	no coding variation
209-0038	failure to convert	0.062 5	0.25 (W24)	<u>4x</u>	0.06	> 0.48 (W24)	<u>> 8x</u>	Pre-XDR	no coding variation
209-0050	failure to convert	0.031 3	0.50 (W24)	<u>16x</u>	0.06	0.48 (W24)	<u>8x</u>	Pre-XDR	no coding variation
209-0182	failure to convert	0.062 5	0.25 (W24)	<u>4x</u>	0.06	> 0.48 (W24)	<u>> 8x</u>	XDR	no coding variation
209-0263	relapse	0.031 3	0.25 (W24)	<u>8x</u>	0.06	0.48 (W24)	<u>8x</u>	XDR	no coding variation
209-0128	failure to convert	0.062 5	0.50 (W24)	<u>8x</u>	0.06	> 0.48 (W24)	<u>> 8x</u>	XDR	no coding variation
209-0157	responder	0.031 3	0.50 (W24)	<u>16x</u>	0.06	0.48 (W24)	<u>8x</u>	XDR	no coding variation
209-0267	failure to convert	0.062 5	1 (W24)	<u>16x</u>	0.06	> 0.48 (W24)	<u>> 8x</u>	XDR	no coding variation

BL = baseline; F = fold increase in MIC compared with baseline (derived from the non-rounded MIC values); W = week
Subjects for whom baseline and post-baseline isolates were genotypically different were excluded from this table.

^a In the no overruling analysis, the discontinuation information was not taken into account and conversion status prior to discontinuation is used.

^b All Available Data Selection: analyses for the Phase IIb trials based on this data selection took into account all available data in the interim database (i.e., up to the cut-off date of the analyses for the trials **C208 Stage 2** and **C209**) or in the final database (for trial **C208 Stage 1**).

2.6 IN VIVO EFFICACY STUDIES

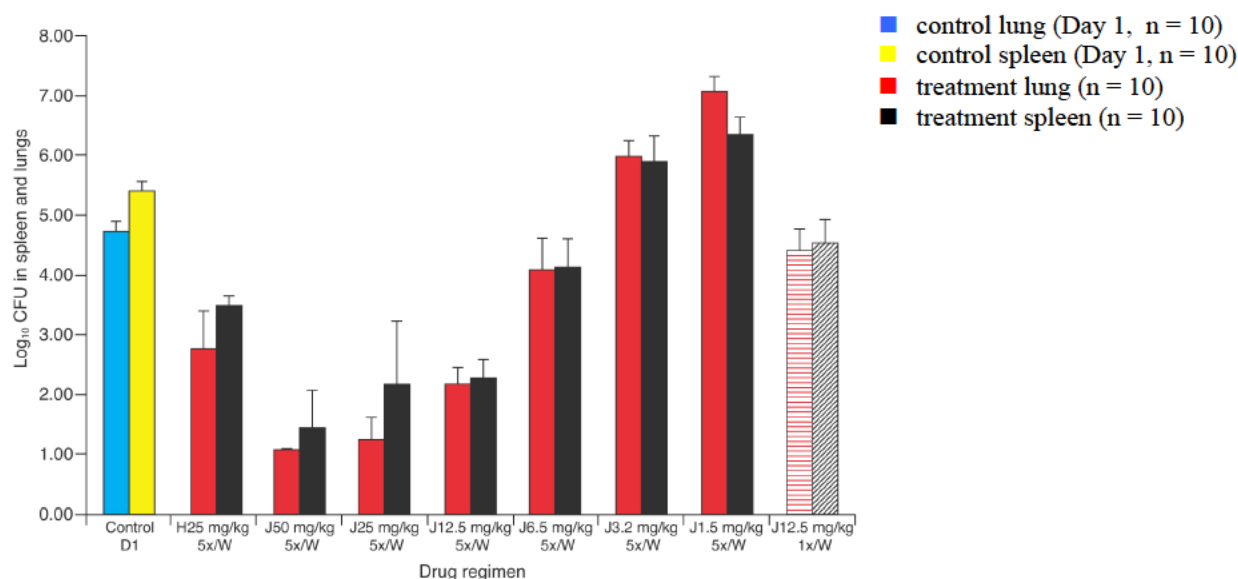
Two murine models are used for assessment of new anti-TB drugs, the non-established (or acute) and the established TB infection models. A guinea pig model was also used to assess the activity of bedaquiline against *M. tuberculosis*.

In both murine models, female Swiss mice are intravenously infected with 2×10^7 CFU of *M. tuberculosis* strain H37Rv. This strain is susceptible to all anti-TB drugs and its bedaquiline MIC is 0.03 µg/mL. In the non-established TB infection model, treatment starts the day after infection with *M. tuberculosis*, while in the established TB infection model, treatment starts approximately 2 weeks after infection. In the latter model, the TB infection is already established at the start of treatment. The bacterial load in the spleen and lungs at 2 weeks post-infection ranges between 10^7 and 10^8 CFU per organ, similar to the bacterial load observed in human pulmonary TB. In both models, untreated mice are expected to die within 4 weeks of infection.

- The **bactericidal activity** refers to the ability of a drug or drug combination to kill all mycobacteria present at baseline, until culture conversion is achieved, i.e. until no further mycobacteria can be isolated out of the infected organs.
- The **sterilizing activity** refers to the ability of a drug or drug combination to prevent relapses. To assess relapse rates in mice, the animals are kept a further 3 months after stopping all treatment. After this 3-month period, animals are sacrificed, and organs are assessed for any mycobacterial bacilli. The recovery of one or more mycobacterial cells out of an infected organ (lung or spleen) is considered as a relapse.

2.6.1 Bactericidal Activity of Bedaquiline Monotherapy

The bactericidal activity of bedaquiline monotherapy was assessed in the non-established TB infection model. Using oral treatment of bedaquiline for 5 days per week for 4 weeks, the minimal dose of bedaquiline that prevented mouse mortality was 1.5 mg/kg, and the minimum effective dose preventing gross lung lesions was 6.5 mg/kg. In mice receiving doses of 12.5 mg/kg, the bacterial load per organ was reduced from 5 to 2 log units ($p < 0.0014$). Thus, the minimum bactericidal dose was very close to the minimal effective dose. At 25 mg/kg, the activity of bedaquiline was significantly better than at 12.5 mg/kg ($p < 0.0014$). At 12.5 and 25 mg/kg, 4 weeks of treatment with bedaquiline was significantly more active ($p < 0.0014$) than with isoniazid (25 mg/kg), a drug known for its strong early bactericidal activity. Moreover, at 12.5 mg/kg, a once-weekly dose of 25 mg/kg was almost as efficacious as a dose of 6.5 mg/kg given 5 times per week (Figure 16). This is likely a consequence of the long $t_{1/2}$ term allowing maintenance of prolonged exposure throughout the 7-day time-frame²⁹.



J = TMC207, H = isoniazid at 25 mg/kg; D1 = Day 1; 5x/W = 5 times per week, 1x/W = once per week (hatched bars)

Note: values are means \pm standard deviation (SD).

Figure 16 : Minimum Effective Dose of TMC207 After 4 Weeks of Treatment in the Non-established Infection Murine TB Model

2.6.2 Bactericidal Activity of Bedaquiline in Combination With Second-line Anti-TB Drugs

Mice were infected intravenously with 5×10^6 CFU of the drug sensitive H37Rv strain of *M. tuberculosis* (established infection model) and treated 5 times per week with bedaquiline alone, or with bedaquiline combined with various combinations of second-line anti-TB drugs amikacin, pyrazinamide, moxifloxacin and ethionamide. The first line drug combination rifampin-isoniazid-pyrazinamide was added as a positive control. When added to amikacin, pyrazinamide, moxifloxacin and ethionamide, bedaquiline accelerated the bactericidal activity of the drug regimen. Bedaquiline-containing regimens were significantly more active than those that did not contain bedaquiline ($p < 0.05$) except for the amikacin + ethionamide + moxifloxacin + pyrazinamide regimen ($p > 0.05$). In terms of proportion of negative cultures, bedaquiline-containing regimens were significantly more potent in rendering the lungs culture negative than the regimens that did not include bedaquiline ($p < 0.05$). In fact, amikacin + ethionamide + moxifloxacin + pyrazinamide + bedaquiline rendered 100% of the lungs culture negative after 2 months of therapy while the amikacin + ethionamide + moxifloxacin + pyrazinamide regimen rendered only 50% of lungs culture negative ($p = 0.036$).

Table 10: Bactericidal Activity of TMC207 in Combination With Second-line Drugs in the Established Infection Murine TB Model

Regimens ^a	Mean Log CFU Counts \pm SD			
	Spleen at 1 Month	Spleen at 2 Months (Proportion of Mice Negative Cultures/Total No. of Mice)	Lungs at 1 Month	Lungs at 2 Months (Proportion of Mice Negative Cultures/Total No of Mice)
Untreated	6.5 \pm 0.2	-	5.9 \pm 0.5	-
B	2.6 \pm 1.3	1.2 \pm 0.5 (0/8)	2.9 \pm 0.9	0.2 \pm 0.3 (6/8)
RHZ	4.5 \pm 0.3	1.9 \pm 0.5 (1/10)	3.7 \pm 0.4	1.0 \pm 0.5 (0/10)
RHZB	1.9 \pm 0.31	0.1 \pm 0.2 (4/10)	1.8 \pm 0.4	0 \pm 0 (10/10)
AEMZ	3.2 \pm 0.5	1.6 \pm 0.4 (1/10)	2.9 \pm 0.2	0.1 \pm 0.1 (5/10)
AEZ	4.0 \pm 0.3	2.8 \pm 0.3 (0/10)	3.7 \pm 0.2	1.2 \pm 0.3 (0/10)
AMZ	3.6 \pm 0.2	1.9 \pm 0.5 (0/10)	3.4 \pm 0.3	0.8 \pm 0.6 (0/10)
AEZB	1.2 \pm 0.2	0.1 \pm 0.1 (7/9)	0.2 \pm 0.3	0 \pm 0 (9/9)
AMZB	1.2 \pm 0.2	0 \pm 0 (8/8)	0.2 \pm 0.3	0 \pm 0 (8/8)
AEMZB	1.2 \pm 0.3	0 \pm 0 (8/8)	0.5 \pm 0.4	0 \pm 0 (8/8)

B = bedaquiline; R = rifampin; H = isoniazid; Z = pyrazinamide; A = amikacin; E = ethionamide; M = moxifloxacin
SD = standard deviation

^a Drugs were administered 5 times/week: rifampin 10 mg/kg; TMC207 25 mg/kg; isoniazid 25 mg/kg; pyrazinamide 150 mg/kg; amikacin 150 mg/kg; ethionamide 50 mg/kg; moxifloxacin 100 mg/kg

This study was the first one in which a regimen without isoniazid and rifampin was able to reach lung and spleen culture conversion within 2 months of therapy. These observations suggested that adding bedaquiline to an MDR-TB regimen accelerates the bactericidal activity of the background regimen and has the potential to significantly shorten the time to culture conversion in patients.

Bactericidal activities were also demonstrated for the combination of bedaquiline with first line anti-TB drugs in the established TB infection model as well as in a guinea pig model.

2.6.3 Sterilizing Activity of Bedaquiline in Combination With Second-line Anti-TB Drugs

A study assessing relapse rates after treatment of mice with second-line drugs with or without bedaquiline was performed. Female Swiss mice were infected with 5.6 log CFU of *M. tuberculosis* H37Rv, and treatment started 14 days later, when the CFU count had increased to 7.1 log. Positive control regimens were 6 months of rifampin + isoniazid + pyrazinamide (first

line regimen) and 6 months of amikacin + ethionamide + moxifloxacin + pyrazinamide (second line regimen). Test regimens were 6 months of bedaquiline + moxifloxacin + pyrazinamide and 6 months of bedaquiline + amikacin + ethionamide + moxifloxacin + pyrazinamide. Relapse rates were assessed 3 months after treatment completion ([Table 11](#)).

Table 11: Proportion of Mice With Relapses 3 Months After Treatment Completion (Lung Data)

Regimen	Total Treatment duration	Relapses at 3 Months Post-Treatment
2 (RHZ) + 4 (RH)	6 Months	3/28 (11%)
2 (BRZ) + 2 (BR)	4 Months	3/19 (16%)
2 (AEMZ) + 4 (ME)	6 Months	11/19 (58%)
2 (AEMZ) + 7 (ME)	9 Months	8/16 (50%)
2 (AEMZ) + 10 (ME)	12 Months	4/18 (22%)
2 (BZM) + 2 (BM)	4 Months	8/20 (40%)
2 (BZM) + 4 (BM)	6 Months	2/19 (11%)
2 (BZM) + 7 (BM)	9 Months	5/20 (25%)
2 (BAEMZ) + 4 (BEM)	6 Months	5/18 (28%)
2 (BAEZ) + 4 (BE)	6 Months	9/20 (45%)
2 (BAEM) + 4 (BEM)	6 Months	10/20 (50%)
6 (BM)	6 Months	9/20 (45%)
6 (BZ)	6 Months	4/18 (22%)

A = amikacin; E = ethionamide; B = bedaquiline; M = moxifloxacin; R = rifampin; H = isoniazid; Z = pyrazinamide
ND = not done, NA = not applicable

Lung culture negativity was obtained after 4 months for the bedaquiline + moxifloxacin + pyrazinamide regimen, and after 6 months for the other regimens (data not shown). Relapse rates 3 months after the end of 6 months of treatment with 2 (rifampin + isoniazid + pyrazinamide) + 4 (rifampin + isoniazid), 2 (amikacin + ethionamide + moxifloxacin + pyrazinamide) + 4 (ethionamide + moxifloxacin), 2 (bedaquiline + amikacin + ethionamide + moxifloxacin + pyrazinamide) + 4 (bedaquiline + ethionamide + moxifloxacin) and 2 (bedaquiline + moxifloxacin + pyrazinamide) + 4 (bedaquiline + moxifloxacin) were 11%, 58%, 28% and 11%, respectively ([Table 11](#)). The bedaquiline + moxifloxacin + pyrazinamide regimen, omitting both rifampin and isoniazid, was as effective after 6 months as rifampin + isoniazid + pyrazinamide. Adding bedaquiline to amikacin + ethionamide + moxifloxacin + pyrazinamide improved the

sterilizing efficacy of this second-line regimen. Both bedaquiline + moxifloxacin + pyrazinamide and bedaquiline + amikacin + ethionamide + moxifloxacin + pyrazinamide may shorten treatment duration of MDR-TB⁶¹.

Bedaquiline was also shown to increase the sterilizing efficacy of the first line regimen rifampin + isoniazid + pyrazinamide in the mouse model described above.

2.7 ESTABLISHMENT OF BEDAQUILINE BREAKPOINTS

The following breakpoints are proposed for both bedaquiline 7H11 agar MIC and REMA MIC.

Table 12: Proposed MIC Interpretive Criteria for TMC207

Pathogen	TMC207 MIC (µg/mL)	
	7H11 Agar	REMA
	Susceptible Only (S)	Susceptible Only (S)
<i>M. tuberculosis</i>	≤ 0.5	≤ 0.25

Bedaquiline REMA MIC interpretive criteria were determined based on correlation of 7H11 agar MIC values and REMA MIC values from clinical data. The bedaquiline REMA MIC results from testing of the clinical *M. tuberculosis* isolates were used to construct scattergrams which correlated agar MIC and the clinical isolate REMA MIC values. Error rates were calculated as described in the CLSI M23 guideline⁶⁵. The REMA MIC interpretive criteria presented in the scattergrams were chosen to produce error rates that were within the suggested CLSI guideline. Additional validation of REMA clinical MIC breakpoints included the MIC₉₀ (and MIC₉₅) and MIC distribution for all *M. tuberculosis* resistance subtypes, and microbiologic outcomes by baseline REMA MICs.

For the 7H11 agar method the proposed interpretive criteria were justified as follows:

2.7.1 MIC Distributions

The overall microbial MIC distributions for the preclinical MDR-TB *M. tuberculosis* isolates as well as MDR-TB isolates from subjects in the C208 and C209 trials are shown in Figure 17. The MIC distribution showed a unimodal pattern consistent with the absence of a resistance subpopulation. MIC distributions of Pre-XDR- and XDR-TB were similar to that of MDR-TB.

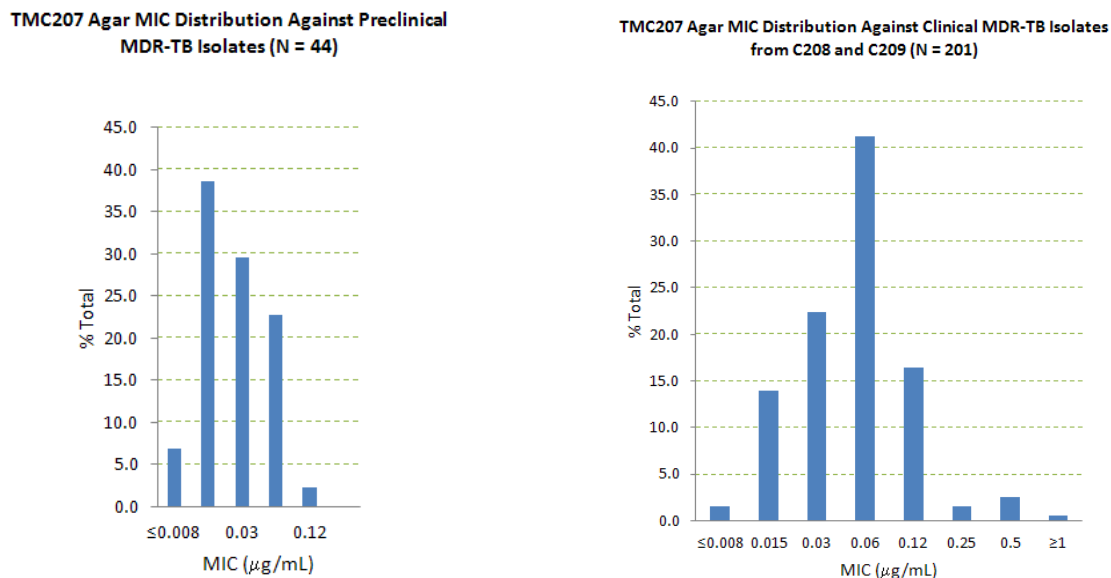


Figure 17: C208 and C209: MIC Distribution of MDR-TB Preclinical Isolates and Clinical Isolates

2.7.2 Pharmacokinetics and Pharmacodynamics (PK/PD)

Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of M2. The PK/PD response was investigated in the murine model of TB infection following oral administration of different doses of bedaquiline or M2 at various dosing frequencies for 6 weeks starting 2 weeks after intravenous infection with *M. tuberculosis*⁶⁶.

In mice, exposure of M2 was 2 to 7 times higher than that of bedaquiline. The exposure to M2 in MDR-TB infected human subjects following repeated administration of bedaquiline is about 25% to 30% of that of bedaquiline. As M2 is also active against *M. tuberculosis*, albeit with 3-to 6-fold lower potency than the parent drug, these differences in exposure complicate the extrapolation of PK/PD findings from the mouse model to patients because the relative contribution of bedaquiline and M2 to overall efficacy is difficult to distinguish. In addition, bedaquiline is highly protein and tissue bound, hindering the assessment of free drug plasma levels. Given these differences between the mouse model and human, PK/PD parameters could not be used to simulate potential target attainment rates for various MIC values based on the clinical dose. Therefore, PK/PD breakpoints were not assessed for bedaquiline.

2.7.3 Correlation of Bedaquiline Agar MIC and Microbiologic Outcome

A critical component in establishing final breakpoints involves correlation of bedaquiline MIC data from the of causative mycobacterial isolates identified in the Phase IIb trials **C208** and **C209** with microbiologic outcomes in these trials (Table 13). Evaluation of the outcomes by MIC from the **C208** and **C209** trials examining culture conversion rates at 24 weeks provide support for a clinical susceptible breakpoint of ≤ 0.5 $\mu\text{g/mL}$ for *M. tuberculosis*. Because of the lack of clinical experience with isolates of *M. tuberculosis* with MICs > 0.5 $\mu\text{g/mL}$, a susceptible only breakpoint of ≤ 0.5 $\mu\text{g/mL}$ is proposed.

Table 13: C208 and C209: Culture Conversion Rates (Week 24 Data Selection, No Overruling for Discontinuation) at Week 24 Versus Baseline TMC207 MIC for mITT Subjects (Agar Method)

	TMC207/BR 24-Week 24 Data Selection ^{a,b}			
Baseline TMC207 MIC ($\mu\text{g/mL}$)	C208 Stage 1 n/N (%)	C208 Stage 2 n/N (%)	C209 n/N (%)	C208 Stage 2 & C209 n/N (%)
≤ 0.008	1/1 (100)	1/1 (100)	1/1 (100)	2/2 (100)
0.015	1/2 (50.0)	5/5 (100)	10/13 (76.9)	15/18 (83.3)
0.03	5/5 (100)	16/17 (94.1)	24/32 (75.0)	40/49 (81.6)
0.06	7/7 (100)	13/24 (54.2)	67/81 (82.7)	80/105 (76.2)
0.12	2/2 (100)	7/7 (100)	28/34 (82.4)	35/41 (85.4)
0.25	0	1/2 (50.0)	0	1/2 (50.0)
0.5	0/1 (0)	1/1 (100)	3/4 (75.0)	4/5 (80.0)
≥ 1	1/1 (100)	0	0/1 (0)	0/1 (0)

N = number of subjects with data; n = numbers of subjects with that result

^a Week 24 Data Selection: analyses based on this data selection took into account all available data up to and including Week 24. If the last assessment in the Week-24 window was an unconfirmed negative or positive value, the first not missing/contaminated result outside this window (if available) was taken into account to get confirmation.

^b In the no overruling analysis, the discontinuation information was not taken into account and conversion status prior to discontinuation is used.

3 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

After oral administration, bedaquiline is well absorbed in the preclinical species. The absolute bioavailability was approximately 36%, 40% and 79% in the dog, monkey and rat, respectively. There was no indication that transport of bedaquiline was affected by an apically located efflux

transporter such as P-gp, and bedaquiline did not significantly inhibit P-gp. Bedaquiline was slowly metabolized, mainly by *N*-demethylation to M2, followed by a second *N*-demethylation to M3. Cytochrome P450 (CYP3A4) was the major CYP involved in the metabolism of bedaquiline. M2 was the main circulating metabolite in all species. Upon repeated administration, the plasma exposure to M2 relative to bedaquiline was 2- to 7-times higher in mice, while it was generally similar to 2-fold lower in rats and dogs and 3 to 4-fold lower in humans.

Bedaquiline was extensively bound to plasma proteins in mice, rats, dogs, monkeys, rabbits and humans. At a concentration of 5 µg/mL the plasma protein binding (PPB) was > 99.9% in all animal species and humans. Bedaquiline distributed rapidly and extensively to tissues as a result of its cationic amphiphilic drug (CAD) properties, with generally major tissue uptake in adrenal glands, lung, spleen, liver, lymph nodes, thymus and fat. Brain uptake was low. Following repeated dose administration, tissue uptake was extensive even at the low doses corresponding to the NOAEL (dogs) or LOAEL (rats). Concentrations of M2 in tissues were generally higher than those of bedaquiline, in agreement with its stronger CAD properties. Both bedaquiline and M2 were slowly eliminated with multiphasic plasma concentration decreases and a terminal half-life up to more than 1 month in dogs after single administration. The administered dose was mainly eliminated in feces. Both after single and repeated administration, the tissue concentrations decreased in parallel to the plasma concentrations after stopping the treatment.

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. Phospholipidosis was 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 is a generalized condition characterized by the accumulation of phospholipids and drug (usually cationic amphiphilic drugs) within cells (lysosomes), resulting in lysosomal lamellar bodies, which are visible at the ultrastructural level^{67,68}.

Phospholipidosis is mainly regarded as an adaptive phenomenon rather than a toxic response. It is described to be slowly reversible upon treatment cessation⁶⁷ and this was confirmed for

bedaquiline by at least partial recovery seen in dog⁶⁸ and rat studies (no recovery assessment in mice). Phospholipidosis was seen in rats (minimal) at exposures similar to the clinical exposure for bedaquiline and M2. In dogs, phospholipidosis was seen at 3- and 6 fold higher exposures compared to those in humans for bedaquiline and M2, respectively.

At NOAEL/LOAEL in dogs and rats (no and minimal phospholipidosis, respectively), bedaquiline and M2 exposures are similar to those in human at the recommended clinical doses. Therefore phospholipidosis is expected to be minimal in humans, if present at all. Importantly, there were no indications for functional consequences of phospholipidosis based on in vitro assessment of macrophage function or in vivo assessment of the immune function in rats. Moreover, compared to the exposure of bedaquiline, the relative exposure of M2, which is a stronger phospholipidosis inducer than bedaquiline in vitro, is lower in human than in preclinical species. After the initial 2-week treatment with daily administration of 400 mg of the drug, bedaquiline is administered intermittently (t.i.w.) at a lower dose (200 mg), thereby avoiding the accumulation of bedaquiline or M2, and further limiting the potential for induction of phospholipidosis, in agreement with the better tolerance of intermittent treatment in dogs.

In addition to changes related to phospholipidosis, the main organs affected by repeated administration of bedaquiline (in one or more species) were skeletal muscle, heart, stomach, pancreas and liver. The latter finding was associated with transaminase increases but no bilirubin changes or cholestasis.

After treatment cessation or dose reduction in animals, all indications of toxicity exhibited at least partial to good recovery, despite a slow elimination of bedaquiline and its major metabolite M2.

Nonclinical safety pharmacology studies showed that bedaquiline and M2 moderately inhibited the rapidly activating delayed-rectifier potassium current (IKr) in vitro in the human ether-à-go-go-related gene (hERG) model. In vivo ECG evaluations were part of repeat-dose toxicity studies in dogs up to 9 month of duration. QT prolongations were absent in all of these studies, with exception of the 2/6-month study. In this study, bedaquiline was administered daily by the p.o. route, via gavage at 10 or 40/20 mg/kg or twice weekly at 140 mg/kg. A low daily dose of 10 mg/kg/day or an intermittent dose of 140 mg/kg twice weekly during 6 months did not show any effect on QT or heart rate. Increased QT-intervals (up to 25%) coinciding with a decreased

heart rate (up to 22%) were noted in ECGs of dogs administered 40 mg/kg/day after 2 months. After correction for heart rate using Fridericia's formula, an increase in QTc-intervals (up to 16%) was noted. After lowering the dose to 20 mg/kg/day, the QT interval prolongation and decreased heart rate were only present to a limited extent and QTc intervals were no longer prolonged when corrected for heart rate. At the end of the 6-month dosing period, there was no evidence of altered ECG parameters. No QT/QTc interval changes were observed after 9-month administration in dogs up to 18 mg/kg/day. In dogs, at the NOAEL of the QT prolongation, the exposures are approximately 8- and 9-fold higher than the clinical exposures for bedaquiline and M2, respectively. The QT prolongation is a finding with clinically relevant implications.

4 OVERVIEW OF CLINICAL PHARMACOLOGY

4.1 PHARMACOKINETICS

4.1.1 Pharmacokinetics of Bedaquiline in Healthy Subjects

Bedaquiline showed dose-proportional PK when administered as an oral formulation at single doses of between 10 and 700 mg and multiple doses between 50 and 400 mg q.d. for 14 days. The rate of bedaquiline absorption was not influenced by the dose; the median t_{\max} was 5 hours at all doses tested. Food increased the relative bioavailability of bedaquiline by about 2-fold compared to administration under fasted conditions. Based on these results, it was recommended to take bedaquiline with food in all trials in TB-infected patients.

Bedaquiline displayed a multi-phasic distribution and elimination profile, with a long elimination half-life that was independent of the dose administered ([Figure 18](#)). The long elimination half-life of bedaquiline did not drive the short-term accumulation observed in plasma upon multiple-dose administration. The mean accumulation index for bedaquiline AUC_{24h} after 2 weeks of q.d. dosing was about 2-fold across the doses studied, which is considerably less than what could be expected based on the terminal elimination half-life ($t_{1/2,term}$) of bedaquiline of about 5.5 months as estimated in patients with MDR-TB. The concept of the effective half-life has been used to describe the half-life associated with accumulation in plasma. For bedaquiline, the observed accumulation of approximately 2-fold after 2 weeks of q.d. dosing corresponds to an effective half-life of approximately 24 hours.

The urinary excretion of unchanged bedaquiline was 0.01% of the dose, indicating that renal clearance of unchanged drug is insignificant.

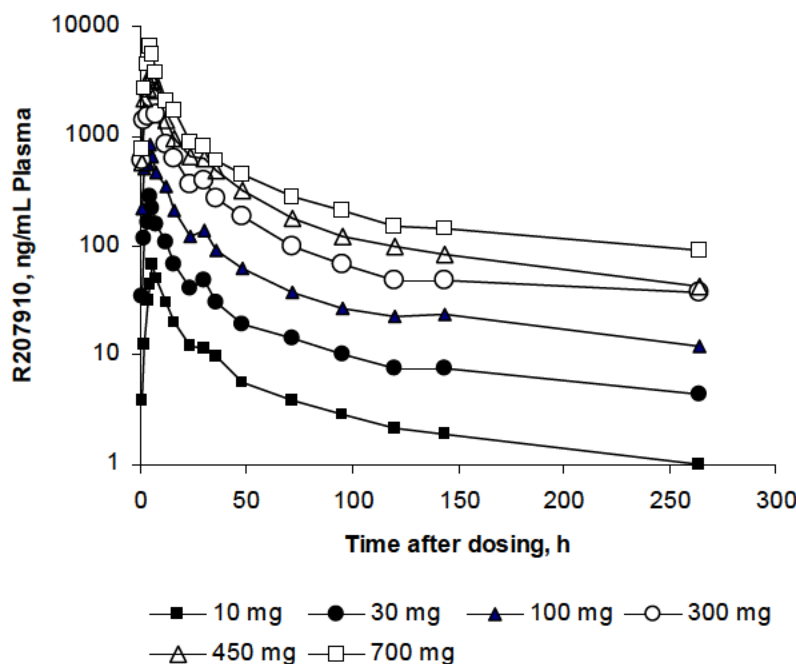


Figure 18: Mean Plasma Concentration-Time Profiles of TMC207 Following Single Oral Dose Administration in Healthy Male Subjects Under Fed Conditions

4.1.2 Multiple-Dose Pharmacokinetics of Bedaquiline in MDR-TB Infected Subjects

In the Phase IIb trials bedaquiline was administered in combination with a multidrug MDR-TB regimen. Bedaquiline was administered as the uncoated tablet (F001, which is the intended commercial formulation) in the Phase IIb trials (Stages 1 and 2 of **C208** and **C209**) in subjects with MDR-TB. The proposed therapeutic regimen for bedaquiline is 400 mg q.d. for 2 weeks followed by 200 mg TIW for the remainder of the treatment period.

Bedaquiline administered at a dose of 400 mg q.d. in Weeks 1 to 2 resulted in higher mean plasma concentrations of bedaquiline and its main metabolite M2 than when administered at a dose of 200 mg t.i.w. from Weeks 3 onwards (until Week 8 for **C208 Stage 1** and Week 24 for **C208 Stage 2** and **C209**), consistent with the longer dosing interval and lower dose per intake from Weeks 3 onwards ([Table 14](#)). The exposure to M2 relative to bedaquiline was similar throughout the bedaquiline treatment period as indicated by the mean plasma AUC_T ratios for M2 versus bedaquiline at Week 2 (0.31) and Week 24 (0.26) in **C208 Stage 2**.

Table 14: C208 Stage 2: Mean (\pm SD) Observed Pharmacokinetic Parameters of TMC207 and M2 at Weeks 2 and 24

		Results C208 Stage 2	
		TMC207	M2
Week 2 (n = 26) ^a	C _{min} (ng/mL)	728 \pm 257	332 \pm 122
	C _{max} (ng/mL)	2763 \pm 1185	467 \pm 157
	C _{ss,avg} (ng/mL)	1371 \pm 529	383 \pm 130
Week 24 (n = 17) ^b	C _{min} (ng/mL)	356 \pm 170	120 \pm 57
	C _{max} (ng/mL)	1267 \pm 435	178 \pm 71
	C _{ss,avg} (ng/mL)	584 \pm 197	152 \pm 53

C_{min} = minimum plasma concentration, C_{max} = maximum plasma concentration, C_{ss,avg} = average plasma concentration over the dosing interval

^a n = 30 for C_{min}, n = 29 for C_{max}

^b n = 18 for C_{min}, n = 19 for C_{max}

Based upon plasma concentration measurements taken during a 2-year follow-up period after the last dose of bedaquiline (200 mg t.i.w.) in **Stage 1** of trial **C208**, the mean elimination $t_{1/2,term}$ was about 5.5 months for bedaquiline and M2. The observed long $t_{1/2,term}$ values for bedaquiline and M2 can likely be explained by the slow release of bedaquiline and M2 from peripheral tissue compartments. Both bedaquiline and M2 have shown extensive distribution in various tissues in nonclinical species, which is likely a result of the CAD characteristics of these compounds as discussed above.

4.2 DRUG-DRUG INTERACTIONS

Bedaquiline is metabolized primarily by CYP3A4 into M2. Coadministration of bedaquiline and drugs that induce CYP3A (e.g., rifampin) may decrease bedaquiline plasma concentrations and reduce its therapeutic effect. Conversely, coadministration of bedaquiline and moderate or strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline which could potentially increase the risk of adverse reactions. Based on in vitro data, bedaquiline does not significantly inhibit the activity of any of the CYP450 enzymes tested (CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5 and CYP4A) and does not induce CYP1A2, CYP2C9, CYP2C19 CYP3A4 activities.

In the Phase I DDI trials, bedaquiline was coadministered with drugs from various classes, including CYP3A inducers and inhibitors. The results of these studies are summarized in [Table 15](#) (effect on bedaquiline) and [Table 16](#) (effect on coadministered agents).

Table 15: Drug Interactions: Plasma Pharmacokinetic Parameters for TMC207 in the Presence of Coadministered Drugs

Coadministered Drug Dose/Schedule (Trial)	TMC207 Dose/Schedule Analyte	N	PK Effect ^a	Mean Ratio (90% CI) of <u>TMC207</u> 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	<u>TMC207</u> 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	<u>TMC207</u> 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	<u>TMC207</u> 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	<u>TMC207</u> 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	<u>TMC207</u> 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.

Table 16: Drug Interactions: Plasma Pharmacokinetic Parameters for Coadministered Drugs in the Presence of TMC207

Coadministered Drug Dose/Schedule Analyte (Trial)	TMC207 Dose/Schedule	N	PK Effect ^a	Mean Ratio (90% CI) of <u>Coadministered Drug</u> Pharmacokinetic Parameters With/Without TMC207 No Effect = 1		
				C _{max}	AUC	C _{min}
Anti-Tuberculosis Drugs						
<u>Rifampin</u> ^b 600 mg q.d. 7 days	300 mg single dose	16	↓	0.73 (0.65 - 0.81)	0.57 (0.53 - 0.62)	-
<u>Isoniazid</u> 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)
<u>Pyrazinamide</u> 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						
<u>Ketoconazole</u> 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)
<u>Lopinavir</u> 400 mg q.d. 24 days	400 mg single dose	13	↓	-	-	0.79 ^c (0.72 - 0.87)
		13	↓	-	-	0.86 ^c (0.78 - 0.94) ^f
<u>Ritonavir</u> 100 mg q.d. 24 days						
<u>Nevirapine</u> 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.

Rifampin

Rifampin is a potent inducer of CYP450 enzymes, including CYP3A4, which likely explains the reduction in bedaquiline exposure by 52%. Due to the possibility of a reduction of the therapeutic effect of bedaquiline due to a decrease in systemic exposure, the combination of bedaquiline and rifampin or other potent CYP3A4 inducers should be avoided.

Exposure to rifampin was 43% lower after co-administration with single-dose bedaquiline. Although these findings may suggest an effect of coadministration of bedaquiline on the PK of

rifampin, it should be noted that these changes are based on a comparison of rifampin PK after the first dose and after 6 subsequent days of dosing with 600 mg q.d. in a single-sequence crossover design. These results can therefore more likely be explained by auto-induction of its metabolism by rifampin, which has been reported to reduce rifampin exposure by approximately 40% after repeated dosing of 600 mg q.d. compared to the pre-induced state⁶⁹.

Isoniazid and Pyrazinamide

The combination of multiple-dose bedaquiline (400 mg qd for 15 days) with multiple-dose isoniazid/ pyrazinamide (300/2000 mg q.d. coadministered from day 11 to 15) in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid, or pyrazinamide. No dose adjustments are required when isoniazid or pyrazinamide and bedaquiline are coadministered.

Ketoconazole

Coadministration of multiple-dose bedaquiline (400 mg qd) and multiple-dose ketoconazole (400 mg q.d.) for 4 days in healthy subjects increased the bedaquiline exposure (AUC_{24h}) by 22%, which can likely be explained by CYP3A inhibition by ketoconazole.

Although CYP3A4 is the primary enzyme involved in the metabolism of bedaquiline, only a modest impact of potent CYP3A4 inhibition by ketoconazole was observed. This can possibly be explained by binding of bedaquiline to intracellular proteins and phospholipids, which may limit the availability of bedaquiline for metabolic enzymes, resulting in a low clearance and consequently a limited impact of metabolic inhibition. Furthermore, because of the long elimination $t_{1/2,term}$ of bedaquiline, steady-state concentrations were not achieved prior to pharmacokinetic sampling. Thus, the full interaction potential could not be detected during the short-term coadministration of ketoconazole, which may also explain the modest changes in exposure to bedaquiline. It has been previously reported that short-term drug-drug interaction trials with long half-life substrates may result in an underestimation of the potential effects after chronic coadministration of a metabolic inhibitor⁷⁰. Since the impact of prolonged CYP3A4 inhibition on bedaquiline exposure is unknown, coadministration of moderate and strong CYP3A4 inhibitors, such as ketoconazole, for more than 2 weeks is not recommended.

Antiretroviral Agents

Lopinavir/ritonavir (C110 trial)

Lopinavir/ritonavir is a (boosted) PI used in combination with other agents for the treatment of HIV infection. In a drug interaction trial of single-dose bedaquiline and multiple-dose lopinavir/ritonavir (400/100 mg twice daily [b.i.d.]), exposure (AUC) to bedaquiline was increased by 22%, while the mean C_{\max} remained comparable. When lopinavir/ritonavir was co-administered with bedaquiline, the mean C_{0h} for lopinavir and ritonavir decreased by 21% and 14%, respectively, relative to administration of lopinavir/ritonavir alone. No dose-adjustment of lopinavir/ritonavir or bedaquiline is recommended when these drugs are co-administered, based on the results of the C110 trial. Clinical data on the combined use of lopinavir/ritonavir and bedaquiline in HIV/MDR-TB co-infected patients are currently not available. In the planned Phase III trial (**C210**), the use of lopinavir/ritonavir is allowed in order to collect safety and efficacy data for the combined use of bedaquiline and lopinavir/ritonavir in HIV/MDR-TB co-infected subjects.

Nevirapine (C117 trial)

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that is commonly used as part of initial HIV ARV therapy. Coadministration of multiple-dose nevirapine (200 mg b.i.d.) with single-dose bedaquiline in HIV-1 infected subjects did not result in clinically relevant changes in the exposure to bedaquiline. No dose-adjustment of nevirapine or bedaquiline is recommended when these drugs are coadministered, based on the results of the C117 trial. Clinical data on the combined use of nevirapine and bedaquiline in HIV/MDR-TB co-infected patients are currently not available.

In addition to the Phase I DDI studies, the effect of bedaquiline on the PK of selected anti-TB drugs was investigated in **Stage 1** of the placebo-controlled **C208** Phase IIb trial in subjects with MDR-TB, the results of which are shown in [Table 17](#).

Overall, there was no apparent major effect of bedaquiline on the PK of these anti-TB drugs in the BR, comprising ethambutol, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone. No dose adjustments are required when any of these drugs and bedaquiline are coadministered.

Dose normalized C_{\max} and AUC_{24h} values for kanamycin were 1.3- and 1.5-fold higher, respectively, when coadministered with bedaquiline. The apparent interaction between

kanamycin and bedaquiline can likely be explained by differences in CL_{CR} , the mean value for which was notably higher in the placebo group (112 mL/min) than in the bedaquiline group (91 mL/min). Since kanamycin is largely eliminated by glomerular filtration⁷¹, exposure to kanamycin is dependent on renal function.

Table 17: Drug Interactions: Plasma Pharmacokinetic Parameters for Background Regimen Anti-TB Drugs in the Presence of TMC207 from Trial C208 (Stage 1)

Coadministered Drug Dose/Schedule Analyte (Trial)	TMC207 Dose/Schedule	N	PK Effect ^a	Mean Ratio (90% CI) of <u>Background Regimen Anti-TB Drug</u> Pharmacokinetic Parameters With/Without TMC207 No Effect = 1		
				C _{max}	AUC	C _{min}
Anti-Tuberculosis Drugs						
<u>Pyrazinamide</u> 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)
<u>Ethambutol</u> 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)
<u>Kanamycin</u> 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)	-
<u>Ofloxacin</u> 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)	-
<u>Cycloserine/ Terizidone</u> 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.

4.3 IMPACT OF INTRINSIC FACTORS ON BEDAQUILINE PHARMACOKINETICS

The potential effects of intrinsic factors on bedaquiline PK were assessed using a population PK model, including data from the Phase II studies in TB-infected patients⁷². In this analysis, the

covariates of age, sex, race, weight (body mass index [BMI]), HIV co-infection, TB type, baseline albumin, and creatinine clearance (CLcr) were evaluated.

4.3.1 Age

The covariate of age was not found to influence the PK parameters of bedaquiline. In the dataset for this analysis, the median age was 32.5 years (range: 18 to 68 years).

4.3.2 Sex

The apparent volume of distribution (V_c/F) was lower in females (138 L) than males (164 L), which may be explained by a difference in body size. However, the difference in V_c/F between females and males was less than 20%, which is expected to have a minimum effect on exposure before steady-state is reached. In the dataset for this analysis, there were 331 males and 149 females.

4.3.3 Race

The estimate for apparent oral clearance (CL/F) was 2.78 L/h in non-Black and 4.23 L/h in Black subjects. Black male and female subjects were therefore predicted to have lower exposures than non-Black male and female subjects. The simulated exposure at steady-state for bedaquiline for a typical Black subject was predicted to be about 34% lower than for a non-Black subject. In the dataset for this analysis, there were 149 Black subjects, 134 Caucasian subjects, 99 Asian subjects, 41 Hispanic subjects, and 57 subjects with race classified as “other”.

These results show that exposure to bedaquiline is generally lower in Black subjects compared to subjects from other race categories. However, this was not considered to be clinically relevant based on the similar clinical outcome in the subset of this subgroup who did not discontinue the trial prematurely by Week 24 in the Phase II studies. This is also supported by the lack of any clear relationship between the exposure to bedaquiline and efficacy.

4.3.4 Body Weight

The covariate of BMI, which correlated with body weight, was not found to influence the PK parameters of bedaquiline. In the dataset for this analysis, the median BMI was 20.7 kg/m² (range: 13.1 to 36.8 kg/m²).

4.3.5 HIV Co-infection

The covariate of HIV co-infection was not found to influence the PK parameters of bedaquiline. In the dataset for this analysis, there were 438 subjects with no HIV co-infection and 35 subjects with HIV co-infection (7 subjects had unknown HIV status).

4.3.6 Extent of Resistance in *M. tuberculosis* Strain

The bioavailability in healthy subjects and DS-TB infected subjects was 2.03-fold higher than in MDR-TB and (pre-)XDR-TB infected subjects. In the dataset for this analysis, there were 111 subjects with no TB infection, 50 DS-TB infected subjects, 160 MDR-TB infected subjects, 60 Pre-XDR-TB infected subjects, and 40 XDR-TB infected subjects (59 subjects with TB had unknown extent of resistance).

4.3.7 Renal Impairment

Renal excretion of unchanged bedaquiline has a minimal contribution to the overall elimination of bedaquiline. In trial CDE-102, only negligible amounts of bedaquiline were recovered as UD after repeated dosing in healthy subjects. However, it has been shown that renal impairment may influence the PK of non-renally eliminated drugs, possibly by affecting drug-metabolizing enzymes and transporters⁷³.

To explore the potential impact of reduced renal function on the PK of bedaquiline, the relationship between creatinine clearance (CL_{cr}) and CL/F of bedaquiline was evaluated in a covariate analysis in the population PK model. Subjects with advanced renal impairment were excluded from the clinical trials. In the dataset for this analysis, the median CL_{cr} was 108 mL/min (range: 39.8 to 227 mL/min). Within this range of CL_{cr} values, no relationship with bedaquiline PK was observed.

4.3.8 Hepatic Impairment

After single-dose administration of bedaquiline to 8 subjects with moderate hepatic impairment (Child-Pugh B) (trial C112), exposure (AUC_{72h}) to both bedaquiline and M2 was 19% lower compared to 8 healthy subjects in this trial. For both bedaquiline and M2, the ranges of individual values for these parameters largely overlapped between subjects with moderate hepatic impairment and healthy subjects.

Because liver disease state (i.e., cirrhosis) may result in lower plasma concentrations of α_1 -acid glycoprotein and albumin, and bedaquiline is highly bound to plasma proteins, lower protein concentrations in subjects with moderate hepatic impairment compared to the healthy controls could have contributed to the observed differences in exposure to bedaquiline between these groups. The mean albumin concentrations were indeed lower in subjects with moderate hepatic impairment (36.4 g/L) compared to healthy control subjects (41.2 g/L). If the lower total bedaquiline plasma exposure in subjects with moderate hepatic impairment is indeed related to the lower plasma protein concentrations in this group, this may result in an increased unbound fraction of bedaquiline in plasma, which may in turn result in a higher hepatic clearance. The absolute unbound (active) concentration of bedaquiline in plasma, however, is expected to be unchanged.

The modest changes in exposure are not considered to be clinically relevant given the absence of clear exposure-response relationships for bedaquiline, and therefore no adjustment of the bedaquiline dose is needed in subjects with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and its use is not recommended in this population.

4.4 RATIONALE FOR DOSE SELECTION AND TREATMENT DURATION

The bedaquiline dosing regimen consisted first of a 8-week investigational treatment period in the **C208 Stage 1** trial (400 mg q.d. for 2 weeks, followed by 200 mg t.i.w. for a further 6 weeks). Trial **C208 Stage 2** built upon safety and efficacy established in **Stage 1** and the investigational treatment period was extended to 24-weeks (400 mg q.d. for 2 weeks, followed by 200 mg t.i.w. for a further 22 weeks) (this was later also used in the **C209** trial). This dosing regimen was based on nonclinical safety and efficacy in mice, as well as results from the previous clinical trials with bedaquiline, i.e., **Phase I** trials (providing safety and pharmacokinetic data) and the Phase IIa trial **C202** in subjects with DS-TB (providing safety, pharmacokinetic, and antimycobacterial activity data of bedaquiline).

To guide dose selection for the **C208** trial, a population pharmacokinetic model for bedaquiline was developed to simulate bedaquiline exposure resulting from various dosing schedules that would (1) control continued increase of plasma concentrations inherent to the long terminal

elimination half-life of bedaquiline, (2) maintain exposure below the safety threshold determined in nonclinical studies, and (3) maintain a high enough exposure to achieve antimycobacterial activity.

Nonclinical data suggested that bedaquiline dosing should be in the range of linear PK to avoid over-proportional tissue distribution and potential toxicity. Furthermore, nonclinical toxicity studies showed that intermittent dosing of bedaquiline was better tolerated than daily dosing of the same total weekly dose. This observation may be related to the lower tissue distribution of bedaquiline and M2 during intermittent dosing versus daily dosing.

Based on the results of the population pharmacokinetic model and nonclinical data, the proposed dosing regimen for trial **C208** started with a loading dose phase of 400 mg q.d. for 2 weeks. This dose was the highest dose tested during multiple-dose administration in several **Phase I** trials and was generally well tolerated during 2 weeks of daily dosing. Furthermore, a 400-mg dose is still within the range of linear PK in humans and a 400-mg daily dose administered as 7-day monotherapy to DS-TB infected subjects (i.e., the highest dose tested) in trial **C202** showed statistically significant eEBA activity and was therefore further explored in the **C208** trial. After the loading phase, 200 mg was to be dosed intermittently at 3 times/week (t.i.w.) during the subsequent investigational dosing period in order to restrict the continued increase in plasma concentrations and thus limit potential toxicity, while maintaining antimycobacterial activity. The bedaquiline dose regimen that was used in the **C208** and **C209** trials was found to be well tolerated and effective. Furthermore, the results of pharmacokinetic/pharmacodynamic analyses of the **C208** (**Stage 1** and **Stage 2**) and **C209** trials indicated that there is no clear relationship between plasma concentrations of bedaquiline associated with the proposed dosing regimen and the observed antimycobacterial activity or safety of bedaquiline. These findings indicate that adequate exposure is generally achieved with the bedaquiline dosing regimen of 400 mg q.d. for 2 weeks followed by 200 mg t.i.w.

After the loading phase, 200 mg was to be dosed intermittently at 3 times/week (t.i.w.) during the subsequent investigational dosing period in order to restrict the continued increase in plasma concentrations and thus limit potential toxicity, while maintaining antimycobacterial activity. The treatment duration of bedaquiline that was used in the Phase IIb trials was increased from 8 week (C208-Stage 1) to 24 weeks (C208 Stage 2 and C209) based on availability of supportive preclinical toxicity data and encouraging clinical safety and efficacy data.

The 24-week bedaquiline dose regimen that was used in the **C208** and **C209** trials was found to be well tolerated and effective. Furthermore, the results of pharmacokinetic/pharmacodynamic analyses of the **C208** (**Stage 1** and **Stage 2**) and **C209** trials indicated that there is no clear relationship between plasma concentrations of bedaquiline associated with the proposed therapeutic dosing regimen and the observed antimycobacterial activity or safety of bedaquiline. These findings indicate that adequate exposure is generally achieved with the bedaquiline dosing regimen of 400 mg q.d. for 2 weeks followed by 200 mg t.i.w.

4.5 CLINICAL PHARMACOLOGY CONCLUSIONS

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. The recommended dose of bedaquiline for the treatment of pulmonary MDR-TB in adults is 400 mg q.d. for 2 weeks, followed by 200 mg t.i.w. for a total of 24 weeks with food and in combination with other anti-TB drugs.

Bedaquiline is primarily subjected to oxidative metabolism leading to the formation of M2. The M2 metabolite is not thought to contribute significantly to clinical efficacy given its lower exposure (about 23% to 31%) in humans and less antimycobacterial activity (3-to 6-fold lower) compared to the parent compound.

The results of the final population pharmacokinetic model for bedaquiline showed that age, sex, body weight, and HIV co-infection did not influence the pharmacokinetic parameters of bedaquiline. Race did have an influence: black subjects had lower bedaquiline exposures than subjects from other race categories. However, this was not considered to be clinically relevant based on the similar clinical outcome in the subset of this subgroup in the Phase II studies who did not discontinue prematurely by week 24 from the trials.

No adjustment of the bedaquiline dose is needed in subjects with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and its use is not recommended in this population.

No bedaquiline dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment or end-stage renal disease requiring hemodialysis or peritoneal dialysis, bedaquiline should be used with caution.

An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other drugs that prolong the QT interval cannot be excluded. Therefore, caution is recommended when prescribing bedaquiline concomitantly with medications with a known risk of QT prolongation. Such caution should also be taken during concomitant clofazimine use. Concomitant administration of bedaquiline with fluoroquinolone antibiotics that have a potential for significant QT prolongation (gatifloxacin, moxifloxacin, and sparflaxacin) should be avoided.

Bedaquiline is metabolized by CYP3A4 and its exposure may therefore be reduced during co-administration with CYP3A4 inducers and increased during co-administration with CYP3A4 inhibitors. The following medications should therefore be avoided during administration of bedaquiline:

- The systemic use of moderate and strong CYP3A4 inhibitors for more than 14 consecutive days (allowing short-term treatment);
- The systemic use of rifamycins (rifampin, rifapentine, and rifabutin) or other potent CYP3A4 inducers.

5 CLINICAL EFFICACY

5.1 PROOF-OF-PRINCIPLE PHASE IIA TRIAL: TMC207-C202

5.1.1 Design

Trial **C202** was a Phase IIa, proof-of-principle, open-label, randomized trial in treatment-naïve subjects with sputum smear-positive pulmonary DS-TB. This trial assessed bactericidal activity of 3 different doses of bedaquiline compared to standard doses of rifampin or isoniazid. Short-term safety, tolerability, and the PK of bedaquiline were also evaluated.

Subjects with pulmonary *M. tuberculosis* infection who were treatment-naïve (or had not received treatment in the last 3 years), were sputum smear-positive, and were not resistant to rifampin at screening were eligible for the trial.

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 and all doses (up to and including 400 mg q.d.) had been shown to be generally safe and well-tolerated in healthy volunteers.

The primary endpoint used to assess the activity of the drugs was the degree of reduction in the sputum viable CFU count over a 7-day period (i.e., eEBA).

5.1.2 Population

The trial was performed at 2 centers in South Africa. In total, 75 subjects were randomized and treated: 15, 16, and 14 subjects received bedaquiline at 25 mg, 100 mg, and 400 mg q.d., respectively, 15 subjects received rifampin 600 mg q.d., and 15 subjects received isoniazid 300 mg q.d.. All subjects were treated for 7 days, except for 8 subjects who prematurely discontinued the trial for various reasons (i.e., 1 subject treated with bedaquiline 25 mg, 2 subjects treated with bedaquiline 100 mg, 1 subject treated with bedaquiline 400 mg, and 4 subjects treated with isoniazid 300 mg).

There were no relevant differences between randomization groups (ITT population) with respect to any of the demographic parameters or baseline disease characteristics. The majority of subjects (60.0%) were male; median age was 34.0 years (range: 18 - 61 years). More than half of the subjects (57.3%) were Black, the others were of mixed origin.

Although all subjects were proven to be infected with strains susceptible to rifampin at screening (using the FASTPlaque TB response test), DST (using the MGIT960 SIRE Kit system) at baseline (Day -1) indicated resistance to rifampin and isoniazid in 1 subject and to isoniazid alone in 3 other subjects. None of these subjects were included in the rifampin or isoniazid treatment groups. In addition, isolates of 3 subjects were resistant to streptomycin at baseline; all isolates were susceptible to ethambutol at baseline. All *M. tuberculosis* isolates had a bedaquiline MIC at baseline that was 0.06 µg/mL when tested using the agar method (posthoc analysis).

5.1.3 Bactericidal Activity Results

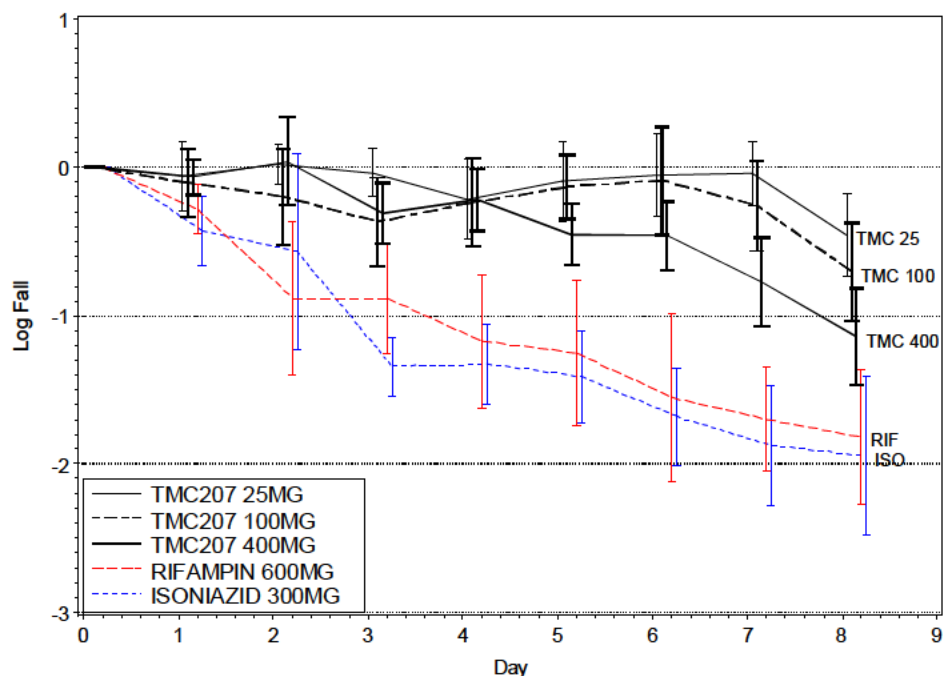
In trial **C202**, 16-hour overnight sputum samples were collected daily in order to determine the degree of reduction in the sputum viable CFU count over a 7-day period (eEBA).

