BRIEFING PACKAGE
Division of Anti-Infective Products
Office of Antimicrobial Products
CDER, FDA

NDA 204-384

Sirturo™
(bedaquiline 100 mg tablets)
For the treatment of adults (≥ 18 years) as part of combination therapy of pulmonary multi-drug resistant tuberculosis (MDRTB)

Applicant: Janssen Research and Development, L.L.C

FDA Anti-Infective Drugs Advisory Committee Meeting
Silver Spring, MD
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1 INTRODUCTION

The emergence of multi-drug resistance in *Mycobacterium tuberculosis* (MDRTB) threatens to erode the progress made in the worldwide control of tuberculosis, presents considerable challenges in the management of HIV co-infected patients, and increases the duration, complexity, and toxicity of treatment. Bedaquiline is the first in the diarylquinoline class of compounds developed to address the need for new therapies to treat MDRTB. The drug inhibits mycobacterial adenosine 5'-triphosphate (ATP) synthase and is intended as part of combination therapy for MDRTB, defined as organisms resistant to both isoniazid and rifampin, two first-line drugs for tuberculosis. No other antimycobacterial agents in current use share this mechanism of action; bedaquiline's activity against this distinct antimycobacterial target lends to the drug's potential use in the setting of drug resistant tuberculosis.

This new drug application (NDA) is submitted under 21 CFR 314.500 (Subpart H) and the applicant seeks an accelerated approval based on evidence that bedaquiline affords an advantage over existing therapy for a surrogate endpoint reasonably likely to predict clinical benefit: time to sputum culture conversion up to week 24 evaluated in two separate stages of a phase 2 study. The utility of sputum culture conversion as a surrogate for durable cure has been previously discussed in FDA sponsored public discussions[1, 2]. The plans for traditional approval of bedaquiline will ultimately be based on the results of an ongoing Phase 3, randomized, placebo-controlled clinical trial confirming superiority in culture conversion 60 weeks after randomization (i.e., after 36 weeks of treatment and 24 weeks of treatment-free follow-up) for bedaquiline added to a background regimen compared with background regimen alone. This briefing document presents the early evidence of safety and effectiveness of bedaquiline in the treatment of adults (≥ 18 years) as part of combination therapy of pulmonary MDRTB. The AIDAC discussion will focus on the benefits and risks of bedaquiline in the treatment of MDRTB and approaches to maximize benefits and minimize risks. In addition, we look forward to AIDAC discussion of clinical implications of the surrogate endpoint.

1.1 Product

Sirturo™ (bedaquiline) tablets, 100 mg, are uncoated, immediate release tablets for oral administration. Each tablet contains 120.89 mg of bedaquiline fumarate drug substance, which is equivalent to 100 mg of bedaquiline free base. Bedaquiline is intended to be used as part of a combination treatment regimen for treatment of MDRTB.

1.2 MDRTB and its Treatment

[1] June 3, 2009 Meeting of the Anti-Infective Drugs Advisory Committee on Development of Drugs for MDRTB, information available at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm126290.htm
[2] 21 CFR 314.500 Subpart H: Accelerated Approval

The proposed indication for bedaquiline is treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* as part of combination therapy in adults (≥ 18 years). MDR *M. tuberculosis* is resistant to the isoniazid and rifampin, the two drugs which serve as the essential backbone of the standard 6 month therapy that has proven highly effective in treatment-adherent patients with drug-susceptible TB (DS-TB). Multidrug resistant isolates of *M. tuberculosis* that have developed resistance to an injectable aminoglycoside and to a fluoroquinolone are classified as extensively drug resistant TB (XDRTB); multidrug resistant strains that have become resistant to either an aminoglycoside or a fluoroquinolone are called pre-XDRTB.

Published estimates of treatment outcomes with optimized MDRTB treatment are similarly variable and may have improved with early diagnosis and increased experience. Early estimates of mortality were as high as 100%[3]. Recent reports on sputum conversion indicates some improvement in outcomes approaching those of drug sensitive TB, even in resource limited settings, with sputum conversion rates as high as 89%. [4, 5]

Nonetheless, treatment for resistant TB is complex, costly, toxic and prolonged, requiring at least 5 second-line drugs for up to 2 years. Second-line drugs include injectable drugs (amikacin, kanamycin, capreomycin) and oral fluoroquinolones (FQs) and other second line drugs; the optimal use of which has not been well studied in randomized controlled trials and whose safety when used in concert with various doses and regimens is not sufficiently described.

2 PRECLINICAL

Bedaquiline is administered at 400 mg once a day for two weeks followed by 22 weeks of intermittent dosing (200 mg three times a week) for the treatment of tuberculosis infection in MDRTB patients. The highest exposures observed during the intermittent dosing were measured after 8 weeks of treatment, where the mean $AUC_{(0\text{-}24h)}$ value was 22 µg*h/mL for bedaquiline and 6 µg*h/mL for the metabolite M2. Mean C_{max} levels were as high as 3.3 µg/mL during Week 2 (daily dosing phase) but steady state plasma levels were about 0.9 µg/mL at Week 8. These exposure data in man were derived from trial TMC207-C208. The safety implications of nonclinical studies were based on the exposure data achieved with the proposed dose.

2.1 MICROBIOLOGY

2.1.1 MECHANISM OF ACTION

[3] Small PM, Shafer RW, Hopewell PC et al. (1993) Exogenous re-infection with multidrug resistant Mycobacterium tuberculosis in patients with advanced HIV disease. N Engl J Med, 328, 1137–44

[4] Kurbatova, E Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. Tuberculosis (Edinb) 92(5):397-403 (2012),

[5] Hafkin Drug-resistant tuberculosis in sub-saharan Africa.J et al Curr Infect Dis Rep. 2010 Jan;12(1):36-45.

The mechanism of action of bedaquiline is different from that of other anti-mycobacterial agents. Bedaquiline inhibits the proton pump of mycobacterial ATP-synthase 3 by binding to the subunit c of the enzyme. Subunit c of ATP synthase is responsible for the flow of protons (H^+ or Na^{++}) from the intercristae region in mitochondria and the periplasmic space in bacteria to the mitochondrial matrix and the bacterial cytoplasm, respectively. Bedaquiline thereby inhibits the production of energy in mycobacterial cells, resulting in cell death. This activity appears to be selective towards mycobacterial ATP synthase relative to eukaryotic mitochondria; bedaquiline IC_{50} for mycobacterial strains was 0.01 μM compared to an IC_{50} >200 μM for human cancer cells, demonstrating that bedaquiline has a > 20,000-fold lower affinity for human mitochondrial ATP synthase than it has for the mycobacterial ATP synthase.

Bedaquiline inhibits both actively replicating and non-replicating wild-type and resistant *M. tuberculosis.* One study submitted in the NDAshowed that bedaquiline killed dormant cells found in latent tuberculosis even though there are low cellular ATP levels during this phase of growth.[6]

2.1.2 MECHANISM OF RESISTANCE

2.1.2.1 Mutations in the *atpE* gene

The results of studies suggest a potential for development of resistance at low concentrations of bedaquiline. The main resistance mechanism is due to substitutions in at least six different amino acids in the *atpE* gene. The rate of mutation against bedaquiline decreases with increased bedaquiline concentrations. At a concentration of 0.3 mcg/ml (10 X the MIC), the mutation rates ranged from 4.7×10^{-7} to 8.9×10^{-9} mutations per cell division. At a concentration of 1.0 mcg/mL (30 X the MIC), the mutations rates ranged from 3.9×10^{-8} to 2.4×10^{-9} mutations per cell division whereas no resistant mutants were obtained at 3 mcg/mL (100 X the MIC). It appears that bedaquiline is bacteriostatic at low concentrations, allowing the bacilli to live long enough to mutate whereas the higher concentrations of the drug killed the bacteria. Sixteen percent of the *M. tuberculosis H37Rv* mutants demonstrated mutations in amino acid residues alanine 63 to proline (Ala63→ Pro). The substitution of Ala63 → Pro results in the greatest effect in the mycobacterial subunit c. This mutation caused an increase in the MIC value for *M. tuberculosis* by 133-fold.

2.1.2.2 Expression of the Efflux Pump

Some mycobacterial isolates resistant to bedaquiline do not show mutations in the *atpE* gene, but rather show an overexpression of the efflux pump, a second putative mechanism of resistance to bedaquiline shared with resistance to clofazimine.

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[6] Koul, A., L. et al. 2008. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed ATP homeostasis. J. Biol. Chem. 283:25273–25280

2.1.2.3 Cross-Resistance

Cross resistance was tested against other drugs (isoniazid, rifampin, streptomycin, ethambutol, pyrazinamide, or fluoroquinolones, PA-824, amikacin, moxifloxacin). The resistant mutant BK12 and susceptible strains of H37Rv were used in determining cross-resistance. No cross-resistance was found between bedaquiline and the drugs listed above.

2.1.3 ANTIMICROBIAL ACTIVITY

2.1.3.1 In vitro

The inhibitory concentrations for the parent drug bedaquiline for 50% and 90% of preclinical isolates (MIC_{50} and MIC_{90}) of *M. tuberculosis* were 0.03 and 0.06 μg/mL, respectively, for both drug susceptible (DS-TB) and MDRTB isolates. Bedaquiline is highly bound to plasma proteins and the inhibitory concentrations increase several fold when testing is performed in the presence of serum. N-monodesmethylmetabolite (M2), the main circulating metabolite of bedaquiline is 4 to 6 times less active against *M. tuberculosis* than the parent compound. M2 is metabolized to the bacteriologically inactive N-didesmethyl M3 metabolite.

Bedaquiline has a narrow spectrum of activity and appears to be specific for *Mycobacterium* species. Tests of efficacy involving other selected gram-positive and gram-negative bacteria showed a lack of inhibition even to large doses of this drug. The activity of bedaquiline against preclinical isolates of *M. tuberculosis* is shown in the applicant's table below (Table 1). Limited data were presented to assess in vitro activity against other relevant human mycobacterial pathogens.

Table 1 Minimum Inhibitory Concentrations of Bedaquiline by *M. tuberculosis* Resistance Subtype

MTB Resistance Subtype	N	Bedaquiline MIC (μg/mL)			
		MIC Range	MIC_{50}	MIC_{90}	MIC_{95}
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
MDRTB	44	≤ 0.008 - 0.12	0.03	0.06	0.06

N = number of strains
Modified from NDA 204-384

Bedaquiline's bactericidal activity appears to be time-dependent rather than concentration-dependent. Reduction in bacterial load of 3 log units was observed after 12 days when *M. tuberculosis* in log-phase growth was exposed to 10 X MIC bedaquiline concentrations. Further reductions in bacterial growth were not seen with bedaquiline concentrations 100 X the MIC. A post-antibacterial effect (PAE) of 9 hours for bedaquiline has been reported based on parallel in vitro experiments demonstrating a PAE of 11 hours for isoniazid.

M. tuberculosis bacilli lie dormant and evade the immune system by intracellular residence within the phagolysozome. Mouse peritoneal macrophages and J774A.1 cells were used to investigate the intracellular and extracellular activity of bedaquiline. Bedaquiline achieved effective intracellular concentrations against *M. tuberculosis*. The bactericidal effect of bedaquiline was slow extracellularly whereas it was rapid intracellularly and showed inhibition in a concentration dependent way.

2.1.3.2 In vivo/ Animal Studies

The accepted treatment protocol for mycobacterial infections is the use of multiple drugs. It is, therefore, important to examine the interactions between the drugs. No effect on mycobacterial activity was demonstrated in vitro when bedaquiline was combined with rifampin versus bedaquiline or rifampin alone against *M. tuberculosis* H37Rv in a murine model. Conversely, while 22% of mice were culture negative after 2 months of bedaquiline monotherapy compared to none of PZA monotherapy treated mice, PZA combined with bedaquiline resulted in 100% culture negativity, indicating synergy ($p = 0.001$).

The bactericidal and sterilizing activity of bedaquiline as monotherapy and in combination with first line drugs was investigated in the murine model. In these studies, the bactericidal activity obtained after 2 months of therapy with rifampin (R) +isoniazid (H)+ pyrazinamide (Z) was similar to 1 month of bedaquiline containing regimens (bedaquiline + HZ and bedaquiline + RZ). As well, 34 months of treatment with bedaquiline-containing regimens was as effective as 6 month standard regimen, and more effective than 4 months of treatment with moxifloxacin (M) + RZ. When added to second line drugs amikacin (A), Z, M and ethionamide (E), bedaquiline accelerated and augmented the bactericidal activity of the regimen (Table 2).

Table 2. Bactericidal Activity of Bedaquiline in Combination with Second-line Drugs in the Established Infection Murine TB Model

Regimens[a]	Mean Log CFU Counts ± 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 ± 0.2	-	5.9 ± 0.5	-
J	2.6 ± 1.3	1.2 ± 0.5 (0/8)	2.9 ± 0.9	0.2 ± 0.3 (6/8)
RHZ	4.5 ± 0.3	1.9 ± 0.5 (1/10)	3.7 ± 0.4	1.0 ± 0.5 (0/10)
RHZJ	1.9 ± 0.31	0.1 ± 0.2 (4/10)	1.8 ± 0.4	0 ± 0 (10/10)
AEMZ	3.2 ± 0.5	1.6 ± 0.4 (1/10)	2.9 ± 0.2	0.1 ± 0.1 (5/10)
AEZ	4.0 ± 0.3	2.8 ± 0.3 (0/10)	3.7 ± 0.2	1.2 ± 0.3 (0/10)
AMZ	3.6 ± 0.2	1.9 ± 0.5 (0/10)	3.4 ± 0.3	0.8 ± 0.6 (0/10)
AEZJ	1.2 ± 0.2	0.1 ± 0.1 (7/9)	0.2 ± 0.3	0 ± 0 (9/9)
AMZJ	1.2 ± 0.2	0 ± 0 (8/8)	0.2 ± 0.3	0 ± 0 (8/8)
AEMZJ	1.2 ± 0.3	0 ± 0 (8/8)	0.5 ± 0.4	0 ± 0 (8/8)

J = bedaquiline; M = MXF; R = RMP; H = INH; Z = PZA; A = AMK; E =ETH; M = MXF SD = standard deviation [a] Drugs were administered 5 times/week: RMP 10 mg/kg; bedaquiline 25 mg/kg; INH 25 mg/kg; PZA 150 mg/kg; AMK150 mg/kg; ETH 50 mg/kg; MXF 100 mg/kg

Source: Table from NDA 204384

Bedaquiline augmented the sterilizing activity of second line drug regimens based on reduced relapse rates 3 months after the end of 6 months of treatment with the following drug combinations:

Table 3. Sterilizing Activity of Bedaquiline in Combination with Second-line Drugs in the Established Infection Murine TB Model

Drug Combination	Relapse Rate (%)
2AEMZ 4EM	58
2AEMZJ 4EMJ	28
2 MZJ 4 MJ	11
2HRZ, 4HR	11

Source: Table from NDA 204384

Compared to the demonstrated relapse rates of the standard regimen of 2HRZ4HR, bedaquiline MZ and bedaquiline AEMZ showed potential in shortening treatment duration for resistant tuberculosis, based on these findings from a murine TB infection model.

Pharmacokinetic studies in Swiss mice indicated that the AUC correlated better with a reduction in CFU than any other PK parameter. The MIC_{50} and MIC_{90} of bedaquiline against *M. tuberculosis* H37Rv infected female Swiss mice were 0.03 mcg/mL and 0.06 mcg/mL respectively. These MICs did not change when MDR-TB isolates were evaluated. No difference was observed in the MIC to bedaquiline between susceptible and resistant mycobacterial strains.

2.1.4 Activity against Clinical Isolates in Study 208 and 209

Study C208

The MIC of bedaquiline for baseline isolates in Study 208 was tested by 7H11 solid agar and REMA. The MIC_{90} for susceptibility tests performed on 7H11 agar was 0.12 mcg/mL and for the Resazurin Microtitre Assay liquid (REMA) test the MIC_{90} was 0.125 mcg/mL. A comparison of susceptibility testing between the solid and liquid culture methods was performed to establish the criteria for susceptibility testing for both methods which are widely used for mycobacteria. Following exposure to anti-TB treatment, susceptibility testing was performed against 11 paired isolates. Two isolates from the bedaquiline arm and nine from the placebo arm were tested by REMA. One from the bedaquiline arm and nine from the placebo group were tested by 7H11 agar. Of three isolates that showed a four fold increase in MIC to bedaquiline, one was isolated from a bedaquiline-treated patient, whereas the other two were from placebo-treated patients. This patient had an MDR (RH) isolate whereas the endpoint isolate was found to be pre-XDR.

Table 4. FDA Analysis of Bedaquiline MIC ranges by Susceptibility test method at Baseline and Follow-up

Parameter	Range of MICs mcg/mL	
	REMA	7H11 AGAR
Baseline	0.0078 to 0.25 µg/mL	0.0075 to > 0.48 µg/mL
Follow-up	0.0156 to 0.0625 µg/mL	0.0075 to 0.24 µg/mL
MIC_{50} of baseline isolates	0.0313	0.03
MIC_{90} of baseline isolates	0.125	0.12

A four-fold MIC shift in bedaquiline was observed in paired clinical isolates in 13 of 28 bedaquiline/BR-treated subjects with paired MIC data in trials C208 Stage 1, C208 Stage 2 and C209. Out of these 13 subjects, genotyping showed that 3 isolates at baseline and post-baseline were genetically different and are ineligible for this resistance-development analysis.

A total of 9 of the remaining 10 bedaquiline/BR-treated subjects failed to convert or relapsed (4 were preXDR and 5 were XDR) following bedaquiline treatment. The MIC shift in REMA was more extreme than that observed with the agar method.
The 4 pre-XDR-TB infected subjects' isolates had 4- to 16-fold increases in REMA MICs and 4- to > 8-fold increases in agar MICs. All four patients failed to convert.
The 5 XDR-TB infected subjects' isolates had 4- to 16-fold increases in REMA MICs, and 8- to > 8-fold increases in agar MICs. Three of these subjects failed to convert, 1 relapsed and 1 was considered a responder. The patient with a four fold bedaquiline MIC shift from C208 Stage 1 was identified by the agar method (from 0.06 to 0.24 mcg/mL) and not confirmed in the retested REMA data. Patients with infection with pre-XDR and XDR strains are less likely to convert.

Study C209
One of the objectives of Study 209 was to determine the MIC of bedaquiline against isolates resistant and susceptible to other anti-mycobacterial drugs. The results showed that there was no difference in the susceptibility to bedaquiline of strains resistant and susceptible to other anti-mycobacterial drugs; the MIC of both groups ranged from 0.03 to 0.06 mcg/mL.

2.1.5 PROVISIONAL INTERPRETIVE CRITERIA = SUSCEPTIBLE

The determination of the breakpoint for bedaquiline included the MIC results of pre-clinical isolates. No pre-clinical isolate was found with an MIC that was > 0.5 mcg/mL of bedaquiline; therefore, the 7H11 agar breakpoint was set at ≤ 0.5 mcg/mL. When the REMA method was used, only one isolate resulted in an MIC of > 0.25 mcg/ leading to the REMA breakpoint of ≤ 0.25 mcg/mL.

Isolates of *M. tuberculosis* with MICs equal to, or lower than these breakpoints are described as "susceptible" to bedaquiline and are likely to be inhibited in vivo by the

relevant concentration of the drug at the infection site. In the C208 study, the average plasma concentration for a 400 mg dose of bedaquiline after 2 weeks was 1.37 mcg/mL; MICs of bedaquiline defined by either method are lower than the drug concentration achieved in plasma and bedaquiline at the 400 mg dose should inhibit the growth of *M. tuberculosis* isolates.

Results of both agar and REMA susceptibility testing methods indicated that there was no correlation between the MIC values and proposed breakpoints and the clinical outcome. Of the subjects who failed in study C208, none had MICs >0.5 mcg/mL. Of the twenty-nine subjects who failed in study C209, only two had MICs >0.5 mcg/mL when the susceptibilities were performed on agar. For the REMA method in study C208, no MIC of the failures was above 0.25 mcg/mL and only 3/29 in C209 were above 0.25 mcg/mL. The isolate from one of the subjects who failed had MICs as low as 0.015 mcg/mL (agar) and ≤ 0.008 mcg/mL (REMA). On the other hand, none of the subjects with successful outcomes had *M. tuberculosis* MICs > 0.5 mcg/mL (agar) or > 0.25 mcg/mL(REMA). Therefore resistance, as defined by values that are greater than the breakpoints, was not demonstrated to play a role in treatment failures with bedaquiline treatment in these small studies.

Table 5 Provisional Susceptibility Breakpoints for Bedaquiline based on Agar and REMA

	Bedaquiline MIC (mcg/mL)	
	REMA	7H11 AGAR
Pathogen	Susceptible Only (S)	Susceptible Only (S)
M. tuberculosis	≤0.5	< 0.25

Source: Table from NDA 204384

2.2 NONCLINICAL TOXICOLOGY PROGRAM

In vitro receptor binding studies showed that bedaquiline inhibited binding to histamine2 receptors (by 87%), sodium channels (by 71%) and dopamine transporters (by 54%) at a concentration of 10 μM (5.6 μg/mL); off-target effects mediated by these receptors are a possibility.

In test species, bedaquiline bioavailability was between 36 and 79%, and drug achieved maximum plasma concentrations between 0.5 and 8 hours after dosing. Bedaquiline is metabolized (mainly by cytochrome P450 (CYP 3A4) to its major metabolite, M2, via *N*-demethylation. Another metabolite, M3, is produced by the subsequent *N*-demethylation of M2. Bedaquiline is extensively bound to proteins, with plasma protein binding above 99.9% for all species, including humans. It is very slowly eliminated from the plasma, with extensive distribution to tissues (volume of distribution Vd_{ss} 60 times total body water). Tissues with the highest accumulation of drug were the adrenal gland, lung, spleen, liver, lymph nodes and thymus. Tissue concentrations of metabolite M2 were higher than those of the parent compound. Elimination half life ranged from 2 days in mice to 50 days in dogs. Drug is excreted predominantly in the feces, with only 1-4% excreted via urine. In bedaquiline-treated dams which had recently given birth, levels of bedaquiline and its metabolite M2 in milk were 4- to 12 times higher than plasma levels.

The nonclinical toxicology program was comprehensive, and included *in vitro* and *in vivo* studies using mice, rats, dogs, rabbits and guinea pig. The applicant evaluated the effects of bedaquiline administration for up to 3 months in mice, 6 months in rats and 9 months in dogs via daily and intermittent dosing (two or three times weekly). There were also evaluations of genotoxic potential, fertility, embryofetal toxicity, pre- and postnatal development, local tolerance, immunotoxicity and mechanistic studies.

2.2.1 ADVERSE EVENTS OF SPECIAL CONCERN

2.2.1.1 Cardiotoxicity

Bedaquiline was shown to inhibit IKr in hERG transfected kidney cells with an IC_{50} of 0.2 mcg/mL for both bedaquiline and its metabolite M2. By comparison, the positive control astemizole, which is known to cause prolonged QT, inhibited IKr with an IC_{50} in the nanomolar range. Effects on IKs were slight/moderate even at bedaquiline concentrations up to 5.5 mcg/mL or M2 concentrations up to 1.6 mcg/mL. Bedaquiline did not increase the QT or QTc interval at plasma bedaquiline levels up to 3.6 mcg/mL in the anesthetized guinea pig. QT or QTc interval was also not increased in conscious telemetered dogs after single oral or intravenous dosing. In a mechanistic study (#1408-008), dogs dosed with 100 mg/kg bedaquiline for six days showed no increases in QT interval. Based on data from another study (Exp 5612), mean $AUC_{(0\text{-}24h)}$ in this study was estimated to be about 100 µg*h/mL, which is much higher than clinical exposures. When dogs were then treated with 100 mg/kg moxifloxacin on Day 7, there was no real difference between the effect of moxifloxacin alone (+17 % compared to control) and the effect of moxifloxacin +bedaquiline, where the QT prolongation was +20 % compared to control.

In one six month dog study, dogs experienced slight increases in the QTc interval (+12 to +16 %, depending on the formula used to correct the QT after two months of dosing at 40 mg/kg/day ($AUC_{(0\text{-}24h)}$ estimated at 150 mcg*h/mL). After the dose was lowered to 20 mg/kg/day, ($AUC_{(0\text{-}24h)}$ estimated at about 130 mcg*h/mL), there was no further evidence of increased QTc interval. There were also no effects on cardiovascular parameters at the end of the six months of dosing at 40/20 mg/kg/day or at any time during the six month dosing period in dogs treated at 10 mg/kg/day ($AUC_{(0\text{-}24h)}$ estimated at about 86 mcg*h/mL) or twice weekly at 140 mg/kg ($AUC_{(0\text{-}24h)}$ estimated at about 170 mcg*h/mL).

The relevance of the QT prolongation to the drug administration is also unclear since animals were in very poor condition at this 40 mg/kg/day dose, with adverse effects including vomiting, decreased activity and a 30 % reduction in body weight. This dose appeared to be above the maximum tolerated dose.

Cardiac troponin (cTnI) was used as a biomarker of cardiac toxicity and was increased at several time points in the 40/20 mg/kg/day dogs and those dosed twice weekly at 140 mg/kg. Cardiac lesions in the 6-month mechanistic study in dogs consisted of minimal

multifocal lymphohistiocytic infiltrates with degeneration of cardiomyocytes and/or minimal to slight endocardial fibrosis. These changes were associated with elevated levels of total CK and cTnI.

No similar EKG changes or cardiac lesions were detected in a 9 month dog study using a lower dose (18 mg/kg/day) despite substantial exposure ($AUC_{(0\text{-}24h)}$ about 154 µg*h/mL at week 13) and despite increases in cardiac troponins. Clearly increases in cardiac troponins do not always indicate cardiac damage. No adverse cardiac effects were observed in dogs treated at 10 mg/kg/day, a dose which resulted in exposures 4 times the clinical exposure.

No consistent QT increases were seen in the nonclinical studies. The clinical studies serve as the basis for assessing this risk in patients with TB.

2.2.1.2 PHOSPHOLIPIDOSIS

Bedaquiline and its active metabolites are considered cationic, amphiphilic drugs (CAD) and, as such, induced phospholipidosis in drug-treated animals, mainly in cells of the monocytic phagocytic system (MPS). After bedaquiline administration, all species tested showed the accumulation of pigment-laden and/or foamy macrophages, mostly in the lymph nodes, spleen, lungs, liver, stomach, skeletal muscle, pancreas and/or uterus. Under electron microscopic examination, phospholipidosis was characterized by the prominent presence of intracytoplasmic lamellar inclusions in the affected tissues.

The excessive accumulation of phospholipids in cells; ultrastructural appearance of membranous lamellar inclusions; accumulation of the inducing drug in association with the increased phospholipids; and reversibility of alterations after discontinuance of drug treatment are classic features of phospholipidosis. These features are also observed with several other drugs, including perhexiline, amiodarone, fluoxetine and gentamicin.

Phospholipidosis developed very quickly with bedaquiline foamy vacuolization seen even after single doses in mice. Findings are more frequent and severe with increasing dose and increasing dosing duration. A NOAEL was not determined for a number of studies as a result of the presence of foamy macrophages and pigment-laden macrophages even at the lowest doses. These findings were slowly reversible upon treatment cessation and at least partial recovery was seen in dog and rat studies with recovery arms. The applicant also conducted in vitro studies which showed that M2 and M3 were more cytotoxic and stronger phospholipidosis-inducers than bedaquiline.

To address the potential for interactions with other phospholipidogenic drugs, the effect of a combined treatment with bedaquiline and clofazimine on in vitro drug-induced phospholipidosis was evaluated. The combined treatment of bedaquiline and clofazimine resulted in an additive effect on drug-induced phospholipidosis: the total fluorescence (or accumulated fluorescent phospholipids) in the cells treated with the combination of

bedaquiline and clofazimine equaled the sum of the fluorescence in the cells incubated with bedaquiline and clofazimine separately.

Although phospholipidosis develops very quickly at high doses and at low doses with prolonged administration, it is observed with many commonly used drugs. Since it is reversible and has not been shown to result in any functional changes, phospholipidosis may be considered to have a favorable risk/benefit ratio in the treatment of TB. When selecting drugs for combination regimens which include bedaquiline, the phospholipidogenic potential of the other drug(s) should be carefully evaluated given the additivity of this effect.

2.2.1.3 MUSCULAR DEGENERATION

Degenerative changes in skeletal muscles were seen in mice, rats and dogs treated with high doses of bedaquiline. For example, minimal fibrohistiocytic infiltration and muscle fiber degeneration were observed in the tongue and, to a lesser extent, in the quadriceps in rats treated for 13 weeks with bedaquiline at high doses (24 mg/kg). However, this myopathy was not detected at the end of a 12 week reversibility period in rats which were treated with bedaquiline for six months at 20 mg/kg/day, a dose which resulting in exposures ($AUC_{(0\text{-}24h)}$) of about 31 µg*h/mL, which was higher than exposures obtained in the clinical trial, (about 22 µg*h/mL). Other adverse effects, including the liver and thyroid hypertrophy, also disappeared during the reversibility period.

Since the bedaquiline-induced muscle damage is reversible, and since rhabdomyolysis is a known risk factor with other approved drugs (such as the cholesterol-lowering drug simvastatin), the risk of adverse muscle effects may not be unreasonable in treating a disease which may be otherwise fatal.

2.2.1.4 STOMACH

In several studies, bedaquiline administration was associated with damage to the stomach lining. For example, in a one month study in rat, degeneration of the fundic glands with cellular debris in the glandular lumen was observed in the stomach at high doses (40 and 160 mg/kg/day). The animals appeared to be able to recover from the stomach injury. The degeneration and necrosis of the fundic mucosa of the stomach observed in one dog study of bedaquiline at 40 mg/kg/day after 13 weeks was no longer seen in dogs given 40/20 mg/kg/day after 26 weeks. The absence of this finding at the end of 26 weeks at the reduced dose suggests that patients are also likely to recover from the adverse effects on the stomach.