During the 7 days of treatment, the eEBA was found to be greater in the rifampin and isoniazid groups compared to the bedaquiline groups. Over a period of 7 days, mean values for eEBA were -0.01, -0.04 and -0.11 \log_{10} CFU/day for the bedaquiline 25 mg, 100 mg and 400 mg groups, respectively. Corresponding values for the control groups were -0.24 \log_{10} CFU/day for the rifampin group and -0.27 \log_{10} CFU/day for the isoniazid group.

Over a period of 2 days, mean values for EBA were 0.01, -0.10 and 0.02 \log_{10} CFU/day for the bedaquiline 25 mg, 100 mg and 400 mg groups, respectively. Corresponding values for the control groups were -0.44 \log_{10} CFU/day for the rifampin group and -0.28 \log_{10} CFU/day for the isoniazid group.

[Figure 19](#) shows changes from baseline in \log_{10} sputum CFU counts over time in the 5 treatment groups. No statistically significant changes from baseline in \log_{10} sputum CFU counts during the 7 days of treatment were observed with the lower doses of bedaquiline (25 mg and 100 mg). The 400 mg bedaquiline treatment group showed a statistically significant decrease from baseline on Days 3, 5, 6 and 7. On Day 7, mean changes from baseline in \log_{10} sputum CFU counts for the bedaquiline 25 mg, 100 mg and 400 mg group were -0.04 (p-value > 0.05), -0.26 (p-value > 0.05), and -0.77 (p-value < 0.05), respectively. For the control treatments, the mean changes from baseline on Day 7 were -1.70 (p-value < 0.05) and -1.88 (p-value < 0.05) for the rifampin and isoniazid groups, respectively.

The subjects treated with rifampin and isoniazid showed bactericidal response from Day 1 onwards, while the bactericidal response in the bedaquiline 400 mg group was apparent from Day 4 onwards.



Note: Day 8 log₁₀ CFU counts are affected by standard TB treatment, which was initiated on Day 8

Figure 19: Changes in log₁₀ Sputum CFU Counts From Baseline Over Time With 95% CI

5.1.4 C202 Summary and Conclusion

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.

There seemed to be a delay in onset of bactericidal activity for subjects receiving bedaquiline 400 mg q.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 log₁₀ sputum CFU counts was smaller for the bedaquiline 400 mg group compared to the rifampin and isoniazid groups.

5.2 PHASE IIB EFFICACY ENDPOINTS BASED ON MGIT CULTURES

As per the Protocol, culture conversion is defined as having 2 consecutive negative MGIT cultures from spot sputa collected at least 28 days apart. All intermediate cultures have to be

negative as well (as applicable). Prior to unblinding the requirement of 28 days is changed into 25 days to accommodate for the scheduled visit windows. This definition has been used for all efficacy analyses in **C208** and **C209** with the only exception of the 8 week analysis of Stage 1 because of the short investigational treatment period (see Section [5.3.1.3](#)).

The time to conversion is defined as the first of the two consecutive negative sputum cultures, provided that during the analysis window no relapse occurs and the patient does not drop out.

Patients who drop out prior to finalizing their treatment with bedaquiline or placebo are censored at their last visit. This is referred to as the Primary Analysis Method.

Based on comments received from the FDA prior to trial start, a sensitivity analysis was added in which subjects who drop out prior to finalizing their treatment with bedaquiline or placebo are carried forward as not converting through the 24 week treatment period. This is referred to as the End-Censored (M=F) Analysis Method.

Note that this End-Censored (M=F) Analysis Method only differs from the Primary Analysis Method on the censoring time for dropout subjects.

Another secondary time to event analysis was added in which subjects who drop out and for whom sputum culture conversion had occurred were not censored. In other words, subjects for whom sputum culture conversion had occurred were not considered as a failure due to dropout.

Examples of how subjects are handled in these analyses are provided in [Appendix 3](#).

After the primary analysis (and unblinding of treatment codes) and in preparation of the 72 Week interim analysis, some additional analysis definitions were added. The above 3 analyses were carried forward with the only difference that the censoring time of the second method for drop out subjects was set to the end of the considered analysis window (e.g. 72 weeks).

Secondly, mutually exclusive categories for treatment failure were defined as follows:

1. *Failure to convert*: subjects in whom sputum culture conversion (as defined above) has not been observed

2. *Relapse*: subjects in whom sputum culture conversion (as defined above) has been observed but for whom a confirmed positive sputum culture was observed at later time points. Please note:
 - a. that this definition is independent from whether the subject was on or off treatment at time of relapse.
 - b. We do not distinguish between relapse or reinfection as this information was not available at time of the NDA.
 - c. In case a subject drops out/completion, we conservatively do not require a confirmed positive sputum culture for the last sample, i.e., one positive culture suffices, to categorize the subject as a relapse for subjects who drop out or complete the trial after having a single positive sputum culture.
3. *Discontinued but converted*: subjects who discontinue after sputum culture conversion.

5.3 PHASE IIB PLACEBO-CONTROLLED TRIAL: TMC207-C208

5.3.1 TMC207-C208 Stage 1 (Exploratory)

5.3.1.1 ANALYSES

The primary analysis of **Stage 1** was performed when all **Stage 1** subjects had completed 8 weeks of double-blind treatment with bedaquiline or placebo (or had discontinued earlier). The final analysis of **Stage 1** was performed when all **Stage 1** subjects had completed the trial (or had discontinued earlier) and included an evaluation of the BR treatment period and the subsequent treatment-free follow-up period of at least 8 weeks (2 months).

Stage 1 subjects with XDR-TB at baseline (for whom second-line DST results only became available after randomization) or who developed XDR-TB during treatment were to be withdrawn and treated for XDR-TB as per national treatment guidelines.

5.3.1.2 POPULATION

Stage 1 of trial **C208** was performed at 6 sites in South Africa. In total, 47 subjects were randomized and treated (i.e., ITT population), of whom 23 subjects received bedaquiline and 24 subjects received placebo. The mITT population consisted of 44 subjects after excluding

3 subjects from the ITT population, i.e., 2 subjects (one in each group) who were found to be XDR-TB at baseline and 1 subject (in the bedaquiline group) who was considered not evaluable for efficacy due to negative MGIT culture results at all time points including baseline.

There were no relevant differences between randomization groups (ITT population) with respect to any of the demographic parameters or baseline disease characteristics (Table 18). Note that among these parameters, lung cavitation was a stratification factor during randomization. The majority of subjects (74.5%) were male; median age at screening was 33.0 years (range: 18 - 57 years). More than half of the subjects (55.3%) were Black, 2.1% were Caucasian, and 42.6% were of other (i.e., mixed or colored) ethnic origin. The majority had cavitation in one lung (57.4%) or in both lungs (27.7%) (Table 18).

Based on DST (agar proportion method) at the central laboratory, 31 subjects (66.0%) in the ITT population were infected with an MDR_{H&R}-TB strain, 6 subjects (12.8%) were infected with a Pre-XDR-TB strain. Two subjects (4.3%) were infected with an XDR-TB strain at baseline and were excluded from the mITT population. None of the **Stage 1** subjects had DS-TB at baseline. Three of the 6 (50.0%) Pre-XDR-TB isolates were resistant to kanamycin and/or CAP (i.e., SLI-Pre-XDR-TB) and 3 isolates (50.0%) were resistant to ofloxacin (i.e., FQ-Pre-XDR-TB). The extent of resistance of the *M. tuberculosis* strain at baseline could not be determined from central laboratory DST results for 5 subjects (21.7%) in the bedaquiline group and for 3 subjects (12.5%) in the placebo group. However, the isolates of these subjects were confirmed resistant to rifampin and isoniazid by either rapid screen tests and/or the subject's medical history (based on previous DST) and were included in the mITT population.

Three subjects in each group were HIV-infected. Abnormally low albumin (grade 1 to grade 3) at baseline was observed in 56.5% of subjects in the bedaquiline group and 58.3% of subjects in the placebo group.

Demographic data and baseline disease characteristics for the mITT population were similar to those of the ITT population.

Table 18: C208 Stage 1: Demographics and Baseline Disease Characteristics – ITT

Parameter Value	TMC207/BR N = 23	Placebo/BR N = 24
Gender, n (%)		
Female	5 (21.7)	7 (29.2)
Male	18 (78.3)	17 (70.8)
Age at screening, years		
Median (range)	33.0 (18-57)	33.0 (19-57)
Ethnic origin, n (%)		
Black	13 (56.5)	13 (54.2)
Caucasian/White	0	1 (4.2)
Other (mixed or colored)	10 (43.5)	10 (41.7)
Lung cavitation^a (as stratified), n (%)		
Cavitation in both lungs	6 (26.1)	7 (29.2)
Cavitation in one lung only	14 (60.9)	13 (54.2)
No Cavitation	3 (13.0)	4 (16.7)
HIV status at screening, n (%)		
Negative	20 (87.0)	21 (87.5)
Positive	3 (13.0)	3 (12.5)
Extent of resistance of <i>M. tuberculosis</i> strain, n (%)		
DS-TB	0	0
MDR-TB ^b	23 (100)	24 (100)
<i>MDR_{H&R}-TB</i>	15 (65.2)	16 (66.7)
<i>Pre-XDR-TB</i>	2 (8.7)	4 (16.7)
<i>XDR-TB</i>	1 (4.3)	1 (4.2)
Albumin grade at baseline, n (%)		
Grade 0	10 (43.5)	10 (41.7)
Grade 1	4 (17.4)	5 (20.8)
Grade 2	7 (30.4)	8 (33.3)
Grade 3	2 (8.7)	1 (4.2)

N = number of subjects with data; n = number of observations

^a Cavitation defined as the presence of at least one cavity ≥ 2 cm

^b No central DST results were available to determine extent of resistance for 8 (17.0%) subjects (i.e., 5 [21.7%] in the TMC207 group and 3 [12.5%] in the placebo group) in the ITT population. These subjects were considered MDR based on rapid screen tests and/or the subject's medical history (based on previous DST).

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Drug susceptibility testing showed that most subjects in the mITT population (91.9%) were infected with isolates susceptible to ethionamide, kanamycin, and ofloxacin at baseline (Table 19). These individual drugs were used in the BR of > 93.0% of **Stage 1** subjects during investigational treatment. The lowest rates of susceptibility were observed for streptomycin (21.6%), ethambutol (35.1%), and pyrazinamide (34.2%), i.e., 3 first-line anti-TB drugs.

Table 19: C208 Stage 1: Baseline Susceptibility to Anti-TB Drugs – mITT

n (%) of isolates susceptible ^a to	TMC207/BR		Placebo/BR		All Subjects	
	N	n (%)	N	n (%)	N	n (%)
EMB	17	5 (29.4)	20	8 (40.0)	37	13 (35.1)
SM	17	2 (11.8)	20	6 (30.0)	37	8 (21.6)
PZA	17	7 (41.2)	21	6 (28.6)	38	13 (34.2)
ETH	17	15 (88.2)	20	19 (95.0)	37	34 (91.9)
OFL	17	16 (94.1)	20	18 (90.0)	37	34 (91.9)
KAN	17	16 (94.1)	20	18 (90.0)	37	34 (91.9)
CAP	17	17 (100)	20	19 (95.0)	37	36 (97.3)

N = number of subjects with data; n = number of subjects susceptible to the specified drug; EMB = ethambutol; SM = streptomycin; PZA = pyrazinamide; ETH = ethionamide; OFL = ofloxacin; KAN = kanamycin

^a Based on the agar proportion method (and the MGIT 960 system for pyrazinamide). Cycloserine was not tested due to poor reproducibility of the results.

Data on file, Janssen Research and Development

About half of all **Stage 1** subjects prematurely discontinued the trial by Week 104 (i.e., trial end for **Stage 1**): 10 subjects (43.5%) in the bedaquiline group and 13 subjects (54.2%) in the placebo group ([Table 20](#)). The major reasons for discontinuation in both groups were noncompliance (4 subjects in each group) and withdrawal of consent (3 subjects in the bedaquiline group and 4 subjects in the placebo group). Five subjects (3 subjects in the bedaquiline group and 2 subjects in the placebo group) discontinued during the 8-week investigational treatment period (including 1 subject in each group with XDR-TB at baseline); the other 18 subjects discontinued during the BR treatment period or the treatment-free follow-up period. Two of these 18 subjects (both in the placebo group) developed XDR-TB postbaseline per the investigator and were withdrawn in order to start XDR-TB treatment, as was foreseen in the protocol.

Table 20: C208 Stage 1: Completion/Withdrawal in - ITT

Trial Termination Type Reason, n (%)	TMC207/BR N = 23	Placebo N = 24	All Subjects N = 47
Completed	13 (56.5)	11 (45.8)	24 (51.1)
Discontinued	10 (43.5)	13 (54.2)	23 (48.9)
Adverse event (fatal myocardial infarction)	1 (4.3)	0	1 (2.1)
Subject lost to follow-up	1 (4.3)	1 (4.2)	2 (4.3)
Subject non-compliant	4 (17.4)	4 (16.7)	8 (17.0)
Subject withdrew consent	3 (13.0)	4 (16.7)	7 (14.9)
Other	1 (4.3) ^a	4 (16.7) ^b	5 (10.6)

N = total number of subjects; n = number of subjects with that observation

^a subject had XDR-TB at baseline

^b 1 subject had XDR-TB at baseline, 2 developed XDR-TB per the investigator during trial, and 1 transferred out

Data on file, Janssen Research and Development

The median (range) total duration of the Investigational Treatment phase (i.e., from date of first bedaquiline/placebo intake until date of last bedaquiline/placebo intake + 1 week) for subjects in the ITT population was 9.00 (1.9 - 9.3) weeks in the bedaquiline group and 9.00 (1.9 - 9.9) weeks in the placebo group. The median (range) total duration of the Overall Treatment phase (i.e., from date of first bedaquiline/placebo intake until date of last intake of any trial drug + 1 week) was longer in the bedaquiline group (85.14 [2.0 - 109.3] weeks) than in the placebo group 63.00 [2.0 - 108.9] weeks). This is most likely a reflection of the higher level of premature discontinuation in the placebo group.

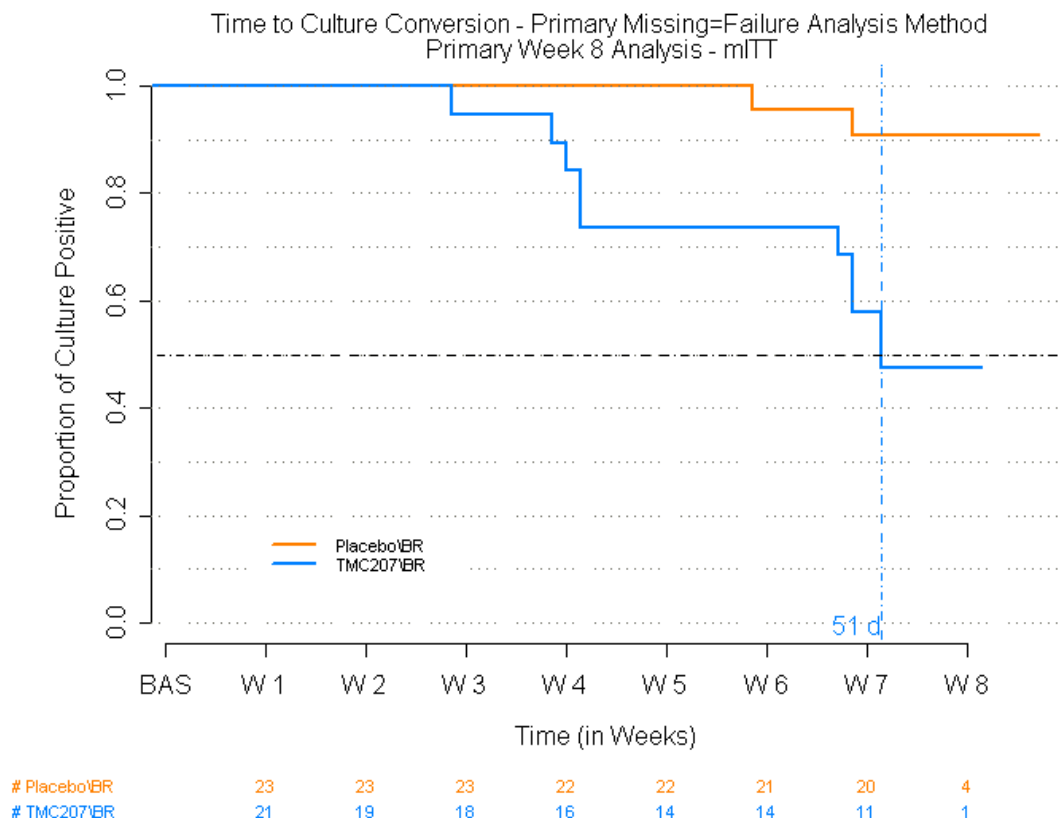
During the investigational treatment period, the BR was similar in both treatment groups. Ethionamide, kanamycin (or the allowed alternative aminoglycoside amikacin), and pyrazinamide were used in the BR of all **Stage 1** subjects. Ofloxacin was used in the BR of all subjects except one whose isolate was resistant to ofloxacin at baseline. Cycloserine was taken by 34.0% and TRD (i.e., a pro-drug of CS) by 25.5% of **Stage 1** subjects during this period. A frequently taken alternative for CS/TRD in the BR was ethambutol (taken by 61.7% during the investigational treatment period), which was permissible in case of intolerance to CS/TRD and if there was no resistance to ethambutol. The most frequently used BR during this period consisted of ethionamide, kanamycin, pyrazinamide, ofloxacin, and ethambutol.

5.3.1.3 PRIMARY EFFICACY ENDPOINT: TIME TO CULTURE CONVERSION DURING THE 8-WEEK TREATMENT PERIOD

The primary efficacy endpoint was time to culture conversion in MGIT during the 8-week investigational treatment period. Note that due to the short duration of the investigational treatment period (with bedaquiline or placebo) in **C208 Stage 1**, a subject was considered to have achieved culture conversion if at least the 2 last assessments during this 8-week period were negative. The time to culture conversion using data up to Week 8 according to the primary missing = failure analysis method is shown in [Figure 20](#). Of note, MGIT cultures were taken weekly during the first 8 weeks.

More subjects in the bedaquiline group achieved culture conversion at Week 8 compared to subjects in the placebo group (47.6% versus 8.7%). Moreover, culture conversion was attained earlier for subjects in the bedaquiline group compared to subjects in the placebo group. The results of a Cox proportional hazards model with lung cavitation and pooled center as covariates

also showed a statistically significant difference in time to sputum conversion between the treatment groups ($p = 0.0034$) in favor of the bedaquiline group (hazard ratio [95% CI]: 11.77 [2.26; 61.23]). Of note, pooling of centers was done prior to unblinding of the treatment codes.



#: number of subjects at risk (i.e., culture positive subjects ongoing in the trial at the corresponding time point)
Note: The intersection of horizontal dotted line and the TMC207 group represents the median time to sputum culture conversion.

Data on file, Janssen Research and Development

Figure 20: C208 Stage 1: Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (Primary Week 8 Analysis, Primary Missing = Failure Analysis Method) – mITT

5.3.1.4 SECONDARY EFFICACY ENDPOINTS

5.3.1.4.1 Time to Culture Conversion at Week 24

As a secondary efficacy endpoint and to enable comparison with **C208 Stage 2** data, time to culture conversion for **C208 Stage 1** subjects was also analyzed at Week 24 (i.e., after 8 weeks of investigational treatment followed by 16 weeks of BR only) using the original definition of culture conversion, see Section 5.2.

Culture conversion was achieved considerably faster and was seen more frequently in the bedaquiline group compared to the placebo group: median time to culture conversion was 70 days in the bedaquiline group and 126 days in the placebo group. The results of a Cox proportional hazards model with lung cavitation and pooled center as covariates also showed a statistically significant difference in time to sputum conversion between the treatment groups ($p = 0.0022$) in favor of the bedaquiline group (hazard ratio [95% CI]: 3.14 [1.51; 6.53]).

The results of the sensitivity analysis (end-censored missing = failure method) showed similar results as observed with the primary analysis method, see [Figure 21](#). Time to culture conversion according to the second sensitivity analysis using ‘no overruling for discontinuation’ was not determined for **C208 Stage 1**.

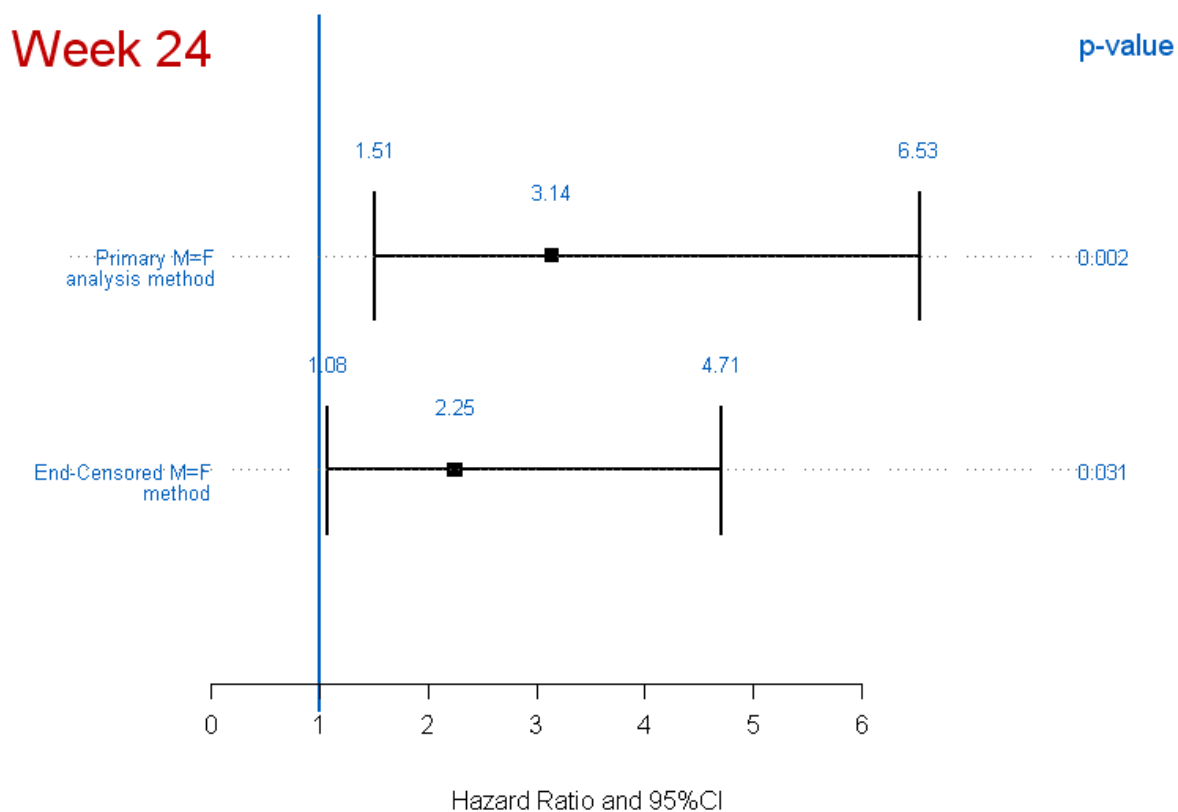


Figure 21: C208 Stage 1: Forest Plot of Hazard Ratio Derived from the Primary M=F Analysis Method and End-Censored M=F Method

5.3.1.4.2 Culture Conversion Rates

The percentage of responders according to the missing = failure response definition (with subjects who prematurely discontinued considered as having not converted) was higher when receiving bedaquiline in addition to the BR compared to placebo in addition to the BR at Week 24 (81.0% versus 65.2%) ([Table 21](#)).

At Week 24, 2 (9.5%) subjects in the bedaquiline group and 1 (4.3%) subject in the placebo group had discontinued the trial while culture converted; consequently, the number of 24-week responders according to the no overruling response definition was 90.5% in the bedaquiline group and 69.6% in the placebo group.

At **Stage 1** trial end (i.e., Week 104), 52.4% and 43.5% of subjects in the bedaquiline and placebo group, respectively, were considered overall responders according to the missing = failure response definition, i.e., they had completed the trial and their microbiological status was ‘converted’ at trial end. The observed decreased treatment effect at trial end (compared to what was observed at Week 24) was largely due to a higher percentage of subjects in the bedaquiline group compared to the placebo group who discontinued while their microbiological status was ‘culture converted’ (28.6% versus 8.7%, subjects indicated as ‘discontinued but converted’).

At trial end, subcategories for non-responders other than ‘discontinued but converted’ favored bedaquiline treatment: 9.5% (bedaquiline) versus 30.4% (placebo) of subjects failed to culture convert during the entire trial and 9.5% (bedaquiline, 2 subjects) versus 17.4% (placebo, 4 subjects) of subjects were considered to have had relapse.

Overall responder rates when using the no overruling response definition also indicated a clear difference between the bedaquiline group and the placebo group (81.0% versus 52.2% of responders, respectively) in favor of bedaquiline treatment.

Table 21: C208 Stage 1: Culture Conversion Rates – mITT

Time Point Microbiological Status, n (%)	Missing = Failure ^a		No Overruling ^b	
	TMC207/BR N = 21	Placebo/BR N = 23	TMC207/BR N = 21	Placebo/BR N = 23
Week 8 8-week responder ^c	10 (47.6)	2 (8.7)	10 (47.6)	2 (8.7)
Week 24 24-week responder	17 (81.0)	15 (65.2)	19 (90.5)	16 (69.6)
Week 104 (Stage 1 Trial End)				
Overall responder	11 (52.4)	10 (43.5) ^c	17 (81.0)	12 (52.2)
Overall non-responder	10 (47.6)	13 (56.5)	4 (19.0)	11 (47.8)
↳ Failure to culture convert	↳ 2 (9.5)	↳ 7 (30.4)	↳ 2 (9.5)	↳ 7 (30.4)
↳ Relapse ^d	↳ 2 (9.5)	↳ 4 (17.4) ^e	↳ 2 (9.5)	↳ 4 (17.4)
↳ Discontinued but converted	↳ 6 (28.6)	↳ 2 (8.7)		

N = number of subjects in population; n = number of subjects with that result

^a A subject was considered responder (missing = failure) if at least 2 cultures from sputa collected at least 25 days apart were MGIT culture negative (as well as all intermediate cultures), this culture negativity was not followed by a confirmed positive MGIT culture (or a single positive sputum result after which the subject completed the trial), and the subject did not discontinue up to the time point being analyzed.

^b A subject was considered responder (no overruling) if at least 2 cultures from sputa collected at least 25 days apart were MGIT culture negative (as well as all intermediate cultures) and this culture negativity was not followed by a confirmed positive MGIT culture (or a single positive sputum result after which the subject completed or discontinued the trial) up to the time point being analyzed.

^c A subject was considered 8-week responder if at least the 2 last assessments during the 8-week investigational treatment period were MGIT culture negative and the subject did not discontinue during these 8 weeks.

^d No information on genotype was available for any of the recurrences; therefore, all recurrences are considered relapses. All 6 relapses in **C208 Stage 1** occurred while on treatment.

^e One subject in the placebo group had a single positive MGIT result at trial end and was considered responder in the final analysis of **C208 Stage 1**. However, to be consistent with the definition of relapse used in the **C208 Stage 2** and **C209** analyses, this subject is included as a relapser in the Summary of Clinical Efficacy resulting in a lower number of responders (10 subjects, 43.5%) than in the final **Stage 1** CSR (11 subjects, 47.8%).

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All relapses in **C208 Stage 1** were observed after Week 24 while subjects were on BR treatment, both in the bedaquiline (2 subjects) and placebo (4 subjects) treatment group.

For 1 of the 2 subjects in the bedaquiline group with relapse, the event was observed one day after a BR treatment interruption of more than 2.5 months during which no anti-TB drugs were taken. Three **Stage 1** subjects with relapse (1 in the bedaquiline group and 2 in the placebo group) were infected with a MDR_{H&R}-TB strain at baseline, the remaining 3 **Stage 1** relapsers had Pre-XDR-TB strains at baseline. Isolates from 2 subjects with MDR_{H&R}-TB (1 in each treatment group) acquired resistance to at least one of the tested anti-TB drugs during the trial.

5.3.2 C208 Stage 2 (Pivotal)

5.3.2.1 ANALYSES

The primary efficacy analysis of **Stage 2** was performed when all **Stage 2** subjects had completed 24 weeks of double-blind treatment with bedaquiline or placebo (or had discontinued earlier) and included data up to 12 July 2010. In order to include efficacy data from a large part of the BR treatment period of **Stage 2** in the NDA submission, an interim analysis of **Stage 2** was performed with an efficacy data cut-off date of 10 May 2011. At this cut-off date, all **Stage 2** subjects had completed the Week 72 visit or had discontinued.

The final analysis of **Stage 2** is completed, and includes an evaluation of the complete BR treatment period and subsequent treatment-free follow-up period, report writing is ongoing. The final analysis clinical study report will be submitted to the FDA under the IND by mid November 2012

5.3.2.2 POPULATION

Stage 2 of trial **C208** was conducted at 15 sites in Asia, South Africa, Eastern Europe, and South America that enrolled at least one subject. Overall, 161 subjects were randomized but 1 subject did not start treatment due to adverse event(s) (grade 3 nausea, vomiting, and dizziness). The ITT population thus included 160 subjects, of whom 79 subjects received bedaquiline and 81 subjects received placebo ([Table 24](#)). The mITT population consisted of 66 subjects in each randomization group after excluding 13 subjects (16.5%) treated with bedaquiline and 15 subjects (18.5%) with placebo who did not have MDR_{H&R}-TB or Pre-XDR-TB at baseline or for whom MGIT results were considered not evaluable ([Table 24](#)). Note that **Stage 2** subjects for whom the MDR status (resistance to at least isoniazid and rifampin) at baseline could not be confirmed based on central DST results or subject's medical history (based on previous DST) (i.e., 4 subjects in the placebo group) were also excluded from the mITT population. Twenty subjects (12 in the bedaquiline group and 8 in the placebo group) did not have isoniazid and rifampin resistance confirmed at the central lab; they were considered MDR subjects based on medical history (based on previous DST) and were included in the mITT population.

At the efficacy cut-off date of 10 May 2011, in the mITT population, 14 subjects (21.2%) in the bedaquiline group and 23 subjects (34.8%) in the placebo group had a major protocol deviation.

These subjects were excluded from the PP population that consisted of 52 and 43 subjects in the bedaquiline and placebo group, respectively (Table 24). The most frequently reported major protocol deviations were related to missed doses of one or more of the BR drugs.

Subject disposition **TMC207-C208-Stage 2** is provided in Table 22. A tabulation of the number of subjects at each visit (Week) is provided in Table 23.

Table 22: C208 Stage 2: Subject Disposition in Trial TMC207

N (%)	All subjects		ITT		mITT		PP	
	TMC207/ BR N = 80	Placebo/ BR N = 81	TMC207/ BR N = 79	Placebo/ BR N = 81	TMC207/ BR N = 66	Placebo/ BR N = 66	TMC207/ BR N = 49	Placebo/ BR N = 40
Screened	80 (100)	81 (100)	79 (100)	81 (100)	66 (100)	66 (100)	49 (100)	40 (100)
Randomized but not treated	1 (1.3)	0	0	0	0	0	0	0
Randomized and treated	79 (98.8)	81 (100)	79 (100)	81 (100)	66 (100)	66 (100)	49 (100)	40 (100)
Unblinded for rollover phase	1 (1.3)	2 (2.5)	1 (1.3)	2 (2.5)	1 (1.5)	1 (1.5)	0	1 (2.5)
Enrolled in rollover phase	0	1 (1.2)	0	1 (1.2)	0	1 (1.5)	0	1 (2.5)

N = number of subjects

Subjects eligible for rollover were unblinded after 24 weeks

Data on file, Janssen Research and Development

Table 23: C208 Stage 2: Tabulation of Number of Subjects at Each Visit – ITT and mITT

Phase Analysis timepoint n (%)	ITT		mITT	
	TMC207/BR N = 79	Placebo/BR N = 81	TMC207/BR N = 66	Placebo/BR N = 66
Screening Screening	79 (100)	81 (100)	66 (100)	66 (100)
Overall treatment				
Baseline	79 (100)	81 (100)	66 (100)	66 (100)
Week 1	78 (98.7)	80 (98.8)	66 (100)	65 (98.5)
Week 2	76 (96.2)	78 (96.3)	64 (97.0)	63 (95.5)
Week 3	77 (97.5)	77 (95.1)	65 (98.5)	63 (95.5)
Week 4	74 (93.7)	75 (92.6)	63 (95.5)	60 (90.9)
Week 5	75 (94.9)	76 (93.8)	64 (97.0)	62 (93.9)
Week 6	73 (92.4)	75 (92.6)	63 (95.5)	62 (93.9)
Week 7	73 (92.4)	76 (93.8)	62 (93.9)	62 (93.9)
Week 8	72 (91.1)	76 (93.8)	62 (93.9)	62 (93.9)
Week 10	69 (87.3)	74 (91.4)	60 (90.9)	60 (90.9)
Week 12	66 (83.5)	74 (91.4)	58 (87.9)	61 (92.4)
Week 14	67 (84.8)	73 (90.1)	59 (89.4)	61 (92.4)
Week 16	65 (82.3)	72 (88.9)	58 (87.9)	59 (89.4)
Week 18	63 (79.7)	69 (85.2)	56 (84.8)	58 (87.9)
Week 20	64 (81.0)	66 (81.5)	57 (86.4)	55 (83.3)
Week 22	64 (81.0)	64 (79.0)	57 (86.4)	54 (81.8)
Week 24	62 (78.5)	64 (79.0)	55 (83.3)	54 (81.8)
Week 28	61 (77.2)	61 (75.3)	54 (81.8)	53 (80.3)
Week 32	60 (75.9)	61 (75.3)	53 (80.3)	53 (80.3)
Week 36	62 (78.5)	59 (72.8)	55 (83.3)	51 (77.3)
Week 48	61 (77.2)	57 (70.4)	54 (81.8)	49 (74.2)
Week 60	58 (73.4)	55 (67.9)	51 (77.3)	47 (71.2)
Week 72	57 (72.2)	51 (63.0)	50 (75.8)	43 (65.2)
Week 84	53 (67.1)	51 (63.0)	46 (69.7)	43 (65.2)
Week 96	38 (48.1)	36 (44.4)	31 (47.0)	30 (45.5)
Week 108	19 (24.1)	23 (28.4)	18 (27.3)	19 (28.8)
Week 120	4 (5.1)	16 (19.8)	3 (4.5)	13 (19.7)
Follow-up Follow-up	22 (27.8)	16 (19.8)	19 (28.8)	12 (18.2)

Data on file, Janssen Research and Development

Table 24: C208 Stage 2: Analysis Populations and Reasons for Exclusion of Subjects

Population, N Reason for exclusion	TMC207/BR	Placebo/BR
ITT	79	81
Subject not MDR _{H&R} -TB or Pre-XDR-TB ^{a,b}	7 (8.9)	12 (14.8)
MGIT results not evaluable ^c	6 (7.6)	3 (3.7)
Total (excluded from mITT)	13 (16.5)	15 (18.5)
mITT^d	66	66
Total with major protocol violation (excluded from PP)	14 (21.2)	23 (34.8)
PP (interim analysis)	52	43

N = number of subjects

^a Subjects had DS-TB or XDR-TB at baseline or MDR-TB status could not be confirmed based on central DST results or subject's medical history (based on previous DST).

^b One subject in each treatment group had 2 reasons for exclusion from the mITT population; these subjects are counted only once and are included in the "subject not MDR_{H&R}-TB or Pre-XDR-TB" category rather than the "MGIT results not evaluable" category.

^c Subjects' MGIT culture results did not allow for primary efficacy evaluation; i.e., MGIT was negative at baseline or no MGIT results were available during the first 8 weeks after first intake

^d Four subjects in the TMC207 group and 5 subjects in the placebo group for whom no MGIT results were available at baseline were included in the mITT population based on positive MGIT results during the first week of intake.

Data on file, Janssen Research and Development

There were no relevant differences between randomization groups (ITT population) with respect to any of the demographic parameters or baseline disease characteristics apart from HIV status and baseline albumin levels (Table 25). Note that among these parameters, lung cavitation was a stratification factor.

The majority of subjects (63.1%) were male; median age at screening was 34.0 years (range: 18 - 63 years). Subjects were of various ethnic origins: 35.0% of subjects were Black, 17.5% were Hispanic, 12.5% were Caucasian, 9.4% were Asian, and 25.6% were of other (primarily mixed) ethnic origin (Table 25). All but 2 of the 56 Black subjects were enrolled at sites in South Africa; most other subjects enrolled in South Africa were of mixed race which was classified as "other".

Cavitary disease was common. Most subjects had cavitation in one lung (61.9%); cavitation in both lungs was observed in 18.1% of subjects (Table 25).

Based on central DST results, 86 subjects (55.1%) in the ITT population were infected with an MDR_{H&R}-TB strain and 28 subjects (17.9%) were infected with a Pre-XDR-TB strain (Table 25). Eighteen of the 28 (64.3%) Pre-XDR-TB isolates were resistant to kanamycin and/or CAP (i.e.,

SLI-Pre-XDR-TB) and 10 isolates (35.7%) were resistant to ofloxacin (i.e., FQ-Pre-XDR-TB). Eight subjects (5.1%) had DS-TB and 7 subjects (4.5%) had XDR-TB at baseline; these subjects were excluded from the mITT population together with 4 subjects (in the placebo group) for whom the MDR status (resistance to at least isoniazid and rifampin) could not be confirmed. For 27 (17.3%) subjects in the ITT population, no central DST results were available to determine extent of resistance but these subjects were considered MDR based on their medical history (based on previous DST).

More HIV-infected subjects were observed in the placebo group (19.8%) than in the bedaquiline group (10.1%). Mean (range) CD4+ cell count in these subjects was 494.6×10^6 cells/L (340 - 692×10^6 cells/L) in the bedaquiline group and 455.1×10^6 cells/L (310 - 670×10^6 cells/L) in the placebo group. All HIV-infected subjects had a CD4+ cell count $> 300 \times 10^6$ cells/L suggesting reasonable immunologic competence; the numerical difference in number of these subjects in the two groups was therefore not considered clinically significant. Abnormally low albumin (grade 1 to grade 3) at baseline was observed somewhat more in the placebo group (55.6% of subjects) than in the bedaquiline group (40.5% of subjects), mainly due to more subjects with grade 2 decreased albumin in the placebo group (35.8% versus 20.3%). Decreases in albumin of grade 3 were observed in 5.1% of subjects in the bedaquiline group and in 1.2% of subjects in the placebo group ([Table 25](#)). Of the 8 HIV-infected subjects in the bedaquiline group, 2 had normal albumin levels at baseline, 1 had grade 1 decreased albumin levels, 4 had grade 2 decreased albumin levels and 1 had grade 3 decreased albumin levels at baseline. Of the 16 HIV-infected subjects in the placebo group, 3 had normal albumin levels at baseline, 4 had grade 1 decreased albumin levels and 9 had grade 2 decreased albumin levels at baseline. Based on medical history at screening, 13 subjects (8.1%) reported diabetes mellitus (6 subjects in the bedaquiline group and 7 subjects in the placebo group).

Demographic data and baseline disease characteristics for the mITT population were similar to those of the ITT population ([Table 25](#)).

Table 25: C208 Stage 2: Demographics and Baseline Disease Characteristics -ITT/mITT

Parameter Value	ITT		mITT	
	TMC207/BR N = 79	Placebo/BR N = 81	TMC207/BR N = 66	Placebo/BR N = 66
Gender, n (%)				
Female	27 (34.2)	32 (39.5)	21 (31.8)	26 (39.4)
Male	52 (65.8)	49 (60.5)	45 (68.2)	40 (60.6)
Age at screening, years				
Median (range)	31.0 (18-63)	35.0 (18-61)	31.0 (18-63)	34.0 (18-57)
Ethnic origin, n (%)				
Black	29 (36.7)	27 (33.3)	24 (36.4)	25 (37.9)
Caucasian/White	8 (10.1)	12 (14.8)	6 (9.1)	8 (12.1)
Hispanic	13 (16.5)	15 (18.5)	12 (18.2)	10 (15.2)
Asian	9 (11.4)	6 (7.4)	9 (13.6)	6 (9.1)
Other	20 (25.3)	21 (25.9)	15 (22.7)	17 (25.8)
Lung cavitation^a (as stratified), n (%)				
Cavitation in both lungs	13 (16.5)	16 (19.8)	12 (18.2)	15 (22.7)
Cavitation in one lung only	50 (63.3)	49 (60.5)	42 (63.6)	41 (62.1)
No Cavitation	16 (20.3)	16 (19.8)	12 (18.2)	10 (15.2)
HIV status at screening, n (%)				
Negative	71 (89.9)	65 (80.2)	61 (92.4)	52 (78.8)
Positive	8 (10.1)	16 (19.8)	5 (7.6)	14 (21.2)
Body mass index (kg/m²)				
n	79	81	66	66
Mean (SD)	20.0 (3.43)	19.9 (3.70)	19.9 (3.39)	19.7 (3.70)
Body mass index (kg/m²)				
< 18	26 (32.9)	32 (39.5)	24 (36.4)	29 (43.9)
≥18-<20	16 (20.3)	18 (22.2)	10 (15.2)	13 (19.7)
≥20-<25	31 (39.2)	22 (27.2)	28 (42.4)	18 (27.3)
≥25	6 (7.6)	9 (11.1)	4 (6.1)	6 (9.1)
Extent of resistance of <i>M. tuberculosis</i> strain, n (%)	N = 79	N = 77	N = 66	N = 66
DS-TB	4 (5.1)	4 (5.2)	0	0
MDR-TB ^b	75 (94.9)	73 (94.8)	66 (100)	66 (100)
MDR _{H&R} -TB	40 (50.6)	46 (59.7)	39 (59.1)	45 (68.2)
Pre-XDR-TB	16 (20.3)	12 (15.6)	15 (22.7)	12 (18.2)
XDR-TB	3 (3.8)	4 (5.2)	0	0
Albumin grade at baseline, n (%)				
Grade 0	47 (59.5)	36 (44.4)	38 (57.6)	24 (36.4)
Grade 1	12 (15.2)	15 (18.5)	11 (16.7)	14 (21.2)
Grade 2	16 (20.3)	29 (35.8)	14 (21.2)	27 (40.9)
Grade 3	4 (5.1)	1 (1.2)	3 (4.5)	1 (1.5)

N = number of subjects with data; n = number of observations

^a Cavitation defined as the presence of at least one cavity ≥ 2 cm

^b No central DST results were available to determine extent of resistance for 27 (17.3%) subjects (i.e., 16 [20.3%] in the TMC207 group and 11 [14.3%] in the placebo group) in the ITT population and for 21 (15.9%) subjects (i.e., 12 [18.2%] in the TMC207 group and 9 [13.6%] in the placebo group) in the mITT population. These subjects were considered MDR based on their medical history (based on previous DST).

Data on file, Janssen Research and Development

Results from DST at baseline showed that most **Stage 2** subjects in the mITT population ($\geq 87.4\%$) were infected with isolates susceptible to ethionamide, kanamycin, and ofloxacin. These individual drugs were used in the BR of $\geq 73.5\%$ of **Stage 2** subjects during investigational treatment. The lowest rates of susceptibility were observed for the first-line anti-TB drugs streptomycin (20.5%), pyrazinamide (37.7%), and ethambutol (40.2%) ([Table 26](#)). Somewhat more isolates from subjects in the placebo group compared to the bedaquiline group were susceptible to ethambutol (46.6% versus 33.3%) and to pyrazinamide (43.1% versus 32.1%) ([Table 26](#)).

According to proportion method DST results, regardless of whether or not subjects were taking the tested anti-TB drugs at baseline, the majority of subjects in the mITT population (96.3% in the bedaquiline group and 92.9% in the placebo group) were infected with an *M. tuberculosis* strain susceptible to at least 3 tested anti-TB drugs; 40.7% in the bedaquiline group and 55.4% in the placebo group were infected with an *M. tuberculosis* strain susceptible to at least 5 of the tested drugs.

Table 26: C208 Stage 2: Baseline Susceptibility to Anti-TB Drugs – mITT

n (%) of isolates susceptible ^a to	TMC207/BR		Placebo/BR		All Subjects	
	N	n (%)	N	n (%)	N	n (%)
EMB	54	18 (33.3)	58	27 (46.6)	112	45 (40.2)
SM	54	9 (16.7)	58	14 (24.1)	112	23 (20.5)
PZA	56	18 (32.1)	58	25 (43.1)	114	43 (37.7)
ETH	54	50 (92.6)	57	51 (89.5)	111	101 (91.0)
OFL	54	48 (88.9)	57	53 (93.0)	111	101 (91.0)
KAN	54	47 (87.0)	57	50 (87.7)	111	97 (87.4)
CAP	54	47 (87.0)	57	50 (87.7)	111	97 (87.4)

N = number of subjects with data; n = number of subjects susceptible to the specified drug; EMB = ethambutol; SM = streptomycin; PZA = pyrazinamide; ETH = ethionamide; OFL = ofloxacin; KAN = kanamycin

^a Based on the agar proportion method (and the MGIT 960 system for pyrazinamide). Cycloserine was not tested due to poor reproducibility of the results.

Data on file, Janssen Research and Development

Up to the data cut-off date of the interim analysis, 57 subjects (35.6%) in the ITT population had discontinued the trial prematurely: 34.2% of subjects in the bedaquiline group and 37.0% of subjects in the placebo group ([Table 27](#)). The main reasons for premature discontinuation were the occurrence of one or more adverse events and withdrawal of consent, but withdrawal of consent accounted for less than a third of premature discontinuations in both treatment groups (6 of 27 subjects in the bedaquiline group and 7 of 30 subjects in the placebo group). Thirty subjects (18.8%; i.e., 13 bedaquiline subjects and 17 placebo subjects) had discontinued the trial

prior to Week 24 and therefore did not complete intake of bedaquiline or placebo as planned. At the cut-off date, all **Stage 2** subjects had completed the Week 72 visit or had discontinued earlier, 23.8% of subjects had completed the trial (including the treatment-free follow-up period of at least 24 weeks), and 40.0% of subjects were ongoing.

Table 27: C208 Stage 2: Completion/Withdrawal - ITT

Trial Termination Type^a Reason, n (%)	TMC207/BR N = 79	Placebo/BR N = 81	All Subjects N = 160
Completed	18 (22.8)	20 (24.7)	38 (23.8)
Ongoing	34 (43.0)	30 (37.0)	64 (40.0)
Discontinued	27 (34.2)	30 (37.0)	57 (35.6)
Adverse event	7 (8.9)	6 (7.4)	13 (8.1)
Subject ineligible to continue the trial	2 (2.5)	6 (7.4)	8 (5.0)
Subject lost to follow-up	5 (6.3)	3 (3.7)	8 (5.0)
Subject non-compliant	3 (3.8)	6 (7.4)	9 (5.6)
Subject withdrew consent	6 (7.6)	7 (8.6)	13 (8.1)
Subject is pregnant	3 (3.8)	2 (2.5)	5 (3.1)
Other	1 (1.3)	0	1 (0.6)
Rollover	0	1 (1.2)	1 (0.6)

N = number of evaluable subjects; n = number of subjects with that result

^a Using all available data up to the data cut-off date of the interim analysis.

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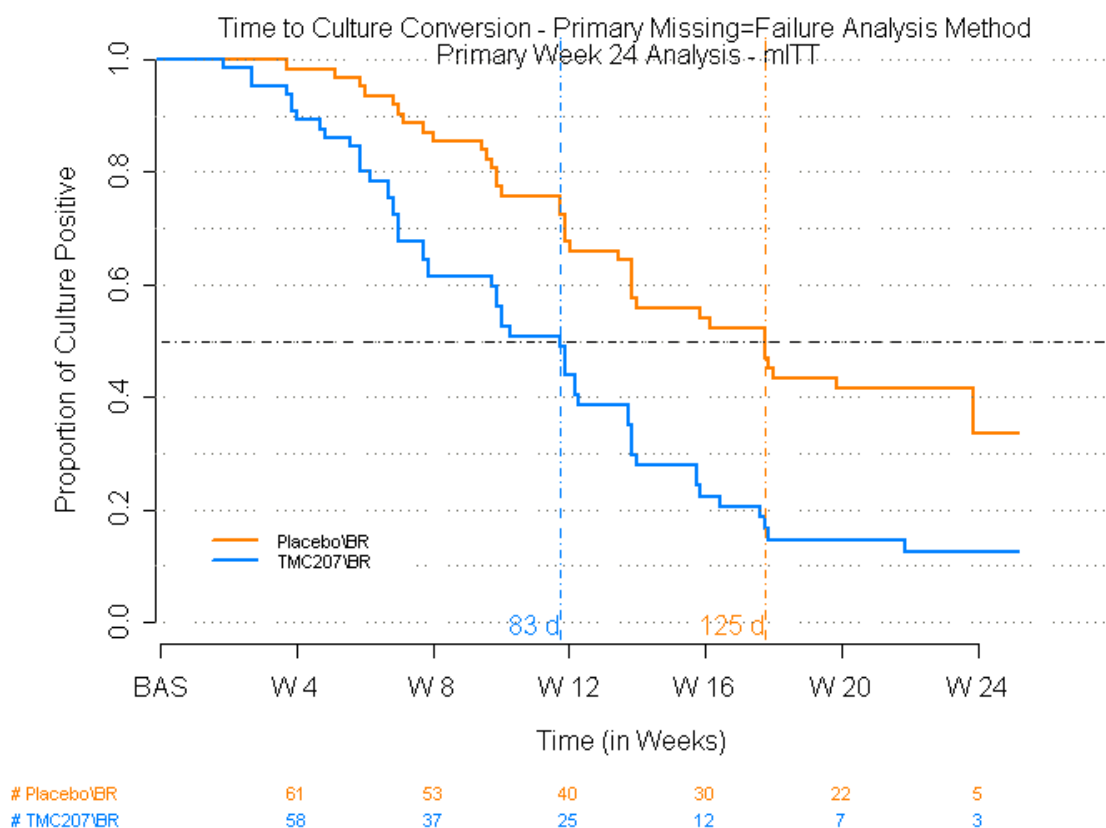
The most frequently used anti-TB drugs in the baseline BR (i.e., within the first 2 weeks of investigational treatment) for subjects in the ITT population were fluoroquinolones (99.4%; mainly ofloxacin: 74.4%), aminoglycosides (95.6%; mainly kanamycin: 62.5%), pyrazinamide (93.1%), ethionamide (84.4%), 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 CS and TRD) were taken by < 30.0% of ITT subjects.

According to agar proportion method DST results, isolates of 75.9% of subjects in the bedaquiline group and of 80.4% of subjects in the placebo group (mITT population) were susceptible to at least 3 drugs in their baseline BR. Additionally, 7.4% of subjects in the bedaquiline group and 17.9% of subjects in the placebo group had isolates susceptible to at least 5 drugs in their baseline BR. Isolates from all subjects were susceptible to at least 1 drug in their baseline BR.

5.3.2.3 PRIMARY EFFICACY ENDPOINT: TIME TO CULTURE CONVERSION DURING THE 24-WEEK TREATMENT PERIOD (PRIMARY WEEK 24 EFFICACY ANALYSIS)

Time to culture conversion during the 24-week treatment period with bedaquiline or placebo was the primary outcome parameter for **Stage 2** of trial **C208** and was analyzed during the primary (Week 24) efficacy analysis that was performed when all subjects had completed their 24-week treatment with bedaquiline or placebo (or had discontinued earlier).

The time to culture conversion according to the primary analysis method (i.e., with subjects who discontinued during the 24-week period being considered as not converted and their time to culture conversion assigned to the last MGIT culture result) is shown in [Figure 22](#).



#: number of subjects at risk (i.e., culture positive subjects ongoing in the trial at the corresponding time point)

Note: The intersection of horizontal dotted line and each treatment arm represents the median time to sputum culture conversion.

Data on file, Janssen Research and Development

Figure 22: C208 Stage 2: Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (Primary Week 24 Efficacy Analysis, Primary Missing = Failure Analysis Method) – mITT

Culture conversion was considerably faster in the bedaquiline group than in the placebo group: median time to culture conversion was 83 days in the bedaquiline group and 125 days in the placebo group. Comparison of treatment groups using a Cox proportional hazards model with lung cavitation and pooled center as covariates also showed statistically significantly faster conversion ($p < 0.0001$) with bedaquiline treatment as compared to placebo treatment when added to a preferred BR for 24 weeks (hazard ratio [95% CI]: 2.44 [1.57; 3.80]).

The results of the sensitivity analysis (end-censored missing = failure method) showed similar results as observed with the primary missing = failure analysis method. Time to culture conversion according to the second sensitivity analysis using ‘no overruling for discontinuation’ was not determined during the primary Week 24 efficacy analysis of **C208 Stage 2**; this analysis method was included in the interim analysis of **C208 Stage 2**.

5.3.2.4 SECONDARY EFFICACY ENDPOINTS

5.3.2.4.1 Time to Culture Conversion at Week 24 (Interim Analysis / 24-Week Data Selection)

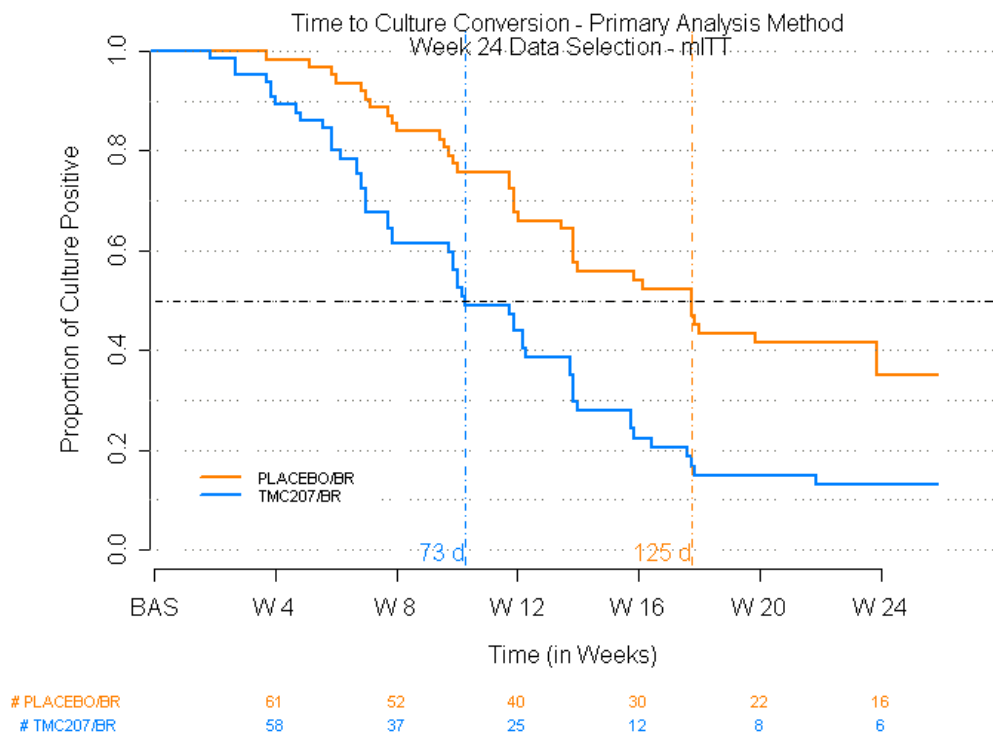
The Sponsor was unblinded to treatment code for the primary efficacy analysis. For the interim analysis, data collection and database lock was performed up to the efficacy cut-off date of 10 May 2011. However, individual subject treatment information was not revealed to the investigators and subjects to allow objective collection of safety information during the rest of the trial.