2.2.1.5 PANCREAS

In several studies, focal to multifocal chronic pancreatitis with acinar cell atrophy was observed in mice and dogs. The pancreatic changes appear to be dose and duration related since pancreatitis was detected earlier (at 13 weeks) at the high dose, (40

mg/kg/day) but was also seen at lower doses after a longer duration of treatment (26 weeks at 10 and 40/20 mg/kg/day).

2.2.1.6 LIVER

In addition to the phospholipidosis noted above, hepatocellular centrilobular hypertrophy was seen at high doses in all species and was often accompanied by increased liver weight and increases in liver enzymes. Single cell necrosis was also observed in mice. Although some changes, such as liver hypertrophy, were not detected at the end of a reversibility period in the recovery studies, in some instances, signs of phospholipidosis persisted, although diminished. Given the reversibility and the ability to monitor this effect, the risk benefit to a TB patient is judged to be favorable.

2.2.1.7 OTHER FINDINGS

Bedaquiline showed no evidence of genotoxicity, when evaluated in an in vitro non-mammalian reverse mutation (Ames) test, an in vitro mammalian (mouse lymphoma) forward mutation assay and an in vivo mouse bone marrow micronucleus assay.

Bedaquiline showed no adverse effects on mating, or fertility and it was not teratogenic. A two-year oral carcinogenicity study is ongoing and results will be available after the due date for this NDA.

3 CLINICAL

3.1 CLINICAL PHARMACOLOGY

3.1.1 SUMMARY OF PHARMACOKINETICS

The clinical pharmacology program consisted of 16 trials that evaluated the PK, drug interactions and PK/PD of bedaquiline. Pharmacokinetic parameters of bedaquiline are summarized in Table 6 for healthy volunteers.

Table 6. Pharmacokinetic parameters of bedaquiline in healthy volunteers

PK Property	PK Parameter	
Dose-proportionality	PK dose-proportional for doses 10 – 700 mg	
Absorption	T_{max} (median)	~5 hr
	$t_{1/2\ term}$	~ 4-5 months
	Food Effect	High fat meal increased C_{max} and AUC by 2-fold.
Distribution	Protein Binding	> 99%
Metabolism	Pathways	Metabolized to M2 and M3 by CYP3A4.

Excretion	Fecal excretion is the major route of elimination.

Source: FDA Clinical Pharmacology Review

3.1.1.1 Absorption

The exposure to bedaquiline increases approximately 2-fold when administered under fed conditions. Bedaquiline is recommended to be administered with food to ensure optimal absorption and exposure. The effect of food on exposure of bedaquiline was determined based on a standard meal as opposed to the high fat meal that is usually recommended per the FDA guidance.

3.1.1.2 Distribution

After reaching C_{max}, bedaquiline concentrations decline tri-exponentially with a long terminal half-life ($t_{1/2, term}$) of approximately 4-5 months; however, the effective half-life of bedaquiline is approximately 24-30 hours, based on the approximately 2-fold accumulation after 2 weeks of daily dosing. Bedaquiline is highly protein bound (>99%) in human plasma. The apparent volume of distribution of bedaquiline in the central compartment was estimated to be around 164 L. The apparent volume of distribution in the peripheral compartments was estimated to be around 178 L, 3010 L, and 7350 L, indicating that bedaquiline is extensively distributed in the body.

3.1.1.3 Metabolism

In vitro studies indicate CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline and the formation of the major metabolite, *N*-monodesmethyl bedaquiline (M2). The minor metabolite, M3, was formed by further *N*-demethylation of M2. (Note: M2 is 4-6 fold less active against *M. tuberculosis* than its parent, bedaquiline; M3 is virtually inactive against *M. tuberculosis.*)

Across Phase 1 studies with single-dose (700 mg; Trial CDE-101) and multiple-dose (50-400 mg once daily for 14 days; Trial CDE-102) bedaquiline in healthy volunteers, M2 was the major metabolite detected in the plasma, which represented approximately 20% of the bedaquiline AUC (Mean $t_{1/2\ term}$ of M2 is ~5.5 months.)

3.1.1.4 Excretion

Based on preclinical studies, bedaquiline is mainly eliminated in feces. In Phase 1 studies in healthy volunteers, the extent of unchanged bedaquiline excreted in the urine was determined to be <0.001% of the administered dose.

3.1.2 INTRINSIC FACTORS

3.1.2.1 Age

The pharmacokinetics of bedaquiline in pediatric patients have not been evaluated. The median age of the patients in the clinical trials was around 32 years. The pharmacokinetics of bedaquiline in elderly and young adults was not determined.

3.1.2.2 Gender

The oral clearance of bedaquiline was not shown to be different between men and women. In a population pharmacokinetic analysis of TB patients treated with bedaquiline, no clinically relevant differences in exposure between men and women were observed.

3.1.2.3 Race

Black patients have an apparent clearance of bedaquiline that is 52% higher than subjects of other races. In a population pharmacokinetic analysis of TB patients treated with bedaquiline, systemic exposure (AUC) to bedaquiline was projected to be 34% lower in African American patients than in patients from other race categories. This lower systemic exposure was not considered to be clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed in clinical trials at the doses studied. Furthermore, response rates in black patients that completed the bedaquiline treatment period were comparable to other race categories in the clinical trials. Notably, the numbers of black subjects were small, and the response rate for the bedaquiline-treated black subjects was the same as that for the placebo-treated subjects, although for this subgroup the placebo response rate was high.

3.1.2.4 Renal Impairment

Bedaquiline is not eliminated by the kidney as evidenced by the relative absence of measurable urine concentrations in the Phase I trials. Bedaquiline is recommended to be administered without dose adjustment to patients with mild to moderate renal impairment and is recommended to be administered with caution in patients with severe renal impairment.

3.1.2.5 Hepatic Impairment

A hepatic impairment trial indicated that no dosage adjustment is needed in patients with mild and moderate hepatic impairment. Bedaquiline is not recommended to be used in patients with severe hepatic impairment.

3.1.3 EXTRINSIC FACTORS

3.1.3.1 CYP450-based drug interactions

Rifampin: Co-administration with 600 mg rifampin (a potent CYP3A4 inducer) reduced bedaquiline C_{max} and $AUC_{0\text{-}336h}$ by approximately 50% in healthy male volunteers receiving single oral dose of bedaquiline (300 mg). Therefore, co-administration of bedaquiline and rifamycins (rifampin, rifapentine, and rifabutin) or other potent CYP3A4 inducers used systemically should be avoided.

Ketoconazole: Co-administration with ketoconazole (a strong CYP3A4 inhibitor), 400 mg daily for 3 days, increased mean bedaquiline C_{max} and $AUC_{0\text{-}24h}$ by 1.09- and 1.22-fold in healthy male volunteers receiving repeated doses of bedaquiline (400 mg daily). It is recommended that the combination of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided.

Isoniazid/Pyrazinamide: Co-administration of the combination of multiple-dose bedaquiline with multiple-dose isoniazid/pyrazinamide (300/2000 mg once daily) in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose adjustment of isoniazid or pyrazinamide is needed when co-administered with bedaquiline.

Nevirapine: Co-administration of multiple-doses of nevirapine (200 mg twice daily) with single-dose bedaquiline did not result in clinically relevant changes in the exposure to bedaquiline in HIV positive patients. No dosage adjustment is needed for bedaquiline when co-administered with Nevirapine.

Kaletra: Following co-administration of a single-dose bedaquiline and multiple-dose lopinavir/ritonavir (400/100 mg twice daily), exposure (AUC) to bedaquiline was increased by 22% while the mean C_{max} remained comparable. No dosage adjustment is needed for bedaquiline when co-administered with Kaletra.

Background regimen drugs for the treatment of MDRTB: In a placebo-controlled trial in patients with MDRTB, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

3.1.3.2 Transporter-based drug interactions

Bedaquiline and M2 are not substrates of P-glycoprotein transport processes. At clinically relevant concentrations, bedaquiline (<5 mcg/mL) and M2 (<0.5 mcg/mL) do not inhibit P-glycoprotein transport processes. At high concentrations (100 μM [~55 mcg/mL]), bedaquiline marginally inhibited P-glycoprotein transport of ^{3}H-paclitaxel. At high concentrations (100 μM [54.2 mcg/mL]), M2 substantially inhibited P-gp dependent transport of ^{3}H-paclitaxel: the basolateral to apical over apical to basolateral paclitaxel

transepithelial transport ratio was reduced from 55.7 to 8.58 with M2, compared with a ratio of 3.45 with verapamil (100 μM).

3.1.4 DOSE/EXPOSURE-RESPONSE RELATIONSHIP AND RATIONALE FOR DOSE SELECTION

The recommended dosage of bedaquiline for MDRTB is:

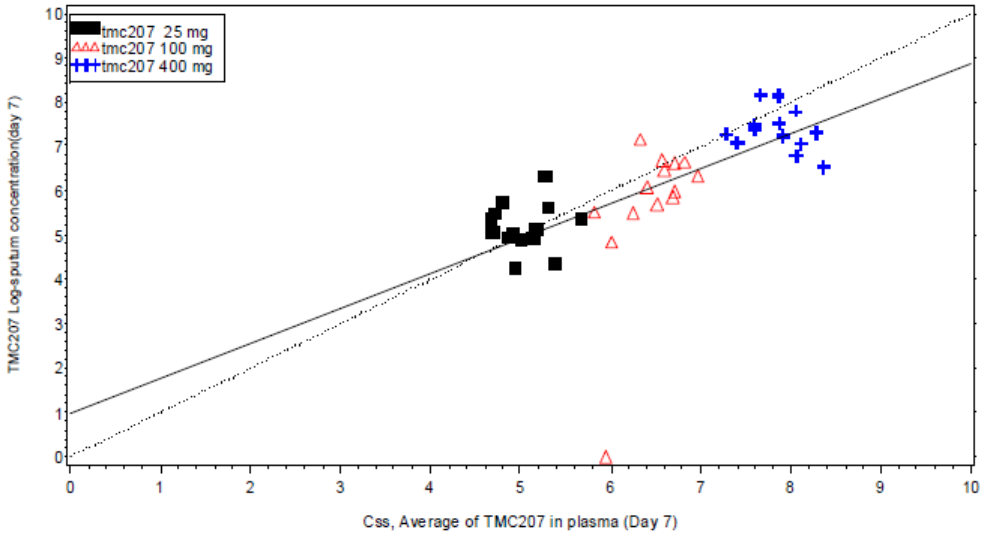
- Weeks 1-2: 400 mg (4 tablets of 100 mg) once daily
- Weeks 3-24: 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses).

The total duration of treatment with bedaquiline is 24 weeks, and bedaquiline should be taken with food.

3.1.4.1 Efficacy

The surrogate endpoint in this drug development program is the time to sputum conversion. The sputum concentrations achieved with bedaquiline in the proof of principle trial C202 and the dose response with respect to the change in $\log_{10}$ sputum CFU counts from baseline (95% CI) over time is represented in the applicant's Figures 1 and 2 below. The 400 mg daily dose administered as 7-day monotherapy to DS-TB infected subjects in trial C202 showed statistically significant early bactericidal activity and provides the basis for the recommended dosage of bedaquiline.

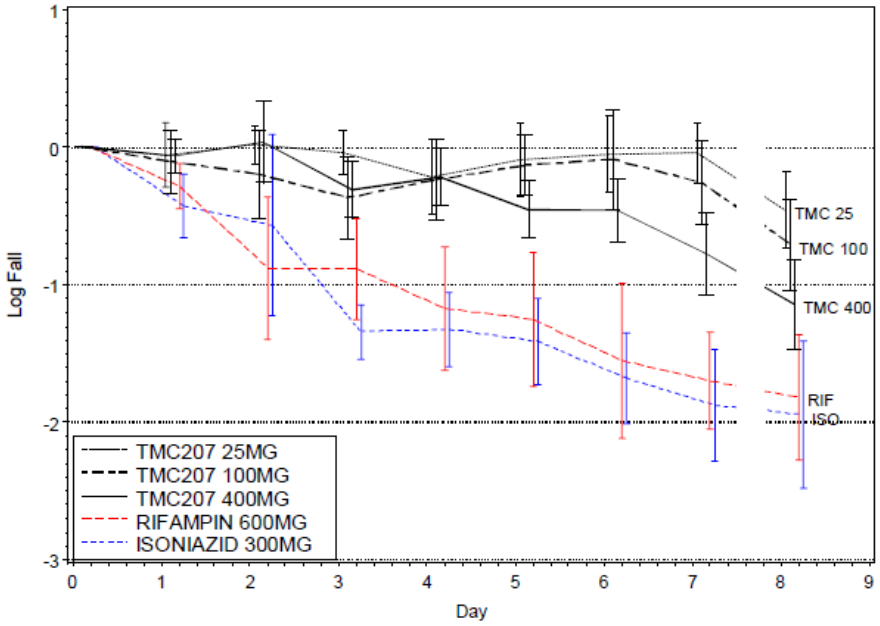
Figure 1. Bedaquiline Sputum Concentration (log scale) Versus C_{ss}, Average Plasma Concentration (log scale)



Dotted line is line of unity, solid line is regression line (slope = 0.79, r^2 = 0.44)

Source: NDA 204 384

Figure 2: Changes in log_{10} Sputum CFU Counts From Baseline Over Time With 95% CI



Note: Day 8 log_{10} sputum CFU counts are affected by standard TB treatment which was initiated on Day 8

Source: NDA 204 384

The exposure-response relationship analyses conducted using data from the Phase 2 trials indicated that no discernible relationship exists between systemic concentrations and time to sputum conversion, indicating that the dose of bedaquiline used in the Phase 2 trials was at the top of the dose-response curve.

3.1.4.2 Safety

No clear and consistent relationship was identified between exposure and incidence of most frequently reported AEs (> 10% subjects) after bedaquiline treatment, including, nausea, arthralgia, headache, chest pain, hemoptysis, and unilateral deafness.

3.2 CLINICAL EFFICACY

The efficacy data are from two Phase 2 trials. StudyC208 is double-blind, randomized, placebo-controlled superiority trial, conducted in 2 consecutive but completely separate stages: an exploratory stage (Stage 1) and a proof-of efficacy stage (Stage 2) and Study C209 is an open-label, single-arm trial.

3.2.1 SUMMARY OF EFFICACY FROM C208

3.2.1.1 STUDY DESIGN AND ENDPOINTS

The comparative efficacy data are from the two separate stages of one Phase 2 trial. Study C208 is double-blind, randomized, placebo-controlled superiority trial, conducted in 2 consecutive but completely separate stages: an exploratory stage (Stage 1) and a proof-of efficacy stage (Stage 2). In Stage 1, subjects were treated with bedaquiline (also referred to as TMC) or placebo for 8 weeks on top of a background regimen given for 18 to 24 months. Final follow-up for Stage 1 was 104 (=8+96) weeks. Stage 2 subjects were treated with bedaquiline or placebo for 24 weeks on top of a background regimen given for 18 to 24 months. Follow-up continues out to 96 weeks after the end of the bedaquiline/placebo treatment period (24+96=120 weeks) and approximately 6 months after the end of all TB treatment. Stage 1 is complete and Stage 2 is ongoing but has complete follow-up out to 72 weeks on all subjects unless they discontinued study prior to 72 weeks.

The primary endpoint for both studies was time to sputum culture conversion (SCC) at the end of the bedaquiline/placebo treatment period. Time to SCC was based on the qualitative assessment of culture growth in mycobacteria growth indicator tube (MGIT) using spot sputum samples. The following details were used to determine time to SCC:

- Sputum culture conversion was defined as 2 consecutive negative cultures from sputa. Sputa had to be collected at least 25 days apart for Stage 2 and all analyses past 8 weeks in Stage 1. All intermediate cultures have to be negative as well. Sputum culture conversion was overruled when followed by a confirmed positive MGIT culture result (defined as 2 consecutive visits with positive sputum results,

not taking into account intermittent missing or contaminated results, or a single positive sputum result after which the subject discontinued or completed).

- Time to SCC was calculated as the interval in days between the date of treatment initiation for MDRTB and the date of the first of the 2 consecutive negative sputum cultures.
- Subjects who discontinued before the end of the analyzed time period were to be considered treatment failures (i.e., no culture conversion event) and their time to SCC was censored at their last assessment with sputum culture (missing = failure).

FDA reviewed the protocol and agreed with the design and planned analysis of the study.

3.2.1.2 PATIENT DISPOSITION

During Stage 1, 47 subjects were randomized to receive either bedaquiline (n = 23) or placebo (n = 24). Six investigators in South Africa participated in this stage. The rate of study discontinuation was high at 44% for bedaquiline and 54% for placebo; however, 83% and 92% had data available for the primary efficacy analysis at week 8.

During Stage 2, 161 subjects were randomized to receive either bedaquiline (n = 80) or placebo (n = 81). Study sites were located in Eastern Europe, Asia, South America, and South Africa. One subject randomized to bedaquiline but not treated was removed from all efficacy analyses. Given the double-blind design, this was considered acceptable. Subjects were excluded from a modified intent to treat (mITT) population due to infection with DS or XDRTB or unconfirmed MDRTB status. Additional subjects were removed if they did not have a positive baseline culture or no post-baseline measurement. Note that one subject was removed from the mITT population due to no post-baseline values. Given that this subject was removed based on post-baseline/post-treatment information, the removal could potentially introduce bias into the study. An additional analysis was conducted including this one bedaquiline subject as a treatment failure (i.e. no sputum culture conversion).

The following table (Table 7) contains the information on subjects included in Stage 2. The discontinuation rate for bedaquiline and placebo were 32% and 35% respectively. Note that 82% and 86% (or 57 and 54 subjects) in each group had microbiological culture data available for the primary efficacy analysis at week 24.

Table 7. Patient Disposition and Inclusion in the Analytic Populations in C208 -Stage 2

	Bedaquiline	Placebo
Randomized	80	81
Randomized and treated (ITT)	79	81
Excluded from mITT	13	15
mITT	66	66
Completed	15 (22.7)	14 (21.2)
Ongoing	30 (45.5)	28 (42.4)
Discontinued	21 (31.8)	23 (34.8)
Rollover		1 (1.5)

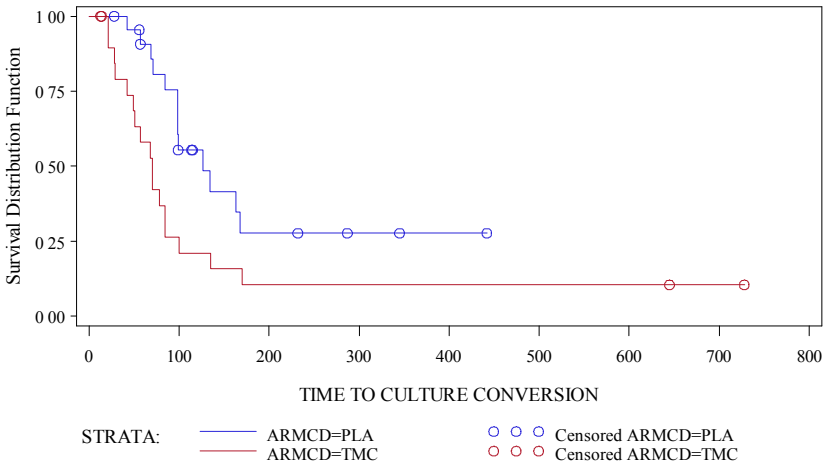
Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 107

3.2.1.3 RESULTS

Stage 1 primary results

The Stage 1 primary efficacy results of time to sputum culture conversion by 8 weeks was faster in the bedaquiline group compared to the placebo group (log-rank test p-value=0.0019). This significance remained in an analysis of the 24 week data as well as the full study data when all subjects had reached week 96 or discontinued earlier (log-rank test p-value=0.0152). The Kaplan-Meier curves for time to culture conversion for the final analysis are shown in Figure 3.

Figure 3. Stage 1 Kaplan-Meier Survival Curves for Final Analysis-mITT



Source: Plot based on data from NDA 204,384. Original Submission

Stage 1 analysis of culture conversion rates at Week 8 showed a statistically significantly higher rate for bedaquiline than for placebo with a difference of 38.9% at Week 8. The results of analyses of culture conversion rates at the later time points were no longer significant (Table 8).

Table 8. C208 - Stage 1 Culture Conversion Rates in the mITT Population

Microbiologic Status	Bedaquiline N=21	Placebo N=23	p-value, exact 95% CI
Week 8 Treatment success	10/21 (47.6%)	2/23 (8.7%)	0.004 [12.3%, 63.1%]
Week 24 Treatment success	17/21 (81.0%)	15/23 (65.2%)	0.293 [-11.9%, 41.9%]
Final Treatment success	17/21 (81.0%)	13/23 (56.5%)	0.102 [-4.8%, 50.3%]

Source: Modified from NDA 204,384. Original Submission. Study Report – Stage 1 – Final Update. p. 103, 105 and from submitted data

Stage 2 primary results

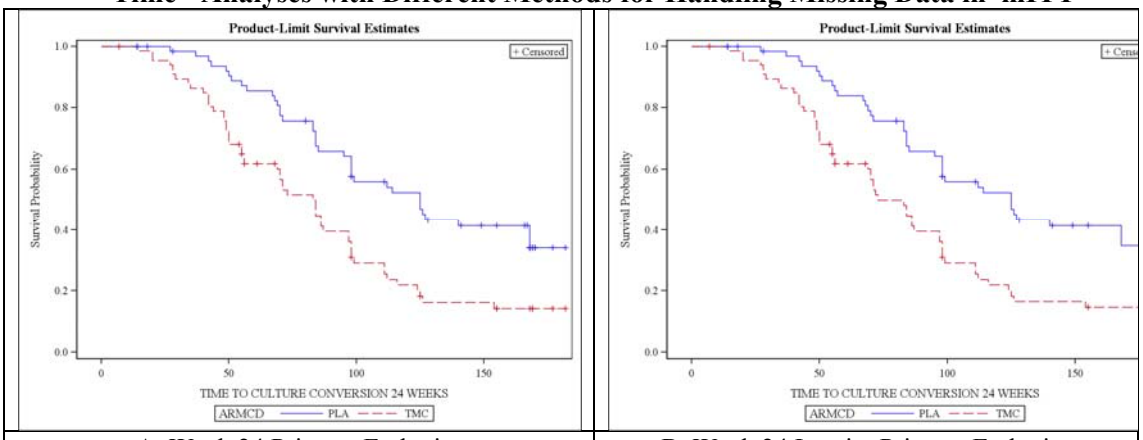
The Stage 2 primary efficacy analysis showed that time to sputum culture conversion was faster and was seen more frequently in the bedaquiline group compared to the placebo group (with a median time to culture conversion of 83 days in the bedaquiline group versus 125 days in the placebo group). A Cox proportional hazards model with covariates of treatment, lung cavitation, and pooled center (region) showed a statistically significant treatment effect for bedaquiline over placebo (hazard ratio = 2.44 [95% CI: 1.57, 3.80]). The following table (Table 9) reports the primary results and the results of the sensitivity analyses with different methods for handling missing data.

Table 9 C208-Stage 2 Treatment Effect (Relative Risk to Culture Conversion) Estimated from Cox Proportional Hazards Models on Week 24 Time to Culture Conversion, mITT

Endpoint	Relative Risk	95% CI	p-value
Stage 2 Primary Endpoint	2.44	1.57, 3.80	<0.0001
Interim Primary Endpoint	2.41	1.55, 3.75	<0.0001
Interim End-censored	2.22	1.43, 3.43	0.0003
Interim Sensitivity 2	1.98	1.30, 3.02	0.0015

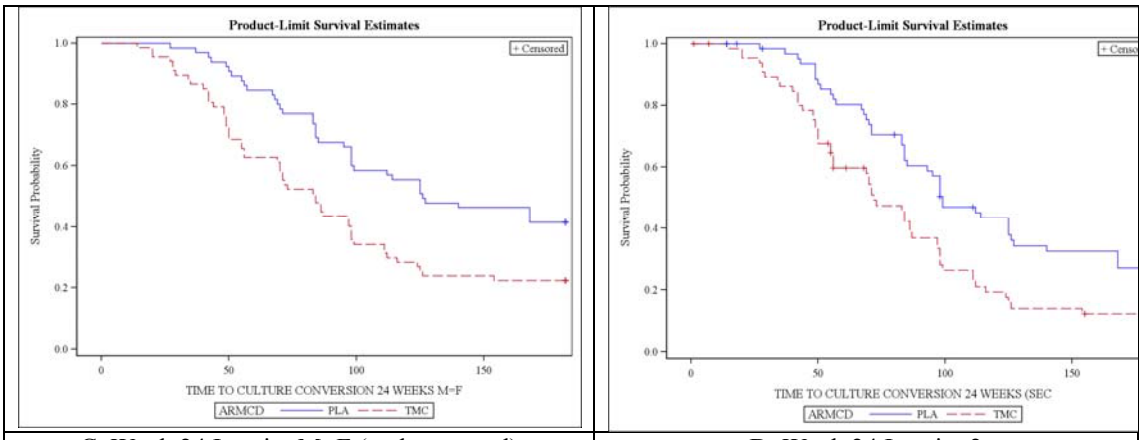
Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 143, 145, 147, 148

Figure 4A –D. Stage 2 Kaplan-Meier Plots: Proportions of Culture Positive Subjects Over Time - Analyses with Different Methods for Handling Missing Data in mITT



A. Week 24 Primary Endpoint (censored at last MGIT assessment)

B. Week 24 Interim Primary Endpoint (Last MGIT or end-censored)



C. Week 24 Interim M=F (end-censored)	D. Week 24 Interim 2 (No overruling by discontinuation)

Source: Modified from NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis.

The following table (Table 10) shows the treatment effect of bedaquiline from the Cox proportional hazards models of the Week 72 data with three methods for handling missing data. There was a statistically significant treatment effect from each of the endpoints. However, compared with the results from Week 24 data analyses, the treatment effect was slightly reduced.

Table 10. C208 - Stage 2 Treatment Effect (Relative Risk to Culture Conversion) Estimated from Cox Proportional Hazards Models on Week 72 Time to Culture Conversion, mITT

Endpoint	Relative Risk	95% CI	p-value
Interim Primary	1.65	1.05, 2.59	0.0290
Interim End-censored	1.56	1.00, 2.43	0.0487
Interim Sensitivity 2	1.86	1.22, 2.82	0.0036

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 159, 160, 161

Stage 2 analyses of culture conversion rates at Week 24 (Table 11) showed a statistically significantly higher rate for bedaquiline than for placebo with a difference of 21% in culture conversion rates at Week 24. Similar to Stage 1, the results of analyses of culture conversion rates at the later time point at Week 72 were no longer significant.

Table 11. C208 - Stage 2 Culture Conversion Rates at Week 24 – mITT

Microbiologic Status	Bedaquiline N=66	Placebo N=66	p-value 95% CI
Week 24 Treatment success	52/66 (79%)	38/66 (58%)	0.009 [5.7%, 36.7%]
Week 72 Treatment success	47/66 (71%)	37/66 (56%)	0.070 [-1.1%, 31.4%]

Source: Modified from NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 144, 164

As stated above, the applicant's definition of the mITT population excluded subjects based on post-baseline information. One subject (Subject 4135) in the bedaquiline group had positive culture result at baseline but no culture results afterwards and was excluded from the mITT population. An analysis was conducted in which this subject was included in the mITT population as a failure (censored at Day 182). There remains a

significant difference in culture conversion between the two groups and the p-value from the log-rank test was 0.0003. Compared with the applicant's primary analysis, the cure rate in the bedaquiline group was changed from 79% to 78% and the p-value from Chi-square test was changed from 0.008 to 0.0135.

Additional analyses of Stage 2

Reason for failure in the primary analysis

Subjects could have been considered a failure in the primary analysis due to lack of sputum conversion or due to discontinuation. Table 12 contains a breakdown of the reason for failure for the primary 24 week results of sputum culture conversion.

Table 12 C208-Stage 2 Culture Conversion Rates at Week 24 – mITT

Microbiologic Status	Bedaquiline N=66	Placebo N=66	p-value 95% CI
Week 24 Treatment success	52/66 (79%)	38/66 (58%)	0.009 [5.7%, 36.7%]
Week 24 Treatment failure	14	28	
Failure due to lack of conversion	5	16	
Failure due to discontinuation	9	12	

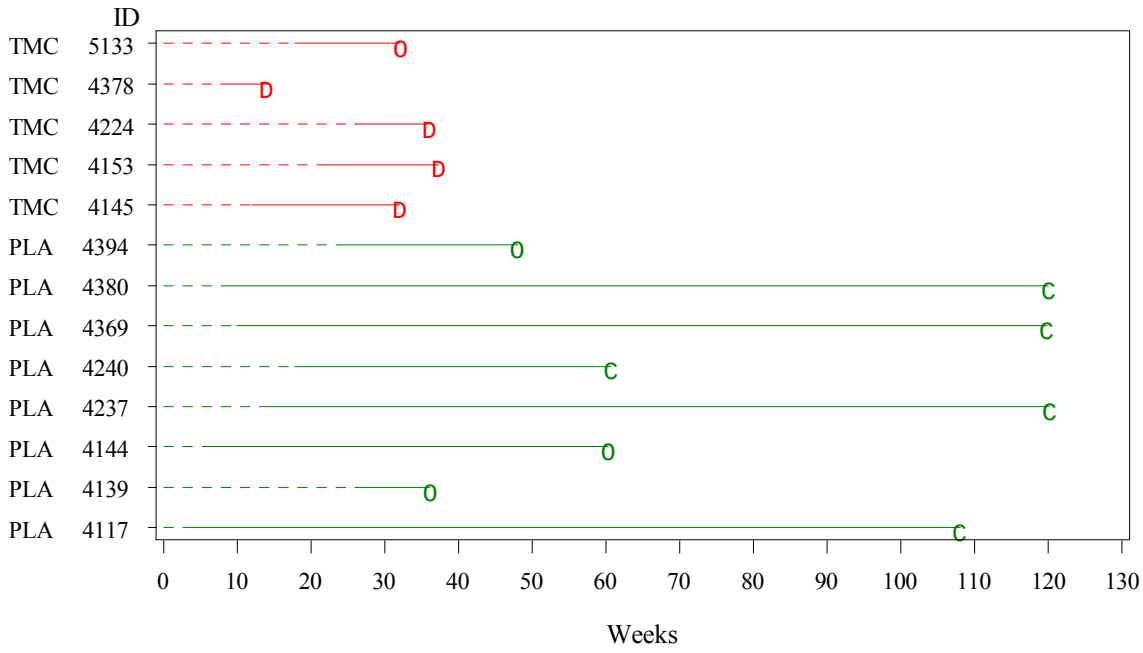
Source: Modified from NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 144 and submitted data.