For the interim analysis performed for the NDA, time to culture conversion was first determined using the 24-week data selection (i.e., using data from the first 24 weeks only) as a major co-primary efficacy endpoint. Time to culture conversion was again analyzed according to the primary analysis method as well as two sensitivity analyses (‘end-censored missing = failure’ and ‘no overruling for discontinuation’ methods). The results are presented below and are similar to those determined during the primary efficacy analysis. There are minor variations due to additional information that became available during this interim analysis.

Time to culture conversion according to the primary missing = failure method is shown in [Figure 23](#). The results are similar to those obtained during the primary Week 24 efficacy analysis. Median time to culture conversion for the mITT population according to the primary

missing = failure analysis method was 73 days for subjects in the bedaquiline group and 125 days for subjects in the placebo group. Compared to the primary Week 24 efficacy analysis with median times of respectively 83 days and 125 days, a shift in median of 10 days was observed for the bedaquiline group. On a subject level, a two-week shift in time to culture conversion is noted for 2 subjects. One subject (placebo group) shifts from 70 days in the primary Week 24 efficacy analysis to 56 days in the 24-week data selection of the interim analysis. Another subject (bedaquiline group) shifts from 84 days in the primary Week 24 efficacy analysis to 72 days in the interim analysis. These changes are due to samples (at Days 56 and 72, respectively) with time to growth of 42 days or higher that were considered positive in the primary analysis, while in the interim analysis these samples were considered negative. The shift for one subject causes the change in median for the bedaquiline group. It is important to note that, although there is a small shift in median time to conversion, culture conversion rates at Week 24 are identical in both analyses.

The results of a Cox proportional hazards model with lung cavitation and pooled center as covariates showed a statistically significant difference in time to sputum conversion between the treatment groups ($p < 0.0001$) in favor of the bedaquiline group (hazard ratio [95% CI]: 2.41 [1.55; 3.75]). These values are similar to those obtained during the primary Week 24 efficacy analysis. Of note, pooling of centers was done prior to unblinding of the treatment codes.



#: number of subjects at risk (i.e., culture positive subjects ongoing in the trial at the corresponding time point)
Note: The intersection of horizontal dotted line and each treatment arm represents the median time to sputum culture conversion.

Data on file, Janssen Research and Development

Figure 23: C208 Stage 2: Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (Interim Analysis / 24-Week Data Selection, Primary Missing = Failure Analysis Method) – mITT

The results of two sensitivity analyses (end-censored missing = failure method, and ‘no overruling for discontinuation’) also showed similar results as observed with the primary missing = failure analysis method (Figure 24). The time to culture conversion (MGIT) according to the no overruling for discontinuation method is shown in Figure 25.

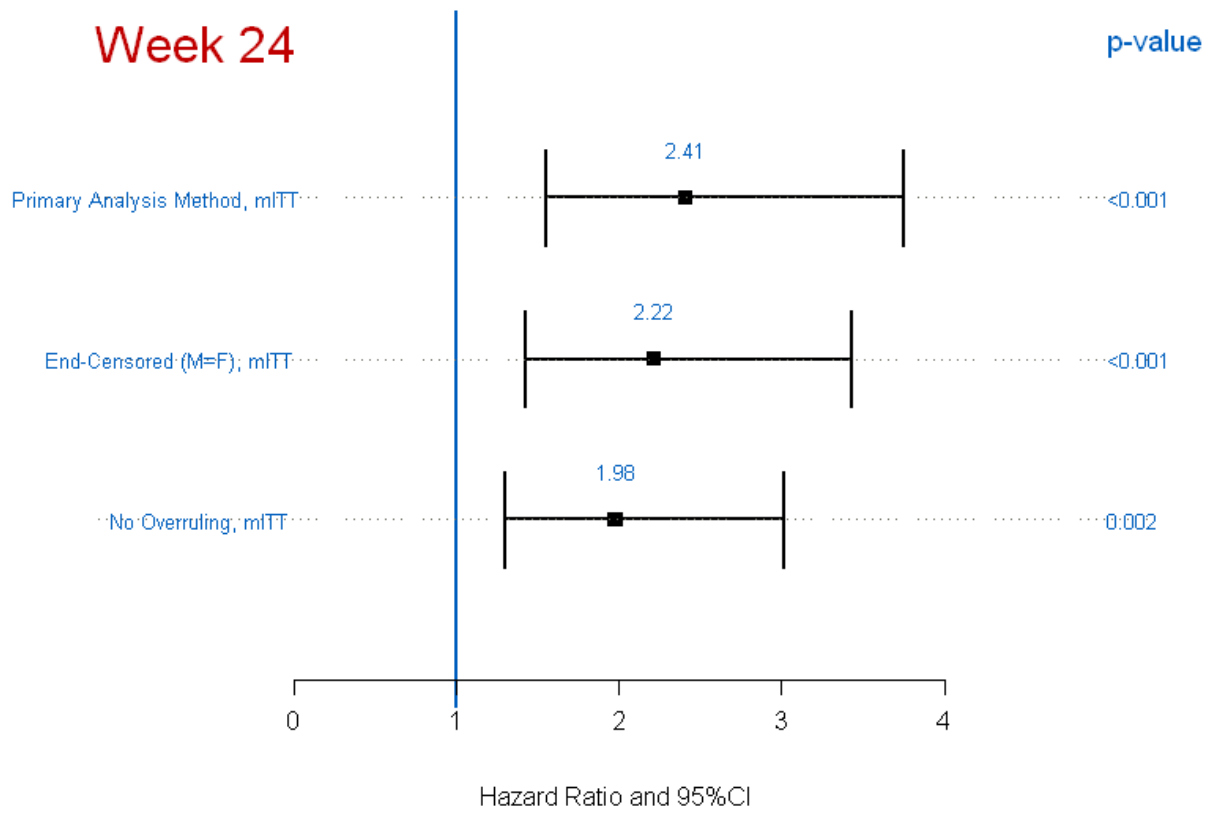
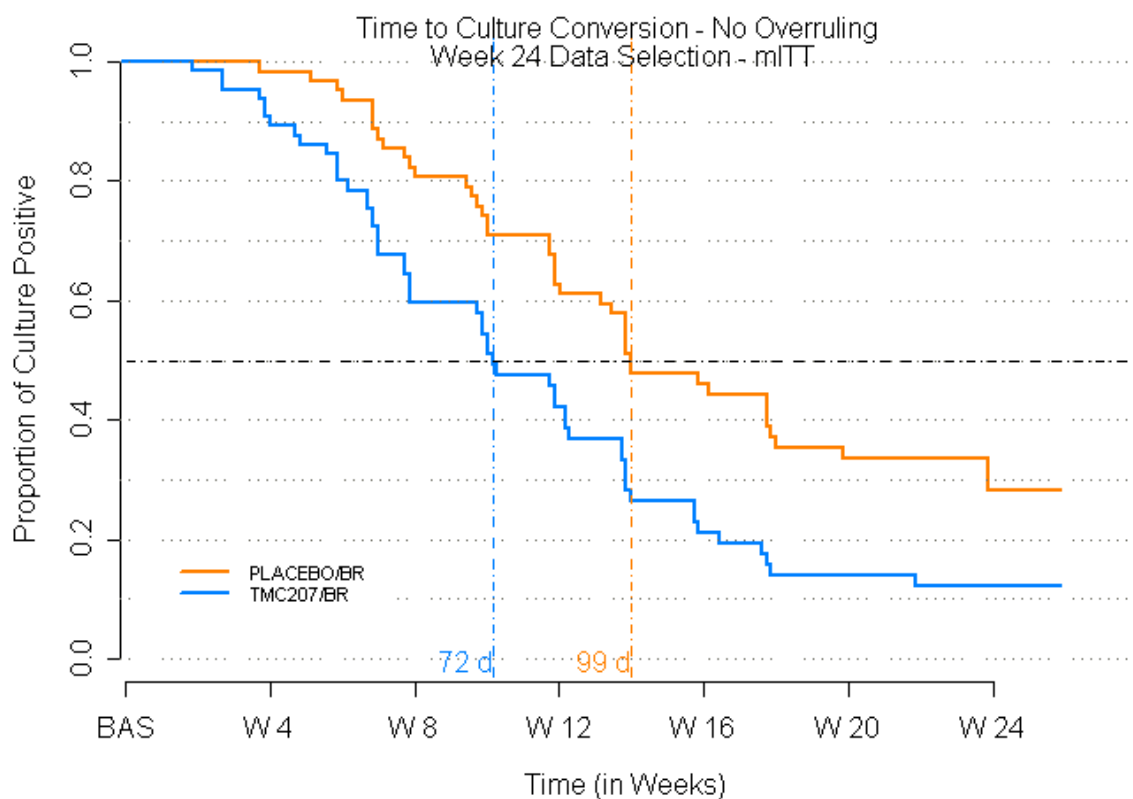


Figure 24: C208 Stage 2: Forest Plot



PLACEBO/BR
TMC207/BR

Time (in Weeks)	W 4	W 8	W 12	W 16	W 20	W 24
# PLACEBO/BR	61	50	37	26	19	16
# TMC207/BR	58	36	24	12	8	6

Placebo/BR, # TMC207/BR: number of subjects at risk.

Of note, culture conversion rates cannot be derived from this figure

Figure 25: C208 Stage 2:Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (Interim Analysis, 24-Week Data Selection, No Overruling for Discontinuation) – mITT

5.3.2.4.2 Culture Conversion Rates

The number of **C208 Stage 2** subjects in the mITT population with culture conversion at Week 24, Week 36, Week 48, Week 60, Week 72, and at the last available assessment time point in the interim analysis is summarized in [Table 28](#) for both responder definitions (missing = failure, and no overruling). The number of non-responders in each subcategory at the last available time point is also included.

When using the ‘missing = failure’ response definition (with subjects who discontinued considered as non-responders), the percentage of responders after 24 weeks of treatment with bedaquiline or placebo in combination with BR was 78.8% in the bedaquiline group and 57.6%

in the placebo group. These results from the interim analysis using the 24-week data selection are identical to the results from the primary Week 24 efficacy analysis.

At the Week 72 visit, the percentage of responders (missing = failure) was 71.2% in the bedaquiline group and 56.1% in the placebo group.

Based on a logistic regression model with only treatment as covariate, the difference in responders (missing = failure) observed between bedaquiline/BR versus placebo/BR treatment groups was statistically significant at Week 24 ($p = 0.008$) and at the last available assessment time point ($p = 0.021$) but not at Week 72 ($p = 0.069$). Note that pooled center and lung cavitation were not included as covariates in this model because of (quasi-)separation.

Conversion rates according to the ‘no overruling’ response definition (in which subjects who discontinued with microbiological status ‘culture converted’ were considered responders) showed a somewhat smaller difference in number of responders between the treatment groups compared to when using the missing = failure response definition. The percentage of 24-week responders (no overruling) was 80.3% in the bedaquiline group and 65.2% in the placebo group. No major changes in conversion rates were observed at later time points; at the last available assessment time point, the percentage of responders (no overruling) was identical to that at Week 24.

Table 28: C208 Stage 2: Culture Conversion Rates (Interim Analysis / All Available Data Selection) – mITT

Time Point Microbiological Status, n (%)	TMC207/BR N = 66	Placebo/BR N = 66	p-value ^c
Week 24			
Responder (missing = failure) ^a	52 (78.8)	38 (57.6)	0.008
Responder (no overruling) ^b	53 (80.3)	43 (65.2)	0.049
Week 36			
Responder (missing = failure) ^a	48 (72.7)	40 (60.6)	0.139
Responder (no overruling) ^b	51 (77.3)	46 (69.7)	0.324
Week 48			
Responder (missing = failure) ^a	49 (74.2)	42 (63.6)	0.187
Responder (no overruling) ^b	53 (80.3)	48 (72.7)	0.305
Week 60			
Responder (missing = failure) ^a	48 (72.7)	39 (59.1)	0.097
Responder (no overruling) ^b	53 (80.3)	46 (69.7)	0.159
Week 72			
Responder (missing = failure) ^a	47 (71.2)	37 (56.1)	0.069
Responder (no overruling) ^b	53 (80.3)	46 (69.7)	0.159
Last Available Time Point^d			
Overall responder (missing = failure) ^a	44 (66.7)	31 (47.0)	0.021
Overall responder (no overruling) ^b	53 (80.3)	43 (65.2)	0.049
Overall non-responder (missing = failure) ^a	22 (33.3)	35 (53.0)	
▶ Failure to culture convert	▶ 8 (12.1)	▶ 15 (22.7)	
▶ Relapse ^e	▶ 5 (7.6)	▶ 8 (12.1)	
▶ Discontinued but converted	▶ 9 (13.6)	▶ 12 (18.2)	
Overall non-responder (no overruling) ^b	13 (19.7)	23 (34.8)	

N = number of subjects in population; n = number of subjects with that result.

^a A subject was considered responder (missing = failure) if at least 2 cultures from sputa collected at least 25 days apart were MGIT culture negative (as well as all intermediate cultures), this culture negativity was not followed by a confirmed positive MGIT culture (or a single positive sputum result after which the subject completed the trial), and the subject did not discontinue up to the time point being analyzed.

^b A subject was considered responder (no overruling) if at least 2 cultures from sputa collected at least 25 days apart were MGIT culture negative (as well as all intermediate cultures) and this culture negativity was not followed by a confirmed positive MGIT culture (or a single positive sputum result after which the subject completed or discontinued the trial) up to the time point being analyzed.

^c Based on a logistic regression model with treatment as covariate.

^d Using the all available data selection up to efficacy data cut-off date of 10 May 2011

Data on file, Janssen Research and Development

At the last available assessment time point prior to 10 May 2011, the percentage of responders (missing = failure) was 66.7% in the bedaquiline group and 47.0% in the placebo group. Among the non-responders, 8 subjects (12.1%) in the bedaquiline group and 15 subjects (22.7%) in the placebo group never achieved culture conversion before the last assessment and 9 subjects (13.6%) in the bedaquiline group and 12 subjects (18.2%) in the placebo group prematurely discontinued while their microbiological status was 'culture converted'. Five subjects (7.6%) in the bedaquiline group and 8 subjects (12.1%) in the placebo group experienced relapse. Given no

information was available on genotype for any of the recurrences at the time of the interim analysis, all recurrences are considered relapses.

In Stage 2 all 13 subjects who relapsed (8 on placebo and 5 on TMC207) had not yet reached the treatment-free follow-up phase. In addition, all but 1 subject (on bedaquiline) relapsed after the investigational phase.

All **Stage 2** subjects with relapse in the bedaquiline group were infected with a MDR_{H&R}-TB strain at baseline; none of these subjects' isolates acquired resistance to any of the tested anti-TB drugs during the trial. In the placebo group, 6 subjects with relapse were infected with an MDR_{H&R}-TB strain at baseline and isolates from 2 of them developed resistance to one or more of the tested anti-TB drugs during the trial. The 2 remaining placebo subjects with relapse were infected with an MDR strain at baseline (i.e., were considered MDR based on medical history [previous DST])

5.3.2.4.3 Time to Smear Conversion and AFB Smear Conversion Rates

As a major secondary efficacy endpoint, time to conversion and conversion rates were also determined using results from AFB smears focusing only on the first 6 months of treatment.

The percentage of 24-week responders using the missing = failure response definition for AFB smear conversion (78.8% in the bedaquiline group and 62.1% in the placebo group) was generally similar to the MGIT conversion rates.

Note that–culture (MGIT) is more sensitive than AFB and is therefore considered the ‘gold standard’⁷⁴.

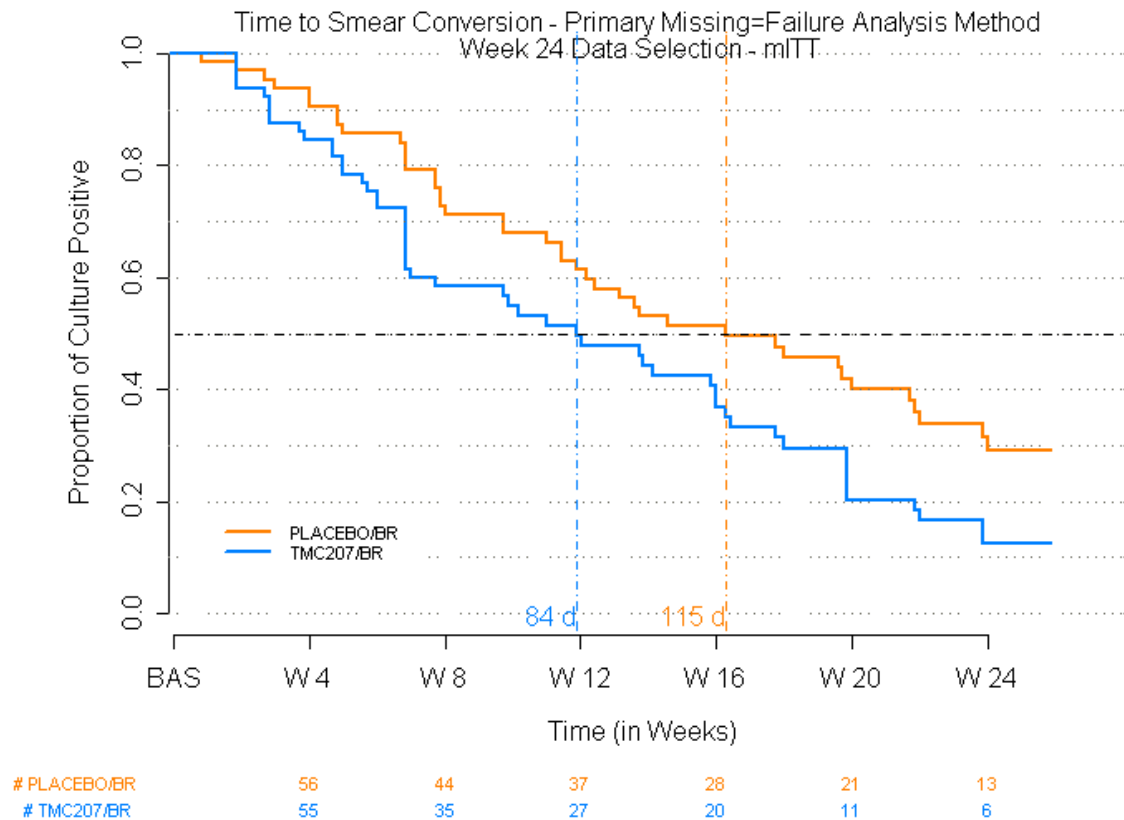


Figure 26 C208 Stage 2: Kaplan-Meier Plot: Proportion of AFB Smear Positive Subjects Over Time (Interim Analysis / 24-Week Data Selection, Primary Missing = Failure Analysis Method) – mITT

5.3.2.5 SUBGROUP ANALYSES

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%).

Culture conversion rates for subgroups at Week 24 are presented in [Table 29](#). There is 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 slightly higher efficacy as compared to MDR-TB patients without bedaquiline addition (73.3% and 62.2 % respectively). Similarly, a clear treatment difference is observed in both the PZA susceptible and resistant subgroups. Strikingly, the subjects on placebo on each of aforementioned subgroups have response rates which are all inferior to the response rates observed in the bedaquiline subgroup. This underscores the magnitude of the relative effect of the addition of bedaquiline to a MDR regimen.

For subgroups by pooled center, lower responder rates were observed in the 3 South African pooled centers compared to the South American site for subjects in the bedaquiline group ([Table 29](#)). The number of subjects in pooled centers Asia and Eastern Europe was below 10 in both treatment arms and therefore no conclusions could be drawn from these results.

An analysis by region was performed because population pharmacokinetic results showed lower exposure of TMC207 in Black subjects compared to the other races in C208 Stage 2 and the majority of subjects enrolled in South Africa designated themselves as Black (about 2/3) or of mixed or colored (about 1/3) race. Results of this analysis by region are provided in [Table 30](#). The lower culture conversion rates (missing = failure) in the region South Africa were likely related to the higher number of discontinuations in South Africa compared to the other regions. Similar findings were observed in C209, see [5.4.4.1](#).

Table 29: C208 Stage 2: Culture Conversion Rates at Week 24 by Subgroups (Interim Analysis / 24-Week Data Selection) – mITT

Parameter	TMC207/BR		Placebo/BR	
	N	24-week responder (missing = failure), n (%)	N	24-week responder (missing = failure), n (%)
Lung Cavitation (as Stratified)				
No cavitation	12	12 (100)	10	8 (80.0)
Cavitation in one lung only	42	30 (71.4)	41	21 (51.2)
Cavitation in both lungs	12	10 (83.3)	15	9 (60.0)
Pooled Center				
Asia	8	8 (100)	4	4 (100)
Eastern Europe	6	3 (50.0)	7	3 (42.9)
South Africa - 1	14	11 (78.6)	17	7 (41.2)
South Africa - 2	13	9 (69.2)	13	11 (84.6)
South Africa - other	10	7 (70.0)	12	6 (50.0)
South America	15	14 (93.3)	13	7 (53.8)
Race				
Black	24	17 (70.8)	25	18 (72.0)
Caucasian/White	6	4 (66.7)	8	4 (50.0)
Hispanic	12	12 (100)	10	5 (50.0)
Oriental/Asian	9	8 (88.9)	6	5 (83.3)
Other	15	11 (73.3)	17	6 (35.3)
Extent of Resistance of <i>M. tuberculosis</i> Strain^a				
MDR _{H&R} -TB	39	32 (82.1)	45	28 (62.2)
Pre-XDR-TB	15	11 (73.3)	12	4 (33.3)
PZA Susceptibility at Baseline (MGIT960)				
Resistant	38	28 (73.7)	33	16 (48.5)
Susceptible	18	16 (88.9)	25	16 (64.0)
HIV Status at Baseline				
Negative	61	48 (78.7)	52	27 (51.9)
Positive	5	4 (80.0)	14	11 (78.6)
Number of Drugs Active in vitro in Baseline BR (agar proportion method)^b				
< 3	13	8 (61.5)	11	5 (45.5)
≥ 3	41	35 (85.4)	45	26 (57.8)
Baseline BMI				
< 18 kg/m ²	24	18 (75.0)	29	17 (58.6)
≥ 18 - < 20 kg/m ²	10	8 (80.0)	13	8 (61.5)
≥ 20 - < 25 kg/m ²	28	22 (78.6)	18	10 (55.6)
≥ 25 kg/m ²	4	4 (100)	6	3 (50.0)
Baseline Albumin Grade				
Grade 0	38	31 (81.6)	24	14 (58.3)
Grade 1	11	9 (81.8)	14	10 (71.4)
Grade 2	14	11 (78.6)	27	13 (48.1)
Grade 3	3	1 (33.3)	1	1 (100)

N = number of subjects; n = number of subjects with observation; PZA = pyrazinamide

^a Extent of resistance based on central DST results was not available for 21 subjects in the mITT population (12 in the TMC207 group and 9 in the placebo group). These subjects were excluded from the subgroup analysis by extent of resistance of *M. tuberculosis* strain.

^b As DST testing was not performed for all anti-TB drugs, some drugs are not accounted for. DST testing was done for isoniazid, rifampin, ethambutol, streptomycin, pyrazinamide, ethionamide, ofloxacin, kanamycin, and capreomycin.

Data on file, Janssen Research and Development

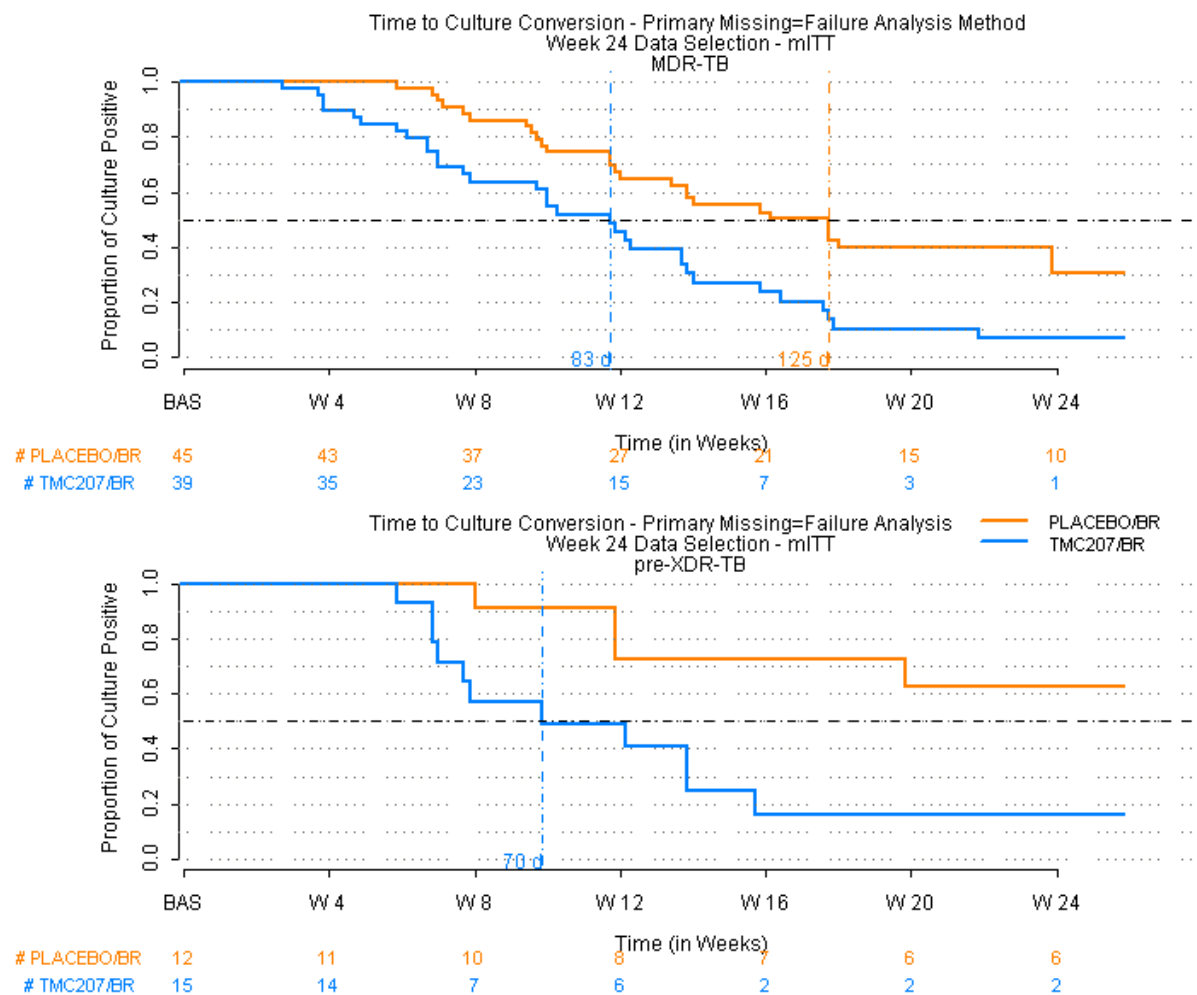
Table 30: Culture Conversion Rates at Week 24 by Region and Trial Discontinuation Before Week 24 (C208 Stage 2, 24-Week Data Selection) – mITT

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

In all subgroup categories, time to culture conversion (24-week data selection, primary missing = failure analysis method) was shorter in the bedaquiline group compared to the placebo group. Differences between subgroups were generally consistent to those observed for culture conversion rates, i.e., subgroups with higher culture conversion rates show shorter time to culture conversion. Time to culture conversion in the MDR-TB and Pre-XDR subgroups are presented in Figure 27.



#: number of subjects at risk

Figure 27: C208 Stage 2: Kaplan-Meier Plot: Proportion of Culture Positive Subjects in Subgroups by Extent of Resistance of *M. tuberculosis* Strain (Figure above: MDR_{H&R}-TB; Figure below: Pre-XDR-TB) (Interim Analysis / 24-Week Data Selection, Primary Missing = Failure Analysis Method) – mITT

As is shown in Table 28, the treatment difference in culture conversion rates observed at Week 24 was higher compared to most subsequent time points which can be explained by a higher number of subjects in the Placebo group converting after week 24. This is also suggested by Figure 28.

In addition, 4 out of the 8 subjects who relapsed in the placebo group, relapsed late (>72 weeks), compared to no (0 out of 5) late relapses in the TMC207 group. Due to these late relapses in the placebo group, the treatment difference of culture conversion rates at the last available time point regains statistical significance.

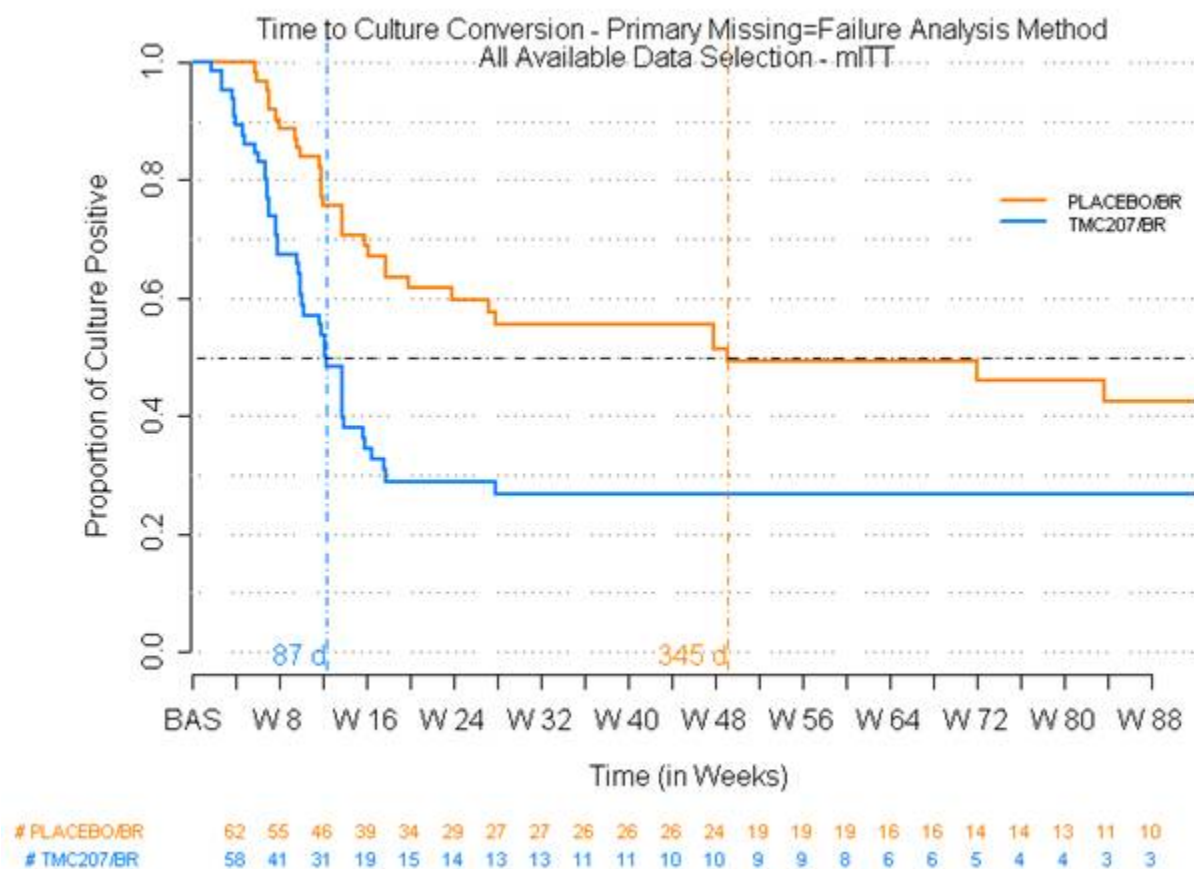


Figure 28: C208 Stage 2: Kaplan-Meier Plot: Time to Culture Conversion (Interim Analysis / All Available Data Selection, Primary Missing = Failure Analysis Method) – mITT

When using the 72-week data selection, similar treatment differences within subgroups were observed for responder rates (missing = failure) compared to the 24-week data selection, except for subgroups by baseline susceptibility to pyrazinamide and baseline albumin grade (Table 31).

Table 31: C208 Stage 2: Culture Conversion Rates 72-Week Data Selection (Missing=Failure) by Subgroups – mITT

	TMC207/BR		Placebo/BR	
	N	n (%)	N	n (%)
Cavitation (as Stratified)				
No cavitations or cavitations < 2 cm	12	9 (75.0)	10	8 (80.0)
Cavitations ≥ 2 cm in one lung only	42	30 (71.4)	41	24 (58.5)
Cavitations ≥ 2 cm in both lungs	12	8 (66.7)	15	5 (33.3)
Pooled Center				
Asia	8	6 (75.0)	4	4 (100)
Eastern Europe	6	4 (66.7)	7	4 (57.1)
South Africa - 1	14	9 (64.3)	17	6 (35.3)
South Africa - 2	13	9 (69.2)	13	9 (69.2)
South Africa - other	10	7 (70.0)	12	6 (50.0)
South America	15	12 (80.0)	13	8 (61.5)
HIV Status at Baseline				
Negative	61	43 (70.5)	52	28 (53.8)
Positive	5	4 (80.0)	14	9 (64.3)
Extent of Resistance of <i>M. tuberculosis</i> Strain				
MDR _{H&R} -TB	39	28 (71.8)	45	28 (62.2)
Pre-XDR-TB	15	10 (66.7)	12	5 (41.7)
Baseline PZA Susceptibility (MGIT960)				
Resistant	38	27 (71.1)	33	14 (42.4)
Susceptible	18	13 (72.2)	25	19 (76.0)
Previous use of First Line Drugs				
No	6	6 (100)	8	5 (62.5)
Yes	60	41 (68.3)	58	32 (55.2)
Number of Potentially Active Drugs in BR at Baseline (AGAR)				
< 3 active drugs	13	7 (53.8)	11	6 (54.5)
≥ 3 active drugs	41	31 (75.6)	45	27 (60.0)
Baseline BMI				
< 18	24	16 (66.7)	29	16 (55.2)
≥18-<20	10	7 (70.0)	13	8 (61.5)
≥20-<25	28	22 (78.6)	18	9 (50.0)
≥25	4	2 (50.0)	6	4 (66.7)
Baseline Albumin Grade				
Grade 0	38	29 (76.3)	24	15 (62.5)
Grade 1	11	9 (81.8)	14	10 (71.4)
Grade 2	14	8 (57.1)	27	11 (40.7)
Grade 3	3	1 (33.3)	1	1 (100)

N = number of subjects; n = number of subjects with observation

Data on file, Janssen research and Development

Information on acquired resistance of anti-TB drugs is summarized in [Table 32](#). Focusing only on acquired resistance to fluoroquinolones, aminoglycosides or capreomycin, fewer patients who were non-responders developed a pre-XDR TB profile in the bedaquiline group (0 versus 7) in Stage 2.

Table 32: C208 Stage 2: Acquired Resistance to Anti-TB Drugs at Endpoint (All Available Data Selection, No Overruling) - mITT

	TMC207	Placebo
mITT	66	66
responders	53	43
paired samples	5	17
additional resistance	1	7
non-responders	13	23
paired samples	5	10
additional resistance	1	7

Data on file, Janssen Research and Development

5.4 SINGLE-ARM, OPEN-LABEL, PHASE IIB TRIAL C209

5.4.1 Analyses

The trial is currently ongoing but all subjects have completed the 24-week investigational treatment period allowing for evaluation of safety, tolerability, and the primary efficacy endpoint (i.e., time to culture conversion in MGIT during the 24-week treatment period with bedaquiline).

An interim analysis was performed including data up 29 March 2011, when all subjects in the trial had completed their 24-week treatment with bedaquiline (or had discontinued earlier). The final analysis will be performed when all subjects have completed the trial (or have discontinued) and will include an evaluation of the entire BR treatment period and the treatment-free follow-up period.

5.4.2 Population

Trial **C209** was performed at 33 sites in Asia, South Africa, Eastern Europe, and South America. Overall, 233 subjects started treatment with bedaquiline in combination with an individualized BR of anti-TB drugs (ITT population). The mITT population, which excluded subjects who had

DS-TB or whose MGIT results did not allow for primary efficacy evaluation (i.e., no positive sputum culture at screening or baseline), consisted of 205 subjects ([Table 33](#)).

Table 33: C209: Analysis Populations and Reasons for Exclusion of Subjects

Population, N Reason, n	TMC207/BR
ITT	233
DS-TB at baseline	3
MGIT results not evaluable ^a	25
Total excluded from mITT	28
mITT	205

N = number of subjects

^a Subjects' MGIT culture results did not allow for primary efficacy evaluation; i.e., MGIT was negative at baseline and screening

Data on file, Janssen Research and Development

The majority of subjects (ITT population) were male (64.4%); median age at screening was 32.0 years (range: 18 - 68 years). Ethnic origin of subjects was mostly Asian (38.6%), Black (32.2%), or Caucasian (25.8%); others were American-Indian or Alaska native (3.4%) ([Table 34](#)). All Black subjects were enrolled at sites in South Africa.

About half of the subjects (51.9%) had cavitation in only one lung; 11.6% had cavitation in both lungs and 36.5% had no cavitation ([Table 34](#)).

Based on DST at the central laboratory, 93 subjects (39.9%) in the ITT population were infected with an MDR_{H&R}-TB strain, 44 subjects (18.9%) were infected with a Pre-XDR-TB strain, and 37 subjects (15.9%) were infected with an XDR-TB strain ([Table 34](#)). Thirteen of the 44 Pre-XDR-TB isolates (29.5%) were resistant to kanamycin and/or capreomycin (i.e., second line injectables [SLI]-Pre-XDR-TB) and 31 isolates (70.5%) were resistant to ofloxacin (i.e., fluoroquinolone [FQ]-Pre-XDR-TB). Three subjects (1.3%) had DS-TB and were withdrawn from the trial per protocol. Isolates from 56 subjects (24.0%) in the ITT population did not have confirmation of isoniazid and rifampin resistance from the central laboratory but were considered MDR based on their medical history (based on previous DST), 32 had evaluable local MGIT results and were included in the mITT population. These subjects were excluded from the subgroup analysis by extent of resistance of *M. tuberculosis* strain.

A large majority of ITT subjects (87.1%) had previously used second-line anti-TB drugs (i.e., were not newly diagnosed for MDR-TB at screening) and most subjects (85.8%) received anti-TB treatment during the Screening phase (i.e., from time of enrollment until one day before

intake of bedaquiline intake). The median (range) duration of anti-TB treatment ongoing at screening in this population was 36.0 (1 - 2639) days. Eleven subjects (4.9%) were HIV infected at screening; all had a CD4+ cell count > 300 cells/ μ L. An abnormally low albumin of at least grade 1 at baseline was observed in 18.5% of subjects. Based on medical history, 17 subjects (7.3%) reported diabetes at screening.

Demographic data and baseline disease characteristics for the mITT population were similar to those of the ITT population ([Table 34](#)). In the mITT population, no correlation was observed between the extent of resistance of the *M. tuberculosis* strain and the level of lung cavitation at baseline ([Table 35](#)).

Table 34: C209: Demographics and Baseline Disease Characteristics – ITT/mITT

Parameter Value	TMC207/BR	
	ITT N = 233	mITT N = 205
Gender, n (%)		
Female	83 (35.6)	73 (35.6)
Male	150 (64.4)	132 (64.4)
Age at screening, years		
Median (Range)	32.0 (18-68)	32.0 (18-68)
Ethnic origin, n (%)		
American-Indian or Alaska Native	8 (3.4)	6 (2.9)
Asian	90 (38.6)	84 (41.0)
Black or African-American	75 (32.2)	67 (32.7)
Caucasian/White	60 (25.8)	48 (23.4)
Lung cavitation^a, n (%)		
Cavitation in both lungs	27 (11.6)	26 (12.7)
Cavitation in one lung only	121 (51.9)	109 (53.2)
No cavitation	85 (36.5)	70 (34.1)
HIV status at screening^b, n (%)	N = 225	N = 198
Negative	214 (95.1)	188 (94.9)
Positive	11 (4.9)	10 (5.1)
Extent of resistance of <i>M. tuberculosis</i> strain, n (%)		
DS-TB	3 (1.3)	0
MDR-TB ^c	230 (98.7)	205 (100)
<i>MDR_{H&R}-TB</i>	93 (39.9)	93 (45.4)
<i>Pre-XDR-TB</i>	44 (18.9)	44 (21.5)
<i>XDR-TB</i>	37 (15.9)	36 (17.6)
Albumin grade at baseline, n (%)		
Grade 0	190 (81.5)	167 (81.5)
Grade 1	19 (8.2)	15 (7.3)
Grade 2	23 (9.9)	22 (10.7)
Grade 3	1 (0.4)	1 (0.5)

N = number of subjects with data, n = number of subjects with that result

^a Cavitation defined as the presence of at least one cavity ≥ 2 cm

^b HIV status was not available for 8 subjects in the ITT population and 7 subjects in the mITT population; the denominator was thus 225 for ITT subjects and 198 for mITT subjects

^c No confirmation of isoniazid and rifampin resistance was available from the central laboratory for 56 (24.0%) subjects in the ITT population and for 32 (15.6%) subjects in the mITT population. These subjects were considered MDR based on their medical history (based on previous DST).

Data on file, Janssen Research and Development

Table 35: C209: Extent of Resistance of *M. tuberculosis* Strain Versus Level of Cavitation – mITT

Level of Cavitation ^a at Baseline, n (%)	TMC207/BR			
	Extent of Resistance of <i>M. tuberculosis</i> Strain ^b			
	MDR _{H&R} -TB N = 93	Pre-XDR-TB N = 44	XDR-TB N = 36	All Subjects N = 173
No cavitation	30 (32.3)	11 (25.0)	15 (41.7)	56 (32.4)
Cavitation in one lung only	49 (52.7)	27 (61.4)	18 (50.0)	94 (54.3)
Cavitation in both lungs	14 (15.1)	6 (13.6)	3 (8.3)	23 (13.3)

N = number of subjects with data; n = number of subjects with that result

^a Cavitation defined as the presence of at least one cavity ≥ 2 cm

^b Extent of resistance was not available for 32 subjects in the mITT population

Data on file, Janssen Research and Development

Susceptibility testing using the agar proportion method showed that most subjects (> 82.0%) in the mITT population were infected with isolates susceptible to capreomycin and ethionamide. Susceptibility to kanamycin and ofloxacin was observed for isolates in 72.9% and 61.4% of subjects. The lowest rates of susceptibility were observed for the first-line anti-TB drugs streptomycin (19.9%), pyrazinamide (21.5%), and ethambutol (22.2%). Susceptibility to all tested anti-TB drugs with validated critical concentrations was lower among Pre-XDR and XDR isolates (Table 36).

The majority of subjects (74.5%) in the mITT population were infected with an *M. tuberculosis* strain susceptible to at least 3 of the anti-TB drugs tested based on the proportion method (only those with validated critical concentrations, i.e., isoniazid, rifampin, ethambutol, streptomycin, pyrazinamide, ethionamide, ofloxacin, kanamycin, and capreomycin); 29.1% were infected with an *M. tuberculosis* strain susceptible to at least 5 drugs.

Table 36: C209: Baseline Susceptibility to Anti-TB Drugs in Subgroups by Extent of Resistance of *M. tuberculosis* Strain and Overall – mITT

n (%) of isolates susceptible ^a to	TMC207/BR							
	MDR _{H&R} -TB		Pre-XDR-TB		XDR-TB		All Subjects	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
EMB	90	27 (30.0)	43	8 (18.6)	34	2 (5.9)	167	37 (22.2)
SM	89	24 (27.0)	43	6 (14.0)	34	3 (8.8)	166	33 (19.9)
PZA	92	26 (28.3)	44	8 (18.2)	36	3 (8.3)	172	37 (21.5)
ETH	90	79 (87.8)	43	35 (81.4)	34	24 (70.6)	167	138 (82.6)
OFL	89	89 (100)	43	13 (30.2)	34	0	166	102 (61.4)
KAN	89	89 (100)	43	32 (74.4)	34	0	166	121 (72.9)
CAP	89	89 (100)	43	34 (79.1)	34	18 (52.9)	166	141 (84.9)

N = number of subjects with data; n = number of subjects susceptible to the specified drug; EMB = ethambutol; SM = streptomycin; PZA = pyrazinamide; ETH = ethionamide; OFL = ofloxacin; KAN = kanamycin

^a Based on the agar proportion method (and the MGIT 960 system for pyrazinamide). Cycloserine was not tested due to poor reproducibility of the results.

Data on file, Janssen Research and Development

Up to the cut-off date of 29 March 2011, 30 (12.9%) subjects in the ITT population had prematurely discontinued the trial (Table 37). The main reasons for premature discontinuation were the occurrence of one or more AEs and withdrawal of consent (each reported for 8 subjects), but both AEs and withdrawal of consent accounted for less than a third of all premature discontinuations (8 of 30 subjects). Twenty subjects (8.6%) had discontinued the trial prior to Week 24 and therefore did not complete intake of bedaquiline as planned. A total of 203 subjects were ongoing in the trial at the database cut-off date. In addition, 133 (57.1%) subjects had completed the Week 36 visit, 55 (23.6%) subjects had completed the Week 48 visit, and 6 (2.6%) subjects had completed the Week 72 visit. None of the subjects had completed the trial at time of data cut-off.

Table 37: C209: Completion/Withdrawal - ITT

Trial Termination Type ^a Reason, n (%)	TMC207/BR N = 233
Completed	0
Ongoing	203 (87.1)
Discontinued	30 (12.9)
Adverse event	8 (3.4)
Subject ineligible to continue the trial	5 (2.1)
Subject lost to follow-up	2 (0.9)
Subject non-compliant	5 (2.1)
Subject withdrew consent	8 (3.4)
Other	2 (0.9)

N = number of evaluable subjects; n = number of subjects with that result

^a Using all available data up to the data cut-off date of the interim analysis.

Data on file, Janssen Research and Development

The majority of subjects in the ITT population (85.8%) received anti-TB treatment during the Screening phase. The most frequently used anti-TB drugs in the baseline BR (i.e., within the first 2 weeks of treatment) for subjects in this population were fluoroquinolones (89.3%; mainly ofloxacin: 52.4%), pyrazinamide (76.0%), aminoglycosides (71.7%; mainly kanamycin: 49.8%), and ethambutol (51.5%). Other baseline BR drugs taken by > 40% of ITT subjects were para-aminosalicylic acid (PAS)-C (46.4%) and ethionamide (42.1%).

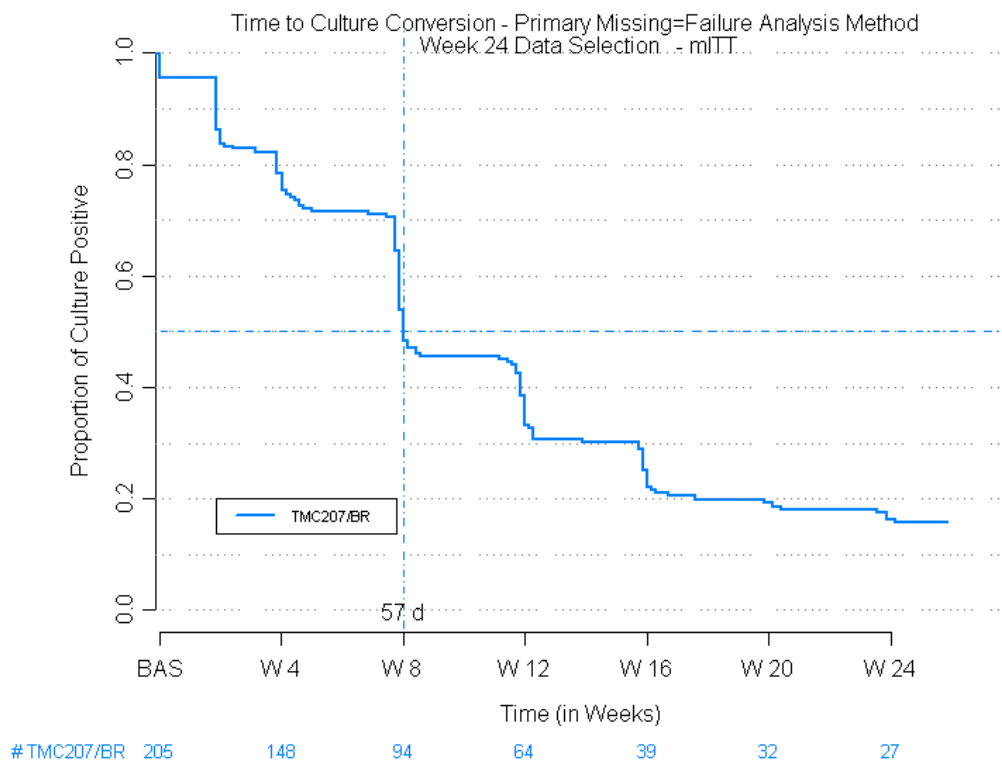
According to agar proportion method DST results (drugs with validated critical concentrations only), 52.7% of subjects in the mITT population had isolates susceptible to at least 3 drugs used in their baseline BR; 4.8% had isolates susceptible to at least 5 drugs in their baseline BR. Isolates from 8.5% of subjects were resistant to all tested drugs in their baseline BR.

5.4.3 Primary Efficacy Endpoint: Time to Culture Conversion at Week 24

The efficacy results presented here are those obtained from the interim analysis of **C209**, which was performed after all subjects had completed 24 weeks of treatment with bedaquiline (or had discontinued earlier). These results have to be interpreted keeping in mind that subjects were allowed to enroll while taking anti-TB drugs (i.e., non-newly diagnosed) and that they did not have to be AFB or culture positive at screening but within 6 months prior to screening. Subjects who were culture negative both at screening and baseline were excluded from the mITT population.

Time to culture conversion during the 24-week treatment period with bedaquiline was the primary efficacy outcome parameter for trial **C209**.

The time to culture conversion according to the primary missing = failure analysis method is shown in [Figure 29](#). Median time to culture conversion for subjects in the mITT population was 57 days.



#: number of subjects at risk (i.e., culture positive subjects ongoing in the trial at the corresponding time point)

Note: The intersection of horizontal dotted line and the TMC207 group represents the median time to sputum culture conversion.

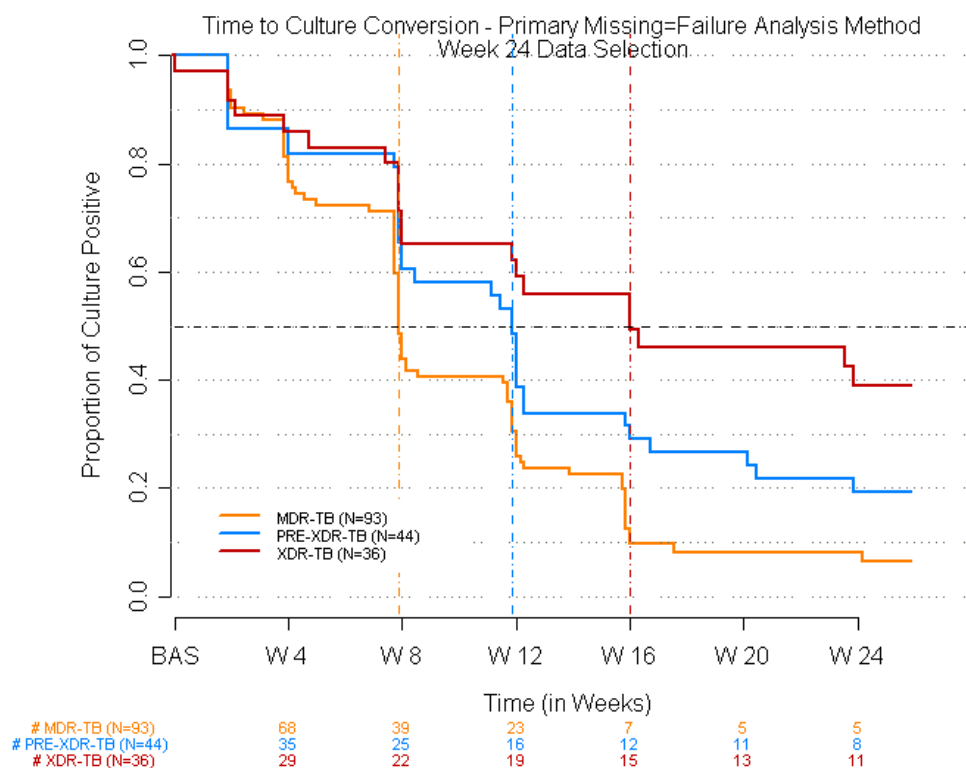
Data on file, Janssen Research and Development

Figure 29: C209: Kaplan-Meier Plot: Proportion of Culture Positive Subjects Over Time (Interim Analysis / 24-Week Data Selection, Primary Missing = Failure Analysis Method) – mITT

The results of sensitivity analyses (the end-censored method and the no overruling for discontinuation method) showed similar results.

The time to culture conversion by extent of resistance of the *M. tuberculosis* strain according to the primary missing = failure analysis method is shown in [Figure 30](#).

For subgroups by extent of resistance of the *M. tuberculosis* strain, median time to culture conversion (24-week data selection, primary missing = failure analysis method) was longer with a higher extent of resistance.



subgroup: number of subjects at risk (i.e., culture positive subjects ongoing in the trial at the corresponding time point); N: total number of subjects in the subgroup.

Note: The intersection of horizontal dotted line and each subgroup represents the median time to sputum culture conversion.

Data on file, Janssen Research and Development

Figure 30: C209: Kaplan-Meier Plot: Proportion of Culture Positive Subjects in Subgroups by Extent of Resistance of *M. tuberculosis* Strain Over Time (Interim Analysis / 24-Week Data Selection, Primary Missing = Failure Analysis Method) – mITT

5.4.4 Secondary Efficacy Endpoints

5.4.4.1 CULTURE CONVERSION RATES

The number of subjects in the mITT population with culture conversion at Week 24 and at the last available assessment time point is summarized in [Table 38](#) for both responder definitions (missing = failure, and no overruling) including subcategories for non-responders at the last available time point.

The percentage of 24-week responders according to the missing = failure response definition (with subjects who discontinued considered as non-responders, regardless of their microbiological status) was 79.5%.

At the last available assessment time point prior to 29 March 2011 (all available data selection), the percentage of responders (missing = failure) was 75.1%. Among the non-responders, 33 subjects (16.1%) never achieved culture conversion before the last assessment and 11 subjects (5.4%) discontinued while their microbiological status was 'culture converted'. Seven subjects (3.4%) experienced relapse, defined as having a confirmed positive sputum culture after prior confirmed culture conversion regardless of whether they were still on anti-TB treatment. No information on genotype was available for any of the recurrences at the time of this interim analysis; therefore, all recurrences are considered relapses.

The number of responders according to the no overruling response definition (with subjects who discontinued while their microbiological status was 'culture converted' were considered responders) was 81.5% at Week 24 and 80.5% at the last available assessment time point.

These numbers are similar to the Kaplan-Meier estimates obtained from the analysis of time to culture conversion.

Table 38: C209: Culture Conversion Rates (Interim Analysis) – mITT

Time Point Microbiological Status, n (%)	TMC207/BR N = 205	
	Missing = Failure ^a	No Overruling ^b
Week 24		
24-week responder	163 (79.5)	167 (81.5)
Last Available Time Point ^c		
Overall responder	154 (75.1)	165 (80.5)
Overall non-responder	51 (24.9)	40 (19.5)
↳ Failure to culture convert	↳ 33 (16.1)	↳ 33 (16.1)
↳ Relapse ^d	↳ 7 (3.4)	↳ 7 (3.4)
↳ Discontinued but converted	↳ 11 (5.4)	

N = number of subjects in population; n = number of subjects with that result; NA = not analyzed

^a A subject was considered responder (missing = failure) if at least 2 cultures from sputa collected at least 25 days apart were MGIT culture negative (as well as all intermediate cultures), this culture negativity was not followed by a confirmed positive MGIT culture (or a single positive sputum result after which the subject completed the trial), and the subject did not discontinue up to the time point being analyzed.

^b A subject was considered responder (no overruling) if at least 2 cultures from sputa collected at least 25 days apart were MGIT culture negative (as well as all intermediate cultures) and this culture negativity was not followed by a confirmed positive MGIT culture (or a single positive sputum result after which the subject completed or discontinued the trial) up to the time point being analyzed.

^c Using the all available data selection up to data cut-off date of 29 March 2011.

^d No information on genotype was available for any of the recurrences at the time of interim analysis; therefore, all recurrences are considered relapses. The 7 relapses occurred while on treatment in 5 subjects, while off treatment in 1 subject, and treatment status at time of relapse was unknown for 1 subject

Data on file, Janssen Research and Development

Results of a subgroup analysis by region are presented in [Table 39](#). Note all but 3 subjects were of Black or African American race in South Africa in the mITT population.

Table 39: Culture Conversion Rates at Week 24 by Region and Trial Discontinuation Before Week 24 (24-Week Data Selection) – mITT

Culture Conversion Rates	C209	
	TMC207/BR	
	N	24-week responder (missing = failure) n (%)
by Region		
Asia (other than China)	31	26 (83.9)
China	50	41 (82.0)
Eastern Europe	41	34 (82.9)
South Africa	70	51 (72.9)
South America	13	11 (84.6)
by Region, Excluding Subjects who Discontinued the Trial Before Week 24		
Asia (other than China)	30	26 (86.7)
China	50	41 (82.0)
Eastern Europe	38	34 (89.5)
South Africa	59	51 (86.4)
South America	11	11 (100)

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

5.4.4.2 TIME TO SMEAR CONVERSION AND AFB SMEAR CONVERSION RATES

Results for time to conversion when using AFB smears were similar compared to when using MGIT cultures. Median time to AFB smear conversion was 58 days for subjects the mITT population (compared to 57 days for MGIT culture conversion).

Smear conversion rates at Week 24 were somewhat lower than MGIT culture conversion rates: 70.2% and 71.2% of subjects were AFB 24-week responders according to the missing = failure and the no overruling definitions, respectively (compared to 79.5% responders with culture conversion at Week 24).

5.5 DURABILITY OF RESPONSE

This section describes the efficacy results that are currently available regarding durability of response in the Phase IIb trials. These results describe persistence of anti-mycobactericidal activity after the end of investigational treatment with bedaquiline or placebo.

To assess durability of response, comparisons were made of culture conversion rates at the end of the trial (for the completed **C208 Stage 1**) or at the last available assessment time point (for the ongoing **C208 Stage 2** and **C209**) versus conversion rates at Week 24. Durability of response was also investigated by using the overall response rates at trial end or at the last available assessment time point, based on the missing = failure response definition and including subcategories for non-responders. The overall response rates based on the no overruling response definition were also used. The ‘missing = failure’ response definition is the most conservative approach to analyze the treatment effect of bedaquiline versus placebo when added to a BR, while the ‘no overruling’ response definition more accurately reflects probable microbiological response because subjects who prematurely discontinued were considered responders if they converted.

Note that in the ongoing trials **C208 Stage 2** and **C209**, all subjects had completed the Week 72 and Week 24 visit, respectively, or had discontinued earlier. Later visits were completed by part of the population in these trials.

In **C208 Stage 2**, the Week 84 visit was completed by 104 subjects (65.0%), i.e., 53 subjects in the bedaquiline group and 51 subjects in the placebo group, and the Week 120 visit was completed by 20 subjects (12.5%), i.e., 4 subjects in the bedaquiline group and 16 subjects in the placebo group. Thirty-eight subjects (23.8%) in the ITT population had completed the trial; i.e., 18 subjects in the bedaquiline group and 20 subjects in the placebo group.

In **C209**, 133 subjects (57.1%) had completed the Week 36 visit and 6 subjects (2.6%) had completed the Week 72 visit. None of the **C209** subjects had completed the trial.

5.5.1.1 DURABILITY OF RESPONSE IN C208 STAGE 1

In the **C208 Stage 1** trial, of the 17 subjects in the bedaquiline group and the 15 subjects in the placebo group who were responders at Week 24, 11 subjects (64.7%) and 10 subjects (66.7%), respectively, were still responders at trial end. Six (35.3%) and 5 (33.3%) of the 24-week responders in the bedaquiline and placebo group, respectively, were non-responders at trial end:

- Of these 6 subjects in the bedaquiline group, 4 subjects had prematurely discontinued the trial while being culture converted and 2 subjects had experienced relapse;

- Of these 5 subjects in the placebo group, 1 subject had discontinued while being culture converted and 4 subjects had experienced relapse.

Thus, the reduction in response rate observed in the bedaquiline group is mainly caused by subjects who discontinued while being converted while the reduction in response rate in the placebo group is mainly caused by subjects who relapse.

No genotyping data were available for any of the 6 cases of recurrence because no sputum samples were provided to the central laboratory at the time of recurrence; therefore, all recurrences were considered relapses. All relapses in **Stage 1** occurred while on treatment, although for 1 of the 2 subjects in the bedaquiline group with relapse, this occurred 1 day after a BR treatment interruption of more than 2.5 months during which no anti-TB drugs were taken.

None of the subjects in either treatment group had confirmed culture conversion beyond Week 24, as all non-responders at Week 24 remained non-responders at trial end.

The total number of overall responders (missing = failure) at **C208 Stage 1** trial end was 11 subjects (52.4%) in the bedaquiline group and 10 subjects (43.5%) in the placebo group. From the non-responders, more subjects in the bedaquiline group (6 subjects, 28.6%) than in the placebo group (2 subjects, 8.7%) had discontinued while being culture converted, and fewer subjects in the bedaquiline group (2 subjects, 9.5%) had ‘failure to culture convert’ during the remaining trial conduct compared to the placebo group (7 subjects, 30.4%). When considering subjects who discontinued while being culture converted as responders (i.e., using the no overruling response definition), the percentage of overall responders at trial end was 81.0% in the bedaquiline group and 52.2% in the placebo group.

5.5.1.2 DURABILITY OF RESPONSE IN C208 STAGE 2

The Sponsor evaluated the durability of the response after Week 24 acknowledging that most of the subjects were still on BR.

In the **C208 Stage 2** trial, of the 52 subjects in the bedaquiline group and the 38 subjects in the placebo group who were responders at Week 24, 43 subjects (82.7%) and 26 subjects (68.4%), respectively, were still responders at the last available time point. In total, 9 (17.3%) and 12 (31.6%) of the 24-week responders in the bedaquiline and placebo group, respectively, were non-responders at the last available time point:

- Of these 9 subjects in the bedaquiline group, 6 subjects had prematurely discontinued the trial while being culture converted at 24 weeks and 3 subjects had experienced relapse;
- Of these 12 subjects in the placebo group, 5 subjects had discontinued while being culture converted at 24 weeks and 7 subjects had experienced relapse.

This suggests the reduction in response rate observed in the bedaquiline group is mainly caused by subjects who discontinue while being converted while the loss of response in the placebo group is mainly caused by subjects who relapse. Furthermore, the loss of response in the placebo group appeared to have occurred mainly after Week 72.

In addition, 3 subjects experienced relapse, either before (1 subject in the bedaquiline group) or after Week 24 (1 subject in either group) and they were defined non-responders at Week 24. Thus, in total 5 subjects (7.6%) in the bedaquiline group and 8 subjects (12.1%) in the placebo group had experienced relapse at the efficacy data cut-off date. All recurrences are considered relapses, because no information on genotype was available for any of the recurrences at the time of the interim analysis. In addition, relapse occurred while on treatment for all 5 subjects in the bedaquiline group and for 6 subjects in the placebo group (1 of whom relapsed after a period of nearly 3 months with only 2 drugs in the BR); relapse occurred while off treatment for 1 placebo subject and treatment status at time of relapse was unknown for 1 other placebo subject.

Culture conversion beyond Week 24 occurred less frequently in the bedaquiline group (1 responder at the last available time point of 14 subjects who were 24-week non-responder, i.e., 7.1%) than in the placebo group (5 responders at the last available time point of 28 subjects who were 24-week non-responder, i.e., 17.9%).

In total, 44 subjects (66.7%) in the bedaquiline group and 31 subjects (47.0%) in the placebo group were considered overall responders (missing = failure) at the last available time point up to the efficacy data cut-off date for **C208 Stage 2** ([Table 40](#)). Among the non-responders, fewer subjects in the bedaquiline group (8 subjects, 12.1%) than in the placebo group (15 subjects, 22.7%) failed to culture convert up to the last available assessment. Fewer subjects in the bedaquiline group had prematurely discontinued while culture converted (9 subjects [13.6%] versus 12 subjects [18.2%] in the placebo group). When considering subjects who discontinued while being culture converted as responders (i.e.; using the no overruling response definition),

the percentage of overall responders at the time of interim analysis was 80.3% in the bedaquiline group and 65.2% in the placebo group.

When looking only at the 29 subjects who had completed **C208 Stage 2** at the efficacy data cut-off date, all 15 subjects (100%) in the bedaquiline group were responders at trial end compared to 8 of 14 completers (57.1%) in the placebo group (Table 40). Of the 6 non-responders at trial end in the placebo group, 5 had experienced relapse and 1 subject failed to convert. In addition, longer overall treatment was observed on average for completers in the placebo group (> 750 days in 10/14 subjects) compared to completers in the bedaquiline group (> 750 days in 4/15 subjects), suggesting that the higher response rate for completers in the latter group is not caused by a longer BR treatment duration.

Table 40: C208 Stage 2: Microbiological Status at Last Available Time Point for all Subjects and for Completers – mITT

Microbiological Status ^a , n (%)	All Stage 2 Subjects		Stage 2 Completers	
	TMC207/BR N = 66	Placebo/BR N = 66	TMC207/BR N = 15	Placebo/BR N = 14
Overall responder (missing = failure)	44 (66.7)	31 (47.0)	15 (100)	8 (57.1)
Overall non-responder (missing = failure)	22 (33.3)	35 (53.0)	0	6 (42.9)
↳ Failure to convert	↳ 8 (12.1)	↳ 15 (22.7)	↳ 0	↳ 1 (7.1)
↳ Relapse ^b	↳ 5 (7.6)	↳ 8 (12.1)	↳ 0	↳ 5 (35.7)
↳ Discontinued but converted	↳ 9 (13.6)	↳ 12 (18.2)	↳ NA	↳ NA
Overall responder (no overruling)	53 (80.3)	43 (65.2)	15 (100)	8 (57.1)

N = number of subjects with data; n = number of subjects with that result; NA: not applicable

^a Using the all available data selection up to efficacy data cut-off date of 10 May 2011. For completers, this time point corresponds to trial end.

^b No information on genotype was available for any of the recurrences at the time of interim analysis; therefore, all recurrences are considered relapses.

Data on file, Janssen Research and Development

5.5.1.3 DURABILITY OF RESPONSE IN C209

The amount of data beyond Week 24 is limited, but the available data suggest that response was durable.

5.6 DRUG SUSCEPTIBILITY TESTING

This section describes the drug susceptibility testing data of the Phase IIb trials. The results are from the ‘all available data selection’ (up to the cut-off dates of the interim analyses for **C208 Stage 2** and **C209**, which includes all available postbaseline DST results), using the

‘no overruling’ response definition (which more accurately reflects probable microbiological response compared to the ‘missing = failure’ response definition as subjects who discontinued but converted are considered responders in the ‘no overruling’ response definition).

5.6.1.1 DRUG SUSCEPTIBILITY TESTING FOR ANTI-TB DRUGS

5.6.1.1.1 Response Rates by Baseline Susceptibility to Tested anti-TB Drugs

In order to explore a possible association between baseline DST results and microbiological response, culture conversion rates were determined for subgroups by DST-related parameters (extent of resistance of *M. tuberculosis* strain at baseline, pyrazinamide susceptibility at baseline, number of drugs active in vitro in the subjects’ baseline BR) in trials **C208 Stage 2** and **C209**.

Note that only DST results from drugs with validated critical concentrations were taken into account. As a consequence of this methodology, results should be interpreted with some caution as subjects may have taken BR drugs for which no validated critical concentration is available.

Also note that because the focus is on the Week 24 time point (for which data are available for all Phase IIb trials), the response rates reflect the bactericidal activity of the regimen and not the sterilizing activity, which is evaluated by looking at durable cure after treatment free follow-up.

For subgroups by extent of resistance of *M. tuberculosis* strain at baseline, higher culture conversion rates at Week 24 were noted for subjects with isolates with a lower degree of resistance. In **C208 Stage 2**, response rates at Week 24 (no overruling response definition) were higher in subjects with MDR_{H&R}-TB compared to Pre-XDR-TB in both treatment groups. Similar results were obtained from **C209**, with a higher 24-week response rate (no overruling) in MDR_{H&R}-TB subjects than in Pre-XDR-TB subjects and also a higher rate in Pre-XDR-TB subjects than in XDR-TB subjects.

When looking at subcategories for Pre-XDR-TB subjects by resistance drug class (i.e., isolates resistant to either second-line injectables [SLI-Pre-XDR-TB] or to fluoroquinolones [FQ-Pre-XDR-TB]), response rates at Week 24 were similar in SLI-Pre-XDR-TB subjects and FQ-Pre-XDR-TB subjects in **C208 Stage 2**, both in the bedaquiline and placebo treatment group. Nonetheless, response rates were higher in the bedaquiline group than in the placebo group in both Pre-XDR-TB subcategories. In **C209**, a higher percentage of subjects with FQ-Pre-XDR-TB were 24-week responder (no overruling) compared to subjects with SLI-Pre-XDR-TB. At

present, there is little published literature describing a potential difference in outcome comparing these 2 Pre-XDR-TB subtypes.

Pyrazinamide, when used as part of a regimen to treat DS-TB, is felt to significantly reduce the number of subjects who relapse after sputum conversion based on pyrazinamides sterilizing activity⁷⁵. To explore the effect of pyrazinamide on MDR-TB treatment response, pyrazinamide susceptibility at baseline was included as a subgroup category in trials **C208 Stage 2** and **C209**.

Subgroups by baseline pyrazinamide susceptibility showed higher conversion rates at Week 24 for subjects whose isolates were susceptible to pyrazinamide at baseline compared to subjects whose isolates were resistant to pyrazinamide at baseline, both in bedaquiline and placebo treatment groups in **C208 Stage 2** and in **C209**. In addition, response rates were higher in the bedaquiline group compared to the placebo group for both pyrazinamide susceptibility subgroups (i.e., pyrazinamide resistant and pyrazinamide susceptible).

For subgroups by number of active drugs (based on in vitro DST, drugs with validated critical concentrations only) in the baseline BR, conversion rates were generally higher for subjects with 3 or more active drugs in their baseline BR than for subjects with < 3 active drugs in the baseline BR. This was observed both in the bedaquiline and placebo treatment groups in **C208 Stage 2** and **C209**. In addition, response rates were generally higher in the bedaquiline group compared to the placebo group. Of note, the fluoroquinolones most often used in the **C208** were different compared to **C209**. However, in this analysis subcategorization of fluoroquinolones based on presumed potency was not done.

In summary, these trends suggest that baseline susceptibility to drugs used in the BR is an important prognostic factor for culture conversion by Week 24.

5.6.1.1.2 Development of Resistance to Anti-TB Drugs During Treatment

Resistance to a certain drug was considered acquired if the subject's isolate was susceptible to the drug at baseline and resistant to the drug at the considered time point. This analysis did not take into account the BR the subject was receiving. Subjects with missing baseline DST results were excluded from this analysis to determine acquired resistance.

In **C208 Stage 1** and **C208 Stage 2**, fewer paired DST results were available for bedaquiline subjects compared to placebo subjects: 1 and 10 mITT subjects in the bedaquiline treatment

groups versus 10 and 27 mITT subjects in the placebo treatment groups of these trials, respectively. In **C209**, paired DST results were available for 17 mITT subjects.

Of the subjects in the bedaquiline treatment groups with paired results, isolates from 1 of 1 subject with paired isolates in **C208 Stage 1**, from 2 of 10 subjects in **C208 Stage 2**, and from 7 of 17 subjects in **C209** acquired resistance to at least 1 of the tested anti-TB drugs (agar proportion method, validated critical concentrations only) during the trial. In the placebo treatment groups, isolates from 5 of 10 **Stage 1** subjects with paired isolates and from 14 of 27 **Stage 2** subjects developed resistance to at least one tested drug.

In the Phase IIb trials, isolates most frequently developed resistance to ofloxacin or ethambutol. Emerging resistance to kanamycin or capreomycin was observed in isolates from at most 1 subject per treatment group and per trial. For the majority of subjects, the anti-TB drugs for which subject's isolates became resistant during the trial were used in the subject's BR.

During **C208 Stage 2**, isolates from bedaquiline subjects appeared less likely to develop a Pre-XDR or XDR resistance pattern compared to placebo subjects: none of the isolates from the bedaquiline subjects and isolates from 7 of the placebo subjects developed a Pre-XDR or XDR resistance profile. During **C208 Stage 1**, isolates from the single subject with paired results in the bedaquiline group and 4 subjects in the placebo group developed a Pre-XDR or XDR resistance profile. During **C209**, 3 subjects with Pre-XDR at baseline developed XDR during the trial.

5.6.1.2 DRUG SUSCEPTIBILITY TESTING FOR BEDAQUILINE

In all Phase II trials, susceptibility of bacterial isolates of *M. tuberculosis* to bedaquiline was tested on 7H11 agar solid medium at different concentrations (0.0075 µg/mL, 0.015 µg/mL, 0.03 µg/mL, 0.06 µg/mL, 0.12 µg/mL, 0.24 µg/mL, and 0.48 µg/mL) to determine a MIC for each isolate. In addition, the MIC of bedaquiline was determined in 7H9 liquid medium using the REMA method. Only DST results for bedaquiline MICs determined on solid medium (7H11 agar) are discussed, as the major conclusions from the agar and REMA methods were similar.

In **C208 Stage 1 and Stage 2**, and **C209**, baseline results for bedaquiline MIC determination using the agar method showed that overall, the MIC₅₀ was 0.06 µg/mL and the MIC₉₀ was 0.12 µg/mL.

5.6.1.2.1 Response Rates by Bedaquiline MIC at Baseline

Culture conversion rates in the Phase IIb trials were evaluated by baseline bedaquiline MIC values from the agar method. No clear trend was noted suggesting a correlation between baseline bedaquiline MIC values and response rate in any of the Phase IIb trials.

5.6.1.2.2 Changes in Bedaquiline MICs During Treatment

As no critical concentrations for bedaquiline were available to determine resistance/susceptibility at the time of data cut-off dates for the interim analyses of the Phase IIb trials, DST results for bedaquiline were presented as the MIC at each time point (agar method). However, the clinical relevance of a 4-fold increase in bedaquiline MIC has not been established.

Paired bedaquiline MIC (agar) results were available for 1, 11, and 16 bedaquiline subjects in the mITT populations of **C208 Stage 1**, **C208 Stage 2**, and **C209**, respectively.

Based on agar method results, a bedaquiline MIC increase of \geq a 4-fold at the last available postbaseline time point was observed in isolates from the single bedaquiline subject with data in **C208 Stage 1**, in isolates from 2 of 11 bedaquiline subjects with data in **C208 Stage 2**, and in isolates from 10 of 16 subjects with data in **C209**.

In **C208 Stage 1**, the subject in the bedaquiline treatment group had a 4-fold increase in bedaquiline MIC (as assessed by agar method, and not confirmed by REMA method) at Week 8 and was infected with an MDR_{H&R}-TB strain at baseline. The subject's isolates additionally developed resistance to other anti-TB drugs, and the subject was a non-responder at Week 8 and had relapse at trial end.

In **C208 Stage 2**, both subjects in the bedaquiline treatment group with a 4-fold increase in bedaquiline MIC (agar) compared to baseline were infected with a Pre-XDR-TB strain at baseline. For one of these subjects, the 4-fold increase was noted at Week 8 and the subject was a responder at the last available time point. Isolates from the second bedaquiline subject who experienced a 4-fold increase in bedaquiline MIC at Week 24, additionally developed resistance

to other anti-TB drugs, and the subject had failed to culture convert at the last available assessment time point.

In **C209**, of the 10 subjects with an at least a 4-fold increase in bedaquiline MIC (agar) compared to baseline, 6 were infected with an XDR strain, 3 with a Pre-XDR strain, and 1 with an MDR_{H&R} strain (genotyping studies are planned to confirm that baseline and post-baseline samples are identical). None of these isolates with at least a 4-fold increases in MIC was shown to have mutations in the *atpE* gene. Isolates from 4 of these 10 subjects had developed resistance to other anti-TB drugs (based on agar proportion method and for drugs with validated critical concentrations only); 3 of them failed to culture convert and 1 had relapse. In the remaining 6 subjects, 4 failed to culture convert and 2 subjects were responders at the last available assessment time point.

5.6.1.2.3 Evaluation of Possible Cross-Resistance Between Bedaquiline and Other Anti-TB Drugs

Possible cross-resistance between bedaquiline and other anti-TB drugs was evaluated in the Phase IIb trials by looking at:

- baseline resistance to anti-TB drugs by baseline bedaquiline MICs;
- acquired resistance to anti-TB drugs by baseline bedaquiline MICs;
- acquired resistance to anti-TB drugs in subjects whose isolates had at least a 4-fold increase in bedaquiline MIC.

No signs of cross-resistance with bedaquiline were observed in any of the Phase IIb trials when considering only the anti-TB drugs for which critical concentrations are available.

5.6.1.2.4 Conclusions for Susceptibility to Bedaquiline

Mycobacterial resistance mechanisms that affect bedaquiline include modification of the *atpE* target gene, the gene encoding a protein of the F₀ subunit of ATP synthase. Such target-based resistance mutations were observed in in vitro experiments, but not in a limited number of strains isolated from clinical trials. Overall, MIC increases for bedaquiline were almost exclusively seen in Pre-XDR and XDR-TB patients

Breakpoint analysis has been performed based on evaluation of microbial populations and correlation with microbiologic outcome from the pivotal **C208** trial and the **C209** trial. Data to support breakpoint selection included the in vitro susceptibility of preclinical and clinical *M. tuberculosis* isolates to bedaquiline and microbiologic outcomes demonstrating favorable culture conversion rates for pathogens with bedaquiline MICs ≤ 0.5 $\mu\text{g/mL}$ when tested by 7H11 agar method. There were no *M. tuberculosis* preclinical isolates with bedaquiline MIC > 0.5 $\mu\text{g/mL}$ when tested by the 7H11 agar method. Isolates of *M. tuberculosis* with bedaquiline MIC (agar) > 0.5 $\mu\text{g/mL}$ were isolated at baseline from only 1 subject. Because of the lack of clinical experience with isolates of *M. tuberculosis* with MICs > 0.5 $\mu\text{g/mL}$, a susceptible only breakpoint of ≤ 0.5 $\mu\text{g/mL}$ is proposed for the 7H11 agar method.

Similarly, there was only 1 subject from whom *M. tuberculosis* with bedaquiline REMA MIC > 0.25 $\mu\text{g/mL}$ was isolated at baseline. Therefore, a susceptible only breakpoint of ≤ 0.25 $\mu\text{g/mL}$ is proposed for the REMA method (Table 41). The breakpoints for both 7H11 agar and REMA MICs are below the average concentrations achievable in humans following administration of 400 mg q.d. of bedaquiline for 2 weeks followed by 200 mg t.i.w. for 22 weeks.

Table 41: Proposed MIC Interpretive Criteria for TMC207

Pathogen	TMC207 MIC ($\mu\text{g/mL}$)	
	7H11 Agar	REMA (7H9 broth)
	Susceptible Only (S)	Susceptible Only (S)
<i>M. tuberculosis</i> ^a	≤ 0.5	≤ 0.25

^a Note that this applies to all MDR *M. tuberculosis* resistance subtypes.

Data on file, Janssen Research and Development

Note that a report of “Susceptible Only” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. Isolates with bedaquiline MICs above the susceptible breakpoint may not indicate the presence of a resistance mechanism. The MIC of the isolate in the non-susceptible range may be within the previously recognized wild-type distribution of susceptibility results; however, there is limited experience with these isolates in clinical trials.

5.6.2 Pharmacokinetic/Pharmacodynamic Relationships for Efficacy Parameters

This section describes the pharmacokinetic/pharmacodynamic relationships for efficacy data in the Phase IIb trials.

Based on **C208 Stage 2** data, the proposed susceptibility breakpoints as determined by the 7H11 agar and REMA assays are below the mean average plasma concentration over the dosing interval (C_{AVG}) observed in subjects following oral administration of 400 mg q.d. of bedaquiline for 2 weeks (mean C_{AVG} = 1.37 $\mu\text{g/ml}$) followed by 200 mg t.i.w. for 22 weeks (mean C_{AVG} = 0.58 $\mu\text{g/ml}$). Protein binding of bedaquiline is > 99.9%, thus the free drug concentration of bedaquiline is less than the bedaquiline MIC_{90} of 0.12 $\mu\text{g/ml}$ derived from all clinical trial MDR-TB isolates (i.e., the overall bedaquiline MIC_{90}). The apparent paradox of superior clinical efficacy when bedaquiline was added to BR in the trial, despite free drug concentrations less than the overall bedaquiline MIC_{90} , supports that plasma concentrations did not correlate with clinical efficacy in the Phase IIb trials with the proposed therapeutic regimen. This paradox was also seen in a mouse model of TB infection in which a dose response was observed following bedaquiline monotherapy despite very low free bedaquiline drug concentrations. These results are further supported by the PK/PD analyses of the Phase IIb trials in which no relationship was seen between exposure to bedaquiline and culture conversion rates in subjects receiving bedaquiline plus BR.

In **Stage 1** of the **C208** trial, no differences in exposure to bedaquiline and M2 in plasma or sputum were observed at both Weeks 2 and 8 between subjects with and without culture conversion.

In **Stage 2** of the **C208** trial, no clear relationship was observed between bedaquiline plasma $\text{AUC}_{24\text{h}}$ and time to culture conversion and culture conversion rates (no overruling for discontinuation method) for both the 24-Week data selection and the all available data selection of the **Stage 2** interim analysis. There was also no clear relationship between culture conversion rates and bedaquiline $\text{AUC}_{24\text{h}}$ quartiles or $\text{AUC}_{24\text{h}}/\text{MIC}$ quartiles (using agar method to determine bedaquiline MIC).

In the **C209** trial, no clear relationship was observed between bedaquiline C_{AVG} and C_{AVG}/MIC values in plasma (using agar method to determine bedaquiline MIC) and the corresponding times to culture conversion (no overruling for discontinuation method, 24-week data selection). At Week 24, somewhat higher conversion rates were observed in higher C_{AVG} quartiles compared to lower C_{AVG} quartiles. This difference appeared to be mainly due to lower response rates in Pre-XDR- and XDR-TB subjects with lower bedaquiline C_{avg} values, although the number of subjects per quartile in these subgroups was small (5 to 17 subjects).

5.7 EFFICACY CONCLUSIONS

The efficacy of bedaquiline for the treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* as part of combination therapy in adults is based on data from:

- One active-controlled, randomized proof-of-principle Phase IIa trial (**C202**) in DS-TB subjects, that evaluated the antimycobacterial activity of monotherapy with bedaquiline for 7 days in 75 subjects with DS-TB infection of whom 45 subjects received bedaquiline monotherapy (the other subjects received monotherapy with either rifampin or isoniazid for 7 days). This trial has been completed;
- Two independent consecutive stages in a placebo-controlled, double-blind, randomized Phase IIb trial in newly diagnosed MDR-TB subjects (including subjects infected with Pre-XDR strains):
 - **C208 Stage 1** (exploratory) including 47 subjects of whom 23 subjects received bedaquiline and 24 subjects received placebo up to 8 weeks in combination with a standardized BR for MDR-TB. **C208 Stage 1** has been completed, and
 - **C208 Stage 2** (pivotal) including 160 subjects of whom 79 subjects received bedaquiline and 81 subjects received placebo up to 24 weeks in combination with a standardized BR for MDR-TB. The 24-week treatment period with bedaquiline of **C208 Stage 2** has been completed and the 96-week follow-up period is ongoing; all subjects have reached at least the Week 72 visit of the trial or discontinued earlier; and
- One single-arm, open-label Phase IIb trial (**C209**) in 233 subjects with newly diagnosed or treatment-experienced MDR-TB infection who received bedaquiline up to 24 weeks in combination with a individualized BR for MDR-TB. Subjects with XDR-TB infection were

allowed to enter the **C209** trial, provided they had at least 3 drugs in their anti-TB regimen to which their *M. tuberculosis* isolate was likely to be susceptible. The 24-week treatment period with bedaquiline of the **C209** trial has been completed and the 96-week follow-up period of this trial is ongoing.

In the Phase IIb trials, bedaquiline was dosed as 400 mg q.d. for the first 2 weeks and as 200 mg t.i.w. for the following 6 weeks in **Stage 1** of the **C208** trial and for 22 weeks in **Stage 2** of the **C208** trial and in the **C209** trial. After the end of bedaquiline (or placebo) intake, the BR was continued during the BR treatment period until a total of 18 to 24 months of therapy was reached (or until at least 12 months of BR therapy was given after the first confirmed negative culture).

The results of **Stage 2** (performed with the proposed 24-week treatment duration with bedaquiline) of the placebo-controlled, double-blind Phase IIb trial **C208** provide the pivotal data for the treatment of MDR-TB with bedaquiline in combination with a BR in adults. The single-arm, open-label Phase IIb trial **C209** (also with the proposed 24-week treatment duration with bedaquiline) provides supporting data.

The subject population in **C208 Stage 2** was generally well-balanced across the bedaquiline and placebo treatment groups. Minor differences between treatment groups were observed with fewer subjects in the bedaquiline group who were HIV positive (10.1% versus 19.8% in the placebo group) and more subjects who had normal albumin levels at baseline (59.5% versus 44.4% in the placebo group). Additionally, isolates of more subjects in the bedaquiline group were resistant to pyrazinamide or to ethambutol at baseline compared to the placebo group. Based on agar proportion DST of anti-TB drugs used in subjects' baseline BR, isolates from 75.9% of subjects in the bedaquiline group and from 80.4% of subjects in the placebo group in the mITT population were susceptible to at least 3 of the drugs used in their baseline BR. The use of drugs in the BR was similar in the bedaquiline and placebo treatment groups.

The **C208** trial was designed to demonstrate superiority in the antibacterial activity of bedaquiline compared to placebo when added to a preferred 5-drug anti-MDR-TB BR. The primary efficacy endpoint in the Phase IIb trials was time to sputum culture conversion, which was determined at the end of the investigational treatment period (i.e., Week 8 for **Stage 1** of the **C208** trial and Week 24 for **Stage 2** of the **C208** trial and for the **C209** trial). This microbiology

endpoint is based on the qualitative assessment of mycobacterial growth in MGIT using spot sputum samples and is a surrogate marker for clinical outcome.

After 24 weeks of MDR-TB treatment, time to sputum culture conversion (the primary efficacy endpoint) was significantly shorter with addition of bedaquiline compared to placebo: median time to culture conversion according to the primary analysis method and using the 24-week data selection in the interim analysis was 73 days in the bedaquiline versus 125 days in the placebo group. Similar results were obtained using this analysis method for the ITT population as well as according to two sensitivity analysis methods ('end-censored missing = failure' and 'no overruling for discontinuation' method) for the mITT population (Table 42).

In the interim analysis as well as in the primary Week 24 efficacy analysis of **C208 Stage 2**, a Cox proportional hazards model adjusting for lung cavitation and pooled center showed a statistically significant difference in time to culture conversion between the treatment groups ($p < 0.0001$) in favor of bedaquiline. In both analyses, an identical number of subjects had culture conversion at Week 24 (i.e., 24-week responders [missing = failure]): 78.8% in the bedaquiline group and 57.6% in the placebo group (Table 42), which was statistically significantly different ($p = 0.008$) based on a logistic regression model with only treatment as covariate.

Table 42: C208 Stage 1, C208 Stage 2 and C209: Median Time to MGIT Culture Conversion and Culture Conversion Rates at Week 24 – mITT

	C208 Stage 1		C208 Stage 2		C209
	TMC207/BR N = 21	Placebo/BR N = 23	TMC207/BR N = 66	Placebo/BR N = 66	TMC207/BR N = 205
Median Time to MGIT Culture Conversion					
<i>Analysis Method</i>					
Primary missing = failure analysis	70 days	126 days	73 days	125 days	57 days
End-censored missing = failure	78 days	129 days	84 days	127 days	57 days
No overruling for discontinuation	NA	NA	72 days	99 days	57 days
Culture Conversion Rates					
Microbiological Status at Week 24, n (%)					
24-week responder (missing = failure)	17 (81.0)	15 (65.2)	52 (78.8)	38 (57.6)	163 (79.5)
24-week responder (no overruling)	19 (90.5)	16 (69.6)	53 (80.3)	43 (65.2)	167 (81.5)

N = number of evaluable subjects; n = number of subjects with that result; NA = not analyzed.

The efficacy results of trial **C208 Stage 2** were robust with consistently better results in the bedaquiline treatment group compared to the placebo treatment group for all microbiological endpoints (except for a secondary endpoint, i.e., change in log₁₀ CFU counts, which was studied

in a subset of subjects) and all different sensitivity analyses. In addition, the 24-week culture conversion rate observed in the placebo group of **C208 Stage 2** (57.6% [missing = failure]) was in line with overall success rates of approximately 60% for new cases of MDR-TB that are reported in the literature².

The superior treatment effect of bedaquiline in **C208 Stage 2** was supported by results from **C208 Stage 1** with a statistically significantly shorter time to culture conversion when using 24-week data ($p = 0.0022$) and higher conversion rates at Week 24 compared to placebo ([Table 42](#)). Therefore, both **Stage 1** and **Stage 2** of the **C208** trial met the primary objective of demonstrating superiority in the antibacterial activity of bedaquiline compared to placebo.

Efficacy results from the **C209** trial were also generally consistent with those of **C208 Stage 2**. In **C209**, a somewhat shorter median time to culture conversion was observed, likely reflecting the fact that most subjects were already receiving anti-TB treatment at screening ([Table 42](#)). The culture conversion rates observed at Week 24 in the **C209** trial were comparable to those of the bedaquiline groups of **C208 Stage 1** and **C208 Stage 2** (approximately 80%).

A somewhat lower response rate has been observed in South Africa in both **C208 Stage 2** and **C209**, where the majority of recruited subjects identified themselves as being Black or of mixed origin. This difference in response rate can likely be explained by a higher number of trial discontinuations before Week 24 in South Africa compared to the other regions, since similar conversion rates were observed across regions among subjects who completed the 24-week bedaquiline treatment period ([Table 30](#)). In addition, in the **C208** trial the incremental benefit of the addition of bedaquiline to the background regimen in South Africa (i.e. a 15.9% higher culture conversion rate at week 24) was similar to treatment difference observed in other regions.

Other secondary endpoints in **C208 Stage 2** also indicated better results with bedaquiline in combination with the preferred BR compared to placebo. When using AFB smear results, time to smear conversion using 24-week data was significantly shorter in the bedaquiline group compared to the placebo group ($p = 0.0383$) and more bedaquiline than placebo subjects had smear conversion at Week 24 (78.8% versus 62.1%).

Susceptibility testing of anti-TB drugs with validated critical concentrations suggested that isolates from subjects treated with bedaquiline, which overall had more baseline resistance to

background drugs, had a lower chance of developing resistance because more subjects treated with bedaquiline converted compared to those treated with placebo. During **C208 Stage 2**, isolates from bedaquiline subjects were less likely to develop a Pre-XDR or XDR resistance pattern compared to placebo subjects. In addition, patients with a Pre-XDR or XDR resistance pattern at baseline were more likely to develop resistance to bedaquiline. No cross-resistance was observed between bedaquiline and anti-TB drugs for which critical concentrations are available.

Although it is premature to establish a critical concentrations for bedaquiline, bedaquiline has shown activity against *M. tuberculosis* with MIC values for drug sensitive as well as drug resistant strains (MDR-, Pre-XDR-, XDR- strains) in the range of 0.008-0.5 µg/mL (agar method). Because of the lack of sufficient clinical experience with isolates of *M. tuberculosis* with bedaquiline MIC > 0.5 µg/mL, a “Susceptible Only” breakpoint of ≤ 0.5 µg/mL (agar) is proposed.

Pharmacokinetic/pharmacodynamic analyses of the Phase IIb trials showed no clear correlation between bedaquiline exposure and time to culture conversion or culture conversion rates.

In conclusion, acknowledging the ongoing status of the Phase IIb trials, the addition of bedaquiline to a 5-drug MDR-TB treatment regimen for 24 weeks resulted in significantly shorter time to conversion, a significantly higher proportion of culture conversion and a lower chance of developing resistance compared to placebo. Importantly, although long-term outcome results with regard to sterilizing activity are currently limited, the improved anti-mycobacterial response at 24 weeks appears durable based on the interim analysis utilizing all available data from these ongoing trials when all subjects had completed Week 72 or discontinued earlier. In general, the efficacy results from trial **C209** are supportive of the results that the addition of bedaquiline to a background regimen improves culture conversion at 24 weeks.

6 CLINICAL SAFETY

The safety and tolerability of bedaquiline for the treatment of pulmonary MDR-TB in adult patients as part of combination therapy is supported by the safety data from 14 trials: 11 completed Phase I trials in non-TB-infected subjects, including the thorough QT trial **TBC1003**, and 3 Phase II trials in TB-infected subjects (1 completed Phase IIa **C202** and 2 completed Phase

I Ib trials **C208 Stage 1** and **2** [1 subject still in rollover] and **C209**). A pooling of the 2 Phase I Ib trials (controlled data in **C208** and uncontrolled data in **C209**) was performed to increase the likelihood of detecting infrequent events due to the higher number of subjects per pooled treatment group and to increase the sample size for subgroup analyses. The Phase I Ib pooled analysis consisted of 2 parts: pooling of the controlled data including data from **C208 Stage 1** and **Stage 2**, and pooling of controlled + uncontrolled data including data from **C208 Stage 1**, **C208 Stage 2**, and **C209**. To complement the safety analysis, information on deaths will be presented up to the cut-off date 15 July 2012, as analyzed and submitted in the Safety Update Report, for trials **C208 Stage 2** and trial **C209**.

6.1 SAFETY AND TOLERABILITY OF BEDAQUILINE IN THE THOROUGH QT TRIAL IN HEALTHY SUBJECTS (TMC207TBC1003)

TBC1003 was a double-blind, single-dose trial in 88 healthy subjects to evaluate the effect of a single supratherapeutic (800 mg) dose bedaquiline on the QT/QTc interval. A total of 44 subjects received bedaquiline.

A schematic overview of the trial is provided in [Figure 31](#).

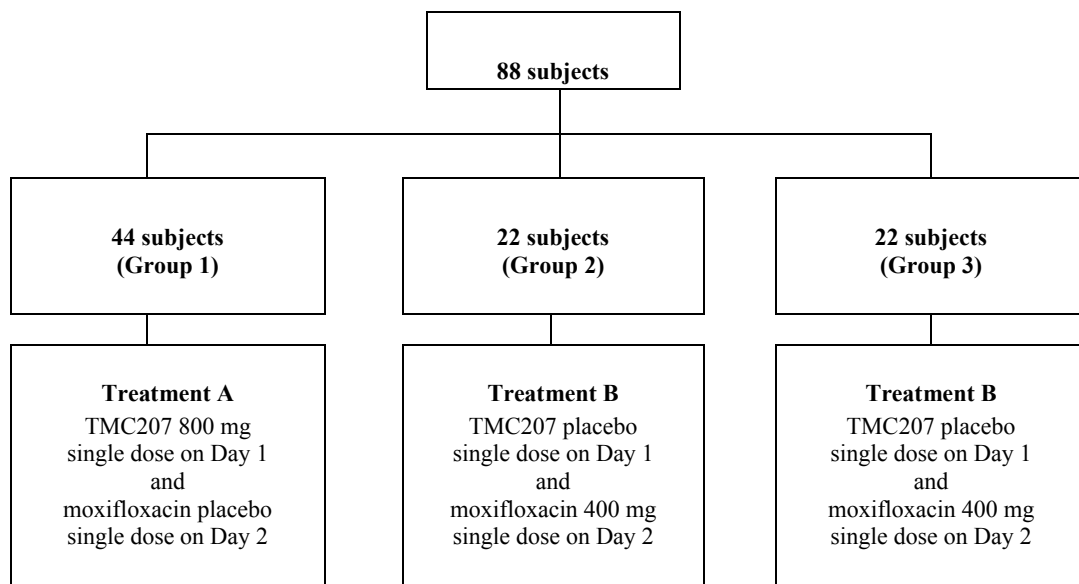


Figure 31: Schematic Overview of Trial TMC207TBC1003

6.1.1 Adverse Events

In this single-dose trial of 800 mg bedaquiline, the most frequently (> 1 subject) reported AEs were nausea, dizziness, and headache in 2 (4.5%) subjects each. During the placebo_{TMC} phase, 1 subject reported dizziness and 1 subject reported headache. Adverse events considered at least possibly related to bedaquiline by the investigator were reported in 4 (9.1%) subjects for bedaquiline, 2 (4.5%) subjects for placebo_{TMC}, 2 (4.5%) subjects for moxifloxacin, and 5 (11.4%) subjects for placebo_{MOX}.

6.1.2 Deaths, Other Serious Adverse Events and Adverse Events Leading to Discontinuation

No deaths or AEs leading to trial discontinuation were reported during the trial.

Two (2.3%) subjects in the trial had a SAE after receiving bedaquiline (Treatment A): one subject had grade 3 headache during the bedaquiline treatment phase and one subject had grade 1 anxiety during follow-up. Both subjects were hospitalized due to the event. Headache was considered possibly related to bedaquiline and doubtfully related to placebo_{MOX} by the investigator. Anxiety was considered doubtfully related to bedaquiline and not related to placebo_{MOX} by the investigator. Concomitant AEs for the subject with the SAE anxiety were palpitations, noncardiac chest pain, and pain.

No other SAEs or AEs of at least grade 3 were reported.

6.1.3 Clinical Laboratory Tests

In the **TMC207TBC1003** trial, all graded treatment-emergent laboratory abnormalities were grade 1 or 2. No graded treatment-emergent laboratory abnormalities were observed following bedaquiline administration.

Two subjects (both Treatment B, i.e., after moxifloxacin administration) each had 2 laboratory abnormalities that were reported as an AE, i.e., blood creatine phosphokinase isoenzym (CPK) increased and blood creatine phosphokinase muscle-brain isoenzym (CPK-MB) increased. These occurred during follow-up.

6.1.4 Cardiovascular Safety (Electrocardiogram)

Holter ECG monitoring was performed continuously for 72 h (3 x 24 h) for each subject on Day -1 (i.e., baseline), Day 1, and Day 2 of Treatments A and B. The largest upper limit of the 90% CIs of the differences between bedaquiline and placebo in time-matched changes from baseline in QTcF was observed 16 h after bedaquiline intake (mean difference: 5.19 ms, 90% confidence interval [CI]: [1.46, 8.92]). This value was below the threshold of 10 ms, indicating that this thorough QT/QTc trial was negative as per ICH E14 guideline.

The results of all sensitivity analyses on the primary analysis were consistent with those of the primary analysis, i.e., the upper limit of the 90% CI was always below 10 ms. The results of the sensitivity analyses using QT corrections for HR other than Fridericia's also confirmed the findings of the primary analysis, except when using Bazett's correction (mean difference: 6.97 ms, 90% CI: [1.88, 12.07]). In accordance with Health Authority guidance (ICH E14) the Fridericia correction method is considered the preferred method to evaluate QT prolongation. The difference between bedaquiline and placebo in time-matched changes from reference in QTcF was comparable between female and male subjects.

Moxifloxacin (400 mg) was included in the trial to document trial sensitivity, i.e., to demonstrate that under the conditions used in this trial, a relevant increase in QTc could be detected. For 4 out of 5 predefined time points of interest, the lower limit of the 98% CIs of the differences between moxifloxacin and placebo in time-matched changes from baseline in QTcF was above 5 ms with the largest value observed at 3 h (mean difference 10.86 ms, 98% CI [8.41, 13.31]). Therefore, the criterion for trial sensitivity was met.

No QTc values above 500 ms or changes in QTc from baseline greater than 60 ms were observed in Holter extracted ECGs and no ECG-related AEs were reported.

One subject (Treatment B) had an abnormal QTcF value between 450 and 480 ms that corresponded to an abnormal QTcF change from baseline between 30 and 60 ms. This subject had a QTcF value of 468 ms corresponding to a change from baseline of 35 ms at the first follow-up visit. At baseline (Day -1), normal QTcF (433 ms) was observed. A second subject (Treatment A) had an abnormal QTcF value between 450 and 480 ms that corresponded to a QTcF change from baseline < 30 ms. This subject had a QTcF value of 457 ms corresponding to a change from baseline of 15 ms 4 h after bedaquiline intake. At baseline (Day -1), QTcF was

normal (442 ms). A third subject (Treatment B) had a QTcF change from baseline of 62 ms, which corresponded to a QTcF value of 418 ms. This occurred following placebo_{TMC} intake and values had decreased the next day (QTcF value: 359 ms; change from baseline: 3 ms).

The mean (SD) of the TMC207 C_{max} and AUC in this study were 8275 (3753) and 71 700 (25 000), respectively, which exceeded the exposure to TMC207 observed in patients after 14 days of 400 mg once-daily dosing (Table 14). No clear relationship was observed between plasma concentrations of bedaquiline or M2 and the change from baseline in QTcF interval.

6.1.5 Combination of Bedaquiline With QT Prolonging Drugs

There is limited information available on the potential for a pharmacodynamic interaction between bedaquiline and drugs that prolong the QT interval of the ECG. An additive or synergistic effect on QT prolongation of bedaquiline when coadministered with other drugs that prolong the QT interval cannot be excluded. Therefore, caution is recommended when prescribing bedaquiline concomitantly with medications with a known risk of QT prolongation. In the event that coadministration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended. Concomitant administration of bedaquiline with fluoroquinolone antibiotics that have a potential for significant QT prolongation (gatifloxacin, moxifloxacin, and sparfloxacin) should be avoided.

In a Phase I DDI trial with ketoconazole (C109), treatment emergent increases in QTcF were observed on single safety ECGs after 3 days of treatment with ketoconazole and after 11 days of treatment with bedaquiline alone. These events occurred in more subjects and were more pronounced in the treatment group that received 3 days of combined treatment with bedaquiline + ketoconazole.

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. Therefore, in the event that co-administration of clofazimine with bedaquiline is necessary, clinical monitoring including frequent ECG assessment is recommended.

The risk of QT interval prolongation in patients treated with bedaquiline may be reduced with:

- 1) Appropriate patient selection, i.e. avoid use in patients with a history of heart failure, a QT interval > 450 ms, patients with a personal or family history of congenital QT prolongation
- 2) Avoiding the concomitant use of QT-prolonging medications
- 3) Performing frequent ECGs.

6.1.6 Conclusions

The **TMC207/TBC1003** trial showed that according to the ICH E14 guidelines, this thorough QT/QTc trial is negative (i.e., the upper limits of all 90% CIs of the differences between bedaquiline and placebo in time-matched changes from baseline in QTcF were below 10 ms) and trial (assay) sensitivity was demonstrated by moxifloxacin control. However, this was a single-dose trial and may not replicate the pharmacodynamic effect on QTcF seen in Phase II studies.

Overall, administration of a single 800-mg dose of bedaquiline was generally well tolerated in this trial.

6.2 SAFETY CONCLUSIONS FROM THE PHASE IIB PLACEBO-CONTROLLED TRIAL: TMC207-C208

In this section, data from the controlled part of the pooled Phase II analysis is presented, which includes data from **C208 Stage 1** and **Stage 2**. This pooled population consists of 102 subjects in the Any bedaquiline group and 105 subjects in the Any placebo group. The 24 Weeks groups contain data from **C208 Stage 2** only while the Any bedaquiline and Any placebo groups contain data from both **C208 Stage 1** (Investigational Treatment period: 8 weeks) and **Stage 2** (Investigational Treatment period: 24 weeks). A high-level summary of pertinent safety information including the mortality results from the final **Stage 2 C208** analysis is presented to provide an overview of the number and causes of deaths.

6.2.1 Adverse Events

During the Investigational Treatment phase, 96.1% of subjects in the Any bedaquiline group and 95.2% subjects in the Any placebo group experienced at least one AE ([Table 43](#)). The most frequently reported AEs in the Any bedaquiline group (> 20.0% of subjects) were nausea (35.3%), arthralgia (29.4%), headache (23.5%), hyperuricemia (22.5%), and vomiting (20.6%).

The incidence of these AEs was generally similar in the Any bedaquiline and the Any placebo groups, except for headache (in 23.5% and 11.4% of subjects, respectively), nausea (35.3% and 25.7%, respectively), and arthralgia (29.4% and 20.0%, respectively).

Most AEs were grade 1 or 2 in severity. During the Investigational Treatment phase, the percentage of subjects with grade 3 or 4 AEs was 27.5% in the Any bedaquiline and 22.9% in the Any placebo group. The most frequently reported grade 3 or 4 AE was hyperuricemia in 10.8% of subjects in the Any bedaquiline group and 13.3% of subjects in the Any placebo group. Other grade 3 or 4 AEs were reported in < 3.0% of subjects in the Any bedaquiline or Any placebo groups. Grade 3 or 4 AEs were considered at least possibly related to bedaquiline/placebo in 8.8% of subjects in the Any bedaquiline group and in 10.5% of subjects in the Any placebo group.

A summary of AEs occurring in at least 10% subjects receiving bedaquiline in the pooling of **Stage 1** and **Stage 2** is provided in [Table 43](#).

Table 43: Pooled C208 Stage 1 and Stage 2: AEs Reported in at Least 10% of Subjects in any Treatment Group During the Investigational Treatment Phase

SOC Preferred term, n (%)	Investigational Treatment Phase			
	Controlled Trials			
	TMC207		Placebo	
	24 Weeks* N = 79	Any* N = 102	24 Weeks* N = 81	Any* N = 105
Any AE	77 (97.5)	98 (96.1)	77 (95.1)	100 (95.2)
Gastrointestinal disorders	50 (63.3)	59 (57.8)	50 (61.7)	59 (56.2)
Nausea	30 (38.0)	36 (35.3)	26 (32.1)	27 (25.7)
Vomiting	20 (25.3)	21 (20.6)	21 (25.9)	24 (22.9)
Abdominal pain upper	9 (11.4)	10 (9.8)	7 (8.6)	8 (7.6)
Gastritis	6 (7.6)	6 (5.9)	13 (16.0)	13 (12.4)
Diarrhea	3 (3.8)	6 (5.9)	11 (13.6)	12 (11.4)
Musculoskeletal and connective tissue disorders	35 (44.3)	41 (40.2)	32 (39.5)	39 (37.1)
Arthralgia	26 (32.9)	30 (29.4)	18 (22.2)	21 (20.0)
Nervous system disorders	32 (40.5)	37 (36.3)	21 (25.9)	24 (22.9)
Headache	22 (27.8)	24 (23.5)	10 (12.3)	12 (11.4)
Dizziness	10 (12.7)	13 (12.7)	10 (12.3)	12 (11.4)
Metabolism and nutrition disorders	30 (38.0)	36 (35.3)	31 (38.3)	34 (32.4)
Hyperuricemia	19 (24.1)	23 (22.5)	26 (32.1)	29 (27.6)
Decreased appetite	8 (10.1)	9 (8.8)	3 (3.7)	4 (3.8)
Ear and labyrinth disorders	24 (30.4)	32 (31.4)	26 (32.1)	37 (35.2)
Deafness unilateral	9 (11.4)	12 (11.8)	6 (7.4)	11 (10.5)
Tinnitus	2 (2.5)	2 (2.0)	10 (12.3)	10 (9.5)
Respiratory, thoracic and mediastinal disorders	25 (31.6)	31 (30.4)	23 (28.4)	30 (28.6)
Hemoptysis	14 (17.7)	17 (16.7)	9 (11.1)	13 (12.4)
Infections and infestations	25 (31.6)	28 (27.5)	28 (34.6)	33 (31.4)
General disorders and administration site conditions	23 (29.1)	26 (25.5)	23 (28.4)	28 (26.7)
Chest pain	9 (11.4)	9 (8.8)	6 (7.4)	8 (7.6)
Injection site pain	4 (5.1)	4 (3.9)	10 (12.3)	10 (9.5)
Skin and subcutaneous tissue disorders	19 (24.1)	25 (24.5)	21 (25.9)	28 (26.7)
Pruritus	10 (12.7)	12 (11.8)	11 (13.6)	13 (12.4)
Investigations	17 (21.5)	19 (18.6)	17 (21.0)	21 (20.0)
Psychiatric disorders	15 (19.0)	16 (15.7)	11 (13.6)	13 (12.4)
Insomnia	11 (13.9)	11 (10.8)	9 (11.1)	10 (9.5)
Eye disorders	10 (12.7)	13 (12.7)	14 (17.3)	15 (14.3)
Blood and lymphatic system disorders	8 (10.1)	9 (8.8)	4 (4.9)	4 (3.8)
Reproductive system and breast disorders	7 (8.9)	8 (7.8)	10 (12.3)	13 (12.4)

N = number of ITT subjects with data, n = number of ITT subjects with this observation

*This pooled population consists of 102 subjects in the Any TMC207 group and 105 subjects in the Any placebo group. The 24 Weeks groups contain data from **C208 Stage 2** only while the Any TMC207 and Any placebo groups contain data from both **C208 Stage 1** (Investigational Treatment period: 8 weeks) and **Stage 2** (Investigational Treatment period: 24 weeks).

Data on file, Janssen Research and Development

6.2.2 Deaths, Other Serious Adverse Events and Adverse Events Leading to Discontinuation

- *Overview of Deaths in the Pooled Stage 1 and Stage 2 C208 Trial*

Upon analysis of Stage 2 of the placebo-controlled Phase IIb trial C208, an imbalance in the number of deaths was identified between the bedaquiline group and the placebo group despite better microbiologic outcomes in the bedaquiline group. Based on this information the Sponsor has chosen to proactively present the mortality information from the completed C208 Stage 2 trial based on the final Topline report which was also submitted in the Safety Update Report. In trial C208 Stage 2, 10/79 subjects in the bedaquiline group died compared to 2/81 subjects in the placebo group. This imbalance remained in the pooled analysis of C208 Stage 1 and Stage 2 in which 12/102 subjects in the Any bedaquiline group and 4/105 subjects in the Any placebo group experienced an SAE leading to death ([Table 44](#)). The reason for the increased overall mortality in the bedaquiline group in this trial is as yet unclear given that the causes of death were varied (only death due to TB was reported more than once), and there was a wide range in time to death since last intake of bedaquiline (range; 115-504 days in C208 Stage 1, 2-911 days in C208 Stage 2), although onset was generally late with only 1 death occurring during the Investigational Treatment phase. In addition, all deaths in the bedaquiline arm were considered not related to study drug by the investigator and none of these subjects had a treatment emergent QTcF ≥ 500 ms or changes in QTcF from baseline > 60 ms.

The analysis of mortality presented below includes both deaths of patients who died while being followed in the trial and deaths reported in a long-term survival analysis of patients who prematurely discontinued the trial.

- ***Deaths During the C208 Trial (Stage 1 and Stage 2)***

Seven (6.9%) subjects in the Any bedaquiline group and 1 subject in the Any placebo group died while being followed in the pooled placebo-controlled trial (**C208 Stage 1 and Stage 2**). Only 1 of these deaths (due to alcohol poisoning) occurred during the Investigational Treatment period with bedaquiline/placebo, the remaining deaths all occurred afterwards. In the Any bedaquiline group, causes of death were myocardial infarction, TB (2 cases), alcohol poisoning, hepatitis and hepatic cirrhosis (1 case), septic shock and peritonitis (1 case), and cerebrovascular accident. In the Any placebo group, cause of death was hemoptysis. The investigator considered all the SAEs leading to death not related to bedaquiline intake in the Any bedaquiline group and doubtfully related to study medication in the Any placebo group. For a summary of these SAEs see [Table 44](#) and [Table 45](#). See [Appendices](#) for individual subject narratives.

- ***Deaths Reported During Long-term Survival Follow-up of Prematurely Withdrawn Subjects***

In the Phase IIb trials (**C208** and **C209**), subjects who prematurely withdrew (unless they withdrew consent) were to be followed for 96 weeks after their last dose of bedaquiline or placebo, or until the last follow-up visit for the last subject in the trial. Investigators were asked to provide minimal information about the survival/clinical outcome of these subjects throughout the follow-up period, approximately every 24 weeks (6 months), unless the subject refused to participate.