3.2.1.4 ANALYSIS OF RELAPSE

The definition of relapse is not a typical definition of relapse since many subjects are still being treated with the background regimen at this point of the analysis of the ongoing study. Relapse for this analysis is defined as having confirmed positive sputum culture after having been defined as converted and without an additional culture conversion prior to the end of the study. In the mITT population, 5 subjects (7.6%) in the bedaquiline group and 8 subjects (12.1%) in the placebo group experienced relapse.

The following figure reports the results for these 13 subjects. The time from onset of treatment to culture conversion (broken line) and time from culture conversion to relapse (solid line) with disposition type (ongoing, discontinued, or completed) in the mITT population is shown in the following figure:

Figure 5. Onset Time of Relapse in Bedaquiline- and Placebo-Treated Patients Relative to Treatment Initiation and Culture Conversion



TMC:Bedaquiline PLA: Placebo C: Completed D: Discontinued O: Ongoing

Source: :Based on NDA 204,384. Original Submission.

The subjects in the placebo group appear to take a longer time from culture conversion to relapse than those in the bedaquiline group. However, the four subjects who relapsed at Week 108 or Week 120 in the placebo group were based on only one positive result at the last visit with microbiological assessment. The results may have been different if more visits had been available and if the subsequent results were negative. If these 4 subjects were excluded, the two treatment arms become more comparable with respect to relapse. The three discontinued subjects in the bedaquiline group discontinued 12 to 45 weeks after relapse.

3.2.1.5 SUBGROUP ANALYSES

Subgroups analyses of Week 24 culture conversion by age, gender, and extent of lung cavitation (i.e. no cavity [or cavitations of <2 cm], cavitation in one lung, or cavitation in both lungs, with cavitation defined as the presence of at least one cavity ≥ 2cm) all showed consistent results of bedaquiline compared to placebo.

Additionally, analyses by baseline TB type (DS, MDR, pre-XDR, XDR, missing) for the intent to treat population also show consistent results (Table 13); however, the numbers of subjects with drug susceptible and XDR-TB were too small to make meaningful comparisons. Failures could be due to microbiological failure to culture conversion or discontinuation by Week 24. The numbers of subjects with failures due to discontinuation by baseline TB type were as follows: in the bedaquiline group, 15 out of 20 failures were due to discontinuation (3, 7, 3, 1, and 1 in the DS, MDR, Pre-XDR, XDR, and Missing TB type subgroups); in the placebo group, 17 out of 35 failures were due to discontinuation (2, 7, 2, and 6 in the DS, MDR, Pre-XDR, and Missing TB type

subgroups). Note in the DS-TB subgroup, all failures on bedaquiline were due to discontinuation and 2 out 3 failures in the placebo group were due to discontinuation.

Table 13. C208- Stage 2 Culture conversion rate at Week 24 by baseline TB susceptibility, ITT

TB type	Bedaquiline	Placebo
DS	1/4 (25.0%)	1/4 (25.0%)
MDR	32/40 (80.0%)	29/46 (63.0%)
Pre-XDR	12/16 (75.0%)	4/12 (33.3%)
XDR	2/3 (66.6%)	3/4 (75.0%)
Missing values	12/16 (75.0%)	9/15 (60.0%)
Total	59/79 (74.7%)	46/81 (56.8%)

Source: based on data from NDA 204,384. Original Submission

Table 14 shows the culture conversion rates by HIV status at baseline. There was an imbalance at randomization in the number of HIV positive subjects randomized to the two arms. The bedaquiline group has only 5 HIV positive subjects so that it is difficult to make any conclusions about HIV status and results. Note, however, that in the placebo group, HIV negative subjects had a lower conversion rate than HIV positive subjects. Therefore, the higher proportion of HIV negative subjects in the bedaquiline (61/66 or 92.4%) group, compared with that in the placebo group (52/66, 78.8%) should not be a concern in overall assessment of bedaquiline efficacy.

Table 14 C208-Stage 2 Culture conversion rate at Week 24 by baseline HIV status, mITT

HIV status	Bedaquiline	Placebo
HIV negative	48/61 (78.7%)	27/52 (51.9%)
HIV positive	4/5 (80.0%)	11/14 (78.6%)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 154

Table 15 contains the week 24 culture conversion results by race and region. The race with the largest sample size is Black; however, it is the only group that did not show a higher success rate on bedaquiline compared to placebo. It appears that this effect is driven by the South African-2 site.

Table 15 C208-Stage 2 Culture conversion rate at Week 24 by Race, mITT

	Bedaquiline	Placebo
Race		
Black	17/24 (70.8%)	18/25 (72.0%)
Caucasian/White	4/6 (66.7%)	4/8 (50.0%)
Hispanic	12/12 (100%)	5/10 (50.0%)
Asian	8/9 (88.9%)	5/6 (83.3%)
Other	11/15 (73.3%)	6/17 (35.3%)
Region		
Asia	8/8 (100%)	4/4 (100%)
Eastern Europe	3/6 (50.0%)	3/7 (42.9%)
South Africa – 1	11/14 (78.6%)	7/17 (41.2%)
South Africa – 2	9/13 (69.2%)	11/13 (84.6%)
South Africa –other	7/10 (70.0%)	6/12 (50.0%)

South America	14/15 (93.3%)	7/13 (53.9%)
Race/Region		
Black/South Africa - 2	8/12 (66.7%)	11/12 (91.7%)
Black/other regions	9/12 (75.0%)	7/13 (53.8%)
Diacon is 'South Africa-1' and Pym is 'South Africa-2'		

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 154

3.2.1.6 CLINICAL ENDPOINTS

No significant effect was seen on the endpoint of weight or chest X-ray.

3.2.2 Study C209 (Supportive Study)

3.2.2.1 Study design

Study C209 is an ongoing Phase II, single-arm, open-label trial to evaluate efficacy, safety, and tolerability of bedaquiline on top of background regimen in the treatment of MDRTB.

Subjects with confirmed pulmonary MDRTB infection were included. Subjects infected with XDRTB were also allowed to enter the trial if they had at least 3 anti-TB drugs in their background regimen to which their *M. tuberculosis* isolate was likely to be susceptible. HIV-infected subjects having a CD4+ count < 250 cells/μL were excluded, compared to 300 cells/μL in Study C208 Stage 2. Unlike in Study C208, HIV-infected subjects receiving antiretroviral drugs (ARVs) were allowed to enter the trial if they met some specific criteria.

The dose, treatment duration, and follow-up duration were the same as in Study C208 Stage 2. The primary efficacy endpoint and main secondary efficacy endpoints were defined the same as in Study C208 Stage 2. The study populations (mITT and ITT) were defined similarly as in the Study C208 Stage 2, but including subjects with XDR-TB.

A Clinical Study Report includes results from planned interim analysis performed when all subjects had completed 24 weeks of treatment with bedaquiline or had discontinued earlier (cut-off date 29 March 2011).

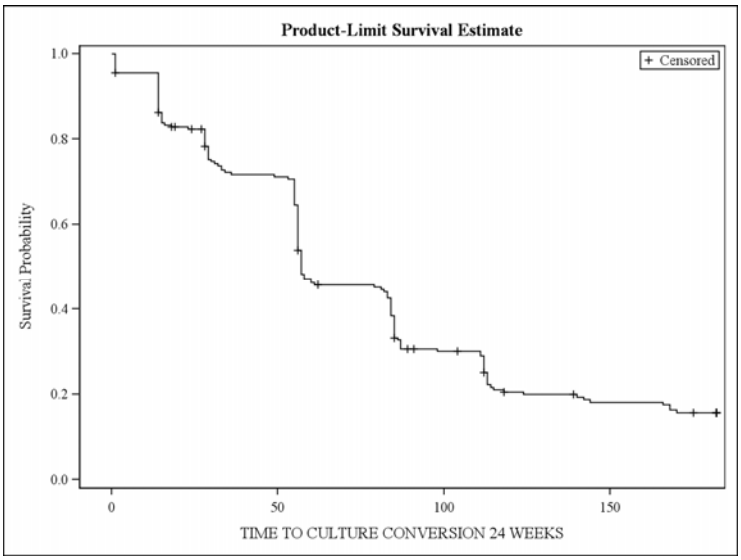
Patient Demographics and Disposition

A total of 294 subjects in Asia, Eastern Europe, South Africa, and South America were screened and 233 were treated (ITT population). The mITT population included 205 subjects. A total of 28 subjects were excluded (3 with DS-TB at baseline and 25 with no positive MGIT at baseline or screening). A total of 203 subjects completed 24-week investigation period and were ongoing, 20 discontinued before Week 24 and 10 discontinued after Week 24. In the ITT population, 37 (15.9%) subjects were infected with XDR-TB, and 11 (4.9%) were HIV-positive.

3.2.2.2 Study C209 primary results

The Kaplan-Meier of the primary efficacy endpoint, time to sputum culture conversion by 24 weeks in the mITT population is depicted in the following graph. Median time to culture conversion for the mITT population was 57 days.

Figure 6. Kaplan-Meier Plot of Proportions of Culture Positive Subjects Over Time



Source: NDA 204,384. Original Submission. Clinical Study Report – Study C209 – p. 112

In the mITT population, 80% (163/205) of subjects achieved culture conversion at the end of Week 24, a secondary efficacy endpoint.

3.3 CLINICAL SAFETY

3.3.1 OVERALL SAFETY EXPERIENCE

The clinical safety information from the phase 1 and phase 2 programs are reviewed separately in this NDA. A total of 265 normal volunteers and 380 TB patients received bedaquiline in the drug development program. Of a total of 337 subjects participating in Phase I trials, 265 were exposed to bedaquiline, including 76 subjects assessed for specific safety issues whose safety data were reviewed separately from the pooled normal volunteer safety data (N=189). In the phase IIa program, 75 patients received 7 days of bedaquiline in a dose ranging, proof-of-concept, early bactericidal study. In the phase IIb program, 23 patients received 8 weeks and 182 patients received 24 weeks of bedaquiline (79 treatment-naïve and 102 treatment-experienced). The safety studies and exposures to bedaquiline in the clinical program for NDA 204384 are shown in Tables 16 and 17. The safety of bedaquiline from studies conducted by other sponsors and the safety of bedaquiline from expanded access programs have not been reviewed for this backgrounder.

Table 16. Bedaquiline safety exposure in Phase 1 Studies

Studies of non-TB subjects in Phase 1 trials	# exposed
5 single-dose Phase I studies*	132
3 multiple-dose Phase I studies*	57
Subtotal of subjects in phase1 studies POOLED for SAFETY	189
Studies Excluded from Pooled Analysis	
C112 single-dose trial (included moderate hepatic impairment)	16
C117 single-dose trial (drug drug interaction in HIV infected)	16
TBC1003 single-dose trial Thorough QT Trial	44
Subtotal of subjects in phase1 studies NOT POOLED for SAFETY	76
Total number of exposed non TB subjects in Phase 1 studies	265

* one trial in each category was placebo controlled
Source: Modified from NDA 204384. Original Submission. Summary of Clinical Safety. p. 49.

Table 17. Bedaquiline safety exposures in Phase 2 Studies with bedaquiline

Studies in TB patients in Phase 2 trials	# exposed
Phase 2a Drug Sensitive TB infected patients in 7 day monotherapy EBA Phase 2b Study 202	45
Phase 2b Multi Drug Resistant TB, treatment-naïve patients, standard 5 drug BR*	
400 mg daily for 2 weeks and 100 mg TIW for 6 weeks C208 Stage 1	23
400 mg daily for 2 weeks and 100 mg TIW for 22 weeks C208 Stage 2	79
Phase 2b Multi Drug Resistant TB, treatment-experienced patients with individualized BR *	
400 mg daily for 2 weeks and 100 mg TIW for 22 weeks in UNCONTROLLED trial C209	233
Total Number of MDR-TB-Infected Patients Exposed to bedaquiline in patients with MDRTB	335
Total Number of DS and MDR TB patients exposed to bedaquiline as monotherapy or in combination	380

*Background regimen consisting of kanamycin, ofloxacin, KAN, ethionamide, pyrazinamide and terizidone provided by the national TB drug program
Source: Modified from NDA 204384. Original Submission. Summary of Clinical Safety

The safety data from the placebo arms in the Phase 1 studies are not represented for comparison in the applicant's and the FDA's pooled analyses. The Applicant did not find it appropriate to make comparative analyses of pooled Phase 1 safety data between placebo- and bedaquiline-exposed subjects. This is because of the relative disparity between the small number of placebo-treated subjects (27 healthy subjects [18 subjects in a Study CDE-101, a single, ascending dose study, and 9 subjects in Study CDE-102, a multiple dose study]) and the number of subjects exposed to bedaquiline (265 healthy subjects). Additionally, there were three studies excluded from the pooled analysis for Phase 1 studies either because the studies enrolled non-healthy subjects (i.e. HIV-infected subjects and subjects with hepatic impairment) or evaluated a bedaquiline dose that was higher (i.e. 800 mg supratherapeutic dose for the QTc study) than the proposed to-be-marketed dose for bedaquiline.

3.3.1.1 Safety in Phase 1 Program

The phase 1 program explored the safety of several formulations of bedaquiline used in development (oral solution, capsules, tablets) from single doses as low as 10 mg of the solution to 800 mg of the to-be-marketed tablet. As such, Phase 1 safety data are not presented in its entirety; the value of the aggregated phase 1 program from a safety perspective is to provide insight into possible safety signals of bedaquiline that were more fully monitored in the phase II program.

The applicant conducted 11 Phase 1 studies to evaluate bedaquiline. Analysis of pooled safety data from 8 Phase 1 studies (5 single-dose studies and 3 multiple-dose studies) enrolling 189 healthy adult subjects, and receiving at least 1 dose of bedaquiline, support the safety and tolerability of bedaquiline either administered alone or with selected other medications. A total of 27 subjects received placebo (18 subjects in a single-dose study and 9 subjects in a multiple-dose study). Some patients may be included in more than one pooled treatment group. The applicant's discussion focused on the group of patients receiving bedaquiline alone, since this group provided the most relevant safety information without the confounding effects of concomitant medications. Comparisons between pooled treatment groups were not done.