The analysis of long-term follow up for survival outcomes in subjects who prematurely discontinued in the pooled trial **C208 (Stage 1 and 2)**, included reports of 8 additional deaths. In **Stage 1**, one subject in the bedaquiline group (pulmonary TB) and 2 subjects in the placebo group (TB related illness and pulmonary TB) died, and in **Stage 2** 4 subjects in the bedaquiline group (3 subjects with TB related illness, 1 subject motor vehicle accident) and 1 subject in the placebo group (TB related illness) died after they discontinued the trial. Review of the reasons for discontinuation from the trial for the subjects that died during the follow-up phase shows that the most common reasons for discontinuation were identification of XDR-TB and non-compliance. Of note, all deaths after premature discontinuation from **Stage 1** and **Stage 2** were due to TB or TB related illness except for 1 bedaquiline subject who died due to a motor vehicle

accident. For a summary of these SAEs see [Table 44](#) and [Table 45](#) below. See [Appendices](#) for individual subject narratives.

Table 44: Pooled C208 Stage 1 and Stage 2 Trials: Overview of Deaths

	TMC207	Placebo
C208 Stage 1	N = 23	N = 24
During Trial	1	0
Follow-up of Premature Withdrawals	1	2
Total	2	2
C208 Stage 2^a	N = 79	N = 81
During Trial	6	1
Follow-up of Premature Withdrawals	4	1
Total	10	2
Pooled C208 Stage 1 and 2	N = 102	N = 105
	12	4

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Table 45: Pooled C208 Stage 1 and Stage 2: Summary of Deaths

C208 Stage 1							
Subject	Treatment Arm	Days Since Last Intake of TMC207/ placebo	Last Culture Conversion Status	Cause of Death	Investigator Causality	Reason for Discontinuation	QTcF \geq 500 ms/ Grade 3 or 4 LFT abnormalities / liver-related AEs
During Trial							
208-3079	TMC207	115	Non-converter	Acute myocardial infarction	not related	-	-/-/-
During Follow-up of Premature Withdrawals							
208-3100	TMC207	504	Non-converter	Pulmonary Tuberculosis	not related ^a	Subject was XDR	-/-/-
208-3010	Placebo	427	Non-converter	TB related illness	not related ^a	Subject developed XDR-TB	-/-/-
208-3049	Placebo	267	Non-converter	Pulmonary Tuberculosis	not related ^a	Subject was XDR	-/-/-
C208 Stage 2							
During Trial							
208-4041	TMC207	2	Converter	Alcohol Poisoning	not related	-	-/-/-
208-4153	TMC207	344	Relapse	Tuberculosis	not related	-	-/-/-
208-4224	TMC207	281	Relapse	Tuberculosis	not related	-	-/-/-
208-5069	TMC207	86	Converter	Hepatitis/hepatic cirrhosis	not related	-	-/+ / +
208-5067	TMC207	513	Converter	Septic shock/peritonitis	not related	-	-/+ / +
208-4399	TMC207	556	Converter	Cerebrovascular accident	not related	-	-/-/-
208-4120	Placebo	105	Non-Converter	Hemoptysis	doubtfully related	-	-/-/-
During Follow-up of Premature Withdrawals							
208-4127	TMC207	787	Non-converter	TB related illness	not related ^b	Non-compliant	-/-/-
208-4378	TMC207	911	Relapse	Motor Vehicle accident	not related ^b	Adverse event (Increased transaminase)	-/+ / +
208-4145	TMC207	262	Relapse	Tuberculosis related illness	not related ^b	Non-compliant	-/-/-
208-4464	TMC207	314	Non-converter	Tuberculosis related illness	not related ^b	Subject developed XDR-TB	-/-/-
208-4155	Placebo	709	Non-converter	Tuberculosis related illness	not related ^b	Non-compliant	-/-/-

^a Information derived from CIOMS (CIOMS forms were submitted for all deaths during the follow-up phase after retrospective request from the Sponsor)

Data on file, Janssen Research and Development

• **Discussion of Mortality in Pooled C208 Trials**

The imbalance in mortality in the pooled C208 trials was driven by the results from the C208 Stage 2 trial. A detailed evaluation of baseline demographics, presence of risk factors for poor treatment outcome, length of follow up, and bedaquiline exposure revealed there are no relevant

differences between the bedaquiline and placebo groups which could provide an explanation for the imbalance in deaths observed (see [Appendix 10](#) for data).

Of note, hepatitis B and C were not checked at screening. Three of the 12 subjects that died during or after participation in the C208 Stage 2 trial had Grade 3 or 4 LFT abnormalities and/or liver related AEs. One of these subjects died due to peritonitis and septic shock, 1 subject died due to hepatitis and hepatic cirrhosis and 1 subject due to a motor vehicle accident. Alcohol-related complications were reported for the first 2 of these subjects, and an additional subject died of alcohol poisoning during the study.

PK/PD relationships

Exposure data is available for 10 out of the 12 subjects that died in trial C208 Stage 2. Based on this analysis, no difference in exposure was observed between survivors and non-survivors (see [Appendix 10](#))

- ***Other SAEs***

During the Investigational Treatment phase of **C208 Stage 1** and **Stage 2**, SAEs were reported in 7 (6.9%) subjects in the Any bedaquiline group and in 2 (1.9%) subjects in the Any placebo group. By preferred term, SAEs occurred in at most 1 subject each in the Any bedaquiline and Any placebo groups. Treatment-related SAEs were reported in 1 subject (abortion spontaneous in the Any placebo group).

- ***AEs Leading to Discontinuation***

One or more AEs led to discontinuation of bedaquiline in 4 (3.9%) subjects and to discontinuation of placebo in 5 (4.8%) subjects. AEs leading to permanent discontinuation of bedaquiline/placebo occurring in > 1 subject in the Any bedaquiline or Any placebo groups were transaminases increased (3 [2.9%] subjects in the Any bedaquiline group and no subjects in the Any placebo group) and pregnancy (no subjects in the Any bedaquiline group and 2 [1.9%] subjects in the Any placebo group). Of the 3 subjects who permanently discontinued bedaquiline treatment due to transaminases increased, one subject died later due to a motor vehicle accident. AEs leading to permanent discontinuation of any BR drug during the Investigational Treatment

phase occurred in 6 (5.9%) subjects in the Any bedaquiline group and 9 (8.6%) subjects in the Any placebo group.

- ***Adverse Events of Special Interest***

The pooled Phase IIb safety database was probed using standardized MedDRA queries (SMQs) ¹ for AEs of interest, which were identified due to their relevance in the target population or their potential importance based on nonclinical and clinical data on bedaquiline and included adverse events related to the liver, QT prolongation, pancreas, muscle and skin.

During the Investigational Treatment phase, AEs identified by the SMQs for **severe cutaneous events** were observed in 2.0% of subjects in the Any bedaquiline group and in 2.9% of subjects in the Any placebo group. None of these events were serious, led to discontinuation or were grade 3 or 4 in severity.

During the Investigational Treatment phase, AEs identified by the SMQ for **acute pancreatitis** were observed in 2.0% of subjects in the Any bedaquiline group and in 1.0% of subjects in the Any placebo group. No AEs with preferred term acute pancreatitis were reported during the Investigational Treatment phase. One subject in each treatment group experienced a grade 3 AE identified by the SMQ for acute pancreatitis. The subject in the Any placebo group discontinued treatment due to this grade 3 AE. No other AEs identified by the SMQ for acute pancreatitis led to discontinuation and none were reported as SAEs. Compared to the Investigational Treatment phase, acute pancreatitis SMQ events during the Overall Treatment phase were considered serious, at least possibly related to bedaquiline/placebo by the investigator, and at least grade 3 in severity each in 1 additional subject in the Any bedaquiline group (3 events of grade 3 SAE pancreatitis acute [starting on Day 278, 376, and 579] considered possibly related to bedaquiline/placebo, except for the last event [starting on Day 579] that was no longer considered related to bedaquiline/placebo by the investigator).

Adverse events identified by the SMQs for **drug-related hepatic disorders** were observed in 8.8% and 1.9% of subjects the Any bedaquiline and Any placebo groups, respectively, during the Investigational Treatment phase. Increases in transaminases accounted for the majority of these reported events of which all but 2 resolved, and there were no reports of severe liver toxicity attributed to bedaquiline. A Hy's law analysis^{30,31} to identify cases of severe liver toxicity

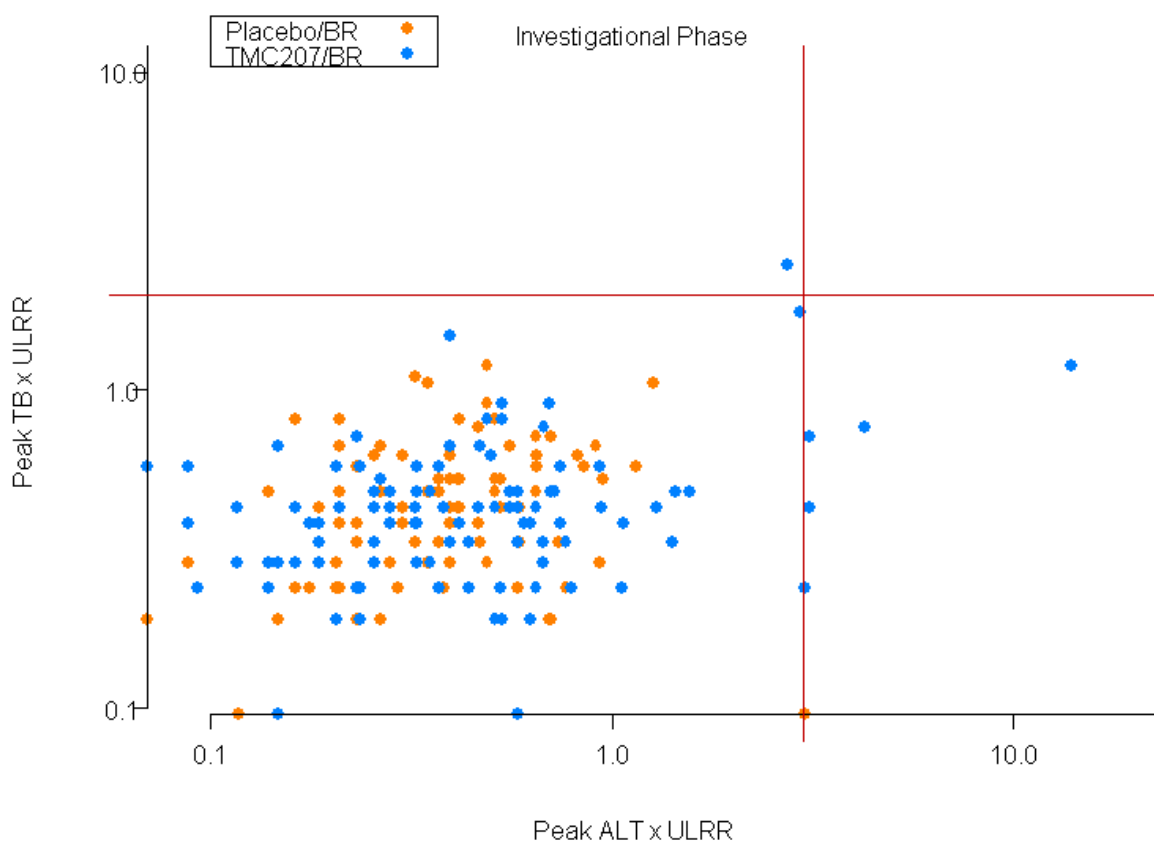
revealed 1 potential case of a patient who experienced concurrent >3 fold elevation of AST and >2 fold elevation in total bilirubin, but was confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background medications (including para-aminosalicylic acid and ethionamide). There were no reported AEs of hepatic failure during the Investigational Treatment phase and no events were reported as an SAE. Drug-related hepatic disorder events led to permanent discontinuation of bedaquiline/placebo in 3 (2.9%) subjects in the Any bedaquiline group and no subjects in the Any placebo group; events of at least grade 3 were reported in 3 (2.9%) subjects in the Any bedaquiline group. One subject (bedaquiline group) in the C208 Stage 2 trial died due to hepatitis/hepatic cirrhosis (see discussion of mortality cases above and [Appendix 4](#) for the narrative). No AEs were identified by the SMQ for **rhabdomyolysis/myopathy** during **C208 Stage 1** and **Stage 2**. AEs identified by the SMQ for Torsade de Pointes/QT prolongation are discussed in Section [6.2.4](#).

6.2.3 Clinical Laboratory Tests

Treatment-emergent graded laboratory toxicities of grade 3 or 4 were observed in $\geq 5.0\%$ of subjects during the Investigational Treatment phase for hyperuricemia (38.6% and 35.6% of subjects in the Any bedaquiline and Any placebo groups, respectively), WBC increased (in 9.9% and 4.8%, respectively), AST increased (6.9% and 0.0%, respectively), plasma prothrombin time (PT) (6.1% and 4.8%, respectively), GGT increased (5.0% and 1.9%, respectively), and ALT increased (5.0% and 1.0%, respectively). Review of the 76 subjects, i.e., 39 subjects in the Any bedaquiline group and 37 subjects in the Any placebo group, with treatment-emergent grade 3 or 4 hyperuricemia showed that in all cases pyrazinamide was part of the BR. Pyrazinamide is well-known to be associated with uric acid increases⁷⁶.

The percentage of subjects with nongraded laboratory abnormalities in the Any bedaquiline group was generally similar to or lower than in the Any placebo group, except for CPK above normal (62.4% and 53.8%, respectively), basophils (%) above normal (16.8% and 10.6%, respectively), monocytes above normal (11.9% and 6.7%, respectively), and lactate dehydrogenase (LDH) above normal (18.8% and 5.8%, respectively). Importantly, there was no difference in the frequency of graded CK abnormalities between groups in the posthoc analysis of graded CPK.

A further analysis of hepatic laboratory parameters for possible cases of severe drug-induced liver toxicity is presented in [Figure 32](#) which shows drug induced severe hepatotoxicity- eDISH plot during the 24 week investigational treatment period⁷⁷. A Hy's law analysis^{30,31} to identify cases of severe drug-induced liver toxicity revealed a single potential case of a patient who experienced concurrent >3 fold elevation of aspartate aminotransferase (AST) and >2 fold elevation in total bilirubin, but was confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background medications (including para-aminosalicylic acid and ethionamide). See [Appendices](#) for a narrative on this subject (208-5067).



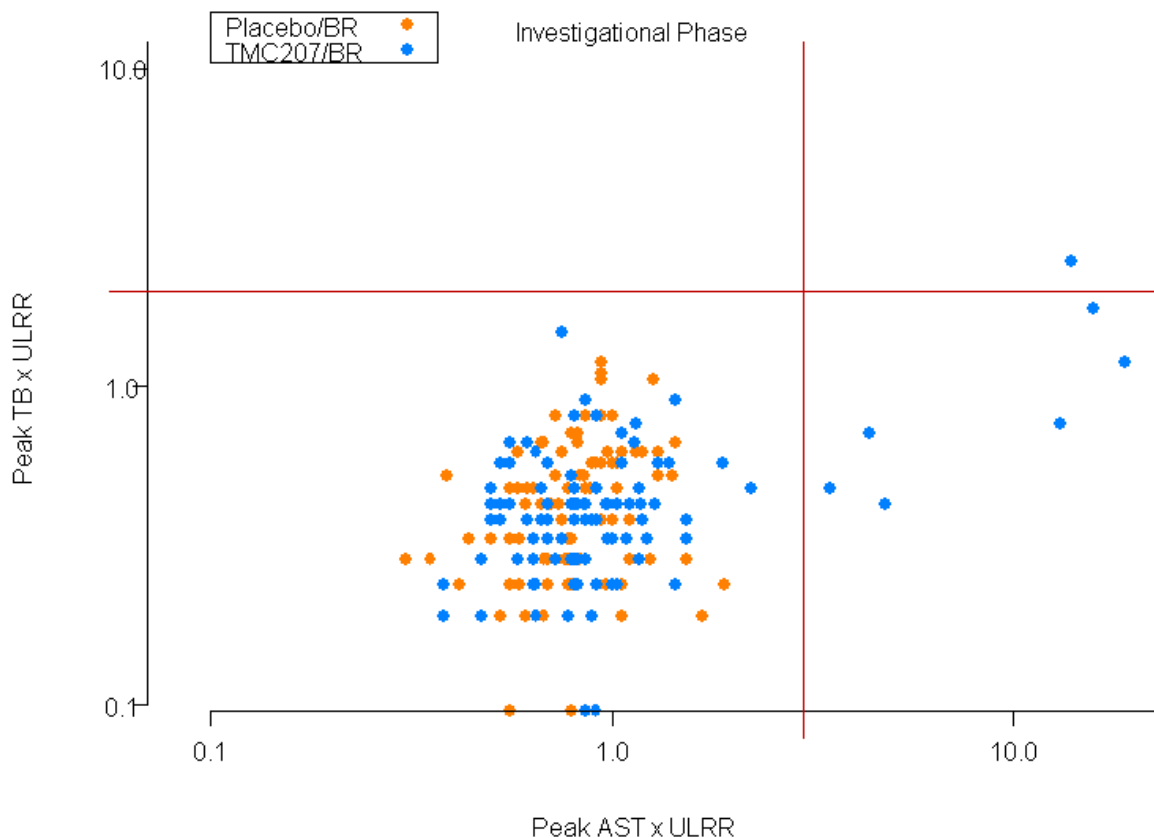


Figure 32: eDish Plots for Controlled Studies, ALT (Top) and AST (Bottom) Investigational Phase

6.2.4 Cardiovascular Safety (Electrocardiogram)

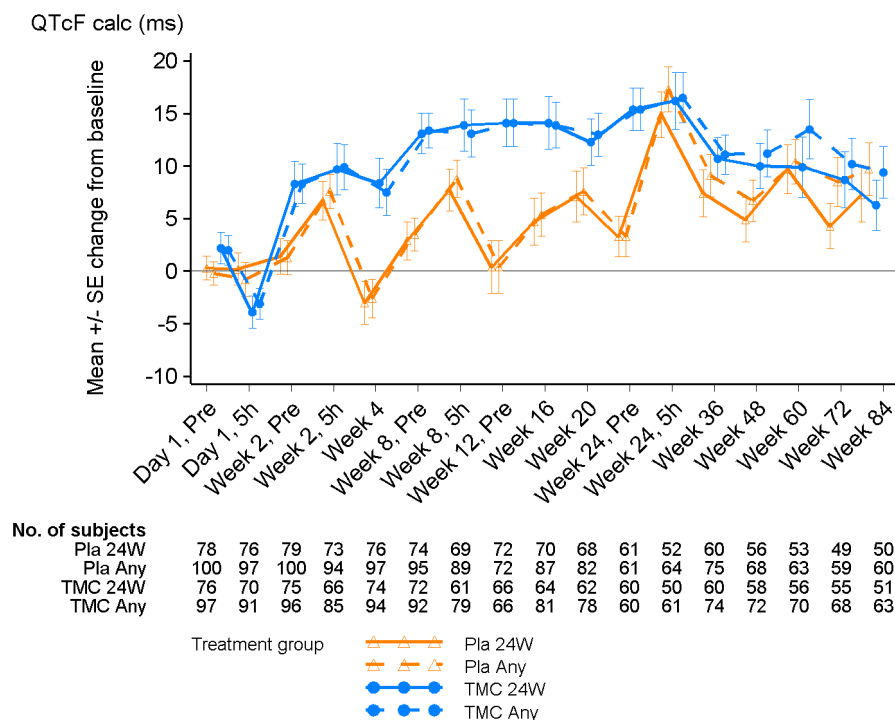
At prespecified time points, triplicate ECGs were taken at predose and 5 h postdose (i.e., bedaquiline t_{\max}). In the Any bedaquiline group, the mean changes from reference in QTcF were comparable between the 5 h postdose assessments and the respective predose assessments, but were greater than the respective predose assessments in the Any placebo group. This suggests there is no direct relationship between bedaquiline C_{\max} and QTcF prolongation.

The changes from reference in QTcF over time in the pooled analysis of **C208 Stage 1** and **Stage 2** during the Overall Treatment phase are presented in [Figure 33](#). Mean changes from reference in QTcF increased gradually over the Investigational Treatment period in the Any bedaquiline

group and decreased thereafter, to become comparable to those in the Any placebo group. In the Any placebo group, mean increases from reference in QTcF also became more pronounced over time but increases were smaller than in the Any bedaquiline group. At Week 84, mean increases from reference were comparable in the 2 groups.

In the Any bedaquiline group, a mean increase from reference in QTcF was observed from the first predose assessment after Day 1 (8.3 ms at Week 2 [pooled analysis]). Mean increases from reference in QTcF grew gradually larger over the first 8 weeks of bedaquiline treatment and then remained more or less stable until Week 24. The largest mean increase from reference in QTcF at a predose time point in the first 24 weeks was 15.4 ms in the Any bedaquiline group (at Week 24) and 7.7 ms in the Any placebo group (at Week 20). After Week 24, QTcF increases in the Any bedaquiline group gradually became less pronounced.

Mean changes from reference in QRS width, and RR- and PR-interval were minor and were not considered clinically relevant. No clinically relevant differences were observed between the Any bedaquiline and Any placebo groups for these parameters.



Note that not all assessment time points of the individual trials are shown in the pooled analysis.

Figure 33: Pooled C208 Stage 1 and Stage 2: Mean (SE) Changes from Reference in QTcF Over Time

During the Investigational Treatment phase in the pooled analysis of **C208 Stage 1** and **Stage 2**, 1 (1.3%) subject in the Any bedaquiline group (CRF ID 208-4385) and no subjects of the placebo group had a QTcF value of more than 500 ms. QTcF values between 480 and 500 ms were observed in 3 (2.9%) subjects in the Any bedaquiline group and in 1 (1.0%) subject in the Any placebo group and QTcF values between 450 and 480 ms were observed in 22.5% and 6.7% of the subjects in the Any bedaquiline and Any placebo groups, respectively. An increase from reference in QTcF of more than 60 ms was observed in 10 (10.1%) subjects in the Any bedaquiline group and 4 (4.0%) subjects in the placebo group. These increases resulted in QTcF values between 450 and 480 ms in 2 of the 10 subjects in the Any bedaquiline group and 1 of 4 subjects in the Any placebo group, in QTcF values between 480 and 500 ms in 3 of the 10 subjects in the Any bedaquiline group and 1 of 4 subjects in the Any placebo group, and in QTcF values > 500 ms in 1 of the 10 subjects in the Any bedaquiline group and in 0 of 4 subjects in the Any placebo group. Increases between 30 to 60 ms were observed in 52.5% and 32.7% of the subjects in the Any bedaquiline and Any placebo groups, respectively. Increases between 30 and

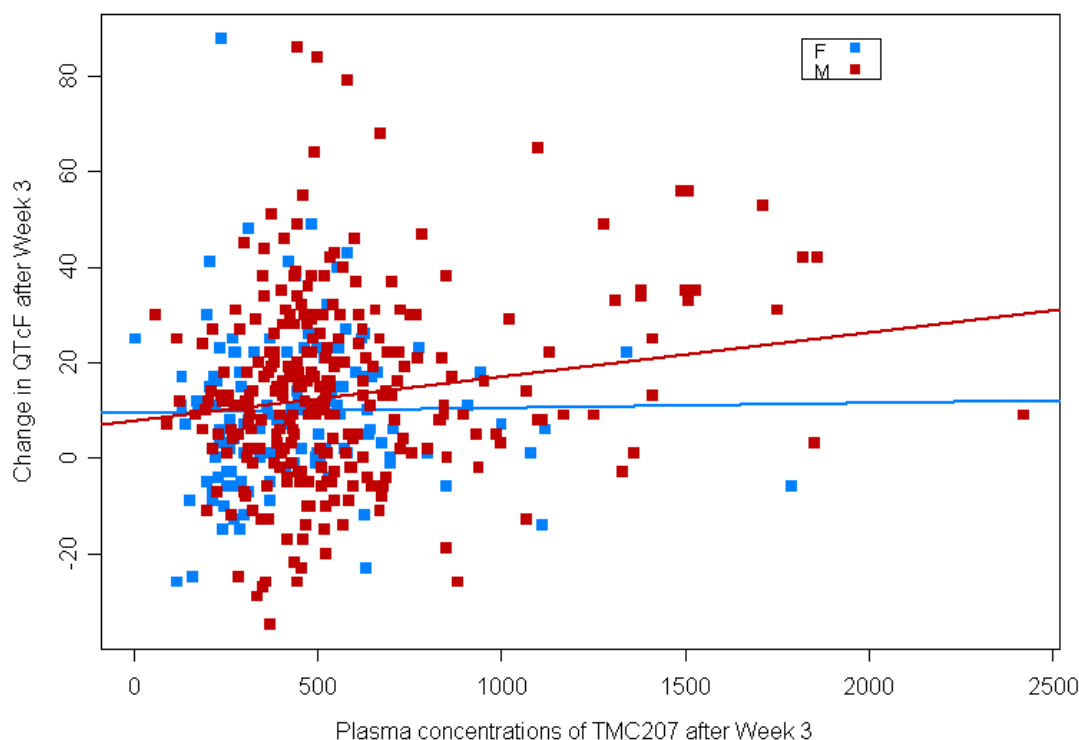
60 ms resulted in QTcF values above 450 ms (all \leq 480 ms) in 15 of 52 subjects with such increases in the Any bedaquiline group and in 2 of 33 subjects with such increases in the Any placebo group.

Abnormalities in HR and PR or QRS intervals occurred with a generally similar incidence in the Any bedaquiline and Any placebo groups.

During the Investigational Treatment phase, AEs identified by the SMQs for Torsade de Pointes/QT prolongation were observed in 3.9% of subjects in the Any bedaquiline group and in 3.8% of subjects in the Any placebo group. No events of Torsade de Pointes were reported and none of the AEs identified by the SMQs for TdP/QT prolongation were serious, led to discontinuation or were grade 3 or 4 in severity.

6.2.5 Pharmacokinetic/Pharmacodynamic Relationships for Safety Parameters

For safety parameters, no relevant differences in median bedaquiline plasma AUC_{24h} were observed for subjects with at least one SAE, grade 4 AE, a Torsade de Pointes/QT prolongation SMQ event, or QTcF abnormalities compared to subjects without these findings. The relationship between QTcF and bedaquiline or M2 plasma concentration was explored graphically by gender. In general, no clear relationship between bedaquiline or M2 plasma concentration up to Week 2 (400 mg q.d.) and after Week 3 (200 mg t.i.w.) and corresponding changes in QTcF was observed in male or female subjects ([Figure 34](#)).



Red line: Regression line (mixed effect model) for male subjects (estimate = 0.009264, R^2 value = 0.0402*)

Blue line: Regression line (mixed effect model) for female subjects (estimate = 0.001026, R^2 value = 0.0003*)

* Ignoring repeated measurement per subject

Figure 34: C208 Stage 2: Scatterplot of TMC207 Plasma Concentration After Week 3 Versus Change in QTcF After Week 3 for Male and Female Subjects

6.2.6 Conclusions

The results of the Pooled **C208 Stage 1** and **Stage 2** trials demonstrate that overall, the treatment with bedaquiline (400 mg q.d. for 2 weeks followed by 200 mg) was generally well tolerated.

During the Investigational Treatment Phase in the pooled **C208** trials, the most frequently reported AEs in the Any bedaquiline group (> 20.0% of subjects) were nausea, arthralgia, headache, hyperuricemia, and vomiting. The incidence of these AEs was similar in the Any bedaquiline and the Any placebo groups, except for headache, nausea, and arthralgia, which occurred more frequently in the Any bedaquiline group. Serious AEs were observed in 7 (6.9%) subjects in the Any bedaquiline group and 2 (1.9%) subjects in the Any placebo group. The incidence of AEs leading to discontinuation and grade 3 or 4 AEs was generally similar in the Any bedaquiline and Any placebo groups.

Overall in the pooled placebo-controlled trials (**Stage 1** and **2**), there was an imbalance in the number of deaths, with 12/102 deaths in the Any bedaquiline group compared to 4/105 deaths in the Any placebo group. This imbalance was driven by the results from the C208 Stage 2 trial. Of these deaths, 1 occurred during the investigational treatment period with bedaquiline/placebo, the remaining deaths occurred afterwards. In the Any bedaquiline group, the causes of death were myocardial infarction, TB (2 cases), alcohol poisoning, hepatitis and hepatic cirrhosis (1 case), septic shock and peritonitis (1 case), and cerebrovascular accident. In the Any placebo group, cause of death was hemoptysis. The investigator considered the SAEs leading to death not related to bedaquiline intake in the Any bedaquiline group and doubtfully related to investigational medication in the Any placebo group. None of these subjects had a treatment emergent QTcF \geq 500 ms.

The analysis of long-term follow up for survival outcomes in subjects who prematurely discontinued in trial **C208 (Stage 1 and 2)**, based on data collection every 24 weeks (6 months) after withdrawal, included reports of 8 additional deaths. In **C208 Stage 1**, one subject in the bedaquiline group (pulmonary TB) and 2 subjects in the placebo group (TB related illness and pulmonary TB) died, and in **Stage 2**, 4 subjects in the bedaquiline group (3 subjects with TB related illness, 1 subject due to a motor vehicle accident) and 1 subject in the placebo group (TB related illness) died after they discontinued the trial. None of these subjects had a treatment emergent QTcF \geq 500 ms.

The incidence of AEs identified by the SMQs for acute pancreatitis, severe cutaneous events, and TdP/QT prolongation was low ($< 4\%$) and generally similar in the Any bedaquiline and Any placebo groups during the Investigational Treatment phase. Events identified by the SMQs for drug related hepatic disorders were reported more frequently in the Any bedaquiline group than in the Any placebo group (8.8% versus 1.9% of subjects). None of these events were reported as an SAE during the Investigational Treatment phase. Drug-related hepatic disorders events led to permanent discontinuation of bedaquiline/placebo in 3 (2.9%) subjects in the Any bedaquiline group and no subjects in the Any placebo group.

Grade 3 or 4 laboratory abnormalities with a higher incidence in the Any bedaquiline group than in the Any placebo group were WBC increased and AST increased. Nongraded laboratory

abnormalities with a higher incidence in the Any bedaquiline group than in the Any placebo group were CPK, basophils (%), monocytes, and LDH above normal.

Analysis for possible cases of severe drug-induced liver injury revealed 1 case of a patient in which the medical assessment is confounded by reported alcoholic hepatitis and concurrent intake of hepatotoxic background medications.

During the Investigational Treatment phase, mean QTcF increases were observed in both the Any bedaquiline and 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 postdose assessments (i.e., bedaquiline t_{\max}) and the respective predose assessments. After the end of the bedaquiline dosing period, QTcF increases in the Any bedaquiline group gradually became less pronounced. 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.

6.3 SAFETY CONCLUSIONS FROM THE PHASE IIB TRIAL TMC207-C209

C209 is an uncontrolled, single-arm Phase Iib trial in 233 newly diagnosed and treatment-experienced MDR-TB subjects. Subjects with XDR-TB were also allowed to enter. bedaquiline dosage was 400 mg q.d. for the first 2 weeks and 200 mg t.i.w. for the following 22 weeks. Upon completion of the 24-week treatment with bedaquiline, subjects were to continue to receive their BR. To provide an oversight of mortality in the **C209** trial, safety information pertaining to deaths analyzed for and submitted in the Safety Update Report, is included in this Briefing Book.

6.3.1 Adverse Events

[Table 46](#) summarizes AEs that occurred in at least 5% of subjects during the Investigational and Overall Treatment Phase.

At least one AE was reported in 88.8% of subjects during the Investigational Treatment phase and AEs were most frequently related to the SOC gastrointestinal disorders (30.9%). The most common AEs were hyperuricaemia, arthralgia, nausea, vomiting, headache, diarrhea, blood uric acid increased, hypokalemia, pruritus, injection site pain, insomnia, and tinnitus. All other AEs occurred in $\leq 5.0\%$ of subjects during the Investigational Treatment phase.

Table 46: C209: Incidence of AEs Reported in > 5.0% of Subjects During the Investigational Treatment Phase

SOC Preferred Term, n (%)	TMC207/BR	
	Investigational Treatment Phase ^a N = 233	Overall Treatment Phase ^b N = 233
Any AE	207 (88.8)	211 (90.6)
Blood and Lymphatic System Disorders	13 (5.6)	15 (6.4)
Cardiac Disorders	16 (6.9)	19 (8.2)
Ear and Labyrinth Disorders	32 (13.7)	36 (15.5)
Tinnitus	13 (5.6)	16 (6.9)
Eye Disorders	26 (11.2)	29 (12.4)
Gastrointestinal Disorders	72 (30.9)	76 (32.6)
Diarrhea	18 (7.7)	21 (9.0)
Nausea	25 (10.7)	26 (11.2)
Vomiting	20 (8.6)	21 (9.0)
General Disorders and Administration Site Conditions	41 (17.6)	48 (20.6)
Injection site pain	13 (5.6)	15 (6.4)
Infections and Infestations	44 (18.9)	57 (24.5)
Investigations	58 (24.9)	61 (26.2)
Blood uric acid increased	16 (6.9)	16 (6.9)
Metabolism and Nutrition Disorders	56 (24.0)	59 (25.3)
Hyperuricaemia	32 (13.7)	32 (13.7)
Hypokalemia	14 (6.0)	15 (6.4)
Musculoskeletal and Connective Tissue Disorders	56 (24.0)	60 (25.8)
Arthralgia	27 (11.6)	29 (12.4)
Nervous System Disorders	42 (18.0)	47 (20.2)
Headache	20 (8.6)	22 (9.4)
Psychiatric Disorders	24 (10.3)	28 (12.0)
Insomnia	13 (5.6)	13 (5.6)
Reproductive System and Breast Disorders	16 (6.9)	19 (8.2)
Respiratory, Thoracic and Mediastinal Disorders	29 (12.4)	36 (15.5)
Skin and Subcutaneous Tissue Disorders	45 (19.3)	45 (19.3)
Pruritus	14 (6.0)	14 (6.0)

N = number of ITT subjects with data, n = number of ITT subjects with this observation

^a The Investigational Treatment phase was defined as follows: from start of TMC207/placebo intake to end of TMC207/placebo intake + 1 week.

^b The Overall Treatment phase was defined as follows: from start of TMC207/placebo intake to the cut-off date (or 1 week after last medication intake in case of early discontinuation).

Data on file, Janssen Research and Development

6.3.2 Deaths, Other Serious Adverse Events and Adverse Events Leading to Discontinuation

- *Overview of Deaths in Trial C209*

In total, since the start of the **C209** trial up to the cut-off date 15 July 2012, 16 subjects have died (12 subjects during the trial and 4 subjects during the survival follow-up phase ([Table 47](#)). None

of the fatal SAEs were considered related to bedaquiline by the investigator, except for renal impairment (after vomiting and dehydration) that was judged doubtfully related to bedaquiline. None had a treatment emergent QTcF \geq 500 ms.

Table 47: Overview of Deaths in Trial C209 (n = 233)

C209*	TMC207
During Trial	12
Follow-up of Premature Withdrawals**	4
Total	16

* cut-off date 15 July 2012

** cut-off date of February 2012

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- ***Deaths During the Trial***

During the trial **C209** up to the cut-off date of 15 July 2012, 12 subjects died due to SAEs, time of death ranged from 12 to 685 days after last bedaquiline intake (median 376 days). Two subjects died due to SAEs (tuberculosis, renal impairment) with onset during the Investigational treatment phase; all other fatal SAEs had an onset after the end of bedaquiline treatment. All SAEs leading to death were considered not related to bedaquiline by the investigator, except for renal impairment after vomiting and dehydration that was judged doubtfully related to bedaquiline. None of these subjects had a treatment emergent QTcF \geq 500 ms. The overall microbiology outcome for 7 of the 12 subjects was failure to convert. See [Table 48](#) for subject specific information.

Table 48: Subject Overview of Deaths While Followed During the Trial C209

Subject ^a	Microbiologic Response	Cause of Death	Days Since Last Study Drug Intake	Investigator causality	QTcF \geq 500 ms/ Grade 3 or 4 LFT abnormalities/ liver-related AEs
209-0024	Non-converter	Tuberculosis	27	Not related	-/-/-
209-0044	Non-converter	Renal impairment	12	Doubtful	-/-/-
209-0001	Non-converter	Tuberculosis	45	Not related	-/-/-
209-0327	Converter	Lung infection	71	Not related	-/-/-
209-0025	Converter	Congestive cardiac failure	262	Not related	-/-/-
209-0021	Non-converter	Pyopneumothorax/ Respiratory failure	476	Not related	-/-/-
209-0038	Non-converter	Tuberculosis	463	Not related	-/-/-
209-0077	Relapse	Tuberculosis	288	Not related	-/-/-
209-0046	Converter	Tuberculosis	632	Not related	-/-/-
209-0156	Non-converter	cardiac arrest (underlying cause pneumonia)	685	Not related	-/-/-
209-0552	Converter	Hemoptysis	479	Not related	-/-/+
209-0225	Non-converter	Hypertension	473	Not related	-/-/-

^a cut-off date 15 July 2012

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• ***Deaths Reported During Long-term Survival Follow-up of Prematurely Withdrawn***

Subjects

The analysis of long-term follow up for survival outcomes in subjects who prematurely discontinued in trial **C209**, based data collection every 24 weeks (6 months) after withdrawal, included 4 additional deaths. Of the 4 subjects who died, date of death was reported for 2 subjects. For those 2 subjects, time of death ranged from 178 to 244 days after last bedaquiline intake (median 211 days) ([Table 49](#)).

Table 49: Subject Overview of Deaths During Follow-up of Premature Withdrawals Trial C209

C209^a						
Subject	Days since last intake	Last culture conversion status	Cause of death	Investigator causality	Reason for Discontinuation	Treatment Emergent QTcF ≥ 500 ms
209-0234	244	Non-converter	Hemoptysis	Not related	MDR-TB related adverse event (QT prolongation ^b)	-
209-0476	<30 ^c	Non-converter	TB related illness	Doubtful	Withdrew consent	-
209-0027	> 18 months ^d	Relapse	TB related illness	Not related	Non-compliance	-
209-0058	178	Non-converter	TB related illness	Not related	Non-compliance	-

^a cut-off date 15 July 2012; NA not applicable

^b QTcF interval at time of AE reporting was 461 ms and was resolved 3 days after discontinuation of TMC207

^c The subject did not complete the full course of investigational treatment

^d Since no specific date of death was reported (only month year) it is not possible to calculate the exact days since last intake of TMC207

Data on file, Janssen Research and Development

- ***PK/PD Conclusions related to Mortality in Trial C209***

Exposure data is available for 10 out of the 16 subjects that died in trial **C209**. No relationship was identified between exposure to bedaquiline and survivor status; median C_{AVG} in survivors was 1075.1ng/mL (range 156-2705) compared to median C_{AVG} in non survivors 968.4 ng/mL (range 210-1620).

By visual inspection no relationship was observed between exposure of bedaquilin and SAEs, Grade 4 AEs and treatment-emergent QTcF abnormalities (see [Appendix 10](#)).

- ***Other SAEs***

One or more SAEs were reported in 14 (6.0%) subjects during the Investigational Treatment phase. By preferred term, these SAEs occurred in 1 (0.4%) subject each and were considered not or doubtfully related to bedaquiline by the investigator, except for ECG QT prolonged that was judged very likely related to bedaquiline in 1 subject.

- ***AEs Leading to Discontinuation***

One or more AEs led to discontinuation of bedaquiline in 6 (2.6%) subjects. By preferred term, these AEs leading to discontinuation of bedaquiline occurred in 1 (0.4%) subject each. Adverse

events led to permanent discontinuation of one or more of the BR drugs in 51 (21.9%) subjects during the trial.

- ***AEs of Special Interest***

AEs identified by the SMQs for acute pancreatitis were observed in 1.3% of subjects during the Investigational Treatment phase. Adverse events identified by the SMQs for drug-related hepatic disorders were observed in 12.0% of subjects. None were reported as SAE or led to permanent discontinuation of bedaquiline; events of at least grade 3 were reported in 8 (3.4%) subjects.

6.3.3 Clinical Laboratory Tests

Treatment-emergent graded laboratory toxicities of grade 3 or 4 were observed during the Investigational Treatment phase for hyperuricemia (9.6%), hyperglycemia (2.6%), increases in AST (3.5%), ALT (2.2%), and GGT (1.3%), increased WBC (1.7%), increased pancreatic amylase (0.9%), and decreased hemoglobin (0.9%). All subjects with treatment-emergent grade 3 or 4 hyperuricemia used pyrazinamide as part of the BR, which is well known to be associated with increases in uric acid. The most frequently observed (in > 10.0%) treatment-emergent nongraded laboratory abnormalities during the Investigational Treatment phase were CPK, pepsinogen I and II, eosinophils (%) and eosinophils count, gastrin, and neutrophils (%) and total neutrophil count above normal, and total cholesterol, red blood cell (RBC) count, and CPK-MB below normal.

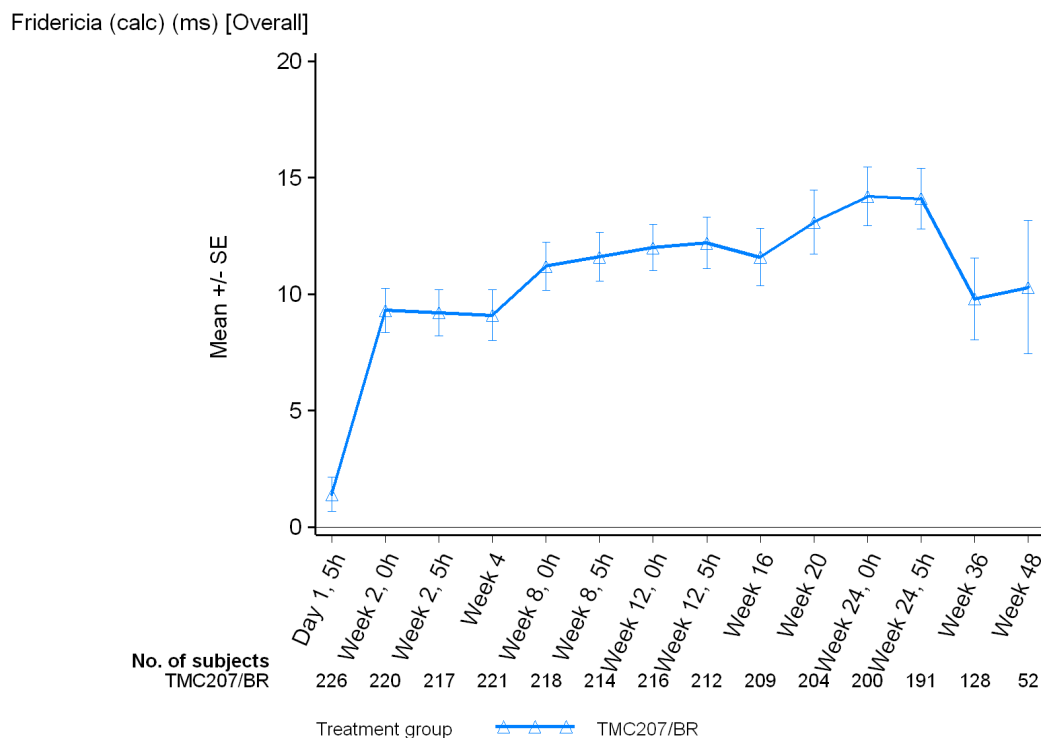
For HIV infected subjects, median viral load at baseline was 4.33 log₁₀ copies/mL (N = 5) and median CD4+ cell count was 570.0 x 10⁶ cells/L (N = 11). At Week 24, a median decrease in viral load of 0.15 log₁₀ copies/mL (N = 4) and a median increase in CD4+ cell count of 44.0 x 10⁶ cells/L was observed (N = 7).

6.3.4 Cardiovascular Safety (Electrocardiogram)

ECG assessments were done at screening, Day -1 (reference, time-matched with Day 1), predose and 5 h postdose (i.e., bedaquiline t_{max}) on Day 1. Thereafter, ECG was assessed every 2 weeks (predose) until Week 4 and every 4 weeks during the remainder of the Investigational Treatment phase, with additional 5 h postdose assessments at Weeks 2, 8, 12, and 24.

Mean changes from reference for QTcF at the 5 h time points were comparable to those at the respective predose time points. Since mean changes from reference in QTcF at the 5 h postdose assessment time points were comparable to those at the respective predose time points, and predose assessments were performed more frequently, further discussion of mean changes in QTcF over time is limited to predose assessments.

Mean changes from reference in QTcF increased during the Investigational Treatment phase (Figure 35). Mean increases from reference in QTcF were observed from the first assessment after Day 1 (9.3 ms at Week 2) with mean increases from reference of more than 10 ms observed from Week 8 (largest mean change from reference: 14.2 ms at Week 24, N = 200). After Week 24, QTcF increases were less pronounced: at Week 36 mean QTcF increase was 9.8 ms (N = 128). Note that after Week 36, data were only available for 52 subjects.



Planned end of TMC207 treatment was Week 24.

Figure 35: C209: Mean (SE) Changes from Reference in QTcF Over Time

During the Investigational Treatment phase, 3 (1.3%) subjects were observed with a QTcF value between 480 ms and 500 ms and 1 (0.4%) subject with a QTcF value of more than 500 ms (514 ms). QTcF increases from reference of more than 60 ms were noted in 9 (3.9%) subjects

and resulted in a QTcF value between 450 and 480 ms in 3 of those 9 subjects, in a QTcF value between 480 and 500 ms in 1 of those 9 subjects, and in a QTcF value > 500 ms in 1 of those 9 subjects. In the remaining 4 subjects with a QTcF increase from reference of more than 60 ms the corresponding QTcF value was normal. QTcF increases from reference of 30 to 60 ms were noted in 84 (36.7%) subjects and resulted in a QTcF value between 450 and 480 ms in 17 of those 84 subjects (20.2%) and in a QTcF value between 480 and 500 ms in 1 of those 84 subjects (1.2%).

AEs identified by the SMQs for Torsade de Pointes/QT prolongation were observed in 2.6% of subjects during the Investigational Treatment phase. There were no reported AEs of Torsade de Pointes. One Torsade de Pointes /QT prolongation event (ECG QT prolonged) was grade 3 in severity and was reported as SAE leading to permanent discontinuation of bedaquiline. In this subject (CRF ID 209-0234), QTcF interval at time of AE reporting was 461 ms; corresponding increase from reference was 11 ms. QTcB was 519 ms with a corresponding change from reference of 38 ms. QTcF and QTcB abnormalities had resolved by the next ECG assessment 3 days later. No other AEs identified by the SMQs for Torsade de Pointes/QT prolongation were reported as SAE, led to permanent discontinuation of bedaquiline, or were considered grade 3 or 4 in severity.

Mean values for RR interval slightly increased during the Investigational Treatment phase, while no consistent or relevant changes were observed for PR interval and for QRS width.

During the Investigational Treatment phase, an abnormally low HR was observed in 6.9% of subjects. The incidence of other abnormalities for HR, PR interval, and QRS width was low.

- ***QTcF Findings During Concomitant use of Clofazimine and Bedaquiline***

A non-GLP study conducted by TB Alliance as part of a discovery program suggested an effect of clofazimine on I_{Kr} in vitro in the human human ether-à-go-go-related gene (hERG) model. In view of this result, a posthoc analysis was performed in **C209** to evaluate QTcF changes in subjects with or without concomitant use of clofazimine and bedaquiline.

The effect of concomitant use of clofazimine and bedaquiline on QTcF findings in **C209** was evaluated using descriptive statistics for changes from reference in QTcF in subgroups by concomitant use of clofazimine. For concomitant use of clofazimine, subjects were included if

they were using clofazimine at Week 24 and had an ECG assessment at Day -1 (reference) and Week 24. The subgroup of subjects without concomitant clofazimine use included subjects who did not use clofazimine at Week 24 and had an ECG assessment at Day -1 (reference) and Week 24. 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 50).

Table 50: C209: Descriptive Statistics for Changes from Reference for QTcF in Subgroups by Concomitant Use of Clofazimine at Week 24

QTcF (calculated) (ms) Time point	Clofazimine Use At Week 24													
	No ^a							Yes ^b						
	N	Mean	SE	SD	Median	Min	Max	N	Mean	SE	SD	Median	Min	Max
Week 24, 0 h	177	12.28	1.229	16.353	13.00	-34.0	67.0	17	31.94	5.735	23.644	27.00	6.0	82.0
Week 24, 5 h	170	12.36	1.258	16.406	11.50	-49.0	60.0	16	28.81	5.672	22.687	29.00	-11.0	82.0

N = number of subjects with data

^a This subgroup included only subjects who did not use clofazimine at Week 24 and had an ECG assessment at Day -1 (reference) and Week 24.

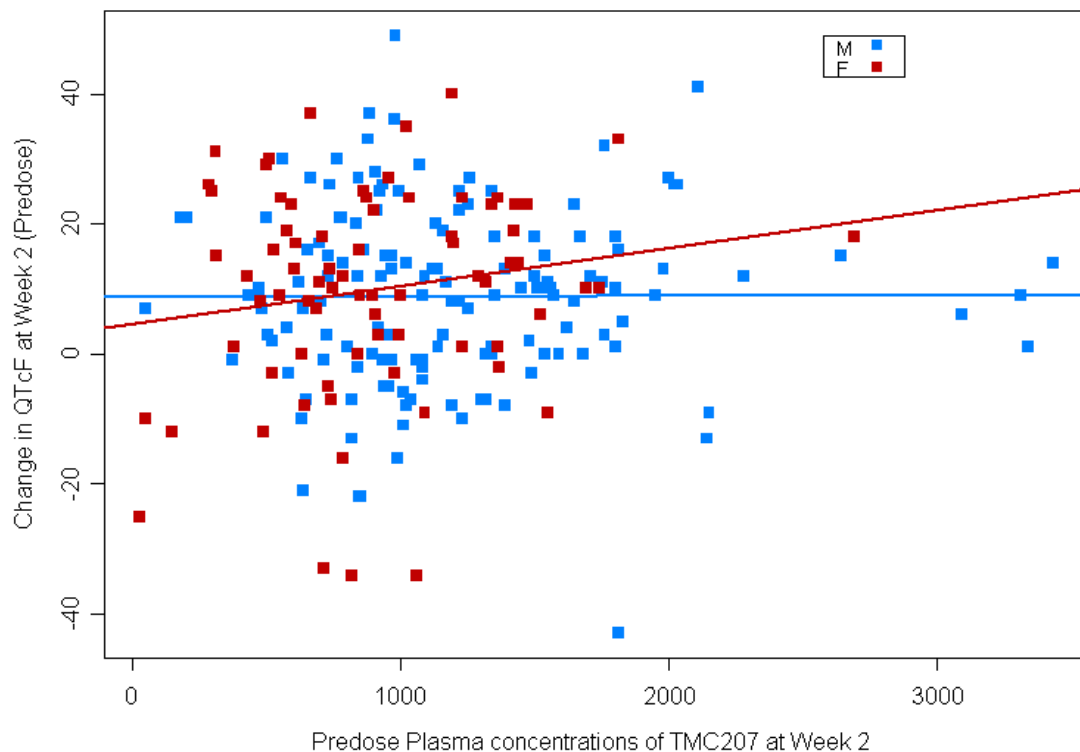
^b This subgroup included only subjects who used clofazimine at Week 24 and had an ECG assessment at Day -1 (reference) and Week 24.

6.3.5 Pharmacokinetic/Pharmacodynamic Relationships for Safety Parameters

Population PK parameters of bedaquiline were tabulated for subjects with or without SAEs, grade 4 AEs, Torsade de Pointes/QT prolongation SMQ events, and treatment-emergent QTcF abnormalities. No relevant differences in median bedaquiline C_{AVG} were observed for subjects with at least one SAE, grade 4 AE, or Torsade de Pointes/QT prolongation SMQ event, or QTcF abnormalities compared to subjects without these findings.

The relationship between QTcF and bedaquiline or M2 plasma concentration was explored graphically by gender. Scatterplots of bedaquiline or M2 plasma concentration versus change in QTcF for male and female subjects are shown in Figure 36 and Figure 37, respectively, for Week 2 and in Figure 38 and Figure 39, respectively, for Weeks 12 and 24.

A trend towards greater QTcF changes with higher bedaquiline or M2 plasma concentrations was observed in male and female subjects.