Table 18. Dose Exposures in the Phase 1 Pooled Studies

Bedaquiline Dose level	Single dose	Multiple dose	All
Up to 100 mg	70	6	76
150 mg		6	6
300 mg	34	0	34
400 mg	16	45	61
450 and 700	6	0	6

Source: Modified from NDA 204384. Original Submission. Summary of Clinical Safety

Of the 57 multiple-dose subjects, 47 received bedaquiline for at least 14 days and 37 subjects received bedaquiline with other medication (INH and PZA = 22 subjects, ketoconazole =15) . A third of subjects (35%) received the 400 mg to-be-marketed dose. Eighteen subjects discontinued the Phase 1 studies prematurely after receiving bedaquiline. Completion rates across single dose and multi-dose studies varied from 85.5% to 96.2%. The most frequent reason for discontinuation was noncompliance (5.3%); subjects reportedly failed to comply with pharmacokinetic sampling.

No deaths or SAEs were reported; 60.3% of subjects developed adverse events (AEs), and 36.5% developed AEs related to bedaquiline. Most AEs were mild, 6.9% of subjects developed at least a Grade 3 severity AE (hyperuricemia n=9, lipase increased n=3, fever n=1,) and only 3 (1.6%) led to drug discontinuation (urinary tract infection, pharyngolaryngeal pain and pyrexia, increased lipase). Events related to the nervous system (24.3%) and gastrointestinal tract (16.9%) were the most common system organ class (SOC) adverse events reported; the most frequent individual adverse event terms were headache (34/189 subjects, 18.0%), and dizziness (10/189 subjects, 5.3%). Other adverse events reported in more than 5% of subjects in the pooled treatment group were dry mouth, diarrhea, fatigue, hyperuricemia, and erythema.

Cardiovascular Safety

To evaluate cardiovascular safety in Phase 1 studies, a resting 12-lead ECG was recorded pre- and post-baseline in all pooled Phase 1 studies. For Studies C110 (open-label, randomized, crossover, drug-drug interaction study with lopinavir/ritonavir) and C111 (open-label, randomized, crossover, bioavailability study), triplicate ECGs were taken. In Study CDE-101 (a single-ascending dose study with a component of food interaction study), a continuous 12-lead ECG was obtained for the first 4 hours postdose.

Cardiac safety in these studies was described in a number of ways:

- AE reports related to the SOC Cardiovascular (including the preferred term ECG QT prolonged, postural orthostatic tachycardia, among others)
- AE report of Prolonged QT (defined by QTcF > 450 ms)

In Phase 1 studies, no subject exposed to bedaquiline, either alone or in combination with other drugs, had a QTcF interval > 500 ms. No subject discontinued treatment due to QT prolongation.

In the study evaluating bedaquiline-ketoconazole coadministration, three patients had increases in their QTcF from baseline (24 to 58 ms from baseline) as AEs with the preferred term ECG QT prolonged (Table 19). The ECG findings resolved after one day and were considered to be possibly related to both bedaquiline and ketoconazole. A greater effect on QTc was noted after repeated dosing with bedaquiline and ketoconazole combined than after repeated dosing of individual drugs. However, none of the QTcF intervals from these patients were > 450 ms and these events were not reported under that category for the combined treatment arm. A single patient in the bedaquiline alone treatment group [1 (6.7%)] was reported in this AE category.

Table 19. ECG findings in for 3 Patients with Prolonged QT in Drug-drug Interaction (DDI) Study with Ketoconazole

	Subject 109-0241	Subject 109-0935	Subject 109-1445
Baseline QTcF value (ms)	425	386	420
Abnormality			
Treatment	TMC207 + ketoconazole	TMC207 + ketoconazole	TMC207 + ketoconazole
Time point	Day 14, 5 h postdose	Day 14, 5 h postdose	Day 14, 5 h postdose
QTcF value (ms)	449	444	448
Increase from baseline in QTcF (ms)	24	58	28

Source: Module 5.3.3.4/TMC207-C109-CSR

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. Table 21. p. 63.

Note that the 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. The average increase of QTcF at 5 h postdose was: 7.6 ms at 5 h postdose after 3 days with ketoconazole treatment alone; 16.4 ms at 5 h postdose after 11 days of bedaquiline treatment alone (400 mg daily), and 28.3 ms at 5 h postdose after 3 days combination of ketoconazole and bedaquiline.

The events reported in this DDI study demonstrate some of the QT prolongation issues associated with bedaquiline. First, QT prolongation was reported in a patient that received bedaquiline alone. As well, mean increases in the QTc interval were greater with combined use of bedaquiline and ketoconazole than with either drug alone. As ketoconazole has the potential to cause QT prolongation, the observation that greater increases in QTcF were observed with multiple doses of bedaquiline and ketoconazole in combination than when these drugs were given independently demonstrate the potential

additive effect of drugs with QT prolonging effects when administered together. This may be attributable to a drug interaction as ketoconazole can increase bedaquiline systemic exposure, or due to additive effects on QT prolongation independent of the drug interaction.

An additional 4 bedaquiline-treated subjects were noted to have a prolonged QTcF interval (QTcF > 450 ms) in other Phase 1 studies:

- 2 subjects (QTcF: 453 & 457 ms) after a single dose of bedaquiline (Study C108 - bioavailability trial)
- 1 subject (QTcF: 452 ms) after multiple doses of 400 mg bedaquiline (Study C104 -DDI w/ INH / PZA)
- 1 subject (QTcF: 481 ms) after receiving bedaquiline with INH and PZA (Study C104).

As the prolongation of QTc interval could translate to abnormalities in vital signs, adverse events related to vital signs were monitored. Three subjects reported Grade 1 AEs of postural orthostatic tachycardia syndrome. Two of these subjects were enrolled in Study C111 (bioavailability study) while one was enrolled in Study C110 (DDI study with lopinavir-ritonavir). The latter patient had a standing pulse rate of 131 bpm. None of the patients experienced clinically significant abnormalities in vital signs (bradycardia, tachycardia, hypotension, etc.).

Summary of findings from the Thorough QT trial C1003:

In this randomized, double-blinded, parallel study, 88 subjects with tuberculosis received either TMC207 or a single oral dose of moxifloxacin 400 mg, and placebo. No significant QTc prolongation effect of TMC207 was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between TMC207 and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established.

The single-dose administration study design was insufficient to achieve exposures of the major metabolite that cover the high-exposure scenario in the clinical setting. Exposure-response data from both study c208 and this dedicated QT study combined with the time course of QTcF compared with the time course of TMC207 and M2 concentrations suggest that an exposure-QTcF relationship exists for the metabolite M2. No exposure-QTcF relationship was evident with TMC207 exposure. The clinically relevant exposure of M2 occurs after 14 days of 400 mg q.d. dosing, owing to the long terminal half-life of the metabolite (5.3 months). QTcF assessment in the dedicated QT study was following a single dose of TMC207 and the Cmax and AUC values for M2 were 1/5.4- and 1/6.4-fold of the exposures to M2 observed in tuberculosis patients in the phase 2 study c208.

3.3.1.2 SAFETY IN PHASE 2A TRIAL C202

Phase 2a Trial (Trial C202)

Trial C202 was a proof-of-principle, open-label, active-controlled, randomized Phase 2 trial in patients with DS-TB. Seventy-five subjects were randomized to 5 groups administered a 7-day study drug treatment regimen. Bedaquiline was given once daily in different doses for each group (25 mg, 100 mg, 400 mg); comparative groups were given INH (300 mg) or rifampin (600 mg) once daily as monotherapy. Of 75 subjects enrolled, 45 received bedaquiline. After the study drug treatment period, subjects in all treatment groups received standard TB treatment regimen for pulmonary DS-TB, based on prevailing national guidelines.

- No deaths occurred from an AE that started during the 7-day investigational study phase (bedaquiline, INH, or RMP) treatment period. Two patients died during the follow-up period, after initiation of a treatment regimen for their DS-TB consisting of RMP, INH, PZA, and EMB,. Neither death was attributable to bedaquiline.
  - a 25 year-old black female who received bedaquiline 400 mg daily for 7 days (7/15 to 7/21/2005) and Kombipak II for treatment of TB (3 tablets daily). She was lost to follow-up for 1 month because she moved residence. She was admitted to the hospital on (b) (6) for retroviral infection (reported as SAEs) and pulmonary TB after she presented with a 1 month history of hemoptysis, general body pains and night sweats. She was wasted and dyspneic but afebrile, with increased JVP, widespread chest crackles, and with tender hepatomegaly. Labs were positive for *M. tuberculosis* sputum culture, and positive serology for HIV with CD4 count of 80. Treatment re-initiated on 7/22/2005 with RMP, INH, PZA, and EMB. She did not improve and died on (b) (6) from HIV and TB.
  - a 41 year-old male who received bedaquiline 400 mg daily for 3 days (13 Sept - 15 Sept 2005) was prematurely withdrawn on D3 because of (+) UA test for cannabinoids. Chest x-ray on enrollment showed extensive pathology of the left lung (cavities, dense infiltration, pleural reaction). The right lung had mild alveolar infiltration and cavitation. The sputum was + for *M. tuberculosis*. Treatment initiated on 16 Sept 2005 with RMP, INH, PZA, and EMB. Patient developed hemoptysis and was referred to a tertiary care hospital where arterial embolization was attempted for hemoptysis. Despite efforts, she died due to massive hemoptysis on (b) (6)

- SAE -Two patients who received INH reported Grade 3 hemoptysis. One patient developed the AE while on INH (discontinued due to the SAE). Another developed the AE during follow-up.

- Adverse Events - A dose related trend in the AE rate was seen: 2 patients (13%) in 25 mg of bedaquiline, 6 patients (38%) in 100 mg of bedaquiline, and 9 (64%) in 400 mg of bedaquiline developed AEs. Seven patients (47%) receiving RMP and 3 (20%) receiving INH reported AEs.

- SOC- Compared to the phase 1 studies, AEs in patients included disease-related events such as hemoptysis from 1 patient (6%) in the 100 mg bedaquiline-treated group, in 3 (21%) patients in the 400 mg bedaquiline-treated group, and 2 (13%) patients in the INH group. Only one patient experienced an AE that was at least Grade 3 in severity. This patient reported Grade 4 hemoptysis that led to premature discontinuation of INH. The rest of the AEs are similar to those reported in phase 1.

To evaluate for cardiovascular safety, ECGs were done at screening, Day -1 (reference), and Day 7 (predose and 5 h postdose). Compared to the control groups treated with RMP and INH and to the other bedaquiline-treated groups, there is a notable increase of > 10 ms in median QTcF value on D7 for the bedaquiline 400 mg dose group. This effect is likely to be attributable to the 400 mg bedaquiline dose as the drug was given alone for the first 7 days. Thus, while the overall safety data from this study indicate that bedaquiline is safe and well-tolerated, the greater increase in QTcF that could be attributed to the 400 mg dose of bedaquiline should be noted. No QTcF values of more than 500 ms were observed in this trial.

3.3.1.3 Phase 2b Trials

The clinical safety database for the Phase 2b trials as of the cut-off date (C208 St 2: June 10, 2011; and C209: 29 March 2011), consisted of 440 TB-infected patients, 335 of whom received bedaquiline. This is summarized in the following table:

Table 20. Summary of bedaquiline Exposure in MDR-TB Patients in Phase 2b Trials

Exposure in TB infected, treatment-naïve subjects in Phase 2b trials	**$N_{bedaquiline}$**
Number of subjects treated with bedaquiline in the Phase 2b trial C208 Stage 1	23
Number of subjects treated with bedaquiline in the Phase 2b trial C208 Stage 2	79
SUBTOTAL MDR-TB- bedaquiline treated subjects in placebo-controlled Phase 2 trials	***102***
Exposure in TB infected, treatment-experienced subjects in Phase 2b trials	
Number of subjects treated with bedaquiline in the Phase 2b trial C209	233
Total Number of MDR-TB-Infected Patients Exposed to bedaquiline	**335**

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 145.

At the time of submission of the NDA, the applicant included the following safety data:

- 8 weeks exposure to bedaquiline/placebo for the C208 Stage 1 data
- 24 weeks exposure to bedaquiline/placebo for the C208 Stage 2 data
- 24 weeks exposure to bedaquiline for the C209 data.

Also at the time of submission, all patients completed up to Week 104 of follow-up for Trial C208 Stage 1 (or discontinued earlier). All patients reached Week 72 (or discontinued earlier) of the trial for Trial C208 Stage 2, with some patients completing the trial at Week 120. All patients reached Week 24 (or discontinued earlier) for Trial C209, with none completing the trial (Week 120).

3.3.1.3.1 Trial C208 Stage 1

This trial was conducted at 6 sites in South Africa. The trial population was 47 patients randomized 1:1, with 23 patients receiving bedaquiline together with a 5-drug background regimen (BR) and 24 patients receiving placebo with the BR. Treatment duration was comparable in both the treatment group (7.13 wks with SD of 2.13 wks) and the placebo group (7.52 wks with SD of 1.69 wks).

Table 21. Exposure in Trial C208 Stage 1

Total Duration (weeks)	**Placebo N = 24**	**Bedaquiline N = 23**
Investigational Treatment Period		
Mean (SD)	7.52 (1.688)	7.13 (2.134)
Median (min; max)	8.00 (0.9; 8.9)	8.00 (0.9; 8.3)
Background Treatment Period		
Mean (SD)	53.16 (38.963)	59.11 (40.478)
Median (min; max)	54.93 (1.0; 100.9)	76.14 (0.1; 101.1)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 1 . p. 151. Module 5.3.5.1/bedaquiline-C208-Stage 1-Anal-GEN/Display GEN.19

Of the 47 randomized patients, 23 patients received bedaquiline and 24 patients received placebo. Twenty-three patients (48.9%) prematurely discontinued the trial: 10 patients (43.5%) in the bedaquiline group and 13 patients 54.2%) in the placebo group. The most frequent reasons for discontinuation were noncompliance (17%) and withdrawal of consent (15%). No relevant differences were noted between the two groups in terms of the reasons for trial discontinuation. One patient discontinued due to a fatal AE and in one patient in each group had XDRTB at baseline and two patients in the placebo group developed XDRTB during the trial.

Baseline demographic and disease characteristics were comparable between treatment groups. Thirty-five (74.5%) patients were male, median age was 33 years, median BMI was 18.3 kg/m^2 and 55.3% were black. (Table22). One patient in each treatment group had XDRTB at baseline. Similar proportions of patients had cavitary disease (20 in both the bedaquiline and the placebo groups). Only 3 patients in each group were HIV-infected with comparable CD4+ cell counts (Table 22).

Table 22. Demographic and Baseline Disease Characteristics for ITT Population for Trial C208 Stage 1

Parameter	**Placebo N = 24**	**Bedaquiline N = 23**	**All Subjects N = 47**

Median (range) Age in years	33.0 (19-57)	33.0 (18-57)	33.0 (18-57)
Median (range) BMI, kg/m2	18.46 (13.8-30.9)	18.31 (14.1-26.9)	18.31 (13.8-30.9)
Gender, Female n (%) **Male n (%)**	7 (29.2) 17 (70.8)	5 (21.7) 18 (78.3)	12 (25.5) 35 (74.5)
Ethnic Origin Black n (%)	13 (54.2)	13 (56.5)	26 (55.3)
Caucasian/White n (%)	1 (4.2)	0	1 (2.1)
Other n (%)	10 (41.7)	10 (43.5)	20 (42.6)
Lung Cavity n (%) **≥ 2 cm in both lungs**	7 (29.2)	6 (26.1)	13 (27.7)
≥ 2 cm in one lung only	13 (54.2)	14 (60.9)	27 (57.4)
No cavity ≥ 2 cm	4 (16.7)	3 (13.0)	7 (14.9)
HIV Negative n (%) **HIV Positive**	21 (87.5) 3 (12.5)	20 (87.0) 3 (13.0)	41 (87.2) 6 (12.8)
Median CD4+ (x10$_6$ cells/L) **in HIV-positive subjects**	375.0 (311-886)	348.0 (310-445)	361.5 (310-886)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 1. p. 93. Display GEN.2, Display GEN.5, Display SAF.13, Listing GEN.6, and Listing SAF.10

The preferred BR for Stage 1 was ETH, KAN, PZA, OFL, and CS/TRD. According to the applicant, no clinically relevant differences in the type and use of BR were noted between the two groups. All patients, except one, used a BR of OFL, ETH, KAN/AMK, and PZA as recommended. The exception did not use OFL because of baseline resistance to OFL. An alternative used for CS/TRD was EMB. Disallowed BR drugs during the Investigational Treatment Phase (dapsone, CAP, clarithromycin, and INH) were taken by patients in the placebo group, not in the bedaquiline group.

Table 23. Background Regimen Used During the Whole Trial in Trial C208 Stage 1

Medication Name, n (%)	Placebo N = 24	Bedaquiline N = 23	All Subjects N = 47
Ethionamide	24 (100)	23 (100)	47 (100)
Aminoglycosides[a]	24 (100)	23 (100)	47 (100)
Pyrazinamide	24 (100)	23 (100)	47 (100)
Ofloxacin	23 (95.8)	23 (100)	46 (97.9)
Ethambutol	17 (70.8)	18 (78.3)	35 (74.5)
Terizidone/cycloserine	18 (75.0)	12 (52.2)	30 (63.8)
Ciprofloxacin	5 (20.8)	4 (17.4)	9 (19.1)
Dapsone	4 (16.7)	0	4 (8.5)
Capreomycin	1 (4.2)	1 (4.3)	2 (4.3)
Para-aminosalicylic acid	2 (8.3)	0	2 (4.3)
Clarithromycin	2 (8.3)	0	2 (4.3)
Kombipak II	0	1 (4.3)	1 (2.1)
Amoxi-clavulanic	1 (4.2)	0	1 (2.1)
Isoniazid[b]	(4.2)	0	1 (2.1)
Moxifloxacin	1 (4.2)	0	1 (2.1)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 1.. p. 98

3.3.1.3.2 Trial C208 Stage II

The trial was conducted in Asia, South Africa, Eastern Europe, and South America, with 15 participating investigators from 23 April 2008 to 10 June 2011. Randomization was stratified by treatment center and extent of lung cavitation. Two hundred eighty-two patients were screened, of which 121 were excluded.

One hundred sixty-one patients were randomized, but one patient did not initiate treatment because of an AE. In all, 160 patients initiated treatment, 79 patients with bedaquiline and 81 patients with placebo, both given in addition to a BR for MDRTB (ITT population). Of these, comparable proportion of patients discontinued prematurely from the trial, with slightly greater number in the placebo group. A similar proportion of patients in both groups discontinued the trial because of adverse events. The disposition of patients and the reasons for premature discontinuation can be seen in the following table.

Table 24. Disposition and Premature Discontinuation of Patients in Trial C208 Stage II

Population/Reason/ n (%)	ITT Population		
	bedaquiline N = 79	Placebo N = 81	All N = 160
Ongoing*	34 (43.0)	30 (37.0)	64 (40.0)
Completed*	18 (22.8)	20 (24.7)	38 (23.8)
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	2 (2.5)	6 (7.4)	8 (5.0)
Subject is pregnant	3 (3.8)	2 (2.5)	5 (3.1)
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)
Other	1 (1.3)	0	1 (0.6)
Rollover	0	1 (1.2)	1 (0.6)

*Represents subjects' last status before cut-off date of 10 June 2011
Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 107.

Patient Demographic Information

The two treatment groups were comparable in terms of patient demographic information. The ITT population consisted of 101 men (63.1% [101/160]) and 59 women (36.9% [59/160]). The median age at screening was 34 years (18-63 years) and mean BMI was 19.9 kg/m^2. A minority of the population was HIV infected in both groups, with the placebo group having a greater proportion of HIV-infected patients than the bedaquiline group (19.8% vs 10.1%, respectively).

Table 25. Demographic Characteristics of Patients Enrolled in Trial C208 Stage II

Demographic Characteristic n (%)	ITT		
	Bedaquiline N = 79	Placebo N = 81	All Subjects N = 160

Demographic Characteristic n (%)	ITT		
	Bedaquiline N = 79	Placebo N = 81	All Subjects N = 160
Age (years) Mean (SD)	36.0 (13.14)	35.8 (11.02)	35.9 (12.08)
Median (Range)	31.0 (18, 63)	35.0 (18, 61)	34.0 (18, 63)
Country (study site)			
Brazil	4 (5.1)	4 (4.9)	8 (5.0)
India	4 (5.1)	1 (1.2)	5 (3.1)
Latvia	5 (6.3)	4 (4.9)	9 (5.6)
Peru	16 (20.3)	17 (21.0)	33 (20.6)
Philippines	1 (1.3)	2 (2.5)	3 (1.9)
Russia	3 (3.8)	7 (8.6)	10 (6.3)
South Africa	43 (54.4)	45 (55.6)	88 (55.0)
Thailand	3 (3.8)	1 (1.2)	4 (2.5)
Ethnic origin			
Black	29 (36.7)	27 (33.3)	56 (35.0)
Caucasian/White	8 (10.1)	12 (14.8)	20 (12.5)
Hispanic	13 (16.5)	15 (18.5)	28 (17.5)
Oriental/Asian	9 (11.4)	6 (7.4)	15 (9.4)
Other	20 (25.3)	21 (25.9)	41 (25.6)
Gender Female	27 (34.2)	32 (39.5)	59 (36.9)
Male	52 (65.8)	49 (60.5)	101 (63.1)
Cavitations (as stratified)	79 (100)	81 (100)	160 (100)
Cavitations . ≥ 2 cm in both lungs	13 (16.5)	16 (19.8)	29 (18.1)
Cavitations . ≥ 2 cm in one lung only	50 (63.3)	49 (60.5)	99 (61.9)
No cavitations or cavitations < 2 cm	16 (20.3)	16 (19.8)	32 (20.0)
Extent of resistance of M. tuberculosis	79 (100)	77 (100)	156 (100)
DS-TB	4 (5.1)	4 (5.2)	8 (5.1)
MDRTB	75 (94.9)	73 (94.8)	148 (94.9)
Pre-XDR-TB	40 (50.6)	46 (59.7)	86 (55.1)
XDR-TB	16 (20.3)	12 (15.6)	28 (17.9)
	3 (3.8)	4 (5.2)	7 (4.5)
Baseline albumin grade	79 (100)	81 (100)	160 (100)
Grade 0	47 (59.5)	36 (44.4)	83 (51.9)
Grade 1	12 (15.2)	15 (18.5)	27 (16.9)
Grade 2	16 (20.3)	29 (35.8)	45 (28.1)
Grade 3	4 (5.1)	1 (1.2)	5 (3.1)
Previous use of first-line drugs(yes)	72 (91.1)	70 (86.4)	142 (88.8)
HIV Negative	71 (89.9)	65 (80.2)	136 (85.0)
HIV Positive	8 (10.1)	16 (19.8)	24 (15.0)
Mean CD4 cell count (HIV positive)	494.6	455.1	468.3
(SD)	-132.66	-125.91	-126.72

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 110

Prior Tuberculosis Treatment

Patients with previous TB treatment were still able to be included in the trial provided they did not receive previous treatment for MDRTB such as aminoglycoside other than streptomycin (SM), any fluoroquinolone, the thioamides (protionamide or ETH), and cycloserine (CS).

A total of 88.8% (142/160) of patients in the ITT population received prior treatment for TB. No significant difference in use of prior TB medications between the bedaquiline and placebo groups was noted. A large proportion of randomized patients received first line anti-TB medications, notably INH (86.1%) and RMP (88.1%). Others include PZA (81.3%), EMB (80.0%), and streptomycin (29.4%).

Table 26. Prior anti-TB drug treatment for Trial C208 Stage II

Previous TB treatment	ITT

Class Treatment n (%)	Bedaquiline/ N = 79	Placebo N = 81	All subjects N = 160
No previous use of TB drug treatment	***7 (8.9)***	***11 (13.6)***	***18 (11.3)***
Any previous use of TB drug treatment	***72 (91.1)***	***70 (86.4)***	***142 (88.8)***
Aminoglycosides	**29 (36.7)**	**18 (22.2)**	**47 (29.4)**
Streptomycin	29 (36.7)	18 (22.2)	47 (29.4)
First-line drugs	**71 (89.9)**	**70 (86.4)**	**141 (88.1)**
Ethambutol	66 (83.5)	62 (76.5)	128 (80.0)
Isoniazid	70 (88.6)	69 (85.2)	139 (86.9)
Pyrazinamide	67 (84.8)	63 (77.8)	130 (81.3)
Rifampicin	71 (89.9)	70 (86.4)	141 (88.1)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 113

Background Regimen (BR)

The preferred BR for Trial C208 Stage II was composed of the following: KAN, OFL, ETH, PZA, and TRD. In case of shortage or of patient tolerability issues, substitutions were permitted:

- AMK could be substituted for KAN (for shortage)
- Protionamide could be substituted for ETH (for shortage)
- EMB could be substituted for TRF/CS (for shortage of intolerance if not resistant to EMB.

The most frequently used drugs in the BR were FQs (99.4%), aminoglycosides (95.6%), PZA (93.1%), ETH (84.4%), and EMB (65.0%) (Table 27). Of the FQs, the most frequently used were OFL (74.4%) and ciprofloxacin (21.3%). Levofloxacin and moxifloxacin were used by 2.5% and 1.3% of patients in the trial, respectively. There were no clinically significant differences between the two groups with their BR.

Table 27. Baseline Background Regimen in the ITT Populations of Trial C208 Stage II

Background regimen Class Treatment n (%)	ITT		
	Bedaquiline/BR N = 79	Placebo /BR N = 81	All Subjects N = 160
Any use of background TB treatment	***79 (100)***	***81 (100)***	***160 (100)***
Aminoglycosides	**76 (96.2)**	**77 (95.1)**	**153 (95.6)**
Amikacin sulfate	19 (24.1)	24 (29.6)	43 (26.9)
Aminoglycosides	10 (12.7)	5 (6.2)	15 (9.4)
Kanamycin	51 (64.6)	49 (60.5)	100 (62.5)
Streptomycin	0	1 (1.2)	1 (0.6)
Fluoroquinolones	**79 (100)**	**80 (98.8)**	**159 (99.4)**
Ciprofloxacin	17 (21.5)	17 (21.0)	34 (21.3)
Levofloxacin	2 (2.5)	2 (2.5)	4 (2.5)
Moxifloxacin	1 (1.3)	1 (1.2)	2 (1.3)
Ofloxacin	59 (74.7)	60 (74.1)	119 (74.4)
Miscellaneous drugs	**79 (100)**	**80 (98.8)**	**159 (99.4)**
Amoxicillin + clavulanic acid	1 (1.3)	0	1 (0.6)
Capreomycin	3 (3.8)	5 (6.2)	8 (5.0)
Cycloserine	18 (22.8)	20 (24.7)	38 (23.8)
Ethambutol	53 (67.1)	51 (63.0)	104 (65.0)

Background regimen Class Treatment n (%)	ITT		
	Bedaquiline/BR N = 79	Placebo /BR N = 81	All Subjects N = 160
Ethionamide	70 (88.6)	65 (80.2)	135 (84.4)
Pas-C	4 (5.1)	8 (9.9)	12 (7.5)
Protionamide	8 (10.1)	13 (16.0)	21 (13.1)
Pyrazinamide	75 (94.9)	74 (91.4)	149 (93.1)
Terizidone	13 (16.5)	16 (19.8)	29 (18.1)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 116

A number of drugs were used in the BR with the permission of the applicant:

- Capreomycin: 10 patients in the bedaquiline group and 12 patients in the placebo group
- INH: 3 patients in both groups
- RMP: 2 patients in the bedaquiline group and 3 patients in the placebo group
- Macrolides: Clarithromycin – 4 patients in the placebo group; azithromycin – 1 patient in the bedaquiline group.

Unlike C208 Stage 1, disallowed medications were also used as part of the BR in both treatment groups:

- Moxifloxacin: 4 patients in the bedaquiline group and 4 patients in the placebo group
    - 2 patients in the bedaquiline group (208-4427 and 208-4423) and 3 patients in the placebo group (208-4033, 208-4036, and 208-4462) were considered major protocol deviations because moxifloxacin was used for > 2 weeks.
    - One of the patients in the placebo group (208-4036) developed abnormalities in QTc during moxifloxacin use (QTcF between 450 and 480 ms). This was reported as a Grade 1 AE ECG QTc interval prolonged.

During the Investigational Treatment phase, BR modifications occurred in 40.5 % of bedaquiline and 45.7% of placebo treated patients. Of these, 1 new drug was added in 21.3%,, two new drugs were added in 10.0% and three new drugs were added in 8.1% of patients' background regimen.

3.3.1.3.3 Trial C209

Trial C209 is a large noncomparative trial that describes the use of bedaquiline in a broader patient population than the controlled C208 trials. This open-label, single-arm trial evaluates the safety, tolerability, and efficacy of bedaquiline in combination with an individualized BR to treat patients with sputum smear-positive pulmonary infection with MDRTB. This study differed from C208 in the following key factors: a greater proportion of the population was treatment experienced, allowed enrollment of preXDR and XDRTB, background therapy was individualized, and had greater numbers of

patients enrolled from Eastern Europe and South America. The main reasons for premature discontinuation were the occurrence of one or more AEs (3.4%) and the withdrawal of consent (3.4%).