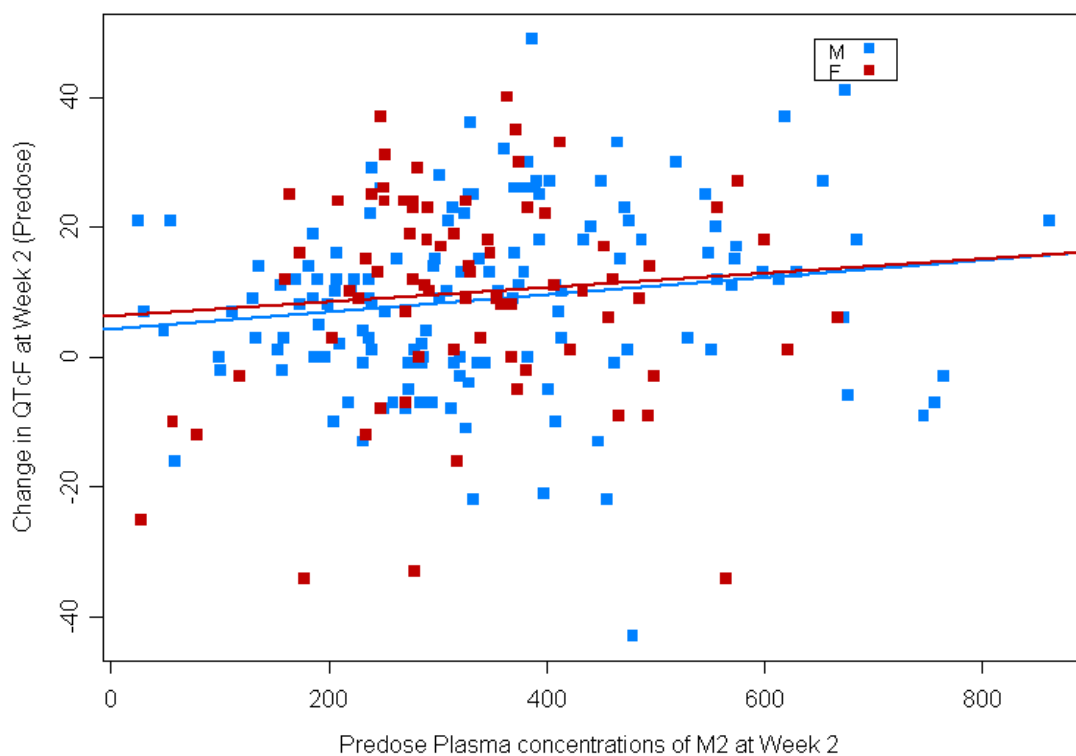


Blue line: Regression line for male subjects (estimate = 0.00012136, $R^2 = 0.0000$)

Red line: Regression line for female subjects (estimate = 0.00586, $R^2 = 0.0279$)

Data on file, Janssen Research and Development

Figure 36: C209: Scatterplot of TMC207 Plasma Concentration at Week 2 Versus Change in QTcF at Week 2 for Male and Female Subjects

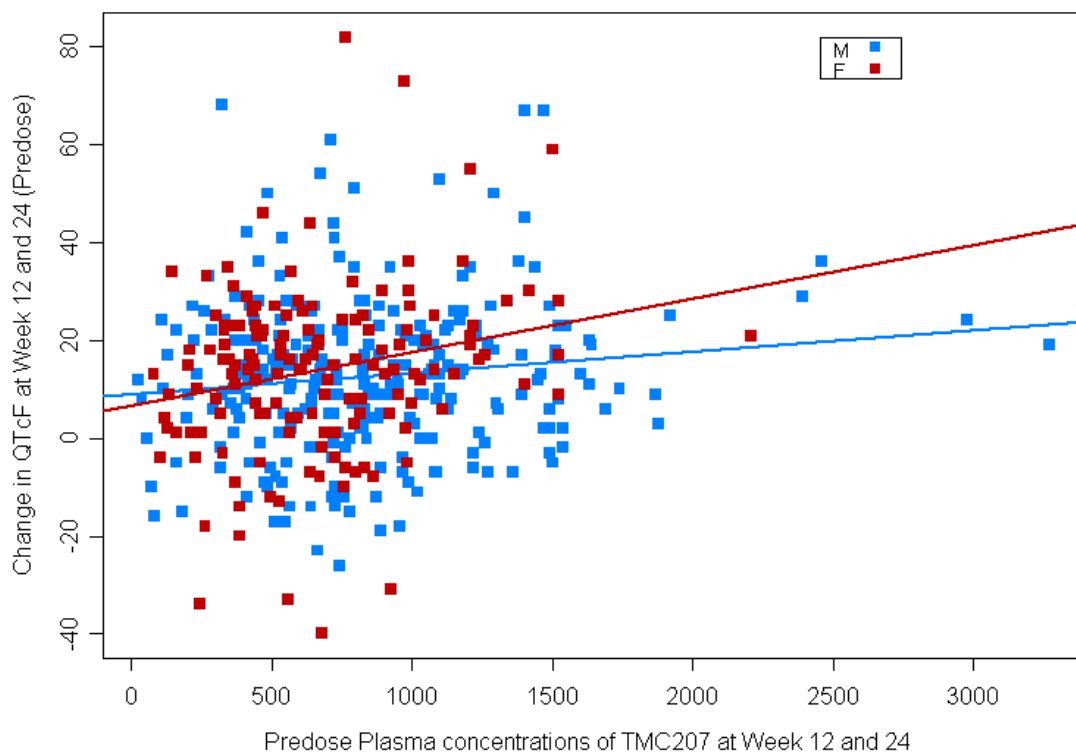


Blue line: Regression line for male subjects (estimate = 0.01310, $R^2 = 0.0241$)

Red line: Regression line for female subjects (estimate = 0.01114, $R^2 = 0.0078$)

Data on file, Janssen Research and Development

Figure 37: C209: Scatterplot of M2 Plasma Concentration at Week 2 (Daily Dosing Period) Versus Change in QTcF at Week 2 for Male and Female Subjects



Blue line: Regression line (mixed model with random subject) for male subjects (estimate = 0.004372, $R^2 = 0.0140^*$)

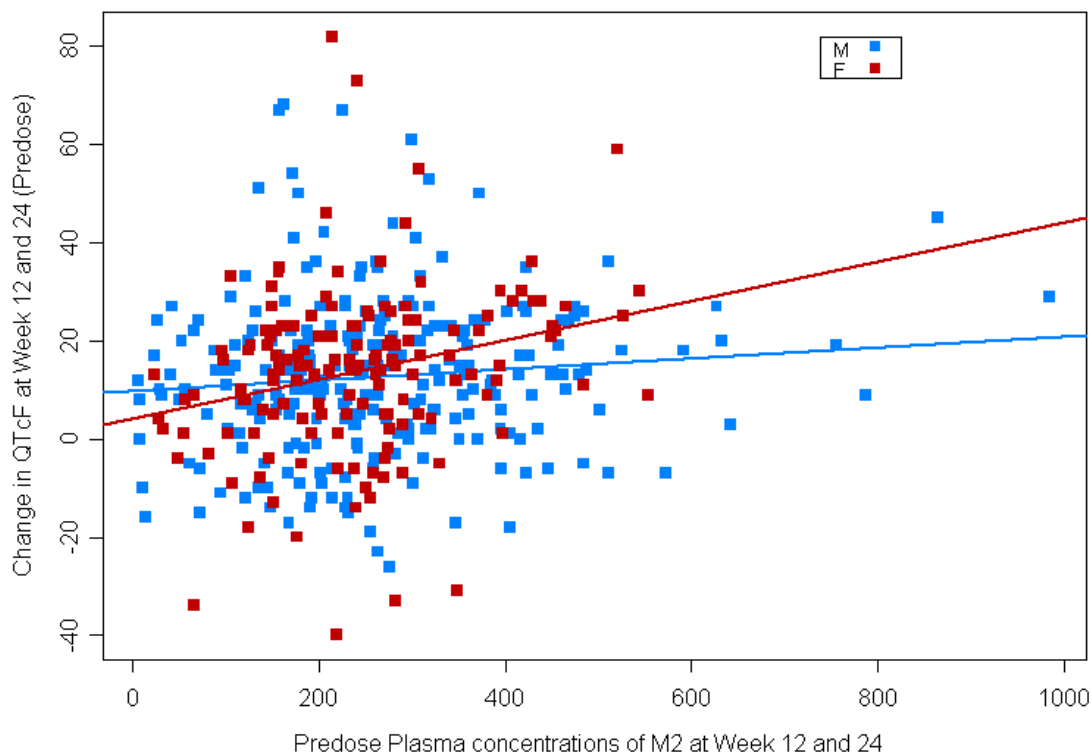
Red line: Regression line (mixed model with random subject) for female subjects (estimate = 0.01096, $R^2 = 0.0470^*$)

* Ignoring repeated measurement per subject

Week 12 and Week 24 are shown on the same graph to include all available data during intermittent dosing.

Data on file, Janssen Research and Development

Figure 38: C209: Scatterplot of TMC207 Plasma Concentration at Week 12 and Week 24 (Intermittent Dosing Period) Versus Change in QTcF at Week 12 and Week 24 for Male and Female Subjects



Blue line: Regression line (mixed model with random subject) for male subjects (estimate = 0.01089, $R^2 = 0.0123^*$)
 Red line: Regression line (mixed model with random subject) for female subjects (estimate = 0.04003, $R^2 = 0.0616^*$)

* Ignoring repeated measurement per subject

Week 12 and Week 24 are shown on the same graph to include all available data during intermittent dosing.

Data on file, Janssen Research and Development

Figure 39: C209: Scatterplot of M2 Plasma Concentration at Week 12 and Week 24 (Intermittent Dosing Period) Versus Change in QTcF at Week 12 and Week 24 for Male and Female Subjects

6.3.6 Conclusions

The results of the **C209** trial demonstrated that, overall, the treatment with bedaquiline of 400 mg q.d. for the first 2 weeks and 200 mg t.i.w for the following 22 weeks was generally well tolerated.

During the 24-week Investigational Treatment phase of **C209**, the most frequently reported AEs (> 5% of subjects) were hyperuricemia, arthralgia, nausea, vomiting, headache, diarrhea, blood uric acid increased, hypokalemia, pruritus, injection site pain, insomnia, and tinnitus.

Severe AEs were reported in 6.0% of subjects, AEs leading to discontinuation in 2.6% of subjects, and grade 3 or 4 AEs were reported in 18.9% of subjects. During the trial, 12 deaths

occurred. All SAEs leading to death were considered not related to bedaquiline by the investigator, except for renal impairment that was judged doubtfully related to bedaquiline and developed after vomiting and dehydration. An additional 4 subjects died during the survival follow-up phase, both described as TB-related, the investigator considered one SAE (hemoptysis) not related to bedaquiline and one SAE (unknown cause) doubtfully related to bedaquiline. None of these subjects had a treatment emergent QTcF ≥ 500 ms.

Adverse events identified by the SMQs for acute pancreatitis and Torsade de Pointes/QT prolongation were observed in at most 2.6% of subjects. Events identified by SMQs for drug related hepatic disorders were reported in 12.0% of subjects during the Investigational Treatment phase. None of the events identified by the SMQs for acute pancreatitis, Torsade de Pointes/QT prolongation, and SMQs for drug related hepatic disorders were considered serious or led to discontinuation of investigational medication, except one grade 3 event of ECG QT prolonged, which was reported as SAE and led to permanent discontinuation of bedaquiline. No AEs were identified by the SMQ for rhabdomyolysis/myopathy during **C209**.

Grade 3 or 4 laboratory abnormalities were observed for hyperuricemia, hyperglycemia, increases in AST, ALT, and GGT, increased WBC, increased pancreatic amylase, and decreased hemoglobin. The most frequent (in $> 10.0\%$) treatment-emergent nongraded laboratory abnormalities during the Investigational Treatment phase were CPK, pepsinogen I and II, eosinophils (%) and eosinophils count, gastrin, neutrophils (%) and total neutrophil count above normal, and total cholesterol, RBC count, and CPK-MB below normal. CPK was analyzed as a nongraded parameter as it is not included in the DMID grading scale.

Mean increases in QTcF were observed from the first assessment after Day 1 (i.e., Week 2), with mean increases from reference of more than 10 ms observed from Week 8. The largest mean increase in QTcF at a predose time point during the first 24 weeks was 14.2 ms (at Week 24; N = 200). After Week 24, QTcF increases were less pronounced: at Week 36 mean QTcF increase was 9.8 ms (N = 128). Mean increases from reference in QTcF were larger in subjects with concomitant CFZ use (Week 24, 0 h: 31.94 ms) than in subjects without concomitant CFZ use (Week 24, 0 h: 12.28 ms).

QTcF values of more than 500 ms were observed in 1 subject. QTcF increases from reference of more than 60 ms were noted in 9 (3.9%) subjects and resulted in QTcF values above 450 ms in 5

of those 9 subjects (including the subject with QTcF > 500 ms). QTcF increases from reference of 30 to 60 ms were noted in 84 (36.3%) subjects and resulted in QTcF values above 450 ms in 18 of those 84 (21.4%) subjects.

A systematic and well-documented approach was used to identify adverse drug reactions (ADRs) for bedaquiline. These were identified from the pooled safety database of the C208 trials, with additional review of safety data from Phase I and Phase IIa trials and the C209 trial. In the **pooled C208 trials**, the most frequently reported ADRs (>20%) in the Any bedaquiline group were nausea, arthralgia, headache, and vomiting. Additional ADRs identified were, in order of frequency: dizziness, transaminases increased, myalgia, diarrhea and ECG QT prolonged. ADRs of at least grade 3 were infrequent, and limited to reports of headache, arthralgia and increased transaminases occurring in at most 2 subjects (see Table 2).

Table 51: Pooled Controlled Phase IIb Trials: Adverse Drug Reactions of at Least Grade 3 During the Investigational Treatment Phase

SOC ADR (grouped term), n (%)	Investigational Treatment phase			
	TMC207		Placebo	
	24 Weeks N = 79	Any N = 102	24 Weeks N = 81	Any N = 105
<i>At least grade 3 ADR</i>	5 (6.3)	5 (4.9)	0	0
Nervous system disorders	1 (1.3)	1 (1.0)	0	0
Headache	1 (1.3)	1 (1.0)	0	0
Hepatobiliary disorders	2 (2.5)	2 (2.0)	0	0
Transaminases increased ^a	2 (2.5)	2 (2.0)	0	0
Musculoskeletal and connective tissue disorders	2 (2.5)	2 (2.0)	0	0
Arthralgia	2 (2.5)	2 (2.0)	0	0

N = number of ITT subjects with data, n = number of ITT subjects with this observation

^a Different AE preferred terms (i.e., transaminases increased, AST increased, ALT increased, hepatic enzyme increased, and hepatic function abnormal) do contribute to this ADR, while for the other ADRs the ADR is the preferred term.

Note: The determination of ADRs was not limited to one trial and consisted of several steps, including review of Pooled Phase I and Phase IIa safety databases.

Data on file, Janssen Research and Development

6.4 OVERALL BEDAQUILINE SAFETY CONCLUSIONS

In the placebo-controlled pooled Phase IIb trials, **C208, Stage 1** and **Stage 2**, the most frequently reported AEs in the bedaquiline group were nausea, arthralgia, headache, hyperuricemia, and vomiting.

Overall, there was an imbalance in the number of deaths in the pooled **Stage 1** and **Stage 2** (Stage 2 final analysis Topline results) **C208** trial. The Sponsor has thus provided preliminary, high-level safety information on all deaths from the Topline results of the final **Stage 2 C208** analysis, which were also presented in the Safety Update Report. In the pooled analysis (**Stage 1** and **Stage 2**) 12 subjects in the Any bedaquiline group and 4 subjects in the Any placebo group experienced a SAE leading to death; causes of death were varied with only death due to TB reported more than once, and none of these subjects had a treatment emergent QTcF ≥ 500 ms. Only 1 death occurred during the Investigational Treatment phase. The imbalance in deaths in the bedaquiline group is primarily driven by the **C208 Stage 2** results in which the imbalance was 10/79 (12.7%) bedaquiline subjects compared to 2/81 (2.5%) placebo subjects.

During the Investigational Treatment phase, mean QTcF increases were observed in both the bedaquiline and placebo groups but they were more pronounced in the bedaquiline group. In the bedaquiline group, a mean increase from reference in QTcF was observed from the first predose assessment after Day 1 (8.3 ms at Week 2). Mean increases from reference in QTcF grew gradually larger over the first 8 weeks of bedaquiline treatment and then remained more or less stable until Week 24. The largest treatment-emergent mean increase from reference in QTcF at a predose time point in the first 24 weeks was 15.4 ms in the bedaquiline group (at Week 24) and 7.7 ms in the placebo group (at Week 20). After Week 24, QTcF increases in the bedaquiline group gradually became less pronounced. QTcF values of more than 500 ms were observed in 1 subject in the bedaquiline group and QTcF values above 450 ms and QTcF increases of 30 to 60 ms and > 60 ms were observed more frequently in the bedaquiline group than in the placebo group.

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. A Hy's law 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 medications.

In the ongoing uncontrolled Phase IIb trial, **C209**, the most frequently reported AEs were hyperuricemia, arthralgia, nausea, vomiting, headache, diarrhea, blood uric acid increased, hypokalemia, pruritus, injection site pain, insomnia, and tinnitus. Up to the cut-off date of 15 July 2012, 16/233 subjects have died. 12 of these cases occurred during the trial and 4 in premature withdrawals.

An additional safety finding in the C209 trial showed that the small subset of patients receiving concomitant clofazimine had larger mean increases in QTcF from reference compared to subjects that did not receive concomitant clofazimine.

In both the controlled and uncontrolled trials, the most frequently reported ADRs in the bedaquiline group were nausea, arthralgia, headache, and vomiting. Additional ADRs identified were, in order of frequency: dizziness, transaminases increased, myalgia, diarrhea and ECG QT prolonged. ADRs of at least grade 3 were infrequent.

In conclusion, bedaquiline administered as 400 mg q.d. for 2 weeks and 200 mg dosed t.i.w. up to an additional 22 weeks was generally well tolerated in adults as part of combination therapy of pulmonary TB due to MDR *M. tuberculosis*. Upon analysis of the pooled placebo-controlled Phase IIb trial (**Stage 1** and **Stage 2**) an imbalance in the number of deaths was identified between the Any bedaquiline group and the Any placebo group despite better microbiologic outcomes in the bedaquiline group. The imbalance in deaths in the bedaquiline group is driven by the **C208 Stage 2** results in which 10/79 bedaquiline subjects compared to 2/81 placebo subjects died. The reason for the increased overall mortality in the bedaquiline group in this trial is as yet unclear given that the causes of death were varied (only death due to TB was reported more than once), and there was a wide range in time to death since last intake of bedaquiline/placebo (range; 115-504 days in **C208 Stage 1**, 2-911 days in **C208 Stage 2**). Only 1 death occurred during the Investigational Treatment phase. In addition, all deaths in the bedaquiline arm were considered not related to study drug by the investigator.

6.5 OVERVIEW OF SAFETY FINDINGS OF STUDIES CONDUCTED WITH BEDAQUILINE (TB ALLIANCE AND EARLY ACCESS PROGRAMS)

6.5.1 Trials Conducted by TB Alliance

The Sponsor has established a collaboration with the Global Alliance for TB Drug Development (TB Alliance) to share expertise and resources in the development of bedaquiline. The Sponsor has granted a license to the TB Alliance for the worldwide development of bedaquiline for DS-TB. Under the terms of the agreement, the Sponsor is responsible for the worldwide development of bedaquiline in the treatment of MDR-TB, while the TB Alliance is responsible for the worldwide development of bedaquiline for DS-TB. Therefore, the current new drug application submitted by the Sponsor is for MDR-TB and not for DS-TB.

Up to 15 March 2012, 2 Phase I trials with bedaquiline have been completed by the TB Alliance, and 1 Phase I trial is ongoing.

No additional safety findings were reported from these studies, with the exception of 5 SAEs of lymphocytopenia in a DDI study with rifabutin, for which lymphopenia is a known ADR⁷⁸. No deaths have been reported in any of the TB Alliance trials.

6.5.2 Early Access Programs

This section presents safety information from programs and studies where subjects who have pulmonary infection due to Pre-XDR or XDR *M. tuberculosis* strains and therefore have limited-to-no treatment options could benefit from bedaquiline treatment:

- CU program TBC3002 (in countries with a legal framework for CU, except in France; initiated in Q2 2011; up to the cutoff date of 15 Jul 2012, 29 subjects were exposed to TMC207);
- EAP TBC3001 (in countries with no legal framework for CU, e.g., Lithuania, Russia; up to the cut-off date of 15 Jul 2012, 17 subjects were exposed to TMC207)
- ATU RRA-5310 and TMC207TBC3003 (in France; up to the cut-off date of 15 Jul 2012, 32 subjects were exposed to TMC207).

Two deaths (1 case general status deterioration, 1 case death following bacterial pneumonia in a destroyed lung) have been reported in the Early Access Programs, no additional safety findings were reported.

7 BENEFITS AND RISKS CONCLUSIONS

7.1 SUMMARY OF BENEFITS

Periodic sputum culture is used to monitor treatment response in MDR-TB, and conversion of cultures from positive to negative for *M. tuberculosis* is the most important indicator of progress, and early sputum conversion has been shown to be a positive predictor of successful treatment outcome⁷⁹.

The addition of bedaquiline to a 5-drug MDR-TB treatment regimen for 24 weeks resulted in significantly shorter time to sputum culture conversion ($p < 0.0001$) and a significantly higher proportion of subjects achieving culture conversion ($p = 0.008$) at Week 24 (78.8% in the bedaquiline group and 57.6% in the placebo group; hazard ratio 2.41(95%CI [1.55-3.75]); $p = 0.008$) (based on the primary analysis method, i.e., missing = failure).

The results of other secondary endpoints and several sensitivity analyses showed robust efficacy of bedaquiline.

The superior treatment effect of bedaquiline as seen in **C208 Stage 2** was supported by results from **Stage 1** of the placebo-controlled **C208** trial. A recent publication⁸⁰ has confirmed that early culture conversion, as seen in **C208 Stage 1**, increased the incidence proportion of cure or treatment completion.

Further supportive data was obtained in the single-arm trial **C209**.

Furthermore, sputum culture conversion rates were also higher in subjects with XDR-TB at baseline than what has been reported in the literature: in **C209**, culture conversion at Week 24 was observed in 20 out of 36 mITT subjects (55.6%) infected with XDR-TB. Reports from literature indicate treatment success rates for HIV-negative XDR-TB of 43.7% and high mortality⁻⁵⁴

In addition, there was a trend for less development of resistance to anti-TB drugs (with validated critical concentrations) in bedaquiline treated patients compared to patients in the placebo group.

The proposed treatment regimen of bedaquiline (400 mg q.d. for 2 weeks and 200 mg dosed t.i.w. up to an additional 22 weeks) added little to the constellation of adverse effects seen in MDR-TB treatment, acknowledging a modest increase in QT and increase in hepatic transaminases. An important safety finding identified upon analysis of trial C208 Stage 2 was an imbalance in the number of deaths between the TMC207 group and the placebo group. No clear explanation to associate mortality and TMC207 exposure in this trial has been identified, given that the causes of death were varied and onset generally late. The overall mortality in this trial was 12.7 % in the TMC207 group, compared to 2.5% in the placebo group. In the literature, mortality of patients being treated for MDR-TB usually exceeds 10%, with a range of 8% to 21%⁸¹. A recently published individual patient data meta-analysis of 9,153 patients with MDR TB reported a mortality rate of 15%¹³.

Bedaquiline has the potential to fulfill an unmet medical need in the treatment of MDR-TB, especially with the increasing incidences of Pre-XDR- and XDR-TB cases that make the need for new TB drugs even more urgent⁴³. Since culture conversion reduces patient infectivity, treatment with bedaquiline will have important public health benefits by reducing the spread of MDR-TB and thus preventing additional secondary cases of MDR-TB. Due to the faster sputum conversion resulting from treatment with bedaquiline, bedaquiline facilitates TB treatment in the community thus obviating the need for prolonged hospitalization that is sometimes required for patients receiving second-line injectable drugs; reduced hospitalizations and monitoring expenses would be welcome to fiscally challenged TB control programs. Prevention of the evolution from MDR-TB to more resistant forms of the disease (Pre-XDR and XDR-TB) that follows the arrest of acquisition of resistance to other 2nd line drugs, would have important medical, public health and

economic benefits because these more resistant forms of TB have higher mortality, are more difficult to treat and rapidly consume limited public health department budgets.

7.2 SUMMARY OF RISKS AND UNANSWERED RISK QUESTIONS

The safety concerns of treatment with bedaquiline include the identified risk of ECG QT prolongation, and the potential risks of pancreatitis, myopathy, myocardial injury, severe hepatotoxicity development or drug resistance, off-label use, and medication error. In addition, a mortality imbalance was observed in the C208 Stage 2 trial.

Although the safety profiles of bedaquiline and placebo when administered with a background MDR-TB regimen are comparable, there are 2 main safety findings associated with bedaquiline treatment, i.e., elevation of transaminases and QT prolongation.

There was a trend for increased hepatic transaminases during treatment with bedaquiline, with a higher percentage of graded laboratory abnormalities in the bedaquiline group than in the placebo group. Furthermore, mean transaminase values increased from baseline during bedaquiline treatment, but returned to within the normal range after Week 24. The majority of grade 3/4 transaminase increased AEs resolved. Of note, no severe cases of liver toxicity were attributed to bedaquiline by the investigators. 1 subject (bedaquiline group) met the laboratory criteria for Hy's Law. Medical assessment suggests the hepatic toxicity in this subject was more likely caused by the background TB regimen and alcohol abuse than by bedaquiline. During bedaquiline treatment liver transaminases can be monitored with routine laboratory testing.

Events of moderate increases in QTcF interval were seen more frequently in the bedaquiline group. Few QTcF increases were considered AEs and only 1 was treatment-limiting and reported as an SAE (ECG QT prolonged). There were no reports of Torsade de Pointes or serious ventricular arrhythmias. A comprehensive clinical assessment of the preclinical safety signals of cardiomyocyte degeneration did not reveal evidence of cardiac muscle injury due to bedaquiline treatment. Analysis of CPK-MB and troponin I showed a pattern of abnormally high values that were similar in the bedaquiline and placebo groups and did not suggest a relationship to bedaquiline dosing. The increase in QTcF interval associated with bedaquiline is considered moderate and is amenable to routine clinical monitoring. As a precaution, an ECG should be obtained prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.

Bedaquiline treatment must be discontinued if the patient develops clinically significant ventricular arrhythmia or a QTcF interval of > 500 ms (confirmed by repeat ECG assessment).

An important finding was the imbalance in the number of deaths between the bedaquiline group and the placebo group reported in **Stage 2** of trial **C208**. No clear explanation to associate increased overall mortality and bedaquiline exposure in this trial has been identified given that the causes of death were varied (only death due to TB was reported more than once), and there was a wide range in time of death since last intake of bedaquiline/placebo, with only 1 death occurring during the Investigational Treatment phase. All deaths were considered not related to bedaquiline by the investigators. In general, the causes of death reported for the majority of the subjects are similar to the causes of death reported from a study from 1963 that utilized autopsies from 295 patients treated for pulmonary TB to ascertain probable causes of death in TB in the pre-and post antibiotic era in the US³².

Although the currently available efficacy results show that treatment including bedaquiline is superior compared to treatment with the BR without bedaquiline, the long-term outcome results with regard to sterilizing activity of bedaquiline are currently limited.

Patient populations for which limited or no data of bedaquiline treatment are currently available, and therefore no efficacy and no safety conclusions can be drawn, include patients with cardiovascular risk factors, severe hepatic insufficiency, severe renal insufficiency, elderly (aged ≥ 65 years), pediatrics (aged < 18 years), nursing mothers, and during pregnancy.

To safeguard bedaquiline's efficacy, bedaquiline should only be administered as part of a MDR-TB regimen. It is recommended that bedaquiline is administered by directly observed therapy (DOT). Bedaquiline should only be used in combination with at least 3 drugs to which the patient's isolate has been shown to be susceptible in vitro. If in vitro testing results are unavailable, treatment may be initiated with bedaquiline in combination with at least 4 other drugs to which the patient's isolate is likely to be susceptible, based on historical data of resistance testing results and previous TB treatment exposure. The total duration of treatment with bedaquiline is 24 weeks (400 mg q.d. for the first 2 weeks and as 200 mg t.i.w. for the following 22 weeks). Throughout treatment with, and following the last intake of bedaquiline, patients should continue to take their companion drugs in accordance with national TB treatment guidelines and local MDR-TB treatment practice. The recommendations in case of missed

dose(s) are as follows: If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From Week 3 onwards, if a dose is missed, patients should take the missed dose, and adjust the dosing schedule to ensure the total dose of bedaquiline during the 7-day period does not exceed 600 mg (taken as 3 intakes of 200 mg per day, at least 24 hours apart).

Because bedaquiline is metabolized by CYP3A4, its exposure may be reduced during co-administration with CYP3A4 inducers (which may reduce its therapeutic effect) and increased during co-administration with CYP3A4 inhibitors (which could potentially increase the risk of adverse reactions). Therefore, the systemic use of moderate and strong CYP3A4 inhibitors for more than 14 consecutive days and of potent CYP3A4 inducers should be avoided during administration of bedaquiline.

7.3 OVERALL BENEFITS/RISKS

The results in the Phase IIb trials with MDR-TB subjects provide robust evidence of improved anti-mycobacterial activity, leading to a significantly shorter time to conversion and a higher proportion of culture conversion, with bedaquiline in combination with a BR of anti-TB drugs, compared a BR without bedaquiline.

Bedaquiline is generally well tolerated. The 2 main safety risks associated with bedaquiline treatment, i.e., elevation of transaminases and QT prolongation, are both moderate, reversible, and can be monitored with routine ECG and laboratory testing. An important safety finding was the imbalance in the number of deaths between the bedaquiline group and the placebo group reported in Stage 2 of trial C208. Analysis does not suggest QT prolongation contributed to the deaths. Two deaths had hepatic injury confounded by alcohol related complications.

The currently proposed risk management includes ongoing monitoring with routine pharmacovigilance practices in collaboration with public health authorities. Additional safety data, including data from treatment of HIV co-infected subjects, will be collected during the planned Phase III controlled trial C210, including 600 patients (300 exposed to bedaquiline). During this trial, both the identified and potential risks of bedaquiline treatment will continue to be carefully monitored. Survival follow up for all subjects, including those who prematurely discontinue the trial (if not withdrawing consent), will be standardized to 2 years after last intake

of bedaquiline/placebo. The Package Insert includes an identification of risks, with warnings and precautions regarding cardiovascular safety and QT prolongation, drug-drug interactions and use in HIV-coinfection; both ECG QT prolonged and transaminases increased are listed as ADRs.

Additional activities that are currently under evaluation or in development to minimize the risk include a communication plan, including a product website, and the setting up a controlled distribution through collaboration with public health authorities including controlled access, and a patient registry.

In conclusion, the results of the clinical development program support the use of bedaquiline, as part of combination therapy, for the treatment of pulmonary tuberculosis due to MDR-TB in adults (≥ 18 years). The recommended regimen of bedaquiline is 400 mg q.d. for 2 weeks, followed by 200 mg t.i.w. for 22 weeks (i.e., a total of 24 weeks). An accelerated approval for bedaquiline would provide broader access to bedaquiline for patients suffering from MDR-TB, who could benefit from a new treatment option that decreases the time to culture conversion and increases the likelihood to culture convert by Week 24 of treatment.

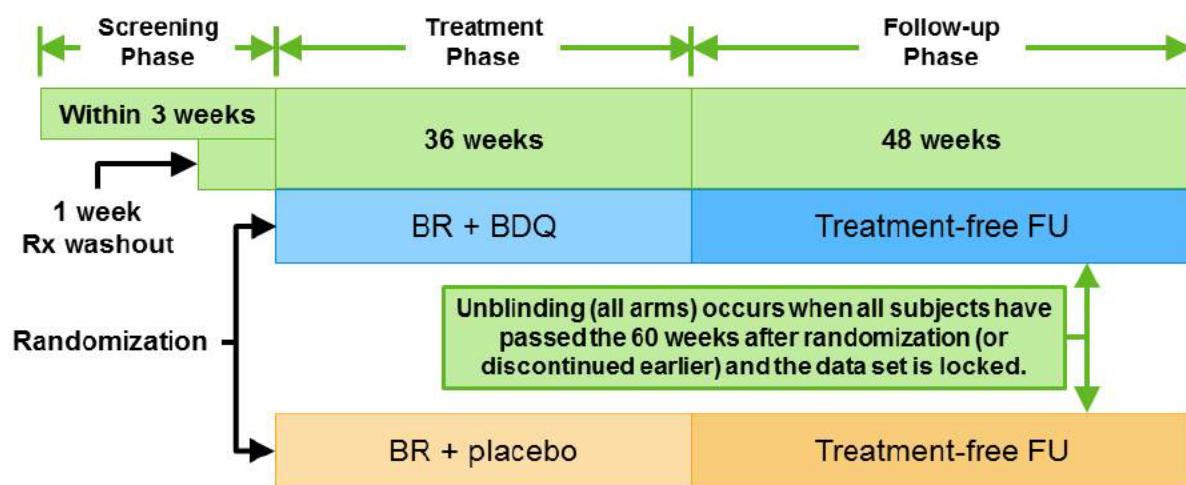
8 PLANNED PHASE III C210 TRIAL

A confirmatory Phase III trial (**C210**) to support the full approval of bedaquiline will be initiated in 2013. Trial **C210** is planned to be conducted in Brazil, Cambodia, China, Colombia, Estonia, Korea, Latvia, Mexico, Peru, the Philippines, Russia, South Africa, Taiwan, Thailand, Turkey, Ukraine, and Vietnam. This trial will utilize a BR comparable to the BR that is currently being evaluated in several countries around the world, as part of the STREAM study⁻³² and based on promising results from an observational study in Bangladesh⁵³. Levofloxacin will replace gatifloxacin or moxifloxacin in the BR given the latter 2 drugs potential for QTc prolongation⁻³⁵. A target of approximately 600 subjects with sputum smear-positive pulmonary infection with MDR-TB or Pre-XDR-TB will receive a BR of MDR-TB therapy and are planned to be randomly assigned in a 1:1 ratio to one of 2 treatment arms (Arms A and B). The 2 randomized treatment arms shorten the overall treatment of MDR TB compared to the WHO standard of care, by providing bedaquiline/placebo (Arm A/Arm B) with a 7-drug BR for 36 weeks. In this way, the study addresses one of the needs expressed by the TB community to explore regimens

of shorter treatment duration and aims to provide confirmatory data that bedaquiline added to a BR improves efficacy. Throughout the **C210** trial, an Independent Data Monitoring Committee will monitor safety and tolerability on a regular basis and make recommendations regarding the continuation, modification, or termination of the trial to the Sponsor.

The Sponsor submitted protocol bedaquiline **C210** entitled “A Phase III Placebo-Controlled, Double-Blind, Randomized Trial to Evaluate the Efficacy and Safety of bedaquiline in Subjects with Sputum Smear-Positive Pulmonary Infection with Multi-Drug Resistant Mycobacterium tuberculosis (MDR-TB)” to the FDA for review under a “Special Protocol Assessment” on 28 December 2011. A Special Protocol Assessment is an agreement between the Sponsor and the FDA indicating that the Sponsor’s proposed trial protocol, including, clinical endpoints and statistical analyses, are acceptable to support regulatory approval of the treatment being evaluated. On 10 February 2012 the Sponsor received FDA’s Special Protocol Agreement.

A schematic overview of the study design is provided in [Figure 40](#).



☆ Unblinding (all arms) occurs when all subjects have passed the 60 weeks after randomization (or discontinued earlier) and the data set is locked.

BR = background regimen; BDQ = bedaquiline; FU = follow-up

Figure 40 C210: Schematic Overview of the Study Design

APPENDICES

APPENDIX 1: TRIAL C208 STAGE 1 AND STAGE 2 TIME AND EVENTS SCHEDULE (TREATMENT AND FOLLOW-UP PERIOD)

Type of Visit	Screening Visit ^a	Stage 1: Treatment Period (8 weeks)										Stage 1: Follow-up Period							
		Stage 2: Treatment Period (24 weeks)																	
		Day -1	Day 1	Day 7	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24
Time of Visit																			
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Informed consent	X																		
Study medication Stage 1 ^b			X	X	X	X	X	X	X	X	X								
Study medication Stage 2 ^b			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BR medication ^{b,c}			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic data	X																		
Pregnancy test ^d	X	X					X				X		X		X		X		X
Inclusion/exclusion criteria	X	X																	
Medical & surgical history/ Concomitant diseases	X																		
Rapid screen test ^{bb}	X																		
Physical examination ^{e,f}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample ^e	X ^h	X			X		X		X		X	X	X	X	X	X	X	X	X
Feces sample	X ^{ee}				X ^{dd}														
Laboratory safety tests ⁱ	X	X			X		X		X		X	X	X	X	X	X	X	X	X
HIV-1 & 2 status	X																		
CD4+ count ^j	X										X				X				X
Vital signs ^{e,k}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG ^e	X ^z	X ^{l,z}	X ^{l,z}	X	X ^{l,z}	X	X	X	X	X	X ^{l,z}	X	X	X	X	X	X	X	X ^{l,z}
Chest X-ray ^m	X										X				X				X
Audiometry		X					X				X		X ^{aa}		X ^{aa}		X ^{aa}		X ^{aa}

Type of Visit	Screening Visit ^a	Stage 1: Treatment Period (8 weeks)										Stage 1: Follow-up Period							
		Stage 2: Treatment Period (24 weeks)																	
Time of Visit		Day −1	Day 1	Day 7	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10	Week 12	Week 14	Week 16	Week 18	Week 20	Week 22	Week 24
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Spot sputum sample (AFB smear, qualitative sputum culture) ^{e,y}	X	X ⁿ		X	X	X	X	X	X	X	X ⁿ	X	X	X	X	X	X	X	X ⁿ
Pooled sputum sample ^o		X		X ^p	X ^p		X ^p		X		X ^p	X ^p	X ^p		X ^p		X		X ^p
Pharmacokinetics ^{e,q}				X	X ^{r,s,t}	X	X	X	X	X	X ^{r,s}	X ^u	X		X ^{r, u}				X ^{r,s,t}

Type of Visit	Stage 1: Follow-up Period, cont'd											In case of withdrawal ^{w,cc}	Follow-up after withdrawal ^x
	Stage 2: Follow-up Period ^{cc}												
Time of Visit	Week 28	Week 32	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96	Week 104 (Stage 1 only)	Week 108 (Stage 2 only)	Week 120 (Stage 2 only)		
Visit	20	21	22	23	24	25	26	27	28		29	X	Y
BR medication ^{b,c}	X	X	X	X	X	X	X	X	X	X	X		
Compliance	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy test ^d			X	X	X	X	X	X	X	X	X	X	X
Physical examination ^{e,f}	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ^g	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample ^e	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety assessments ¹	X	X	X	X	X	X	X	X	X	X	X	X	X
CD4+ count ^l			X	X	X	X	X	X	X	X	X	X	
Vital signs ^{e,k}	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG ^e	X	X	X ^z	X ^z	X	X	X			X	X	X	X
Chest X-ray ^m				X								X	X
Spot sputum sample (AFB smear, qualitative sputum culture) ^{e,y}	X	X	X	X	X ⁿ	X ⁿ	X	X	X	X	X	X	X
Pharmacokinetics ^{e,q}	X ^v	X ^v	X	X	X	X	X	X ^v	X ^u		X ^v		

^a Screening visit has to be performed within 14 days prior to Day 1; the subject must discontinue all TB drugs to allow 7 days washout.

- ^b TMC207 or placebo will be taken orally with water, 10 minutes after completion of a standardized breakfast. BR medication should preferably be taken before breakfast, except on days of sampling for full pharmacokinetic profiling when all study medication (TMC207 or placebo, and BR drugs) will be taken within 10 minutes following completion of breakfast. All study medication administration will be supervised.
- ^c The BR is selected prior to randomization. It is commonly recommended that 18-24 months total therapy be administered; the period may be shortened provided that 12 months of treatment have been given after documentation of sputum culture conversion from positive to negative.
- ^d For female subjects only; serum test at screening, urine test at other visits.
- ^e Assessments are to be made and samples are to be taken before study medication intake. Blood samples for predose pharmacokinetics are to be taken before breakfast within 1 hour before scheduled intake of study medication. ECG readings are to be made within 1 hour before intake of study medication. Single ECG's will be taken, except for the ECG's marked with footnote 'z'
- ^f Includes weight, temperature, and ophthalmologic exam. At screening and at the end of treatment period, the ophthalmologic exam should include a fundoscopic examination. At the other visits, the ophthalmologic exam should include a 'red reflex' of the fundus with an external light source.
- ^g Adverse events will be monitored continuously from signing of informed consent form onwards until the last trial related activity.
- ^h An additional urine sample must be collected for drug screening.
- ⁱ Subjects should have fasted for at least 10 hours (overnight) prior to sampling for laboratory assessments.
- ^j For all subjects at screening and for HIV positive subjects at other timepoints.
- ^k Includes pulse rate, blood pressure, and respiratory rate.
- ^l On Days -1 and 1, and at Weeks 2, 8, and 24, ECGs will be taken at 0 and 5h relative to dosing. On days where no TMC207 or placebo is administered (i.e., Day -1 and Weeks 24 for **Stage 1**; Day -1 for **Stage 2**), ECGs will be taken relative to 8 a.m. (first ECG will be taken at 8 a.m.). ECGs during follow-up will be taken relative to 8 a.m. if possible, after breakfast. At Weeks 8 (for **Stage 1** only) and 24 (for **Stage 2** only), an additional ECG will be taken at 36 and 48h after dosing.
- ^m One radiologist experienced in tuberculosis per site will interpret all chest X-rays. X-rays may be taken more frequently as needed for any evidence of worsening pulmonary health, as determined by the investigator.
- ⁿ *M. tuberculosis* identification will be done on Day -1. Drug susceptibility testing will be done on Day -1, at Weeks 8 and 24, and one year after the last dose of TMC207 or placebo (i.e., at Week 60 for **Stage 1** and Week 72 for **Stage 2**). Additional drug susceptibility assessments are to be made in case of failure to respond to treatment (failure of sputum culture conversion), relapse (having positive sputum culture after having been defined converted with isolation of the same strain of MDR-TB), or new infection/reinfection (initial sputum culture conversion according to protocol definition but subsequent return of sputum culture from negative to positive with isolation of a different strain of MDR-TB).
- ^o Overnight (16h) sputum samples will be collected for quantitative sputum culture and for time to culture positivity (MGIT) in a subset of subjects. This sampling will start on the indicated visit day and will continue until the next morning.
- ^p Sputum concentrations of TMC207 and M2 will be determined in a subset of subjects, in an aliquot of the overnight sputum samples collected on Day 7 and at Weeks 2, 4, and 8 for **Stage 1** and on Day 7 and at Weeks 2, 8, 16, and 24 for **Stage 2**. For subjects in **Stage 1** who remain hospitalized at Weeks 10, 12, 16, and/or 24, additional overnight sputum will be collected for analysis of sputum TMC207 and M2 concentrations.
- ^q Predose (before intake of TMC207 and within 1 hour of the next scheduled intake) sampling for plasma concentrations of TMC207 and M2 will occur weekly up to Week 8 for **Stage 1** subjects, and on Day 7 and Weeks 2, 4, 8, 12, 16, and 24 for **Stage 2** subjects.
- ^r For all **Stage 2** subjects, an additional sample at 5 h after dosing will be collected at Weeks 2 and 24. At Weeks 8 and 16, an additional sample will be collected at anytime postdose.
- ^s At Weeks 2, 8 and 24 for **Stage 1** subjects, and at Weeks 2 and 24 for **Stage 2** subjects, full pharmacokinetics profiling will be performed in all subjects of **Stage 1** and in a subset of subjects in **Stage 2**; pharmacokinetics sampling will occur predose and 1, 3, 5, 6, 8, 12, and 24 h after dosing. At Weeks 8 (for **Stage 1** only) and 24 (for **Stage 2** only), 48-hour pharmacokinetic profiling (i.e., additional samples at 36h and 48h after dosing) will be done.
- ^t At Weeks 2 and 24 during **Stage 1**, the pharmacokinetics of the drugs in the BR will be determined for evaluation of drug-drug interactions.
- ^u Follow-up pharmacokinetic assessments for **Stage 1** subjects at Weeks 10, 12, 16, 24, 36, 48, 60, 72, 84, and 104.

-
- ^v Follow-up pharmacokinetic assessments for **Stage 2** subjects at Weeks 28, 32, 36, 48, 60, 72, 84, 96, and 120.
 - ^w Visit is to be performed at time of withdrawal from the trial or the following morning. Subjects who prematurely discontinue the trial (except for withdrawal of consent) are to be followed for survival until the last follow-up visit for the last subject in the trial. Investigators are asked to provide minimal information about the survival/clinical outcome of subjects, approximately every 6 months.
 - ^x Visit is to be scheduled between 5 and 7 days after withdrawal from the trial (other than withdrawal of consent).
 - ^y At each visit, triplicate spot sputum samples should be taken.
 - ^z At these visits, triplicate ECGs will be taken. At Week 2 and Week 24 of **Stage 2** (full PK days), triplicate ECGs will be taken at each PK timepoint in the subpopulation undergoing full PK profiling.
 - ^{aa} Only for **Stage 2** subjects
 - ^{bb} Resistance should be shown by susceptibility culture OR rapid screen tests. If resistance to rifampin or isoniazid is based on rapid screen tests, these tests need to be repeated at the screening visit and both tests must be positive. Rapid screen test for determination of resistance to rifampin and isoniazid are fast plaque and Genotype MTBDR line probe (both tests need to be positive).
 - ^{cc} Subjects who will be enrolled into the rollover arm will perform the rollover visit. Thereafter they will follow the visit schedule as displayed in the rollover flowchart.
 - ^{dd} During **Stage 2** of the trial, feces will be quantitatively collected over 24h from 12 subjects at the day of dosing
 - ^{ee} At the screening visit a fecal control sample will be collected from two patients, provided patients consent to feces sampling during this visit.

Remark: Cultured specimens will be preserved for genetic sequencing of *M. tuberculosis* isolates in case cured subjects have relapse during the course of the trial, experience reinfection/new infection, or fail their MDR-TB treatment.

[illegible]

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- ^a Subjects who are found eligible to participate in the rollover arm will continue with the visit schedule of this flowchart. For the rollover subjects the withdrawal visit from the main flowchart is the same as the rollover visit of this flowchart.
 - ^b TMC207 will be taken orally with water, 10 minutes after completion of breakfast. All study medication administration will be supervised.
 - ^c Subjects will continue to receive a BR that has been optimized based on the most recent available susceptibility results and local clinical practice. It is commonly recommended that 18-24 months total therapy be administered; the period may be shortened provided that 12 months of treatment have been given after documentation of sputum culture conversion from positive to negative. All study medication administration will be supervised.
 - ^d For female subjects only: urine pregnancy test.
 - ^e Includes weight, temperature, and ophthalmologic exam.
 - ^f Adverse events will be monitored continuously from signing of the Informed Consent Form (ICF) onwards until the last trial-related activity.
 - ^g On days of pharmacokinetic sampling (i.e., Week 2R, Week 12R, and Week 24R), assessments (ECG and vital signs) are to be made and samples (safety blood sample and urine sample) are to be taken before study medication intake. On other days, the safety blood sample should be taken as early as possible on the day of the visit/ Single ECG's will be taken.
 - ^h An additional urine sample must be collected for drug screening.
 - ⁱ Subjects should preferably have fasted for at least 10 hours prior to sampling for laboratory safety tests.
 - ^j For human immunodeficiency virus (HIV)-positive subjects only.
 - ^k Includes pulse rate, blood pressure, and respiratory rate.
 - ^l For determination of TMC207 and M2 plasma concentrations; sample should be taken before TMC207 intake and within 1 hour of the next scheduled intake.
 - ^m At each visit, triplicate spot sputum samples should be taken. During treatment, this should be done before intake of TMC207.
 - ⁿ Drug susceptibility testing will be done on Day 1 and after the last dose of TMC207. Additional drug susceptibility assessments may be made at the discretion of the investigator or treating physician in case of failure to respond to treatment, in order to optimize the patient's subsequent therapy.
 - ^o Visit is to be performed at time of withdrawal from the trial or the following morning. Subjects who prematurely discontinue the trial (except for withdrawal of consent) are to be followed for survival until the last follow-up visit for the last subject in the trial. Investigators are asked to provide minimal information about the survival/clinical outcome of subjects, approximately every 6 months.
 - ^p Visit is to be scheduled between 5 and 7 days after withdrawal from the trial (for reasons other than withdrawal of consent).
 - ^q Subjects with pre-existing XDR-TB for whom second-line susceptibility results only become available after randomization, who were randomized in the group receiving TMC207 and who rollover to the rollover arm of **Stage 2**, will complete the rollover visit and start the visit that matches the visit schedule the patient had reached in the main study before rollover.
 - ^r Total TMC207 treatment should be 24 weeks (pre-existing XDR patients that were on TMC207 will continue TMC207 in the rollover arm).
 - ^s All subjects will be followed for 96 weeks after their last dose of TMC207.

[illegible]

culture) ^m																			
^a	TMC207 will be taken orally with water, after completion of breakfast. TMC207 and BR intake should be supervised using DOTS-Plus according to the country's national TB program DOTS guidelines. Family and community members may be used to verify compliance when the patient is an outpatient.																		
^b	BR per NTP treatment guidelines.																		
^c	Subjects will continue to receive BR until, as commonly recommended, they reach a total treatment duration of approximately 18 to 24 months, including MDR-TB treatment started before intake of TMC207.																		
^d	For female subjects only: serum pregnancy test as screening, urine pregnancy test at other visits.																		
^e	For subjects who were previously diagnosed with MDR-TB and are being treated, the start date and details of their treatment regimen will be recorded, if known.																		
^f	Includes weight, temperature, and ophthalmologic exam. At baseline and Week 24 fundoscopy may be performed at the investigator's discretion.																		
^g	On Day 1 and on days of pharmacokinetic sampling (i.e., Week 2, Week 12, and Week 24), assessments (ECG and vital signs) are to be made and samples (safety blood sample and urine sample) are to be taken before intake of TMC207. On other days, the safety blood sample should be taken as early as possible on the day of the visit. Triplicate ECG's at 0 hours (predose) and 5 hours post-dose will be obtained at Day 1 and Week 2, 8, 12, and 24. Furthermore, a triplicate ECG will be taken at 0 hours and 5 hours relative to 8 a.m. on Day -1. Two additional triplicate ECGs will be taken at Week 36 and 48. Single ECGs will be taken at all other visits for safety assessments.																		
^h	An additional urine sample must be collected for drug screening.																		
ⁱ	Subjects should preferably have fasted for at least 10 hours prior to sampling for laboratory safety tests.																		
^j	For all subjects at screening and for human immunodeficiency virus (HIV)-positive subjects at other time points.																		
^k	Includes blood pressure, pulse rate, and respiratory rate.																		
^l	For determination of TMC207 and M2 plasma concentrations; sample should be taken before intake of TMC207, within 1 hour of the next scheduled intake (i.e., between 23-25 [Week 2], 47-49 or 71-73 hours after the preceding intake).																		
^m	At each visit, triplicate spot sputum samples should be taken. During treatment, this should be done before intake of TMC207.																		
ⁿ	<i>M. tuberculosis</i> identification will be done on Day -1. Drug susceptibility testing will be done on Day -1 and after the last dose of TMC207 (i.e., Week 24). Additional drug susceptibility assessments may be made at the discretion of the investigator or treating physician in case of failure to respond to treatment, in order to optimize the patient's subsequent therapy. <i>Note:</i> If the spot sputum sample is insufficient in quantity to perform susceptibility testing, a pooled sputum sample can be requested from the patient.																		
^o	Visit is to be performed at time of withdrawal from the trial or the following morning. Subjects who prematurely discontinue the trial (except for withdrawal of consent) are to be followed for survival for 24 months or until the last follow-up visit for the last subject in the trial. Investigators are asked to provide minimal information about the survival/clinical outcome of subjects, approximately every 6 months.																		
^p	Visit is to be scheduled between 5 and 7 days after withdrawal from the trial (for reasons other than withdrawal of consent).																		
^q	For HIV-positive subjects only. HIV-positive subjects must bring their most recent viral load results to the screening visit. These results may not be older than 3 months. If prior results are not available or are older than 3 months, then viral load measurement should be repeated at screening at a local lab.																		
^r	Feces will be quantitatively collected over 24 hours from 6 subjects who are enrolled at selected sites in South Africa at the day of dosing.																		
^s	A pre-treatment control sample is to be collected before or at Day -1 from 6 subjects enrolled at selected sites in South Africa provided subjects consent to feces sampling.																		
^t	The chest X-ray is not mandatory at screening when the subject has taken the test within 1 month prior to the screening visit.																		

Note: Unscheduled visits should be planned to assess, confirm, and follow up on clinically relevant adverse events (AEs) or laboratory abnormalities.

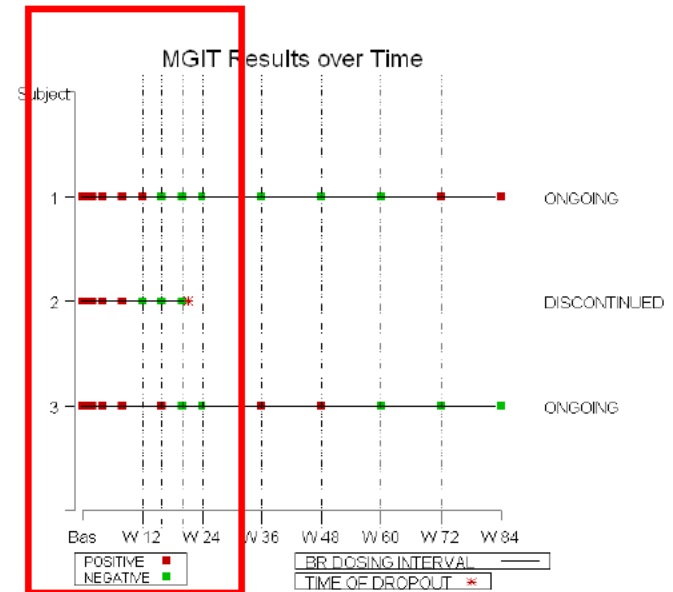
APPENDIX 3: EXAMPLES RESPONSE DEFINITIONS

24 Week Data Selection

For the 24 Week Data Selection, only consider the measurements within the red box. The column that indicates the conversion (Converter?), also indicates the censoring (yes=event, no=censored) in the time to analysis.

Subject	Primary Analysis Method		End-Censored (M=F)		No Overruling	
	Time to	Converter?	Time To	Converter?	Time To	Converter?
1	W16	Yes	W16	Yes	W16	Yes
2	W20*	No	W24*	No	W12	Yes
3	W20	Yes	W20	Yes	W20	Yes

*: censored

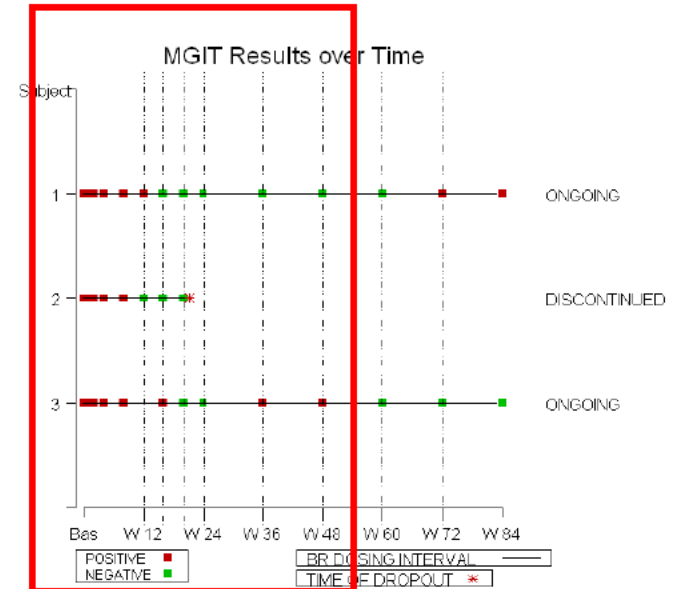


48 Week Data Selection

For the 48 Week Data Selection, only consider the measurements within the red box. The column that indicates the conversion (Converter?), also indicates the censoring (yes=event, no=censored) in the time to analysis.

Subject	Primary Analysis Method		End-Censored (M=F)		No Overruling	
	Time to	Converter?	Time To	Converter?	Time To	Converter?
1	W16	Yes	W16	Yes	W16	Yes
2	W20*	No	W48*	No	W12	Yes
3	W48*	No	W48*	No	W48*	No

*: censored

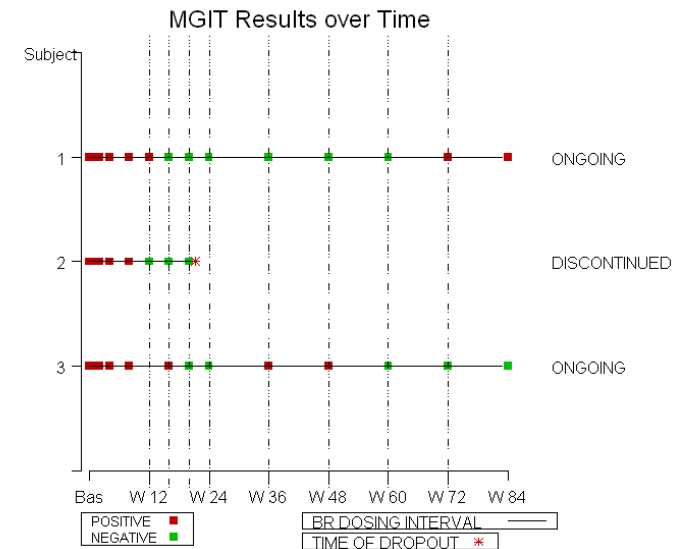


All Available Data Selection

For the All Available Data Selection, consider all the measurements. The column that indicates the conversion (Converter?), also indicates the censoring (yes=event, no=censored) in the time to analysis.

Subject	Primary Analysis Method		End-Censored (M=F)		No Overruling	
	Time to	Converter?	Time To	Converter?	Time To	Converter?
1	W84*	No (Relapser)	W120*	No	W84*	No
2	W20*	No (Disc. But Converted)	W120*	No	W12	Yes
3	W60	Yes	W60	Yes	W60	Yes

*: censored



APPENDIX 4: CLINICAL NARRATIVES FOR DEATHS WHILE FOLLOWED DURING THE TRIAL C208 STAGE 2

SUBJECT 208-4041 (BEDAQUILINE GROUP): ALCOHOL POISONING

Subject 208-4041 (fatal SAE ‘alcohol poisoning’ leading to discontinuation of bedaquiline) was a 54 year old White man infected with an MDR_{H&R} TB strain at baseline. The subject had cavitations of at least 2 cm in one lung only. No relevant past medical history was reported for this subject; active diseases at screening included cough with sputum, fever, and night sweats. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed abnormal cough with sputum. A serology screen for HIV was negative.

The subject was randomized to bedaquiline treatment and started intake on 31 March 2009 in combination with a BR consisting of KAN, OFL, protonamide, PZA, and TRD. He discontinued intake of bedaquiline on 17 July 2009 (Day 109). The subject prematurely discontinued the trial on 19 July 2009 (Day 111) due to a fatal SAE. The last available visit was on 6 July 2009 (Week 14 visit).

On 17 July 2009 (Day 109), the subject had his last intake of bedaquiline as it was the last intake of bedaquiline for that week as per protocol (source: CIOMS). On (b) (6) (Day (b) (6)), the subject left the hospital voluntarily, but did not return the same day. Site personnel started to search for the subject on (b) (6). (b) (6) (Day (b) (6)), the site was contacted by the police stating the subject was found dead at the roadside. An autopsy revealed alcohol intoxication as cause of death proved by a high alcohol concentration in the blood (3.73%). Screening for other drugs was negative (source: CIOMS). The event was reported as a grade 4 SAE and was considered not related to bedaquiline and not related to the BR in the opinion of the investigator.

Other AEs reported during the investigational treatment period were abdominal pain upper, pyrexia, and pruritus.

MGIT results showed a positive MGIT culture at baseline (30 March 2009) and a confirmed conversion to negative at the Week 8 visit (25 May 2009, Day 56). The subject’s last available MGIT assessment (Week 14 visit on 6 July 2009, Day 98) was negative; his overall outcome was non responder (discontinued but culture converted, missing = failure analysis).

SUBJECT 208-4153 (BEDAQUILINE GROUP): TUBERCULOSIS

Subject 208-4153 (fatal SAE ‘tuberculosis’) was a 33 year old woman of a race specified as ‘other’ infected with an MDR_{H&R} TB strain at baseline. The subject had cavitations of at least 2 cm in both lungs. No past medical history was reported for this subject; active diseases at screening included cough, weight loss, and pleuritic pain. She did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed abnormal crepitations of the right midzone, and loss of air at entry of the left apex. A serology screen for HIV was negative.

The subject was randomized to bedaquiline treatment and started intake on 27 August 2009 in combination with a BR consisting of EMB, ETH, KAN, OFL, and PZA. She completed the investigational treatment period as planned without any clinically significant interruption (> 14

days) of the BR; last intake of bedaquiline was on 10 February 2010 (Day 168). The subject died on (b) (6) (Day (b) (6)).

In May 2010 (exact day unknown), the subject experienced worsening of TB. Due to progressive worsening of TB and the non-compliance with the BR, the subject was admitted to the hospital and restarted with treatment for multi-drug resistant TB on (b) (6) (source: CIOMS). The event was reported as a grade 3 SAE and was considered not related to bedaquiline and not related to the BR in the opinion of the investigator. No concomitant medications to treat the event were administered. On (b) (6), the subject died. No autopsy was performed (source: CIOMS).

AEs reported during the investigational treatment period were menorrhagia, dysphagia, subcutaneous abscess (left buttock), gastroenteritis, and anemia.

MGIT results showed a positive MGIT culture at baseline (26 August 2009) and a confirmed conversion to negative at the Week 22 visit (27 January 2010, Day 154). Recurrence was observed at the Week 36 visit (14 May 2010, Day 261), at which time the subject restarted intake of EMB, ETH, OFL, and PZA. The subject's last available MGIT assessment (Week 72 visit on 12 January 2011, Day 504) was positive; her overall outcome was non responder (relapse, missing = failure analysis).

SUBJECT 208-4224 (BEDAQUILINE GROUP): TUBERCULOSIS

Subject 208-4224 (fatal SAE 'tuberculosis') was an 18 year old Black man infected with an MDR_{H&R} TB strain at baseline. The subject had cavitations of at least 2 cm in one lung only. No past medical history was reported for this subject; active diseases at screening included cough, weight loss, and fatigue. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed the subject to be ill-looking, wasted, and mildly distressed with mild respiratory distress and fine crackles. A serology screen for HIV was negative.

The subject was randomized to bedaquiline treatment and started intake on 20 August 2008 in combination with a BR consisting of aminoglycoside antibacterials, CIP, CS, EMB, ETH, and PZA. He completed the investigational treatment period as planned with at least one clinically significant interruption (> 14 days) of the BR (ETH, CS, EMB, OFL, and PZA were stopped from 29 April 2009 till 2 June 2009 and ETH, OFL, EMB, PZA, and TRD from 29 July 2009 till 13 October 2009). Last intake of bedaquiline was on 29 January 2009 (Day 163). The subject died on (b) (6) (Day (b) (6)).

On 28 April 2009 (Day 252), the subject experienced relapse of MDR-TB. On this day, the subject's MGIT assessment (Week 36) was positive. The event was reported as a grade 4 SAE and was considered not related to bedaquiline and not related to the BR in the opinion of the investigator. During this visit, it became clear that the subject was not compliant with his treatment. After extensive counseling, the subject agreed to be compliant from then on (source: CIOMS).

In June 2009 (exact day unknown), the subject experienced cough, decreased appetite, tremor, and weight decreased. Tremor was reported as a grade 1 AE, and cough, decreased appetite and weight decreased as grade 2 AEs. All were considered not related to bedaquiline and doubtfully related to the BR in the opinion of the investigator.

On 7 September 2009, the subject refused to be admitted to the hospital despite being warned about the seriousness of the situation (source: CIOMS). In September 2009 (exact day unknown), the subject experienced non-cardiac chest pain, reported as grade 2 AE that was considered not related to bedaquiline and not related to the BR in the opinion of the investigator. On 15 October 2009, the subject was treated with paracetamol (2 tablets po).

During a home visit on 2 October 2009, the subject still refused to be admitted to the hospital. On 8 October, during another home visit, he finally agreed to be admitted. The subject was admitted to the hospital on (b) (6), and was found with extensive bilateral disease. In October 2009 (exact day unknown), the subject experienced the grade 1 AEs dysphagia, feeling hot, and pyrexia, the grade 2 AEs malaise and edema peripheral, and the grade 3 AE dyspnea. Dyspnea was considered not related to bedaquiline and not related to the BR in the opinion of the investigator, whereas dysphagia, pyrexia, malaise, and edema peripheral were considered not related to bedaquiline and doubtfully related to the BR. Feeling hot was considered not related to bedaquiline and possibly related to the BR.

On 20 and 27 October 2009, his symptoms had improved. However, on 5 November 2009, the subject's dyspnea worsened (source: CIOMS). Dyspnea was treated with ipratropium bromide (unknown dose inhaled once) on 6 November 2009.

On (b) (6) the subject died due to respiratory failure due to extensive bilateral TB (source: CIOMS).

No action was taken towards the BR for any of the events described above. Except for non-cardiac chest pain and dyspnea, no concomitant medications were administered to treat any of the above mentioned AEs.

AEs reported during the investigational treatment period were arthralgia, dizziness, blood creatinine increased, and deafness bilateral.

MGIT results showed a positive MGIT culture at baseline (19 August 2008) and a confirmed conversion to negative at the Week 28 visit (3 March 2009, Day 196). Recurrence was observed at the Week 36 visit (28 April 2009, Day 252). The subject's last available MGIT assessment (Week 60 visit on 13 October 2009, Day 420) was positive; his overall outcome was non responder (relapse) (missing = failure analysis).

SUBJECT 208-5069 (BEDAQUILINE GROUP): HEPATIC CIRRHOSIS, HEPATITIS AND ANEMIA

Subject 208-5069 (fatal grade 3/4 hepatic disorders sub-SMQ SAEs 'hepatic cirrhosis' and 'hepatitis', and SAE 'anemia') was a 63 year old Asian man infected with an *M. tuberculosis* strain resistant to at least RMP and INH (MDR-TB) based on subject's medical history (based on previous DST; central DST results to confirm extent of resistance were not available). The subject had cavitations of at least 2 cm in one lung only. The subject's past medical history included iron deficiency anemia and bronchiectasis; active diseases at screening included mild cough and mild dyspnea. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed decreased breath sound and crackle at right lung. A serology screen for HIV was negative.

At baseline (21 September 2009), normal values were observed of ALT (12 U/L; normal limits: 6-43 U/L), ALP (95 U/L; normal limits: 35-125 U/L), AST (26 U/L; normal limits: 11-36 U/L),

albumin (33 g/L; normal limits: 33-49 g/L), indirect bilirubin (3 µmol/L), and total bilirubin (4 µmol/L).

The subject was randomized to bedaquiline treatment and started intake on 22 September 2009 in combination with a BR consisting of CS, ETH, KAN, OFL, and PZA. He completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of bedaquiline was on 8 March 2010 (Day 168). The subject died on (b) (6) (Day (b) (6)).

On (b) (6) (Day (b) (6)), the subject experienced worsening of anemia and was admitted to the hospital (source: CIOMS). This was reported as a grade 3 SAE and was considered doubtfully related to bedaquiline and possibly related to the BR in the opinion of the investigator. Treatment with the BR was permanently discontinued due to this event. Concomitant medications to treat the event included multivitamins (1 tablet t.i.d. po from 9 March 2010 to an unknown day in April 2010), folic acid (5 mg o.d. po from 11 March to an unknown day in April 2010), neurobion (1 tablet t.i.d. po from 11 March to an unknown day in April 2010), packed human blood cells (3 units IV from 11 March to 12 May 2010), and fero-B-cal (200 mg q.d. po from 5 April to 5 May 2010). The subject recovered from anemia on 5 April 2010 (Day 196), after a duration of 29 days.

At the last laboratory assessment (i.e., follow-up; 5 April 2010), AST was grade 3 (189 U/L), ALT grade 2 (89 U/L), ALP grade 1 (197 U/L), indirect bilirubin (9 µmol/L), and total bilirubin (16 µmol/L).

On (b) (6) (Day (b) (6)), the subject was admitted to the hospital with a 2-month history of fatigue and a one-week history of epigastric pain. In the hospital, diagnosis of hepatitis and hepatic cirrhosis was made (source: CIOMS). Hepatitis and hepatic cirrhosis were reported as grade 3 and 4 SAEs, respectively, considered not related to bedaquiline and not related to the BR in the opinion of the investigator. During admission, the subject had ascites and volume depletion due to liver cirrhosis (source: CIOMS). No concomitant medications were administered to treat hepatitis. Hepatic cirrhosis was treated with multivitamins (1 tablet t.i.d. po from 12 May to 1 June 2010), packed human blood cells (1 unit IV on 18 May 2010), ceftriaxone (2 g q.d. IV from 18 to 23 May 2010), metronidazole (500 mg every 8 hours IV from 18 to 23 May 2010), fero-B-cal (1 tablet o.d. po from 18 to 30 May 2010), ranitidine (1 tablet b.i.d. po from 18 to 30 May 2010, and 50 mg once IV on 21 May 2010), simeticone (1 tablet t.i.d. po from 18 to 30 May 2010), dextrose and sodium chloride injection (80 mL every hour IV from 18 May to 2 June 2010), B-komplex (2 mL q.d. IV from 19 to 23 May 2010), neurobion (1 tablet t.i.d. po from 19 to 30 May 2010), human albumin (50 mL q.d. IV from 20 to 21 May 2010), folic acid (1 tablet q.d. po from 20 May to 1 June 2010), tramadol (1 ampule every 8 hours IV on 21 May 2010, and every 6 hours IV from 30 May to 2 June 2010), furosemide (20 mg q.d. po from 23 May to 1 June 2010, and 40 mg once IV on 30 May and 1 June 2010), spironolactone (50 mg q.d. po from 23 May to 1 June 2010), plasma (4 units IV on 24 May 2010), metoclopramide (1 ampule every 6 hours IV from 24 to 31 May 2010), lorazepam (0.5 mg q.n. po from 25 May to 1 June 2010), sodium chloride (40 mL every hour IV on 28 May 2010), potassium chloride (30 mL 3 times IV on 29 May 2010), and morphine (4 mg twice every 4 hours IV on 2 June 2010).

The subject died on (b) (6) (Day (b) (6)) due to hepatitis and hepatic cirrhosis.

Other AEs reported during the investigational treatment period were chest pain, anorexia, arthralgia, hyperuricemia, myalgia, nausea, and weight decreased.

MGIT results showed a positive MGIT culture at baseline (21 September 2009) and a confirmed conversion to negative at the Week 6 visit (2 November 2009, Day 42). The subject's last available MGIT assessment (2nd follow-up visit on 7 May 2010, Day 228) was negative; his overall outcome was non responder (discontinued but culture converted) (missing = failure analysis).

SUBJECT 208-4399 (BEDAQUILINE GROUP): CEREBROVASCULAR ACCIDENT

Subject 208-4399 (fatal SAE 'cerebrovascular accident') was a 53-year-old man of a race specified as 'other' infected with an *M. tuberculosis* strain resistant to at least RMP and INH (MDR-TB) based on subject's medical history (based on previous DST; central DST results to confirm extent of resistance were not available). The subject had cavitations of at least 2 cm in one lung only. The subject's active diseases at screening included productive cough, exertional dyspnea, and night sweats. No past medical history was reported for this subject. He did not have a history of drug allergy or hypersensitivity. No relevant physical examination abnormalities were reported at screening. A serology screen for HIV was negative.

The subject was randomized to bedaquiline treatment and started intake on 4 August 2009 in combination with a BR consisting of EMB, ETH, KAN, OFL, and PZA. He completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of bedaquiline was on 18 January 2010 (Day 168, Week 24). The subject died on (b) (6) (Day (b) (6)).

At baseline (4 August 2009), supine SBP and DBP were normal (115/80 mmHg). From Week 1 to Week 72 (11 August 2009 to 21 December 2010), supine DBP was either normal or grade 1 increased (range: 74-99 mmHg). Supine SBP was normal or abnormally low from Week 1 to Week 36 (13 April 2010), except at Week 10 (12 October 2009), where supine SBP was grade 1 increased (145 mmHg). On 6 July 2010, supine SBP and DBP were grade 1 increased (146/93 mmHg), which was reported as a grade 1 AE considered not related to bedaquiline and doubtfully related to the BR in the opinion of the investigator. Concomitant medications to treat this event included hydrochlorothiazide (12.5 mg q.d. po from 6 July 2010 to 6 August 2010) and acetylsalicylic acid (1/2 tablet q.d. po from 6 July 2010 to 28 July 2011). The AE hypertension, which was reported during the treatment period with BR alone, had not resolved at time of reporting. From 27 September 2010, supine SBP was normal. ECG interpretation showed premature ventricular systoles on 6 July 2010; no other ECG-related abnormalities were concurrently reported.

During his last visit to the site, on 13 June 2011, the subject's blood pressure was 128/113 mmHg (grade 3 high DBP).

On (b) (6) (Day (b) (6)), the subject experienced possible cerebrovascular accident due to hypertension. According to his family, the subject was not ill just prior to his death. He woke up on the morning of his death, spoke to the family and then went back to bed, where he was found dead later. No autopsy was performed (source: CIOMS).

Cerebrovascular accident was reported as a grade 4 SAE and was considered not related to bedaquiline and not related to the BR in the opinion of the investigator.

AEs reported during the investigational treatment period were arthralgia, back pain, headache, blood uric acid increased, musculoskeletal pain, rash, and deafness.

MGIT results showed a positive MGIT culture at baseline (3 August 2009) and a confirmed conversion to negative at the Week 28 visit (15 February 2010, Day 196). The subject's last available MGIT assessment (Week 96 visit on 13 June 2011, Day 679) was negative; his overall outcome was death but converted.

SUBJECT 208-5067 (BEDAQUILINE GROUP): PERITONITIS AND SEPTIC SHOCK

Subject 208-5067 (grade 3/4 hepatic disorder sub-SMQ event 'hepatitis' and fatal SAEs 'peritonitis' and 'septic shock') was a 43-year-old Asian man infected with a Pre-XDR-TB strain (resistant to RMP and INH as well as to fluoroquinolones [OFL] but susceptible to injectable drugs [CAP and KAN]) at baseline. The subject had cavitations of at least 2 cm in one lung only. No past medical history was reported for this subject. According to the CIOMS forms, the subject had a history of heavy alcohol consumption. Active diseases at screening included mild productive cough, mild dyspnea and HIV. Although HIV was recorded as an active disorder on the medical history page of the Case Report Form (CRF), the subject's HIV serology screen at enrollment was negative. Baseline CD4 count was 844 x 10⁶ cells/L. The subject did not receive ARV therapy during the trial. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed crackle in the left lung.

The subject was randomized to TMC207 treatment and started intake on 25 August 2009 in combination with a BR consisting of AMK sulfate, CS, ETH, OFL, and PZA. On 30 November 2009 (Day 98, Week 14), treatment with OFL and PZA was discontinued and on 18 December 2009 (Day 116, Week 16), treatment with PAS-C was started. On 8 March 2010 (Day 196, Week 28), treatment with AMK sulfate was temporarily discontinued due to AEs (ocular icterus, anorexia, fatigue, and vomiting). Treatment with AMK sulfate and the remaining drugs in the BR (CS, ETH and PAS-C) was permanently discontinued on 12 April 2011 (Day 596, Week 85) due to hepatitis. He completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of TMC207 was on 10 February 2010 (Day 170, Week 24). The subject died on (b) (6) (Day (b) (6)), due to SAEs peritonitis and septic shock). The last available visit was on 28 June 2011 (Follow-up visit).

On 5 March 2011 (Day 558), the subject experienced anorexia and fatigue. These events were reported as grade 2 AEs and considered not related to TMC207 and probably related to the BR in the opinion of the investigator. Additionally, at an unspecified day in March 2011, the subject was also diagnosed with ocular icterus and hepatitis, both reported as grade 3 AEs and considered not related to TMC207 and probably related to the BR. No concomitant medications were given to treat these events. The BR was permanently discontinued due to hepatitis on 12 April 2011. According to the CIOMS report, the subject's concurrent conditions also included alcoholic hepatitis.

At baseline, laboratory results showed normal values for ALT (10 U/L, normal limits: 6-43 U/L), ALP (65 U/L, normal limits: 31-129 U/L), AST (18 U/L, normal limits: 11-36 U/L), GGT (52 U/L, normal limits: 10-61 U/L), lactate dehydrogenase (LDH) (133 U/L, normal limits: 53-234 U/L), and total bilirubin (4 µmol/L, normal limits: 3-21 µmol/L).

During the investigational treatment phase, ALP levels were within normal limits, except from Week 20 to Week 32 (11 January 2010 to 5 April 2010) when ALP levels were grade 1 increased (range: 147-189 U/L), at Week 84 (5 April 2011) (243 U/L, grade 1), and at Follow-up (28 June

2011) (362 U/L, grade 2). ALT levels were within normal limits, except at Week 24 and at Follow-up (8 February 2010 and 28 June 2011) when ALT was grade 2 increased (118 and 97 U/L, respectively). AST levels were within normal limits or at most grade 1 increased from Week 2 to Week 16 (range: 24-43 U/L).

From Week 18 to Follow-up (30 December 2009 to 28 June 2011), AST levels were grade 1 to 4 increased (range: 41-501 U/L). GGT levels were within normal limits or at most grade 1 increased from Week 2 to Week 12 (range: 50-101 U/L). From Week 14 to Follow-up, GGT levels were grade 2 to 4 increased (range: 125-2627 U/L). LDH levels were within normal limits (range: 127-204 U/L), except at Week 24 and at Follow-up when LDH levels were above normal (269 and 265 U/L, respectively). Total bilirubin was within normal limits, except at Week 24 (52 µmol/L, grade 3), at Week 84 (129 µmol/L, grade 4), and at Follow-up (95 U/L, grade 4). Direct bilirubin was within normal limits, except at Week 24 (29 µmol/L, above ULN), at Week 84 (80 µmol/L, above ULN), and at Follow-up (55 µmol/L, above ULN). It should be noted that the laboratory criteria for Hy's law were met at Weeks 24 and 84 (confounded by reported history of heavy alcohol consumption and alcoholic hepatitis, and concomitant BR medications [CS, ETH, and PAS-C] associated with hepatotoxicity.)

No laboratory results were available for March 2011.

On 5 April 2011 (Day 589), vomiting was reported as a grade 1 AE and was considered not related to TMC207 and possibly related to the drugs in the BR. The same day, grade 4 increased total bilirubin (129 µmol/L) and GGT (1240 U/L) were observed, as well as grade 3 increased AST (148 U/L) and grade 1 increased ALP (243 U/L). ALT and LDH were normal. Concomitant medications to treat vomiting included metoclopramide (1 tablet t.i.d. prn po from 12 to 19 April 2011 and 1 tablet t.i.d. po from 19 to 29 April 2011) and multivitamins (1 tablet t.i.d. po from 19 to 29 April 2011).

Due to hepatitis, the drugs in the BR, i.e., AMK sulfate, CS, ETH and PAS-C, were permanently discontinued on 12 April 2011.

At the next laboratory assessment on 28 June 2011, AST, GGT, and total bilirubin were grade 4 increased (357 U/L, 2627 U/L, and 95 µmol/L, respectively), ALP and ALT were grade 2 increased (362 and 97 U/L, respectively), and LDH was above normal (265 U/L).

At an unspecified date in June 2011, anemia was reported as a grade 1 AE, which was considered not related to TMC207 and not related to the BR. The subject was treated with red blood cells (1 unit t.i.d. IV on 8 July 2011).

Anorexia, fatigue, ocular icterus, hepatitis, vomiting, and anemia were not resolved at time of reporting.

On 1 July 2011 (Day 676), the subject started experiencing fever, abdominal pain, nausea and vomiting (source: CIOMS), and he was diagnosed with peritonitis, which was reported as a grade 4 SAE considered not related to TMC207 and the drugs in the BR. On (b) (6) he went to hospital due to worsening of his symptoms. On (b) (6) (Day (b) (6)), the subject was admitted into the surgery unit for bowel exploration due to suspected hollow organ perforation, but the subject died before bowel exploration began (source: CIOMS). The principal diagnosis was peritonitis. Septic shock, anemia, hypomagnesemia and pulmonary TB were considered

comorbidities (source: CIOMS). Septic shock was reported as a grade 4 SAE and was considered not related to TMC207 and not related to the BR.

The subject developed metabolic acidosis, respiratory failure and malnutrition as complications from peritonitis. Severe metabolic acidosis led the subject to have an arrest (source: CIOMS).

Concomitant medications to treat peritonitis and septic shock included dextrose and sodium chloride injection (40 ml once IV on 7 July 2011 and 1000 ml o.d. IV from 7 to 8 July 2011), dopamine (1000 mg once IV on 7 July 2011), potassium chloride (20 meq once IV on 7 July 2011), metoclopramide (10 mg stat IV on 7 July 2011), omeprazole (40 mg o.d. IV on 7 July 2011), sodium chloride (120 mL 91 h IV on 7 July 2011 and 100 mL once IV and 1000 mL 5x IV on 8 July), ceftriaxone (2 g stat then o.d. IV from 7 to 8 July 2011), fenoterol with ipratropium bromide (0.5/1.25 mg stat then 94 h nb from 7 to 8 July 2011), metronidazole (500 mg stat then 98 h IV from 7 to 8 July 2011), diazepam (10 mg stat IV on 8 July 2011), furosemide (40 mg stat IV on 8 July 2011), glucose (500 mL once IV on 8 July 2011), and sodium bicarbonate (50 mL stat IV on 8 July 2011).

AEs reported during the investigational treatment period were presbyopia, chest pain, dyspepsia, diarrhea, anorexia, dizziness, syncope, and headache.

MGIT results showed a positive MGIT culture at baseline (24 August 2009) and a confirmed conversion to negative at the Week 14 visit (30 November 2009, Day 98). The subject's last available MGIT assessment (Follow-up visit on 28 June 2011, Day 673) was negative; his overall outcome was death but converted.

SUBJECT 208-4120 (PLACEBO GROUP): HEMOPTYSIS

Subject 208-4120 (fatal SAE 'hemoptysis') was a 24 year old woman of a race specified as 'other' infected with a pre XDR TB strain (resistant to RMP and INH as well as to injectable drugs [both CAP and KAN] but susceptible to fluoroquinolones [OFL]) at baseline. The subject had cavitations of at least 2 cm in both lungs. No past medical history was reported for this subject; active diseases at screening included night sweats, weight loss, tightness of chest, and cough chest pain. She did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed abnormal crepitations left and right. A serology screen for HIV was negative.

The subject was randomized to placebo treatment and started intake on 26 February 2009 in combination with a BR consisting of EMB, ETH, KAN, OFL, and PZA. She completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of placebo was on 12 August 2009 (Day 168). The subject died on (b) (6) (Day (b) (6)).

On (b) (6) (Day (b) (6)), in the early evening, the subject experienced hemoptysis. The subject experienced another episode of hemoptysis later on the same day, and died. No autopsy was performed (source CIOMS). The event was reported as a grade 3 SAE and was considered doubtfully related to placebo and possibly related to the BR in the opinion of the investigator. No concomitant medications were administered to treat the event.

AEs reported during the investigational treatment period were vomiting, upper respiratory tract infection, neutrophil count increased, muscle spasms, weight decreased, and oral candidiasis.

MGIT results showed a positive MGIT culture at baseline (25 February 2009). No confirmed conversion to negative was observed. The subject's last available MGIT assessment (Week 36 visit on 4 November 2009, Day 252) was positive; her overall outcome was non responder (failure to convert, missing = failure analysis).

APPENDIX 5: CLINICAL MINI-NARRATIVES FOR DEATHS DURING LONG-TERM SURVIVAL FOLLOW-UP OF PREMATURELY WITHDRAWN SUBJECTS TRIAL C208 STAGE 2

SUBJECT 208-4127 (BEDAQUILINE GROUP): TB-RELATED ILLNESS

Subject 208-4127 (bedaquiline group) was a 51-year-old female (race: other) who had cavitations of at least 2 cm in one lung only and who was infected with an MDR_{H&R}-TB strain. Diseases active at screening included headaches, visual disturbances, constipation, arrhythmia, chest pain, asthma, cough, joint pains, night sweats, loss of weight and tiredness. She received bedaquiline in combination with EMB, PZA, ETH, OFL and KAN. First intake of bedaquiline was on 24 Apr 2009. The subject discontinued bedaquiline and BR intake on 22 May 2009 and was withdrawn from the trial due to non-compliance; last contact during the trial was on 30 Jun 2009. No major protocol deviations with regard to interruptions in study medication intake of more than 14 days were reported for this subject. On 18 Jul 2011, i.e., 748 days after trial termination and 787 days after last intake of bedaquiline, the investigator reported that the subject died of TB-related illness. The investigator reported that the subject was re-admitted to hospital for MDR-TB on (b) (6) (source: CIOMS ZA-JNJFOC-20120801148(0)). On 24 Nov 2010, the subject was diagnosed with XDR-TB and XDR-TB treatment was started. On (b) (6), the subject absconded from the hospital. There were no hospital or clinic records of her taking medication during this time, and no record of her location. Based on third party report, the subject died at an unspecified date in 2011 of TB-related illness. No autopsy was performed and no clear cause of death was known but the investigator assumed it to be XDR-TB. The investigator assessed the causality of the SAE as not related to study medication. MGIT results showed no confirmed conversion to negative. The subject's last available MGIT assessment (Day 61) was positive; her overall outcome was categorized as "failure to convert".

SUBJECT 208-4145 (BEDAQUILINE GROUP): TB-RELATED ILLNESS

Subject 208-4145 (bedaquiline group) was a 36-year-old male (race: other) who had cavitations of at least 2 cm in both lungs and who was infected with an MDR_{H&R}-TB strain. Diseases active at screening included gunshot in chest, night sweats, productive cough, loss of weight, and hemoptysis. He received bedaquiline in combination with EMB, PZA, ETH, OFL and KAN. First intake of bedaquiline was on 6 Aug 2009. The subject completed bedaquiline intake on 20 Jan 2010 (Week 24) but was withdrawn from the trial due to non-compliance; last on-treatment visit was Week 36 (14 Apr 2010) and last contact during the trial was on 9 Jun 2010. Last documented BR intake was on 14 Apr 2010. No major protocol deviations with regard to interruptions in study medication intake of more than 14 days were reported but several interruptions in bedaquiline and BR intake of less than 14 days were reported as minor protocol deviations. On 9 Oct 2010, i.e., 122 days after trial termination and 262 days after last intake of bedaquiline, the investigator reported that the subject died of **TB-related illness**. The subject died in hospital (source: CIOMS ZA-JNJFOC-20120703749(3)). No autopsy was performed. Reason for hospitalization was worsening MDR-TB. The death certificate listed cause of death as natural causes (source: CIOMS ZA-JNJFOC-20120703749(3)). The investigator assessed the causality of the SAE as not related to study medication. MGIT results showed a confirmed conversion to negative at the Week 12 visit (Day 84). Recurrence was observed at the Week 32

visit (Day 224). The subject's last available MGIT assessment (Day 308) was positive; his overall outcome was categorized as "relapse".

SUBJECT 208-4378 (BEDAQUILINE GROUP): MOTOR VEHICLE ACCIDENT

Subject 208-4378 (bedaquiline group) was a 36-year-old male (race: Black) who had cavitations of at least 2 cm in one lung only and who was infected with an MDR_{H&R}-TB strain. Diseases active at screening included coughing and night sweats. He received bedaquiline in combination with AMK sulfate, OFL, ETH, EMB, and PZA. During the trial, AMK sulfate was replaced by KAN and EMB by TRD. First intake of bedaquiline was on 30 Oct 2008. The subject discontinued bedaquiline intake on 20 Mar 2009 and was withdrawn from the trial due to an AE (increased transaminase); last contact was on 2 Apr 2009. On 17 Sep 2011, i.e., 898 days after trial termination and 911 days after last intake of bedaquiline, the investigator reported that the subject died due to a motor vehicle accident. The investigator assessed the causality of the SAE as not related to study medication. MGIT results showed a confirmed conversion to negative at the Week 8 visit (Day 54). Recurrence was observed at the Week 14 visit (Day 98). The subject's last available MGIT assessment (Day 155) was negative (single negative result); his overall outcome was categorized as "relapse".

SUBJECT 208-4464 (BEDAQUILINE GROUP): TB-RELATED ILLNESS

Subject 208-4464 (bedaquiline group) was a 30-year-old male (race: other) who had no cavitations or cavitations less than 2 cm who was infected with an XDR-TB strain. Diseases active at screening included varicose veins in lower limbs, anemia, leucocytosis, lymphopenia, and neutrophilia. He received bedaquiline in combination with KAN, ETH, PAS-C, PZA, EMB, MOX, AMK, CS, ciprofloxacin and amoxicillin + clavulanic acid. First intake of bedaquiline was on 21 Aug 2009. The subject discontinued the trial (reason: subject became XDR); the subjects was reported with the minor protocol deviation "selection criteria not met" (inclusion criterium 3 and exclusion criterium 6). Last contact during the trial was on 19 Dec 2009, last intake of study drug was 18 Nov 2009. On 28 Sep 2010, i.e., 283 days after trial termination and 314 days after last intake of bedaquiline, the investigator reported that the subject died of TB-related illness. The subject was reported to have died from complications of XDR-TB. No autopsy was performed (Source: CIOMS PE-JNJFOC-20120605490(1)). The investigator assessed the causality of the SAE as not related to study medication. MGIT results showed no confirmed conversion to negative. The subject's last available MGIT assessment (Day 99) was positive; his overall outcome was categorized as "failure to convert".

SUBJECT 208-4155 (PLACEBO GROUP): TB-RELATED ILLNESS

Subject 208-4155 (placebo group) was a 36-year-old female (race: other) who had cavitations of at least 2 cm in both lungs and who was infected with an MDR_{H&R}-TB strain. Diseases active at screening included painful joints, cough, night sweats, loss of appetite, fatigue, loss of weight and shortness of breath. She received placebo in combination with EMB, PZA, ETH, OFL and KAN. First intake of placebo was on 11 Sep 2009. The subject completed placebo intake on 22 Feb 2010 but was withdrawn from the trial due to non compliance; last documented BR intake was on 29 Jul 2010 and last contact during the trial was on 18 Nov 2010. One interruption in BR intake of more than 14 days was reported as a major protocol deviation. In addition, several interruptions in placebo or BR intake of less than 14 days were reported as minor protocol deviations. On 1 Feb 2012, i.e., 440 days after trial termination and 709 days after last intake of

placebo, the investigator reported that the subject died of TB-related illness. On 19 Nov 2011, the subject restarted treatment for MDR-TB. On (b) (6) the subject was admitted to hospital and on (b) (6) treatment for XDR-TB was started. The subject died from XDR-TB on (b) (6). No autopsy was performed. The investigator assessed the causality of the SAE as not related to study medication. MGIT results showed no confirmed conversion to negative. The subject's last available MGIT assessment (Day 434) was positive; her overall outcome was categorized as "failure to convert".

APPENDIX 6: CLINICAL NARRATIVES FOR DEATHS WHILE BEING FOLLOWED DURING THE TRIAL C208 STAGE 1

SUBJECT C208-3079 (BEDAQUILINE GROUP): MYOCARDIAL INFARCTION

TMC207-TiDP13-C208						
FATAL ADVERSE EVENT SUMMARY						
CRF ID 208-3079						
DEMOGRAPHICS						
Subject: CRF ID 208-3079			Gender: Female			
Age at screening: 33 years			Race: Coloured			
Investigator: Dr. A. Diacon			Country: South Africa			
TREATMENT AS PER PROTOCOL			ACTUAL TREATMENT			
<u>Investigational treatment period:</u> bedaquiline (400 mg q.d. on Week 1-2 and 200 mg t.i.w. from Week 3 to 8) + BR from Week 1 to 8			bedaquiline (Days 1-56): 28 Aug 07 – 22 Oct 07 BR (Days 1-169): EMB, ETH, KAN, OFL, and PZA: 28 Aug 07 – 12 Feb 08 (last intake of any BR med on 12 Feb; background phase until 14 Feb)			
<u>Background treatment period:</u> BR from Week 9 to 104			Trial Termination: 14 Feb 2008			
ADVERSE EVENT LEADING TO DEATH						
<u>Adverse event</u>	<u>Severity</u>	<u>Drug relatedness^a</u>	<u>TB relation</u>	<u>Start</u>	<u>End</u>	
Myocardial infarction	Grade 4	Not related / Not related	No	(b) (6)	(b) (6)	
^a Relatedness to bedaquiline/placebo and to the BR						
BASELINE SUBJECT DATA						
<p>MDR-TB; documented medication resistance: RMP and INH; lung cavity ≥ 2 cm in one lung only;</p> <p>HIV status: positive; urine drug screening: negative.</p> <p>Susceptibility at baseline: resistant to RMP and INH; susceptible to capreomycin, EMB, ETH, KAN, OFL, PZA, and SM.</p> <p>Medical history: nausea, vomiting, and previous pulmonary TB; concomitant diseases at screening: exfoliative dermatitis, HIV, cough, night sweats, weight loss, and pleuritic chest pain.</p> <p>Physical examination at screening and baseline: crepitations, exfoliative dermatitis at trunk and arms, being thin, and marked temporal wasting.</p>						
CLINICAL NARRATIVE						
<p>Subject 208-3079, a 33-year-old HIV-positive female received bedaquiline in addition to a BR consisting of EMB, ETH, KAN, OFL, and PZA from 28 August 2007 onwards. She completed the 8-week investigational treatment period on 22 October 2007. The subject had a documented resistance towards RMP and INH at screening. Susceptibility results confirmed RMP and INH resistance at baseline. Medical history at screening included active exfoliative dermatitis, HIV, cough, night sweats, weight loss, and pleuritic chest pain. Physical examination at screening revealed crepitations, exfoliative dermatitis at trunk and arms, being thin, and marked temporal wasting. The subject was a nonsmoker (source: CIOMS).</p> <p>On (b) (6) i.e., on Day (b) (6) of the trial and during the background treatment period, the subject experienced sudden death. Two days prior to this event, i.e., on (b) (6), the laboratory parameters CK,</p>						

CK-MB, troponin, hemoglobin, platelets, total cholesterol, triglycerides, and electrolytes (K^+ and Ca^{2+}) were within normal limits. An autopsy was performed and showed 100% obstruction of the lumen of the left anterior descending coronary artery, recent infarction of the left ventricle at the apex, anterior wall, and intra-ventricular septum. The autopsy report concluded that the cause of death was consistent with acute myocardial infarction (source: CIOMS). Myocardial infarction was reported as SAE of severity grade 4 and was considered not related to the investigational medication or other drugs in the BR and as not related to TB by the investigator.

Concomitant AEs at the time of death were photosensitivity reaction and soft tissue injury, both of grade 1.

BACKGROUND DATA

Height: 162 cm

Weight: 37 kg

BMI: 14.10 kg/m²

CONCOMITANT NON-TB MEDICATION

<u>Medication</u>	<u>Dosage</u>	<u>Indication</u>	<u>Start</u>	<u>End</u>
Cough syrup	10 mL tds	Coughing (prophylactic)	Pre-trial	27 Aug 07
Ibuprofen	200 mg tds	Pleuritic pain before screening	Pre-trial	27 Aug 07
Diclofenac	25 mg tds	Pleuritic pain before screening	Pre-trial	14 Feb 08
Amoxi-clavulanico	375 mg tds	AE	23 Aug 07	27 Aug 07

CONCOMITANT NON-TB MEDICATION, CONT'D

<u>Medication</u>	<u>Dosage</u>	<u>Indication</u>	<u>Start</u>	<u>End</u>
Pyridoxine	25 mg q.d.	Vitamin supplement (prophylactic)	27 Aug 07	14 Feb 08
B-komplex	2 tablets q.d.	Vitamin supplement	28 Aug 07	14 Feb 08
Clotrimazole	1 application b.i.d.	AE	5 Sep 07	11 Sep 07
Doxycycline	100 mg b.i.d.	Perianal ulcers and vaginal discharge	5 Sep 07	13 Sep 07
Metronidazole	400 mg t.i.d.	Perianal ulcers and vaginal discharge	5 Sep 07	13 Sep 07
Amoxicillin	500 mg t.i.w.	AE	6 Sep 07	17 Sep 07
Fluconazole	200 mg q.d.	AE	19 Sep 07	4 Oct 07
Hydrocortisone	3 application t.i.w.	AE	2 Oct 07	19 Oct 07
Paracetamol	2 tablets t.i.w.	Unknown	3 Oct 07	18 Oct 07
Mebendazole	500 mg q.i.d.	AE	17 Oct 07	17 Oct 07
Theophylline	200 mg q.d.	AE	22 Nov 07	3 Jan 08

OTHER ADVERSE EVENTS

<u>Adverse event</u>	<u>Severity</u>	<u>Drug relatedness^a</u>	<u>TB-relation</u>	<u>Start</u>	<u>End</u>
Pleuritic pain	Grade 2	Not related / Not related	Yes	23 Aug 07	25 Aug 07
Anal ulcer	Grade 1	Not related / Not related	No	5 Sep 07	17 Sep 07
Oral candidiasis	Grade 1	Not related / Not related	No	17 Sep 07	25 Sep 07

Nausea	Grade 1	Possible / Possible	No	26 Sep 07	26 Sep 07
Eczema	Grade 1	Not related / Not related	No	2 Oct 07	10 Oct 07
Helminthic infection	Grade 1	Not related / Not related	No	17 Oct 07	17 Oct 07
Lymphadenopathy	Grade 1	Not related / Not related	Yes	22 Oct 07	8 Nov 07
Chest discomfort	Grade 1	Not related / Not related	Yes	22 Nov 07	3 Jan 08
Photosensitivity reaction	Grade 1	Possible / Probable	No	24 Nov 07	14 Feb 08
Soft tissue injury	Grade 1	Not related / Not related	No	9 Feb 08	14 Feb 08

^a Relatedness to bedaquiline/placebo and to the BR

CLINICAL LABORATORY TESTS

Lab test (units)	Normal limits	Screening (21 Aug 07)	Week 8 (22 Oct 07)	Week 16 (19 Dec 07)
CD4+ (/μL)	404 – 1612	<u>445</u>	<u>563</u>	<u>390</u>

Bold: below normal limits

VITAL SIGNS AND ECG

No abnormalities in vital signs parameters were observed for this subject.

Abnormalities in ECG parameters included QTcB increases between 30 and 60 ms at all assessments (range: 31-60 ms) which resulted in absolute values between 450 and 480 ms at Week 7 (453 ms) and Week 20 (451 ms). QTcF increases of > 60 ms were observed at Week 7 (61 ms) and Week 20 (80 ms) and increases between 30 and 60 ms at all other assessments (range: 34-60 ms); corresponding absolute QTcF values were within normal limits.

Additional ECG abnormalities included negative T waves (possible ischemia) at Day -1 and T wave negativity at Day 1.

M. TUBERCULOSIS MGIT OUTCOME

<u>D-1</u>	<u>W1</u>	<u>W2</u>	<u>W3</u>	<u>W4</u>	<u>W5</u>	<u>W6</u>	<u>W7</u>	<u>W8</u>	<u>W10</u>	<u>W12</u>	<u>W14</u>	<u>W16</u>
+	+	+	+	+	+	+	-	-	-	+	-	-
<u>W18</u>	<u>W20</u>	<u>W22</u>										
-	-	-										

+: positive, -: negative

At the time point corresponding to negative culture conversion, the cell is shaded grey.

APPENDIX 7: CLINICAL MINI-NARRATIVES FOR DEATHS DURING LONG-TERM SURVIVAL FOLLOW-UP OF PREMATURELY WITHDRAWN SUBJECTS TRIAL C208 STAGE 1

SUBJECT 208-3049 (PLACEBO): PULMONARY TB

Subject was a 20-year-old male (race: other) who had no cavitations and who was infected with an XDR-TB strain. The subject had cough, night sweats, weight loss and crepitations active at screening. He received placebo in combination with CAP, ETH, EMB, KAN, OFL, PZA, TRD and dapsons. First intake of placebo was on 10 October 2007, last intake of placebo was on 15 October 2007 and last date of contact was on 23 October 2007. The subject was withdrawn from the trial on 23 October 2007 due to identification of infection with an XDR-TB strain based on results of local susceptibility testing that only became available during the first week of the trial. On (b) (6) i.e., (b) (6) days after trial termination and (b) (6) days after last intake of placebo, the subject died of pulmonary TB.

SUBJECT 208-3100 (BEDAQUILINE): PULMONARY TB

Subject was a 25-year-old male (race: other) who had cavitations of ≥ 2 cm in one lung and who was infected with an XDR-TB strain. The subject had intermittent dizziness, tinea versicolor, intermittent nausea, thoracic scoliosis, intermittent headache, coughing, night sweats and weight loss diseases active at screening. He received bedaquiline in combination with ETH, KAN, OFL, PZA and TRD. First intake of bedaquiline was on 10 October 2007, last intake of bedaquiline was on 15 October 2007 and last date of contact was on 23 October 2007. The subject was withdrawn from the trial on 23 October 2007 due to identification of infection with an XDR-TB strain based on results of local susceptibility testing that only became available during the first week of the trial. On (b) (6) i.e., (b) (6) days after trial termination and (b) (6) days after last intake of bedaquiline, the subject died of pulmonary TB.

SUBJECT 208-3010 (PLACEBO): TB RELATED ILLNESS

Subject was a 19-year-old male (race: Black) who had cavitations of ≥ 2 cm in both lungs and who was infected with an MDR_{H&R}-TB strain. The subject had swelling of both feet, thin wasted lower limbs, peripheral neuropathy, night sweats, cough, tiredness and loss of weight active at screening. He received placebo in combination with EMB, ETH, KAN, OFL, PZA, TRD, amoxi-clavulanico, clarithromycin, dapsons. First intake of placebo was on 19 June 2007, last intake of placebo was on 13 August 2007 and last date of contact was on 28 May 2008. The subject was withdrawn from the trial on 28 May 2008 due to development of XDR-TB per the investigator. On (b) (6) i.e., (b) (6) days after trial termination and (b) (6) days after last intake of placebo, the subject died of TB related illness.

APPENDIX 8: CLINICAL NARRATIVES FOR DEATHS WHILE BEING FOLLOWED DURING THE TRIAL C209

SUBJECT C209-0001: WORSENING OF TUBERCULOSIS

Subject 209-0001 (SAE ‘hallucination’, fatal ‘worsening of tuberculosis’) was a 59-year-old White man infected with an XDR-TB strain (resistant to RMP and INH as well as to injectable drugs [KAN] and fluoroquinolones [OFL]) at baseline. The subject had no cavitations or cavitations smaller than 2 cm. He had been treated previously with second-line anti-TB drugs including augmentin (amoxicillin+clavulanic acid), CAP, moxifloxacin, OFL, PAS-C, protionamide, and TRD. The subject’s past medical history included MDR-TB in 2000 (cured in 2002); active diseases at screening included dyspnea, shortness of breath of grade 2-3, cough with sputum, and anxiety of grade 2-3. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed wasting, anxiety, cough, and dyspnea. A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 1 September 2009 in combination with a BR consisting of augmentin (amoxicillin+clavulanic acid), CAP, protionamide, and TRD. He permanently discontinued intake of bedaquiline on 14 October 2009 (Day 44) due to an SAE (hallucination). The subject died on (b) (6) (Day (b) (6)).

On 14 October 2009 (Day 44), the subject experienced organic hallucinations. He was aggressive and later calmed down but still expressed persecutory delusions (source: CIOMS). The subject was hospitalized on the same day due to hallucination, which was reported as a grade 3 SAE. The event was considered doubtfully related to bedaquiline and possibly related to the BR in the opinion of the investigator. The most likely cause of organic hallucination was considered a combination of drugs (not further specified) (source: CIOMS). On that day, bedaquiline was permanently discontinued and all drugs in the BR were temporarily discontinued due to the event. Concomitant medications to treat hallucination included chlorprothixene (25 mg t.i.d.), diazepam (5 mg t.i.d.), haloperidol (5 mg t.i.d.), and trihexyphenidyl hydrochloride (2 mg t.i.d.) from 14 to 19 October, melperone hydrochloride (25 mg t.i.d.) from 26 October to 27 November, phenazepam (0.5 mg t.i.d.) from 28 October to 27 November, and chlorprothixene (25 mg b.i.d.) from 13 to 16 November. A BR consisting of augmentin, CAP, protionamide, and TRD was reinitiated on 31 October 2009.

On the morning of (b) (6) (Day (b) (6)), the subject’s condition worsened and the subject died on the same day. The cause of death was worsening of tuberculosis infection leading to pulmonary failure. Tuberculosis (verbatim: worsening of TB) was reported as a grade 4 SAE leading to death and was considered not related to bedaquiline or the BR by the investigator. The SAE organic hallucinations had not resolved on the day of death.

Other AEs reported during the investigational treatment period were cor pulmonale, hypokalemia, and hemorrhoids.

MGIT results showed a positive MGIT culture at baseline (31 August 2009) and at the last available assessment (Week 4 visit on 28 September 2009, Day 28). The subject’s overall outcome was non-responder (failure to convert).

SUBJECT C209-0024: TUBERCULOSIS

Subject 209-0024 (fatal ‘tuberculosis’) was a 52-year-old Black woman infected with an XDR-TB strain (resistant to RMP and INH as well as to injectable drugs [KAN] and fluoroquinolones [OFL]) at baseline. The subject had cavitations of at least 2 cm in one lung only. She had been treated previously with second-line anti-TB drugs including ETH, KAN, and OFL. The subject’s past medical history included spleen hypo-echoic lesions on sonography; active diseases at screening included cough, loss of weight, right pleuritic pain, and hemoptysis. She did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed bilateral crepitations and loss of air entry left. A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 18 November 2009 in combination with a BR consisting of EMB, ETH, KAN, OFL, and PZA. She discontinued intake of bedaquiline on 18 January 2010 (Day 62) due to an SAE (tuberculosis). The subject died on (b) (6) (Day (b) (6)).

In early January 2010, the subject became weak and dehydrated (source: CIOMS). Reported AEs were sinusitis and lymphadenitis from 4 to 11 January; neuropathy peripheral from 5 January onwards, and dehydration from 11 to 15 January. All were grade 2 in severity and considered not or doubtfully related to bedaquiline or the BR, except for peripheral neuropathy that was judged possibly related to bedaquiline and the BR by the investigator. Concomitant medications during that period included pyridoxine (25 mg q.d. from 30 September 2009 to 11 February 2010) for nutritional support, metoclopramide hydrochloride (10 mg prn from 30 September 2009 to 14 February 2010), beclometasone dipropionate (2 unknown dose b.i.d. from 7 to 11 January 2010) and chlorphenamine maleate (4 mg q.i.d. from 7 to 11 January 2010) for sinusitis, and electrolyte solutions (3000 mL q4h IV on 15 January 2010) for dehydration. No action towards bedaquiline or the BR was taken for these events. The BR at this time consisted of EMB, ETH, OFL, and PZA; TRD was added on 11 January 2010.

On 18 January 2010 (Day 62), the subject permanently stopped taking bedaquiline and withdrew from the trial due to being too ill (source: CIOMS). Physical examination on this day indicated ongoing crepitations on the right. Tuberculosis (verbatim: XDR-TB) was reported as a grade 4 SAE from that day onwards and was indicated as leading to discontinuation of bedaquiline. All drugs in the BR were permanently discontinued due to this SAE; last intake was recorded on 11 February 2010. (b) (6) days later, on (b) (6) the subject died from tuberculosis, which was considered not related to bedaquiline and the BR in the opinion of the investigator.

No other AEs were reported for this subject.

MGIT results showed a positive MGIT culture at baseline (17 November 2009) and at the last available assessment (Week 8 visit on 18 January 2010, Day 62). The subject’s overall outcome was non-responder (failure to convert).

SUBJECT C209-0025: CARDIAC FAILURE CONGESTIVE

Subject 209-0025 (fatal ‘cardiac failure congestive’ and SAE ‘cor pulmonale’) was a 57-year-old Black woman infected with an MDR_{H&R}-TB strain at baseline. The subject had cavitations of at least 2 cm in one lung only. She had been treated previously with second-line anti-TB drugs including ETH, KAN, and OFL. The subject’s reported past medical history and active diseases at screening did not include relevant events. She did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed malposition of heart (source: CIOMS) and cardiac apex (displaced to lateral midclavicular line), chronic obstructive pulmonary disease (source: CIOMS), and bilateral crepitations (apices posterior right anterior loss air entry). A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 18 November 2009 in combination with a BR consisting of EMB, ETH, KAN, OFL, and PZA. She completed the investigational treatment period without any clinically significant interruption of BR (> 14 days); last intake of bedaquiline was on 4 May 2010 (Day 168). The subject died on (b) (6) (Day (b) (6)). She took EMB, which has been reported to be associated with myocarditis and pericarditis, was taken until 9 January 2011 (Day 418).

On 27 July 2010 (Day 252), the subject experienced hypertension that was reported as a grade 2 AE. Supine SBP and DBP were 169 mmHg (grade 2) and 128 mmHg (grade 3) on this day, respectively. Both had been normal at baseline (Day 1) on 18 November 2009 (supine SBP: 117 mmHg; supine DBP: 83 mmHg) and all other study visits prior to 27 July 2010. No action towards the BR was taken and no concomitant therapy was started to treat hypertension. At the next visit on 18 October 2010 (Day 335), supine SBP and DBP were normal (123 mmHg and 75 mmHg, respectively).

On 29 December 2010 (Day 407), the subject experienced shortness of breath. She was diagnosed with right sided cardiac failure (cor pulmonale) on (b) (6) and was hospitalised on the same day (source: CIOMS). Hypertension was ongoing at that time (supine SBP: 144 mmHg [grade 1]; supine DBP: 101 mmHg [grade 2]). The following day on (b) (6) (Day (b) (6)), the subject experienced congestive cardiac failure. A clinically significant abnormality in ECG parameters had been observed the day before: QTcB was between 450 ms and 480 ms (461 ms); QTcF was within normal limits (418 ms). Both events (cor pulmonale with onset date 29 December 2010 and cardiac failure congestive) were reported as grade 3 SAEs and were treated with furosemide (80 mg b.i.d. IV) from 29 December onwards. Other concomitant medications included pyridoxine hydrochloride (25 mg q.d. until 9 January 2011) for nutritional support and potassium chloride (600 mg t.i.d. from 29 December 2010 onwards) to prevent hypokalemia. Drugs in the BR (EMB, ETH, OFL, PZA, and TRD at start of symptoms of cor pulmonale) were taken until 9 January 2011 and were permanently discontinued due to cardiac failure congestive.

Nine days after onset of congestive cardiac failure, on (b) (6), the subject died from this SAE and had not recovered from cor pulmonale or hypertension. An autopsy was not performed (source: CIOMS).

Hypertension, cor pulmonale, and cardiac failure congestive were considered not related to bedaquiline or the BR in the opinion of the investigator.

Other AEs reported during the investigational treatment period were headache, vomiting, gastritis, constipation, hypokalemia, otitis media viral, deafness bilateral, dyspnea, and insomnia.

MGIT results showed a positive MGIT culture at baseline (17 November 2009) and a confirmed conversion to negative at the Week 4 visit (23 December 2009, Day 36). The subject's MGIT result was positive at the Week 24 visit (4 May 2010, Day 168), negative at the following assessment (Week 36 visit on 27 July 2010, Day 252), and negative at the last available assessment (Week 60 visit on 11 January 2011, Day 420); her overall outcome was non-responder (discontinued with sputum culture conversion).

SUBJECT C209-0044: RENAL IMPAIRMENT

Subject 209-0044 (fatal 'renal impairment', SAE 'dehydration', and SAE 'vomiting' leading to discontinuation of bedaquiline) was a 63 year old Black woman infected with an MDR TB strain at baseline. The subject had cavitations of at least 2 cm in one lung only. She had been treated previously with second line anti-TB drugs including ETH, KAN, OFL, and TRD. No past medical history was reported for this subject; active diseases at screening included dyspepsia, "generalized old age", intermittent dizziness, and smoking. The subject did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed poor air entry right and crepitations right and left. A serology screen for HIV was negative. The subject's potassium level was normal at screening on 23 April 2010 (3.7 mmol/L, normal range: 3.4 5.4 mmol/L) and was grade 2 decreased at baseline on 29 April 2010 (2.9 mmol/L). No abnormalities were observed from urinalysis at screening or baseline.

The subject started treatment with bedaquiline on 30 April 2010 in combination with a BR consisting of ETH, KAN, OFL, PZA, and TRD. She prematurely discontinued intake of bedaquiline on 21 May 2010 (Day 22) due to a SAE (vomiting). The subject died on (b) (6) (Day (b) (6)).

On (b) (6) (Day (b) (6)), the subject experienced vomiting for which she was hospitalized (source: CIOMS). The event was reported as a grade 3 SAE and was considered doubtfully related to bedaquiline and probably related to the BR in the opinion of the investigator. No postbaseline treatment-emergent abnormalities were observed for amylase, lipase, gastrin, or pepsinogen I and II for this subject. The same day, bedaquiline was permanently discontinued due to vomiting; the BR (ETH, KAN, OFL, PZA, and TRD) was continued at that time. Concomitant medications to treat the vomiting included metoclopramide hydrochloride (10 mg t.i.d. po from 25 May 2010 until 2 June 2010). Nevertheless, the vomiting continued and this led to dehydration and renal impairment as reflected by blood results (creatinine was 146 µg/L and potassium was 2.5 mmol/L on 25 May 2010; source: CIOMS). The subject was reported with dehydration and renal impairment on 25 May 2010 (Day 26), both were a grade 4 SAE. Dehydration was considered doubtfully related to bedaquiline and probably related to the BR; renal impairment was considered doubtfully related to bedaquiline and very likely related to the BR. Drugs in the BR were permanently discontinued due to these events: last intake of ETH was on 26 May 2010. On (b) (6) (Day (b) (6)), the subject received electrolyte solutions (1000 ml q8h IV) for dehydration. She died from renal impairment on that same day, after a duration of (b) (6) days.

One other AE was reported during the investigational treatment period: vestibular disorder.

MGIT results showed a positive MGIT culture at baseline (29 April 2010) and at the last available MGIT assessment (Week 2 visit on 13 May 2010, Day 14). The subject's overall outcome was failure to convert.

SUBJECT C209-0327: LUNG INFECTION

Subject 209-0327 (fatal AE 'lung infection', SAE 'emotional disorder') was a 31 year old Asian man infected with a pre XDR TB strain (resistant to RMP and INH as well as to fluoroquinolones [OFL] but susceptible to injectable drugs [CAP and KAN]) at baseline. The subject had cavitations of at least 2 cm in one lung only. He had been treated previously with second-line anti TB drugs including LVX, EMB, PZA, and PAS-C. No past medical history was reported for this subject; active diseases at screening included cough, expectoration chest distress, and chest collapse. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed abnormal cough and left lobe percuss dullness (sic). A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 1 June 2010 in combination with a BR consisting of AMK sulfate, EMB, LVX, protionamide, and PZA. He completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of bedaquiline was on 15 November 2010 (Day 168). The subject died on (b) (6) (Day (b) (6)).

This subject had confirmed culture conversion on 26 July 2010 (Day 56) and had negative MGIT cultures up to the last available culture on 15 November 2010 (Day 168). On 18 December 2010 (Day 201), the subject experienced lung infection. He had more cough and sputum and had become short of breath without any cause (source: CIOMS). The subject was hospitalized on (b) (6). Lung infection was reported as a grade 4 SAE and was considered not related to bedaquiline or the BR in the opinion of the investigator. No action was taken towards the BR, which consisted of EMB, LVX, PZA, and protionamide. Concomitant medications to treat the event included primaxin (1,000 b.i.d. mg IV) from 28 December to 6 January, ambroxol (50 mL b.i.d. IV) from 28 December to 9 January, and acetylcysteine (0.6 g t.i.d. po) from 29 December to 9 January. The BR drugs EMB, levofloxacin, and PZA were replaced with clarithromycin and clofazimine from 30 December onwards; protionamide was continued. Shortness of breath resolved, cough and expectoration lessened (source: CIOMS), and the subject recovered from lung infection on (b) (6) (Day (b) (6)), after a duration of (b) (6) days. He was discharged from hospital the same day (source: CIOMS).

On (b) (6) (Day (b) (6)), the subject was hospitalized again due to lung infection (source: CIOMS). He presented with more cough and expectoration and was short of breath without any cause. The event was reported as a grade 4 SAE and was considered not related to bedaquiline or the BR in the opinion of the investigator. No concomitant medication was reported. During hospitalization, the subject had a mental anomaly and he was diagnosed with emotional disorder on 20 January 2011 (Day 234; source: CIOMS CN-JNJFOC-20110106869[3]). This event caused prolonged hospitalization and was reported as a grade 3 SAE. Emotional disorder was considered not related to bedaquiline or the BR in the opinion of the investigator. Concomitant medication to treat emotional disorder included alprazolam (0.8 mg q.n. po), lorazepam (1 mg b.i.d. po), and risperidone (0.5 mg q.n. po) from 20 to 25 January. The subject had not recovered from the emotional disorder.

On (b) (6) (Day (b) (6)), the subject experienced additional expectoration, cough, and shortness of breath and was treated with meropenem (source: CIOMS). The following day, the subject permanently discontinued all BR drugs (protonamide, clarithromycin, and clofazimine) due to emotional disorder and discharged himself. He died at home on that day (b) (6), Day 2 (b) (6) due to lung infection.

Adverse events reported during the investigational treatment period for this subject were 'white blood cell (WBC) count increased' and 'GGT increased'.

MGIT results showed a positive MGIT culture at baseline (31 May 2010) and a confirmed conversion to negative at the Week 8 visit (26 July 2010, Day 56). The subject's last available assessment at the Week 24 visit (15 November 2010, Day 168) was negative; his overall outcome was "death but converted".

SUBJECT C209-0021: RESPIRATORY FAILURE

Subject 209-0021 (fatal SAE 'respiratory failure' and SAE 'pyopneumothorax') was a 22 year old Black woman infected with an XDR TB strain (resistant to RMP and INH as well as to injectable drugs [CAP and KAN] and fluoroquinolones [OFL]) at baseline. The subject had no cavitations larger than 2 cm. She had been treated previously with second-line anti-TB drugs (including KAN, EMB, PZA, MXF, ETH, PAS-C, and TER). No medical history was reported. The subject's relevant active diseases at screening included pleuritic pain, cough, weight loss, tiredness and intermittent tight chest. She did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed abnormal cough. The subject was a non-smoker (source: CIOMS ZA-JNJFOC-20110511213[2]). A serology screen for HIV was positive. CD4 cell count at baseline was 315 x 106 cells/L; HIV viral load was not reported.

The subject started treatment with bedaquiline on 8 September 2009 in combination with a BR consisting of EMB, ETH, KAN, PAS-C, PZA, and TRD. She completed the investigational treatment period with a clinically significant interruption (> 14 days) of the BR. Last intake of bedaquiline was on 22 February 2010 (Day 168, Week 24). The subject died on (b) (6) (Day (b) (6)).

On 1 November 2010 (Day 420), the subject was reported with worsening of tuberculosis. Tuberculosis was reported as a grade 3 AE and considered not related to bedaquiline and the BR by the investigator. At time of the event, the BR consisted of PAS-C, PZA, TRD, AMK sulfate, augmentin, MXF, INH, and CAP.

On (b) (6) (Day (b) (6)), the subject experienced a severe right pyopneumothorax and was hospitalized (source: CIOMS). Pyopneumothorax was reported as a grade 3 SAE and was considered not related to bedaquiline and the BR in the opinion of the investigator. An intercostal drain was inserted to drain the pus and air (source: CIOMS). At the start of the SAE pyopneumothorax, the subject received a BR consisting of PAS-C, PZA, TRD, AMK sulfate, augmentin, MXF, INH, and CAP. Concomitant medications to treat the event included potassium chloride and sodium chloride (40 mg and 1000 mL, respectively, once IV on 14 May 2011). The subject recovered from pyopneumothorax on (b) (6) after a duration of (b) (6) days. The same day, she had a chest drain removed and was discharged (source: CIOMS). On (b) (6) (Day (b) (6)), the subject experienced respiratory failure for which she was hospitalized the same day (source: CIOMS). This event was reported as a grade 4 SAE considered not related to

bedaquiline or the BR by the investigator. Due to her terminally ill condition including XDR-TB, the subject only received palliative treatment (source: CIOMS). The BR was permanently discontinued due to pyopneumothorax and respiratory failure on 30 May 2010. The subject died on (b) (6). The causes of death were respiratory failure, drug-resistant tuberculosis and immunosuppression (source: CIOMS).

Other AEs reported during the investigational treatment period were oral candidiasis, seasonal rhinitis, pleuritic pain, muscle spasm, and insomnia.

MGIT results showed a positive MGIT culture at baseline (7 September 2009). The subject's last available MGIT assessment (Week 84 visit on 21 April 2011, Day 591) was positive; her overall outcome was failure to convert.

SUBJECT C209-0038: DRUG-RESISTANT TUBERCULOSIS

Subject 209-0038 (SAEs 'pneumothorax' and 'tuberculosis') was a 19 year old Black man infected with a pre XDR TB strain (resistant to RMP and INH as well as to injectable drugs [KAN and CAP] but susceptible to fluoroquinolones [OFL]) at baseline. The subject had cavitations of at least 2 cm in one lung only. He had been treated previously with second-line anti-TB drugs including ETH, KAN, and OFL. The subject's past medical history included diarrhea, constipation, and headache; active diseases at screening included weight loss, sweats, cough, and pleuritic pain bilateral. The subject did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed abnormal wheeze right posterior with poor air entry and "amphoric brr" left apex. A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 2 March 2010 in combination with a BR consisting of EMB, ETH, KAN, OFL, and PZA. He completed the investigational treatment period as planned but with a clinically significant interruption (> 14 days) of BR drugs (from 11 to 31 May 2010); last intake of bedaquiline was on 18 August 2010 (Day 170). The subject discontinued the study on 17 November 2011 (Day 626) due to non-compliance.

On (b) (6) (Day (b) (6)), the subject was hospitalized for treatment of presumed XDR-TB, as the medication was only available in hospital (source: CIOMS ZA-JNJFOC-20110200185[5]). No drug susceptibility results from that day were available at the central lab; however, subsequent susceptibility testing results at the Week 24 visit (18 August 2010, Day 170) confirmed emergence of resistance to OFL, a fluoroquinolone. The subject was resistant to EMB and CAP and susceptible to ETH and PZA at that time point (based on the agar proportion method). He was also observed with a more than 4-fold increase in bedaquiline MIC during investigational treatment, from 0.0625 µg/mL at baseline to 0.5 µg/mL at Week 24 (based on the REMA method). Prior to the event, the subject had interrupted bedaquiline for 6 days (from 18 to 23 May 2010, missed 2 doses during t.i.w. dosing) and all drugs in the BR for more than 2 weeks (from 11 May to 31 May 2010). On 1 June 2010 (Day 92), a BR was re-initiated and consisted of EMB, ETH, OFL, PZA, PAS-C, CAP, and TRZ; pyridoxine was also started on that day.

On (b) (6) (Day (b) (6)), whilst still in hospital, the subject developed pneumothorax, which was reported as a grade 4 SAE. A left intercostal drain was inserted on the same day (source: CIOMS ZA-JNJFOC-20110200185[5]). The event was considered not related to bedaquiline or the BR in the opinion of the investigator. No action was taken towards study medication and no concomitant medications were given to treat this event.

The subject recovered from pneumothorax on 27 February 2011, after a duration of 35 days.

All BR medications were discontinued on 18 May 2011.

As of 10 October 2011 (Day 588), the subject's drug-resistant tuberculosis became worse (source: CIOMS ZA-JNJFOC-20111111419[3]). On the same day, tuberculosis was reported as a grade 3 AE. The subject did not receive BR at that time. On (b) (6) the subject was hospitalized due to continued worsening of the tuberculosis (source: CIOMS) and tuberculosis was reported as a grade 4 SAE. Tuberculosis was considered not related to bedaquiline or the BR in the opinion of the investigator.

On (b) (6) (Day (b) (6)), the subject died due to drug-resistant tuberculosis (source: CIOMS).

Other AEs reported during the investigational treatment period were deafness bilateral and tinnitus.

MGIT results showed a positive MGIT culture at baseline (1 March 2010) and these remained positive up to the last available assessment (Withdrawal visit on 17 November 2011, Day 626). The subject's overall outcome was failure to convert.

SUBJECT C209-0077: WORSENING OF TB

Subject 209-0077 (fatal SAE 'tuberculosis') was a 32 year old Black woman infected with an M. tuberculosis strain resistant to at least RMP and INH (MDR-TB) consistent with the subject's medical history based on previous DST (central DST results to confirm extent of resistance were not available). The subject had cavitations of at least 2 cm in one lung only. She had been treated previously with second-line anti-TB drugs (including KAN, OFL, ETH, and TRD). The subject's active diseases at screening included HIV. No medical history was reported. She did not have a history of drug allergy or hypersensitivity. No findings of physical examination were reported at screening. A serology screen for HIV was not available. CD4 cell count at baseline was 600 x 106 cells/L; HIV viral load was 960 copies/mL.

The subject started treatment with bedaquiline on 8 July 2010 in combination with a BR consisting of ETH/KAN/OFL/PZA/TRD. She completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR. Last intake of bedaquiline was on 22 December 2010 (Day 168). The subject died on (b) (6) (Day (b) (6)).

The subject had started BR at an unspecified date in June 2010 (prior to bedaquiline start). Sputum cultures were negative since 24 June 2010 and radiological improvement was observed. However, the subject was not compliant with her treatment after completion of the investigational treatment phase despite repeated counseling (source: CIOMS). Her sputum cultures became positive on 22 December 2010 (Week 24) and remained so. Her chest X-ray had worsened and she had lost approximately 10 kg in weight. It was concluded that MDR-TB treatment was failing.

Tuberculosis (verbatim: worsening of TB) was reported as a grade 3 SAE and was considered not related to bedaquiline or the BR in the opinion of the investigator. On 22 December 2010, KAN was permanently discontinued due to this SAE.

She was admitted to a private facility on 5 August 2011 for strict monitoring and optimization of her treatment for XDR-TB due to her poor response to MDR TB treatment. A BR consisting of CAP, PAS-C, moxifloxacin, and clofazimine was started. Last recorded intake of this BR was 5 October 2011.

On 6 October 2011, the investigator reported that the subject was chronically non-adherent to her MDR-TB treatment, antiretroviral treatment, and her re-treatment regimen for XDR-TB despite all the counseling and efforts made to help her. In the morning of (b) (6) the subject died in her sleep at home, from worsening of TB. An autopsy was not performed.

Other adverse events reported during the investigational treatment period were vomiting, arthralgia, abdominal pain, diarrhea, and influenza.

MGIT results showed a negative MGIT culture at baseline (8 July 2010), hence the subject was excluded from the mITT population. MGIT cultures remained negative up to the Week 20 visit (24 November 2010, Day 140). A confirmed positive culture was observed at Week 24 (22 December 2010). The subject's last available MGIT assessment (Week 60 visit on 30 August 2011, Day 419) was positive; her overall outcome was relapse.

SUBJECT 209-0046: TUBERCULOSIS

Subject 209-0046 (fatal SAE 'tuberculosis') was a 34 year old Black man infected with an M. tuberculosis strain resistant to at least RMP and INH (MDR-TB) consistent with the subject's medical history based on previous DST (central DST results to confirm extent of resistance were not available). The subject had cavitations of at least 2 cm in one lung only. He had been treated previously with second-line anti-TB drugs (including KAN, OFL, and ETH). No medical history or currently active diseases were reported at screening. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed abnormal left basal crepitations and right basal crepitations axillary (TB) [The sponsor acknowledges the verbatim text was edited for clarity]. A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 14 May 2010 in combination with a BR consisting of EMB/ETH/KAN/OFL/PZA. He completed the investigational treatment period as planned but with a clinically significant interruption (> 14 days) of the BR. The subject completed intake of bedaquiline on 27 October 2010 (Day 167). The subject died on (b) (6) (Source: CIOMS ZA-JNJFOC-20120713032(0)).

Kanamycin was stopped on 6 September 2010. After 15 October 2011, there was no record of EMB, ETH, OFL, and PZA intake, except for 1 dose on 21 December 2011.

At an unspecified date in 2012, the subject experienced worsening of TB. Tuberculosis was reported as an SAE and was considered not related to bedaquiline in the opinion of the investigator. The severity of this SAE and the relation to the BR were not reported. The subject died on (b) (6) It was unknown whether an autopsy was performed.

Herpes zoster was reported as an AE during the investigational treatment period.

MGIT results showed a negative MGIT culture at baseline (13 May 2010) and was therefore excluded from the mITT population. MGIT results remained negative up to the last available assessment (Week 96 visit on 9 March 2012, Day 666) with exception of unconfirmed positive cultures at the Week 2 visit (27 May 2010, Day 14) and the Week 48 visit (12 April 2011, Day 334). The subject's overall outcome was culture conversion.

SUBJECT 209-0156: CARDIAC ARREST

Subject 209-0156 (SAE leading to death 'pneumonia' and SAE 'dyspnea', 'cough' and 'neurotoxicity') was a 59 year old Asian man infected with an XDR TB strain (resistant to RMP and INH as well as to injectable drugs [CAP and KAN] and fluoroquinolones [OFL]) at baseline. The subject had cavitations of at least 2 cm in one lung only. He had been treated previously with second-line anti-TB drugs including augmentin (amoxicillin+clavulanic acid), clarithromycin, CS, KAN, levofloxacin, and PAS-C. The subject's past medical history included tinnitus, blurred vision, finger tingling sense, and right thoracoplasty; active diseases at screening included high tone hearing loss, intermittent sudden flash of heat of whole body, cicatricial bronchiectasis, atelectasis, sputum, cough, dyspnea, tachypnea, and COPD (source CIOMS KR-JNJFOC-20101201394[2]). The subject did not have a history of drug allergy or hypersensitivity. A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 29 December 2009 in combination with a BR consisting of augmentin, CS, KAN, levofloxacin, and PAS-C. He completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of bedaquiline was on 14 June 2010 (Day 168, Week 24). The subject died on (b) (6) (Day (b) (6)).

The subject had active dyspnea at screening for which he was receiving concomitant medication including seretide (1 b.i.d. inh) and tiotropium (18 µg q.d. inh). During the investigational treatment period, the subject experienced several episodes of aggravation of dyspnea, which were reported as an AE dyspnea of severity grade 1 on 8 February 2010 (Day 42) and 11 April 2010 (Day 104) and of severity grade 3 on 14 May 2010 (Day 137). For the latter event of dyspnea, the subject visited an emergency room and was told that he had pneumonia. He subsequently attended the investigator's clinic, where a chest radiograph showed pneumonic consolidation, and he was admitted to hospital on (b) (6) (source: CIOMS KR-JNJFOC-20100506608[1]). Pneumonia was reported as a grade 3 SAE starting on an unknown day in May 2010.

All events of dyspnea and the SAE pneumonia were considered not related to bedaquiline or to the BR in the opinion of the investigator. No action was taken towards study medication for any of these events. Concomitant medications to treat the events of dyspnea included aminophylline (250 mg q.d. IV), fluticasone propionate (2 mg q.d. inh), ipratropium bromide (500 µg q.d. inh), glucose injection (200 or 500 mL q.d. IV), acetylcysteine (300 mg q.d. IV), and/or budesonide (500 µg q.d. inh) on the days of reporting. Pneumonia was treated with concomitant medications including azithromycin (500 mg q.d. po), ceftriaxone (2 g q.d. IV), glucose injection (500 ml q.d. IV), and osmotan (1000 ml b.i.d. IV) on 17 May, methylprednisolone sodium succinate (30 mg t.i.d or b.i.d. IV) from 17 to 24 May, piperacillin/tazobactam (4.5 g t.i.d. IV) and sodium chloride

(100 ml t.i.d. IV) from 17 to 25 May, bactrim (2 b.i.d. po) on 22 and 23 May and from 25 to 27 May, and prednisone (30 or 15 mg q.d. po) from 25 May to 1 June.

The subject recovered from each event of (aggravation of) dyspnea on the same day of reporting, and from pneumonia on (b) (6) (Day (b) (6)) when he was discharged from hospital (source: CIOMS).

After the end of the investigational treatment period, the subject again experienced episodes of aggravation of dyspnea on 22 July 2010 (Day 206) and 25 October 2010 (Day 301), which were reported as a grade 2 and 3 AE, respectively, and from which he recovered on the same day after treatment with concomitant medications (aminophylline, fluticasone propionate, glucose injection, ipratropium bromide, and/or sodium chloride) on the days of reporting. On 1 November 2010 (Day 308) (source: CIOMS KR-JNJFOC-20101201394[2]), 8 April 2011 (Day 466) (source: CIOMS KR-JNJFOC-20110506136[3]) and 8 September 2011 (Day 619) (source: CIOMS: KR-JNJFOC-20110904221[3]), the subject was hospitalized for 3 episodes of aggravated dyspnea that were reported as a grade 3 SAE. Dyspnea was reported to be caused by underlying lung disease (COPD). The first 2 episodes of (aggravation of) dyspnea were considered resolved on 15 November 2010, after a duration of 15 days and 15 April 2011, after a duration of 8 days, respectively. The third episode was considered resolved with sequelae on 21 September 2011 after a duration of 14 days. Concomitant medications to treat the 3 dyspnea SAEs with sequence numbers 14, 20 and 21 are listed below under “Concomitant Medication”.

All 5 episodes of dyspnea described in the above paragraph were considered not related to bedaquiline or the BR in the opinion of the investigator. No action towards drugs in the BR was taken for any event.

On 2 (b) (6) (Day (b) (6)), the subject experienced severe cough and dyspnea (source: CIOMS KR-JNJFOC-20120106130[3]), both reported as grade 3 SAEs. He was hospitalized the same day. The investigator did not consider the SAEs related to the study medication and no action was taken towards drug in the subject’s BR. The risk factors included multi drug resistant TB, bronchiectasis and atelectasis. At the start of the SAEs cough and dyspnea, the subject’s C-reactive protein level (60.8 µg/dL [normal high range: 5 µg/L]) and pCO₂ (47.6 mmHg [normal range: 34 – 45]) were increased, his red blood cell count was slightly low (4.0 millions/mm³ [normal range: 4.5 – 6.3 millions/mm³] on 6 January 2012) and WBC count was normal (6.15 millions/mm³ [normal range: 4 – 10 millions/mm³] on 6 January 2012). To treat the severe cough (sequence number 23) and dyspnea (sequence number 24), the subject received concomitant medication as listed below under “Concomitant Medication”.

On (b) (6) the subject had recovered from the cough after a duration of 27 days and was discharged with the dyspnea not yet resolved (source: CIOMS).

The subject experienced the adverse events of paraesthesia (verbatim: both leg/hand tingling sense), which was considered an adverse reaction of linezolid and hypoesthesia (verbatim: both foot numbness and numbness of fingertips) from December 2010 onwards. After aggravation of tingling sense and difficulty in ambulation, the subject’s condition was reassessed and on 7 April 2012 (Day 831), he was reported with neurotoxicity and aggravation of dyspnea (source: CIOMS KR-JNJFOC-20120405877[3]). Neurotoxicity was reported as a grade 3 SAE, which was considered not related to bedaquiline and possibly related to the BR. The BR consisted of

augmentin, CS, levofloxacin, EMB, and CAP on 6 April 2012, a day before the start of the neurotoxicity. On (b) (6) the subject was hospitalized due to the aggravation of dyspnea and on 16 April, the subject was diagnosed with pneumonia (source: CIOMS). Therefore, the previously reported event of dyspnea was updated to a grade 3 SAE, which was not considered related to study medication. To treat pneumonia, the subject received antibiotics (source: CIOMS). On (b) (6) the subject was transferred from the general ward to the intensive care unit, due to cardiac arrest on (b) (6) and was started on a ventilator. The subject's BR medications were temporarily stopped and then restarted on (b) (6) with the intention of "weaning" on (b) (6) (source: CIOMS). On (b) (6) at 16:00 a further cardiac arrest occurred, the subject was treated with epinephrine, cardiac massage, "ambu bagging" and the ventilator was restarted. The medical team obtained informed consent to not resuscitate (DNR). The subject died from cardiac arrest (underlying cause pneumonia) on (b) (6). An autopsy was not performed (source: CIOMS).

Other AEs reported during the investigational treatment period were infusion site discolouration, dyspepsia, pruritus generalized, pain, oropharyngeal pain, nasopharyngitis, and fatigue.

MGIT results showed a positive MGIT culture at baseline (28 December 2009) and throughout the trial until the last available assessment at the Week 108 visit (8 February 2012, Day 772), except for one unconfirmed negative MGIT culture at the Week 12 visit (22 March 2010, Day 84). The subject's overall outcome was failure to convert.

SUBJECT 209-0225: HYPERTENSION

Subject 209-0225 (SAEs 'cardiac failure', 'cerebral hemorrhage', 'ischemic cerebral infarction' and fatal SAE 'hypertension') was a 46 year old White man infected with an MDR_{H&R} TB strain at baseline. The subject had cavitations of at least 2 cm in one lung only. He had been treated previously with second-line anti-TB drugs including AMK sulfate, OFL, PZA, EMB, and CS. No past medical history was reported for this subject; active diseases at screening included type II diabetes. He did not have a history of drug allergy or hypersensitivity. None of the abnormalities reported upon physical examination at screening were clinically relevant. A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 18 May 2010 in combination with a BR consisting of AMK sulfate, CS, EMB, OFL, and PZA. He completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of bedaquiline was on 12 November 2010 (Day 179, Week 24). The subject prematurely discontinued the trial due to a fatal SAE and died on (b) (6) (Day (b) (6)).

On 2 December 2010 (Day 199), the subject experienced edema peripheral (verbatim: pretibial edema) as observed during physical examination. The event was reported as a grade 3 AE and was considered not related to bedaquiline and the BR in the opinion of the investigator. No action was taken towards drugs in the BR, which consisted of AMK, EMB, OFL, PZA, and cycloserine. On this day, QTcF values were between 450 ms and 500 ms (481 ms at the predose ECG and 464 ms at the 5h postdose ECG), corresponding to changes from reference within normal range (< 30 ms); troponin I was above normal (0.03 µg/L, upper limit: 0.02 µg/L); creatine phosphokinase - muscle-brain isoenzyme (CPK-MB) was within normal limits (2.40 µg/L; normal range: 0.70-4.90 µg/L).

On (b) (6) (Day (b) (6)), the subject presented to the emergency room with dyspnea (source: CIOMS). On examination, the subject had severe pretibial edema and atrial gallop rhythm, pulmonary hypertension, and a ventricular ejection fraction of 30%. The subject was diagnosed with congestive cardiac failure and was scheduled for further investigations. On (b) (6) (Day (b) (6)), he was hospitalized and underwent a coronary angiography and was discharged that night (source: CIOMS TR-JNJFOC-20101204471[10]). No ECG or laboratory results were available from these time points. Cardiac failure was reported as a grade 3 SAE and was considered doubtfully related to bedaquiline and the BR in the opinion of the investigator. No action was taken towards the BR. Edema peripheral and cardiac failure were treated with furosemide (20 mg q.d. po on 10 December 2010 and 20 mg t.i.w. po from 11 December 2010 to 28 February 2012). In addition to oral furosemide, cardiac failure was treated with intravenous furosemide (4 mL q.d.) on 9 December 2010, salutec (2.5 mg q.d. po) from 9 December 2010 to 12 January 2011, acetylsalicylic acid (100 mg q.d. po) from 9 December 2010 to 19 September 2011, sildenafil (25 mg q.d. po) from 31 December 2010 to 24 January 2011, and spironolactone (25 mg q.d. po) from 31 December 2010 to 28 February 2012.

The investigator reported that pulmonary hypertension could be an underlying reason for congestive heart failure and the subject was scheduled to have further examinations (source: CIOMS). On (b) (6) (Day (b) (6)), he was hospitalized for an angiographic examination that showed a negative vasoreactivity test result; he was discharged the same day. Physical examination on 11 March 2011 (Day 298) indicated that pretibial edema was ongoing. The subject had grade 3 increased supine SBP and DBP on that day (190 mmHg and 110 mmHg, respectively), which was not reported as an AE.

On (b) (6) (Day (b) (6)), the subject was unconscious and was admitted to hospital. On 25 August 2011, he had a computerized tomography scan and was diagnosed with intraparenchymal cerebral hemorrhage (source: CIOMS TR-JNJFOC-20101204471[10]). Cerebral hemorrhage was reported as a grade 4 SAE and was considered not related to bedaquiline and the BR in the opinion of the investigator. No action was taken towards the BR. The subject's hematoma was drained by craniotomy (source: CIOMS). On 6 September 2011, the subject recovered from cerebral hemorrhage with sequelae, i.e., right hemiparesis (source: CIOMS), after a duration of 43 days.

On (b) (6) (Day (b) (6)), the subject was hospitalized with ischemic cerebrovascular accident due to an epileptic attack. A computerized cranial tomography was performed and confirmed diagnosis of ischemic cerebrovascular accident (source: CIOMS). Ischemic cerebral infarction was reported as a grade 4 SAE and was considered not related to bedaquiline and not related to the drugs in the BR. No action was taken towards the BR. Concomitant medications to treat this event included acetylsalicylic acid (300 mg q.d. po), enoxaparin sodium (0.4 cc b.i.d. IV), levetiracetam (250 mg b.i.d. po), and pantoprazole sodium sesquihydrate (40 mg q.d. po) from 19 September 2011 to 28 February 2012.

On (b) (6) (Day (b) (6)), the subject developed hypertension. His family reported that he was feeling worse and that he had passed away before the emergency services had arrived at his home (source: CIOMS TR-JNJFOC-20120400577[2]). Hypertension was reported as a grade 4 fatal SAE, considered not related to bedaquiline and the BR in the opinion of the investigator.

Adverse events reported during the investigational treatment period were hyperglycemia, hypertension, blood gastrin increased, blood creatinine increased, GGT increased, and WBC count increased. Grade 3 elevations of SBP and DPB were also noted.

MGIT results for this subject showed a positive MGIT culture at baseline (17 May 2010). The subject's last available assessment (Week 48 visit on 11 March 2011, Day 298) was negative but as only a single negative culture was obtained, his overall outcome was failure to convert.

SUBJECT 209-0552: HEMOPTYSIS

Subject 209-0552 (SAEs 'decreased appetite', 'hyponatremia', hemoptysis, and 'hypovolemic shock' and fatal SAE 'hemoptysis') was a 56 year old Asian man infected with an MDR_{H&R} TB strain at baseline. The subject had cavitations of at least 2 cm in both lungs. He had been treated previously with second-line anti-TB drugs including EMB and PZA. The subject's past medical history included fever, weight loss, and dyspnea; active diseases at screening included anorexia, weakness, bronchospasm, cough, phlegm, and crepitation at left upper lobe. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening confirmed crepitation at left upper lobe. A serology screen for HIV was negative.

The subject started treatment with bedaquiline on 6 October 2010 in combination with a BR consisting of CS, EMB, ETH, KAN, and OFL. He completed the investigational treatment period as planned without any clinically significant interruption (> 14 days) of the BR; last intake of bedaquiline was on 23 March 2011 (Day 169, Week 24). The subject died on (b) (6) (Day (b) (6)).

On 23 February 2011 (Day 141), i.e., during the investigational treatment phase, the subject experienced anorexia and weight decreased. On (b) (6) (Day (b) (6)), he also experienced weakness from hyponatremia and was admitted to hospital for supportive care (source: CIOMS). Decreased appetite (verbatim: anorexia) and hyponatremia were reported as SAEs of severity grade 2 and grade 3, respectively; weight decreased was reported as an AE of severity grade 3. Laboratory results showed a serum sodium level of 128 mmol/L (grade 2 decreased) and an albumin level of 32 g/L (grade 1 decreased) on 23 February; sodium had further decreased to 122 mmol/L on 1 March (source: CIOMS). At baseline, serum sodium was within normal limits (141 mmol/L, normal range: 132 147 mmol/L) and albumin was grade 1 decreased (32 g/L; normal range: 33 49 g/L). No action was taken towards the study medication and no concomitant therapy was started to treat hyponatremia and weight decreased. Concomitant medication to treat decreased appetite included dextrose and sodium chloride injection (1000 mL q.d. IV from 1 to 9 March). All three events were considered doubtfully related to bedaquiline and the BR in the opinion of the investigator, except for weight decreased that was judged possibly related to the BR.

The subject recovered from decreased appetite and hyponatremia on 3 and 10 March 2011, after a duration of 9 and 10 days, respectively. On 4 and 10 March, the subject's sodium level was within normal range (135 mmol/L; source: CIOMS). The subject was discharged from hospital on 11 (b) (6) (Day (b) (6)); source: CIOMS). The subject recovered from weight decreased on 6 September 2011, after a duration of 196 days.

Other AEs reported during the investigational treatment period were myalgia, chest discomfort, tremor, asthenia, palpitations, constipation, agitation, tinea infection, and hemoptysis.

On 17 May 2012, at the Week 84 visit (Day 590) at the clinic, the subject experienced sudden hemoptysis of 40 mL/dL of blood. His vital signs and hemodynamics were stable and physical examination revealed crepitations and rhonchi at the left upper lobe lung field. The subject had a cough and blood in the sputum, for which he was hospitalized for observation (source: CIOMS TH-JNJFOC-20120516728[1]). Laboratory assessments for platelet count and PT were normal on that day. Hemoptysis was reported as a grade 1 SAE and was considered not related to bedaquiline and not related to the BR in the opinion of the investigator. No action was taken towards the BR. A chest X ray showed cavity in the left upper lobe and no new lesions. Hemoptysis was likely from the tuberculosis cavity in the left upper lobe area (source: CIOMS). Concomitant medications to treat this event are listed below (under the heading ‘concomitant medication’; see AE sequence number 23).

The subject’s hematocrit was 34% at admission and 24% on the fourth day of hospitalization. After receiving packed red blood cells his hematocrit increased to 31% (source: CIOMS). The subject’s hemoptysis gradually improved and he was discharged from hospital on (b) (6) with blood stained sputum. On (b) (6) (Day (b) (6)), the subject’s blood stained sputum disappeared (source: CIOMS). Hemoptysis was considered resolved the same day, after a duration of 36 days.

The next day ((b) (6) Day (b) (6)), the subject was hospitalized because he had been experiencing dyspnea and fever for a week as well as loss of appetite, diarrhea, and a cough. A physical examination showed a blood pressure of 92/64 mmHg, a heart rate of 120 bpm, and crepitation in the upper lobe of his lung (source: CIOMS TH-JNJFOC-2012614349[4]). Hypovolemic shock was reported as grade 3 SAE and was considered not related to bedaquiline and not related to the BR. No action was taken towards the BR due to this SAE. The subject was treated with ceftazidime, clindamycin, and intravenous fluid replacement (source: CIOMS). After the IV fluid replacement, his blood pressure increased to 106/58 mmHg and his clinical condition improved. On (b) (6) his blood pressure was stable at 100-135 mmHg systolic and his heart rate was between 90 and 100 bpm (source: CIOMS), and hypovolemic shock was considered resolved, after a duration of 3 days. The subject however complained of generalized weakness and wanted to stay in the hospital (source: CIOMS).

On 7 July 2012 (Day 641), the subject experienced massive hemoptysis with a sudden blood loss of 300 mL. He had good consciousness, but experienced hemodynamic instability. His blood pressure was 70 mmHg systolic, respiratory rate was 49/min, heart rate was 150 bpm, oxygen saturation was 70%, and his hematocrit level was 34% (source: CIOMS TH-JNJFOC-20120614349(1)). No coagulation-related laboratory values were reported. Hemoptysis was reported as a grade 4 SAE and was considered not related to bedaquiline and not related to the drugs in the BR. An endotracheal tube was inserted, the subject was put on a mechanical ventilator and moved to the respiratory intensive care unit. Blood pressure was controlled with dopamine intravenously and one unit of packed red blood cells was transfused (source: CIOMS). On (b) (6) the subject developed dyspnea and hypotension. In order to control his blood pressure, treatment with dopamine was changed into epinephrine; other supportive care was provided. Four days later, the subject suddenly developed massive hemoptysis of 300 mL blood. His heart rate slowed down to 30 bpm and his blood pressure was not measurable. His family decided to stop further life support, and the subject died the same day (source: CIOMS).

MGIT results showed a positive MGIT culture at baseline (5 October 2010) and a confirmed conversion to negative at the Week 16 visit (26 January 2011, Day 113). The subject's last available assessment at the Week 60 visit (22 November 2011, Day 413) was negative; his overall outcome was culture conversion.

APPENDIX 9: CLINICAL MINI-NARRATIVES FOR DEATHS DURING LONG-TERM SURVIVAL FOLLOW-UP OF PREMATURELY WITHDRAWN SUBJECTS TRIAL C209

SUBJECT 209-0234: TB RELATED ILLNESS

Subject 209-0234 was a 32-year-old White man who had cavitations of ≥ 2 cm in one lung and who was infected with an MDR_{H&R}-TB strain at baseline. The subject's medical history active at screening included dyspnea, tachypnea and clubbing. HIV serology screen was negative. He started bedaquiline on 28 May 2010 in combination with a BR consisting of CS, OFL, CAP, PAS-C, clofazimine, ETH, PZA, protionamide, and thioacetazone. The subject prematurely discontinued bedaquiline on 4 Jun 2010 due to QT prolongation and was withdrawn from the trial on 15 Jun 2010 for the same reason. ECG QT prolongation was reported as a grade 3 SAE and considered very likely related to bedaquiline and not related to drugs in the BR by the investigator. The maximum reported QTcF value was 461 ms (on 4 Jun 2010). The event had resolved by the next follow up visit 3 days later. On (b) (6) i.e., (b) (6) days after trial termination and (b) (6) days after last intake of bedaquiline, the subject died of **TB-related illness**. The subject experienced massive **hemoptysis** following a planned pneumonectomy. The investigator considered the causality between bedaquiline and hemoptysis as not related to bedaquiline (source: CIOMS TR-JNJFOC-20110301517[3]). MGIT results showed a positive MGIT culture at baseline (28 May 2010) and up to the last available MGIT assessment (Follow-up visit on 15 Jun 2010, Day 19). The subject's overall outcome was failure to convert.

SUBJECT 209-0476: TB RELATED ILLNESS

Subject 209-0476 was a 20-year-old White man who had cavitations of ≥ 2 cm in one lung and who was infected with a Pre-XDR-TB strain (resistant to RMP and INH as well as to injectable drugs [CAP] but susceptible to fluoroquinolones [OFL]) at baseline. No medical history was reported. HIV serology screen was negative. He started bedaquiline on 4 Oct 2010 in combination with KAN, LFX, PZA, CS, PAS-C and amoxicillin + clavulanic acid. The subject prematurely discontinued bedaquiline intake on 2 Dec 2010 and withdrew consent on 3 Dec 2010. The survival form indicates that the subject died of **TB-related illness** on an unspecified date in December 2010. The investigator considered the causality between death and bedaquiline as doubtfully related (source: CIOMS PC-JNJFOC-20111000323[1]). MGIT results showed a positive MGIT culture at baseline (1 Oct 2010) and remained positive up to the last available MGIT assessment (Week 4 visit on 27 Oct 2011, Day 24). The subject's overall outcome was failure to convert.

SUBJECT 209-0027: TB-RELATED ILLNESS

Subject 209-0027 was a 37-year-old Black woman who had cavitations of ≥ 2 cm in one lung and was infected with an MDR_{H&R}-TB strain at baseline. The subject's active diseases at screening included included night sweats, weight loss, productive cough, and mild hemoptysis. HIV serology screen was negative. The subject started treatment with bedaquiline on 27 Nov 2009 in combination with a BR consisting of ETH, EMB, KAN, OFL, and PZA. She completed the investigational treatment period as planned but with several clinically significant interruptions (> 14 days) of BR drugs; last intake of bedaquiline was on 12 May 2010 (Day 167). The subject was withdrawn from the trial on 28 Nov 2011 (Day 732) due to non-compliance. On 20 Jan 2011 (Day 420), the subject experienced worsening of tuberculosis. Tuberculosis was reported as a grade 3 AE considered not related to bedaquiline or the BR. On (b) (6) (Day (b) (6)), the subject was admitted to a hospital with a diagnosis of pneumonia, reported as a grade 3 SAE and considered not related to bedaquiline and not related to the BR by the investigator. At time of pneumonia diagnosis the subject was not receiving BR. The subject recovered from pneumonia and was discharged from hospital on (b) (6) (source: CIOMS ZA-JNJFOC-20110200290[2]). On 12 Feb 2011, the subject started a BR of EMB, ETH, KAN, OFL, PZA, and TRD. On 13 Apr 2011, the AE tuberculosis was considered resolved. All BR medication was discontinued on 31 Jul 2011; there are no records of BR intake after that date. From 1 Sep 2011 (Day 644) onwards, the subject experienced worsening of tuberculosis, reported as a grade 3 AE considered not related to bedaquiline or the BR by the investigator. On (b) (6) (Day (b) (6)), the subject was admitted to hospital with a lung abscess, reported as a grade 3 SAE (CIOMS ZA-JNJFOC-20111009255[1]). The SAE was considered not related to bedaquiline or the BR by the investigator. The subject was discharged from hospital and was considered recovered from the lung abscess only on (b) (6). The survival form indicates that the subject died of **TB-related illness** at an unspecified date in January 2012. MGIT results showed a positive MGIT culture at baseline (26 Nov 2009) and a confirmed conversion to negative at the Week 16 visit (17 Mar 2010, Day 111). A confirmed positive culture was observed at the Week 36 visit on 5 Aug 2010 (Day 252). MGIT culture results remained positive until Week 96 (3 Oct 2011, Day 676). The subject's MGIT result at the last available assessment (Withdrawal visit on 21 Nov 2011, Day 725) was negative (not confirmed). Her overall outcome was relapse.

SUBJECT C209-0058: WORSENING OF XDR-TB

Subject 209-0058 was a 27-year-old Black woman who had cavitations of ≥ 2 cm in both lungs and who was infected with an XDR-TB strain at baseline. The subject's active diseases at screening included cough. HIV serology screen was negative. The subject started treatment with bedaquiline on 20 Aug 2010 in combination with a BR consisting of ETH, KAN, OFL, PZA, and TRD. The subject was withdrawn from the trial on 31 Jan 2011 (Day 165) due to non-compliance; last intake of bedaquiline was on 10 Jan 2011 (Day 144). The subject was reported to have "absconded from hospital" and was lost to follow-up after (b) (6). On (b) (6) she was readmitted to hospital with severe dyspnea and tachypnea (source: CIOMS ZA-JNJFOC-20120704216[0]). Differential diagnosis included respiratory failure/respiratory infection with XDR-TB tuberculosis as the suspected cause. On (b) (6) i.e., (b) (6) days after trial termination and (b) (6) days after last intake of bedaquiline, the subject died due **worsening of XDR-TB**. An autopsy was not performed. MGIT results showed a positive culture at baseline (19 Aug 2010) and remained positive the last available assessment (Week 20 visit on 5 Jan 2011, Day 139). Her overall outcome was failure to convert.

APPENDIX 10: TRIAL C208 STAGE 2 MORTALITY DATA**Table 52: Demographic Data - Tabulation and Descriptive Statistics (ITT) by Survival Status - Trial C208 Stage 2 Final Analysis**

Parameter Value n (%)	TMC207/BR		Placebo/BR	
	Alive N = 69	Death N = 10	Alive N = 79	Death N = 2
Age (years) at reference date/time				
n	69	10	79	2
Mean (SD)	35.4 (12.97)	41.7 (13.58)	36.0 (11.07)	30.0 (8.49)
Median (Range)	30.0 (19, 63)	39.5 (18, 63)	35.0 (18, 61)	30.0 (24, 36)
Weight (kg)				
n	69	10	79	2
Mean (SD)	56.1 (10.33)	48.6 (10.36)	54.4 (8.55)	41.2 (8.70)
Height (cm)				
n	69	10	79	2
Mean (SD)	166.8 (9.30)	161.3 (11.04)	165.8 (9.41)	158.0 (11.31)
Body mass index (kg/m²)				
n	69	10	79	2
Mean (SD)	20.2 (3.54)	18.5 (2.16)	19.9 (3.71)	16.4 (1.13)
Age (years)	69 (100)	10 (100)	79 (100)	2 (100)
AGE ≤ 45 years	49 (71.0)	6 (60.0)	62 (78.5)	2 (100)
45 < AGE < 65 years	20 (29.0)	4 (40.0)	17 (21.5)	0
Body mass index (kg/m ²)	69 (100)	10 (100)	79 (100)	2 (100)
< 16	7 (10.1)	0	5 (6.3)	1 (50.0)
≥ 16 - < 18	14 (20.3)	5 (50.0)	25 (31.6)	1 (50.0)
≥ 18 - < 20	14 (20.3)	2 (20.0)	18 (22.8)	0
≥ 20 - < 25	28 (40.6)	3 (30.0)	22 (27.8)	0
≥ 25	6 (8.7)	0	9 (11.4)	0
Country	69 (100)	10 (100)	79 (100)	2 (100)
Brazil	4 (5.8)	0	4 (5.1)	0
India	4 (5.8)	0	1 (1.3)	0
Latvia	4 (5.8)	1 (10.0)	4 (5.1)	0
Peru	15 (21.7)	1 (10.0)	17 (21.5)	0
Philippines	1 (1.4)	0	2 (2.5)	0
Russia	3 (4.3)	0	7 (8.9)	0
South Africa	37 (53.6)	6 (60.0)	43 (54.4)	2 (100)
Thailand	1 (1.4)	2 (20.0)	1 (1.3)	0
Ethnic origin	69 (100)	10 (100)	79 (100)	2 (100)
Black	27 (39.1)	2 (20.0)	27 (34.2)	0
Caucasian/white	7 (10.1)	1 (10.0)	12 (15.2)	0
Hispanic	13 (18.8)	0	15 (19.0)	0
Oriental/asian	7 (10.1)	2 (20.0)	6 (7.6)	0
Other	15 (21.7)	5 (50.0)	19 (24.1)	2 (100)
Pooled centre	69 (100)	10 (100)	79 (100)	2 (100)
Asia	6 (8.7)	2 (20.0)	4 (5.1)	0
Eastern Europe	7 (10.1)	1 (10.0)	11 (13.9)	0
South Africa	37 (53.6)	6 (60.0)	43 (54.4)	2 (100)
South Africa - 1	14 (20.3)	3 (30.0)	16 (20.3)	2 (100)
South Africa - 2	13 (18.8)	1 (10.0)	14 (17.7)	0
South Africa - Other	10 (14.5)	2 (20.0)	13 (16.5)	0
South America	19 (27.5)	1 (10.0)	21 (26.6)	0
Sex	69 (100)	10 (100)	79 (100)	2 (100)

Parameter Value n (%)	TMC207/BR		Placebo/BR	
	Alive N = 69	Death N = 10	Alive N = 79	Death N = 2
Female	25 (36.2)	2 (20.0)	30 (38.0)	2 (100)
Male	44 (63.8)	8 (80.0)	49 (62.0)	0

Table 53: Death Data by Pooled Centre (ITT)- Trial C208 Stage 2 Final Analysis

Parameter Value n (%)	TMC207/BR		Placebo/BR	
	Alive N = 69	Death N = 10	Alive N = 79	Death N = 2
Pooled centre	69 (100)	10 (100)	79 (100)	2 (100)
Asia	6 (8.7)	2 (20.0)	4 (5.1)	0
Eastern Europe	7 (10.1)	1 (10.0)	11 (13.9)	0
South Africa	37 (53.6)	6 (60.0)	43 (54.4)	2 (100)
South Africa - 1	14 (20.3)	3 (30.0)	16 (20.3)	2 (100)
South Africa - 2	13 (18.8)	1 (10.0)	14 (17.7)	0
South Africa - Other	10 (14.5)	2 (20.0)	13 (16.5)	0
South America	19 (27.5)	1 (10.0)	21 (26.6)	0

Table 54: Baseline Disease Characteristics by Death Status - Tabulation and Descriptive Statistics - ITT Trial C208 Stage 2 Final Analysis

Parameter Value n (%)	TMC207/BR		Placebo/BR	
	Alive N = 69	Death N = 10	Alive N = 79	Death N = 2
Baseline ALT grade	69 (100)	10 (100)	79 (100)	2 (100)
GRADE 0	58 (84.1)	8 (80.0)	70 (88.6)	1 (50.0)
GRADE 1	10 (14.5)	1 (10.0)	8 (10.1)	1 (50.0)
GRADE 2	1 (1.4)	1 (10.0)	0	0
GRADE 3	0	0	1 (1.3)	0
Baseline AST grade	69 (100)	10 (100)	79 (100)	2 (100)
GRADE 0	61 (88.4)	7 (70.0)	70 (88.6)	1 (50.0)
GRADE 1	7 (10.1)	2 (20.0)	7 (8.9)	1 (50.0)
GRADE 2	0	1 (10.0)	1 (1.3)	0
GRADE 3	1 (1.4)	0	1 (1.3)	0
History of Hepatitis	69 (100)	10 (100)	79 (100)	2 (100)
No	67 (97.1)	10 (100)	75 (94.9)	2 (100)
Yes	2 (2.9)	0	4 (5.1)	0
History of alcohol abuse	69 (100)	10 (100)	79 (100)	2 (100)
No	67 (97.1)	10 (100)	79 (100)	2 (100)
Yes	2 (2.9)	0	0	0
History of Diabetes	69 (100)	10 (100)	79 (100)	2 (100)
No	63 (91.3)	10 (100)	72 (91.1)	2 (100)
Yes	6 (8.7)	0	7 (8.9)	0

Table 55: Baseline Disease Characteristics - Tabulation and Descriptive Statistics by Survival Status - ITT Trial C208 Stage 2 Final Analysis

n (%)	TMC207/BR		Placebo/BR	
	Alive N = 69	Death N = 10	Alive N = 79	Death N = 2
HIV status	69 (100)	10 (100)	79 (100)	2 (100)
Negative	61 (88.4)	10 (100)	63 (79.7)	2 (100)
Positive	8 (11.6)	0	16 (20.3)	0
Cavitations (as stratified)	69 (100)	10 (100)	79 (100)	2 (100)
Cavitations \geq 2 cm in Both Lungs	11 (15.9)	2 (20.0)	15 (19.0)	1 (50.0)
Cavitations \geq 2 cm in One Lung Only	42 (60.9)	8 (80.0)	48 (60.8)	1 (50.0)
No Cavitations or Cavitations $<$ 2 cm	16 (23.2)	0	16 (20.3)	0
Cavitations (x-ray page)	69 (100)	10 (100)	79 (100)	2 (100)
Cavitations \geq 2 cm in Both Lungs	9 (13.0)	2 (20.0)	13 (16.5)	2 (100)
Cavitations \geq 2 cm in One Lung Only	42 (60.9)	7 (70.0)	43 (54.4)	0
No Cavitations or Cavitations $<$ 2 cm	18 (26.1)	1 (10.0)	23 (29.1)	0
Extent of resistance of M. Tuberculosis strain	69 (100)	10 (100)	79 (100)	2 (100)
DS-TB	4 (5.8)	0	4 (5.1)	0
MDR-TB*	65 (94.2)	10 (100)	75 (94.9)	2 (100)
MDR_H&R-TB	34 (49.3)	6 (60.0)	45 (57.0)	1 (50.0)
Pre-XDR-TB	15 (21.7)	1 (10.0)	11 (13.9)	1 (50.0)
XDR-TB	2 (2.9)	1 (10.0)	4 (5.1)	0
Baseline albumin grade	69 (100)	10 (100)	79 (100)	2 (100)
Grade 0	42 (60.9)	5 (50.0)	36 (45.6)	0
Grade 1	12 (17.4)	0	14 (17.7)	1 (50.0)
Grade 2	13 (18.8)	3 (30.0)	28 (35.4)	1 (50.0)
Grade 3	2 (2.9)	2 (20.0)	1 (1.3)	0
Previous use of first line TB drugs	69 (100)	10 (100)	79 (100)	2 (100)
No	7 (10.1)	0	10 (12.7)	1 (50.0)
Yes	62 (89.9)	10 (100)	69 (87.3)	1 (50.0)
PZA susceptibility	57 (100)	8 (100)	66 (100)	2 (100)
Resistant	37 (64.9)	6 (75.0)	35 (53.0)	2 (100)
Susceptible	20 (35.1)	2 (25.0)	31 (47.0)	0
Fluoroquinolone susceptibility	55 (100)	8 (100)	65 (100)	2 (100)
Resistant	8 (14.5)	2 (25.0)	8 (12.3)	0
Susceptible	47 (85.5)	6 (75.0)	57 (87.7)	2 (100)
Injectable drug susceptibility	55 (100)	8 (100)	65 (100)	2 (100)
Resistant	12 (21.8)	1 (12.5)	11 (16.9)	1 (50.0)
Susceptible	43 (78.2)	7 (87.5)	54 (83.1)	1 (50.0)

n (%)	TMC207/BR		Placebo/BR	
	Alive N = 69	Death N = 10	Alive N = 79	Death N = 2
CD4 cell count				
n	67	9	79	2
Mean (SD)	681.0 (296.19)	751.6 (432.71)	669.9 (284.02)	1142.5 (65.76)
Median (Range)	635.0 (127, 1356)	769.0 (232, 1711)	607.0 (291, 1655)	1142.5 (1096, 1189)
CD4 cell count (HIV Negative)				
n	59	9	63	2
Mean (SD)	706.3 (303.75)	751.6 (432.71)	724.5 (287.59)	1142.5 (65.76)
Median (Range)	656.0 (127, 1356)	769.0 (232, 1711)	673.0 (291, 1655)	1142.5 (1096, 1189)
CD4 cell count (HIV Positive)				
n	8	-	16	-
Mean (SD)	494.6 (132.66)	-	455.1 (125.91)	-
Median (Range)	487.0 (340, 692)	-	432.5 (310, 670)	-

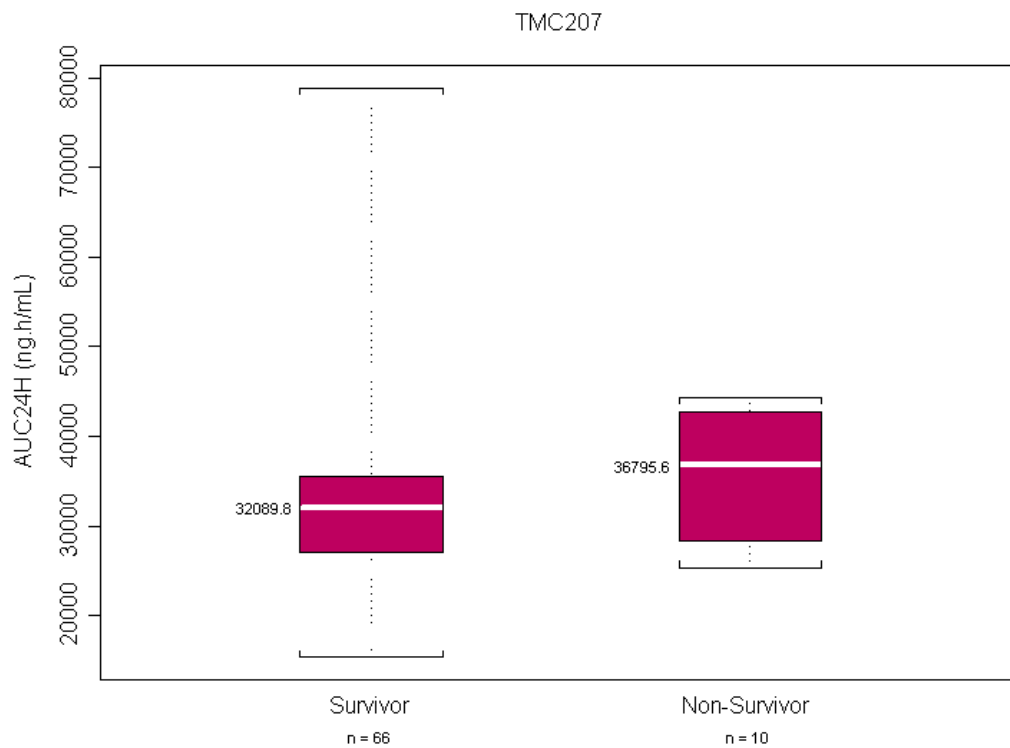
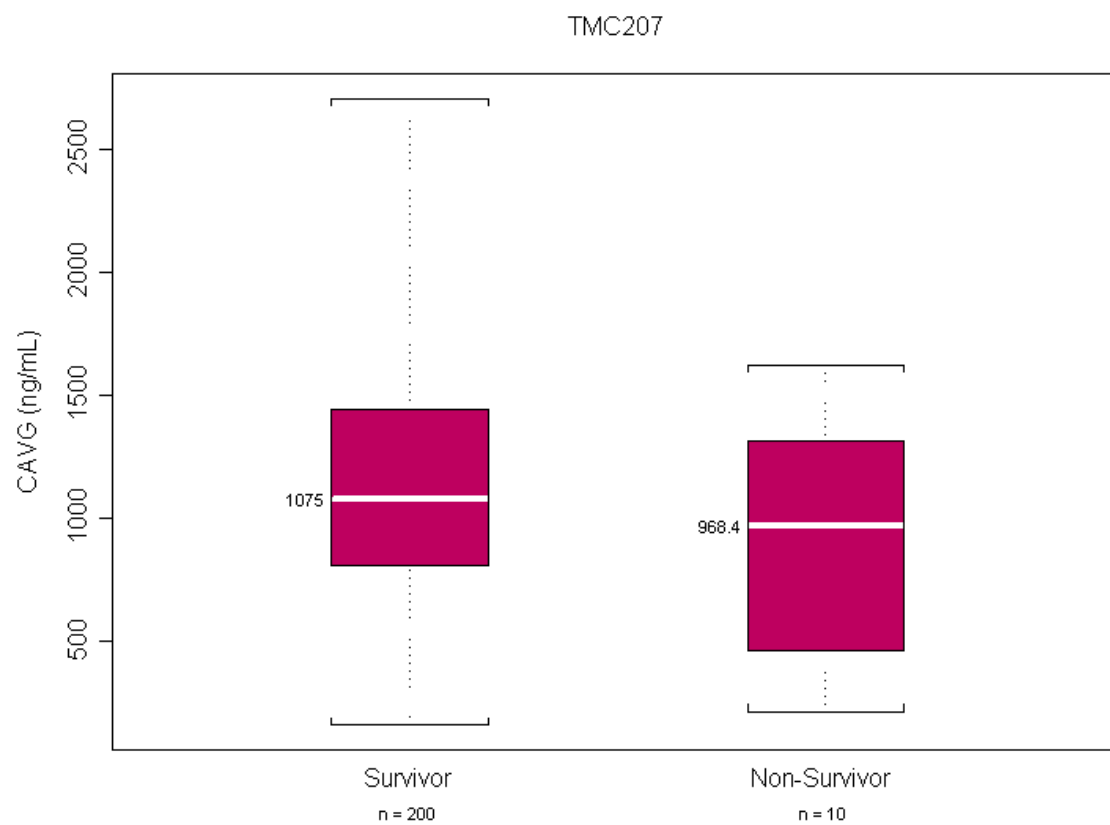
Figure 41: Exposure in Survivors (66) versus Non-Survivors (10)

Figure 42: Exposure in Survivors (200) versus Non-Survivors (10)



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² Publicly available guidelines (e.g. ICH, WHO, FDA, EMEA, NIH, ...) are not routinely submitted, but can be made available upon request.

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