Table 28. Baseline Patient Demographic Information

Baseline Characteristics -Subject Disposition	**ITT N = 233 (%)**
M/F	150 (64.4)/83 (35.6)
Age:	
Mean (SD)	34.6 (12.09)
median (range), years	32.0 (18; 68)
BMI (kg/m2)	
Mean (SD)	20.6 (3.76)
Ethnic origin, n (%)	
American-Indian or Alaska Native	8 (3.4)
Asian	90 (38.6)
Black or African-American	75 (32.2)
White	60 (25.8)
Ethnicity, n (%) Hispanic or Latino	17 (7.3)
Not Hispanic or Latino	216 (92.7)
TB strain, n (%)	
DS-TB	3 (1.3)
Drug resistant TB (all)	230 (98.7)
MDRTB	93 (39.9)
pre-XDR-TB	44 (18.9)
XDR-TB	37 (15.9)
Cavitation n (%) None or cavitations < 2 cm	85 (36.5)
≥ 2 cm in one lung only	121 (51.9)
≥ 2 cm in both lungs	27 (11.6)
HIV Negative n (%)	214 (95.1)
HIV Positive n (%)	11 (4.9)
Previous use of 2nd line drugs	233 (100)
No previous use (newly diagnosed)	30 (12.9)
With previous use (non-newly diagnosed)	203 (87.1)
TB regimen ongoing at screening	200 (85.8)
Median Duration of TB regimen at screening (days)	36.0
Trial participation ongoing, n (%)	203 (87.1)
Discontinuations -Reason	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 noncompliant	5 (2.1)
Subject withdrew consent	8 (3.4)
Other	2 (0.9)

Source: Modified from NDA 204,384. Original Submission. Complete Study Report – Study C209 – Interim analysis. Table 6, p. 80, Table 7, p. 82, Table 8, p. 83

The BR in the initial 2 weeks of the investigational treatment phase was selected by the investigator, and most commonly included FQs (89.3%, mainly OFL 52.4%), PZA (76.0%), aminoglycosides (71.7%, mainly KAN 49.8%), and EMB (51.5%).

Although moxifloxacin and clarithromycin were disallowed concurrently with bedaquiline:

- Moxifloxacin was used by 3 patients for 5 -28 days (use of moxifloxacin for > 14 days in 1 patient was a major protocol deviation) and
- Clarithromycin was used by twelve patients for 2 to > 14 days
- RMP was used concurrently by 5 patients.

The median (range) duration of the investigational treatment phase was 25.0 (1.1-28.3) weeks whereas median (range) duration of the overall treatment phase was 37.9 (1.1-81.1) weeks.

3.3.2 Deaths in the Clinical Program for Bedaquiline

There were no deaths in the Phase 1 program. For the Phase II trials, prior to the safety database cutoff/lock date (C208 St 2: June 10, 2011; and C209: 29 March 2011), a total of 15 deaths were reported in these trials (Trial C202 [Phase IIa], Trial C208 [Phase IIb Stage I, Phase IIb Stage II], and Trial C209). Among 335 patients in the pooled phase 2b trials (Trials C208 Stage 1, Trial C208 Stage 2, and Trial C209) randomized to bedaquiline, 12 patients died (3.6%). These are summarized in Table 29.

Six out of the thirteen deaths in the phase 2b trials were classified as TB-related; three of which occurred in the controlled study C208 (two bedaquiline treated vs 1 placebo treated patient). Of the TB-related deaths in the phase 2 program, five of six were in patients with cavitary lesions, five of six were in subjects with infections due to mycobacterial strains that were susceptible to three or fewer second line drugs and four of six were infected with pre-XDRTB or XDRTB strains.

In the controlled trial C208 Stages 1 and 2, five deaths occurred in the bedaquiline group compared to one death in the placebo group. Excluding the deaths caused by tuberculosis, the role of either bedaquiline or BR in the development of three SAEs could not be ruled out: hepatitis, vomiting, congestive heart failure.

- Patient 208-5069 died on D(b)(6) with diagnoses of hepatitis and hepatic cirrhosis on D228. Hospital records indicated that the patient had a 2 month history of fatigue and a 1 week history of epigastric pain. Patient was diagnosed with alcoholic liver cirrhosis with ascites, volume depletion, and malnutrition. Bedaquiline or the BR could have exacerbated the underlying hepatic pathology.

- Patient 209-0044 died on D(b)(6) during the investigational treatment phase from vomiting and dehydration that caused renal impairment. Bedaquiline or the BR could be related to the vomiting that precipitated the patient's renal impairment.

- Patient 209-0025 died on D(b)(6) post-treatment with bedaquiline from congestive heart failure. At the time of diagnosis, while the QTcF was within normal limits (418 ms), the QTcB was slightly elevated at 450 to 480 ms. Bedaquiline could

have contributed to the persistent QT prolongation and the congestive heart failure.

One patient 208-3079, a 33 year old, HIV+ black female was treated for 56 days with bedaquiline and 169 days with a BR consisting of EMB, ETH, KAN, OFL, PZA. Her baseline ECG showed negative T waves. She had an unwitnessed sudden death on study day (b) (6) ((b) (6) days or ~4 months after her last dose of bedaquiline) two days after the last BR dose. Two days prior her death, laboratory parameters such as CK, CK-MB, and troponin were within normal limits. A postmortem examination showed complete luminal occlusion of the left anterior descending coronary artery with atherosclerotic plaques, with myocardial necrosis consistent with this vessel (L ventricle at the apex, anterior wall, and intraventricular septum.

Table 29. Summary of Deaths in the Phase 2 Trials

Treatment Group/ Trial/ Dose	Patient ID	Details	Timing of Death* (days of trial)	Phase of Trial	Tuberculosis Death/ SAE reported term	FDA Assessment Association w/ Therapy	Causality of Death	Conversion/Response
Trial C208 Stage 1 (8-week course) Bedaquiline Group	208-3079	33 yo, HIV (+) black F; treated for 87 days; baseline ECG negative T wave BR: EMB, ETH, KAN, OFL, PZA	D171 (b) d or ~4 mos post bedaquiline)	Post-treatment	Myocardial Infarction, complete occlusion of LAD	None	SAE	Conversion (Wk 14) Outcome: Non-responder (death)
Trial C208 Stage 2 (24-week course) Bedaquiline Group	208-4041	54 yo white M w/ $MDR_{H\&R}$-TB strain ; treated for 109d; BR: KAN, OFL, Prothionamide, PZA, TRD; 4 active drugs in BR	D(b) (d post-bedaquiline)	Immediate post-treatment phase	Alcohol Poisoning (Grade 4) high alcohol blood concentration(3 73%) unwitnessed death	None	SAE	Conversion (Wk 8) Outcome: Non-responder (discontinuation)
	208-5069	63 yo HIV (-) M w/ cavity due to an INH- and RMP-resistant (at least) strain BR: CS, ETH, KAN, OFL, PZA (susceptibility unavailable); received 168d of bedaquiline	D(b) (b) (6) d post-bedaquiline)	Post-treatment (Follow-up)	D228: Hepatitis (Grade 3) and Hepatic Cirrhosis (Grade 4); On D228, admitted for a alcoholic liver cirrhosis with ascites, volume depletion, malnutrition	Background regimen or bedaquiline could be contributory	SAE	Conversion (Wk 6) Outcome: non-responder (discontinuation)
	208-4153	33 yo F w/ $MDR_{H\&R}$-TB strain susceptible to all Rx in BR (5 active drugs in BR); BR: EMB, ETH, KAN, OFL, PZA; received 168d of bedaquiline, w/ interruption of the BR q other week	D(b) ((b) (6) d post-bedaquiline)	Post-treatment	Tuberculosis AE-Tuberculosis (Grade 3); readmitted to hospital 10 mos after bedaquiline for TB worsening and noncompliance w/ BR	None	SAE	Conversion (Wk 22) with recurrence (Wk 36) Outcome: Non-responder (relapse)
	208-4224	18 yo HIV (-) M w/ $MDR_{H\&R}$-TB strain susceptible to 2 Rx in BR (2 active drugs in BR); BR: CIP, CS, EMB, ETH, PZA; received 163d of bedaquiline; w/ significant interruption of BR; D252 Px relapsed	D(b) (b) d post-bedaquiline)	Post-treatment	Tuberculosis AE- Dyspnea (Grade 3),TB relapse (Grade 4); readmitted to the hospital 8 ½ months after last intake dose of bedaquiline and died 3 weeks later	None	SAE	Conversion (Wk 28) but with recurrence (Wk 60) Outcome: Non-responder (relapse)
Placebo Group	208-4120	24 yo HIV (-) F with bilateral cavities > 2 cm from a pre-XDR TB strain BR: EMB, ETH, KAN, OFL, PZA 2 active drugs in BR	D(b) ((b) d post-placebo)	Post-treatment	Tuberculosis AE-Hemoptysis (Grade 3)	None	SAE	No conversion Outcome: nonresponder
Late Follow-Up (reported between 10 June 2011 and 15 March 2012 bedaquiline Group	208-4399	53 yo HIV (-) M with unilateral cavities > 2 cm from a $MDR_{H\&R}$-TB strain; BR: EMB, ETH, KAN, OFL, PZA (susceptibility unavailable) Completed 168d of bedaquiline;	D (b) (6) (b) (6) d post-bedaquiline	Late Post-treatment	Cerebrovascular Accident (CVA) (Grade 4) probably from hypertension (Grade 3)	None	SAE	Conversion (Wk 28) Outcome: death but converted
	208-5067	43 yo Asian HIV (+) M (HIV serology neg) with unilateral cavities > 2 cm from a pre-XDR TB strain BR: AMK, CS, ETH, OFL, PZA with PAS-C addition ; received 170d of bedaquiline Patient also developed elevation of transaminases and bilirubin (levels fulfilling Hy's Law) (Grade 4) on Wk 24 and Wk 84 as discussed below	D(b) ((b) d post-bedaquiline)	Late Post-treatment	AE-Infectious Peritonitis; Septic Shock (Grade 4)	None	SAE	Conversion (Wk 14) Outcome: death but converted

Treatment Group/ Trial/ Dose	Patient ID	Details	Timing of Death* (days of trial)	Phase of Trial	Tuberculosis Death/ SAE reported term	FDA Assessment Association w/ Therapy	Causality of Death	Conversion/Response
UNCONTROLLED TRIALS								
Uncontrolled Trial (Trial C209) (bedaquiline-treated Group)	209-0024	52 yo HIV (-) F with unilateral cavities > 2 cm from XDR-TB strain BR: KAN, OFL, EMB, ETH, PZA Isolate susceptible to 1 drug in baseline BR; D55, TRD added to BR; discontinued bedaquiline on D62 because of SAE; D86 TB treatment DCed	D(((d post-bedaquiline)	Investigational Treatment Phase	Tuberculosis AE- Tuberculosis (Gr 4)	None	SAE	No conversion Outcome: Non-responder (failure to convert)
	209-0044	63 yo HIV (-) F with > 2 cm unilateral cavities from $MDR_{H\&R}$-TB strain BR: ETH, KAN, OFL, PZA, TRD, prior treatment with ETH, KAN, OFL, TRD Discontinued bedaquiline after D22 for AE	(	Investigational Treatment Phase	Vomiting (Gr 3), Dehydration, and Renal Impairment (Gr 4) D22: Vomiting , Bedaquiline DCed; D26: 4 days post D/C vomiting dehydration and renal impairment; D34: death	Possibly related Investigator: doubtfully related	SAE	No conversion Outcome: Non-responder (failure to convert)
	209-0001	59 yo HIV (-) male with < 2 cm cavities from XDR-TB strain BR: amox/clav, CAP, Prothionamide, TRD; Isolate susceptible to 1 drug in BR; Completed 44d of bedaquiline	((d post-bedaquiline)	Overall Treatment Phase; post-bedaquiline	Tuberculosis AE-Tuberculosis (Gr 4) Organic Hallucinations (Gr 3) likely due to combination of drugs;	None	SAE	No conversion Outcome: Non-responder (failure to convert)
	209-0327	31 yo HIV (-) M with > 2 cm unilateral cavities from pre-XDR TB BR: AMK, EMB, levofloxacin, prothionamide, PZA; Isolate susceptible to 2 drugs in B; completed 168d of bedaquiline; On D213, EMB, levo, PZA repolaced with clarithromycin and clofazimine; improved but on D228, readmission for lung infection	D(b) ((d post-bedaquiline)	Overall Treatment Phase;	Lung Infection (Gr 4) starting D201; patient converted	None	SAE	Conversion (Week 8) Outcome: Non-responder (death but converted)
	209-0025	57 yo HIV (-) F with > 2 cm unilateral cavities due to $MDR_{H\&R}$-TB strain; BR: KAN, OFL, EMB, ETH, PZA; Completed bedaquiline therapy (168d); prior treatment with ETH, KSN, OFL	D(b) (b) (6) post-bedaquiline)	Overall Treatment Phase;	D 420: Gr 3 right-sided congestive cardiac failure ECG: QTcB 450-480ms QTcF w/ normal (418 ms) Shortness of breath	Possibly related	SAE	Conversion (Wk 36) Outcome: Non-responder (discontinuation)
Phase IIa (7-day treatment) (Trial C202) Bedaquiline Group (400 mg once Daily)	202-0109	25 yo, HIV (+) black F; treated for 7d; BR: RMP, INH, PZA, and EMB	D((b d post-bedaquiline)	Post-treatment	Tuberculosis AE -Pulmonary TB Retroviral Infection (D41)	None	SAE	
	202-0036	41 yo M, treated for 3d; d/c'ed study bec of cannabinoids; BR: RMP, INH, PZA, and EMB	D(((d post-bedaquiline)	Post-treatment	Tuberculosis AE- Hemoptysis (Grade 3) (D13)	None	SAE	

Source: FDA Clinical Review of Safety

Hy's Law case (Death due to Infectious Peritonitis and Septic Shock)

Subject 208-5067 was a 43-year-old Asian man with HIV (but HIV serology from trial is negative) and cavitary pre-XDRTB co-infection. At screening, he had a mild productive cough and dyspnea. The patient was also reported to have heavy alcohol consumption. Baseline CD4 count was 844 x 10^6 cells/L. The subject did not receive ARV therapy during the trial. During the trial, the patient was reported to have alcoholic hepatitis as a concurent condition. Bedaquiline was started with a BR consisting of AMK sulfate, CS, ETH, OFL, and PZA. OFL and PZA were discontinued on Week 14 and were replaced with PAS-C on Week 16.

The subject completed the Investigational Treatment phase as planned without any clinically significant interruption; last intake of bedaquiline was on Week 24. AMK sulfate was discontinued on Week 28.

Table 30. Liver transaminase and bilirubin profile of patient fulfilling Hy's Law

Phase Analysis time point	ALT (U/L)	AST (U/L)	Total bilirubin (µmol/L)
Overall treatment			
Baseline	10	18	4
Week 2	9	26	4
Week 4	7	24	4
Week 6	8	24	7
Week 8	7	**43**	12
Week 10	11	**40**	5
Week 12	9	35	10
Week 14	11	30	6
Week 16	11	**40**	5
Week 18	35	**119**	9
Week 20	32	**134**	13
Week 22	21	**94**	11
Week 24	**118**	**501**	**52**
Week 28	35	**226**	14
Week 32	13	**78**	9
Week 48	8	**47**	18
Week 60	29	**122**	15
Week 72	14	**41**	8
Week 84	41	**148**	**129**

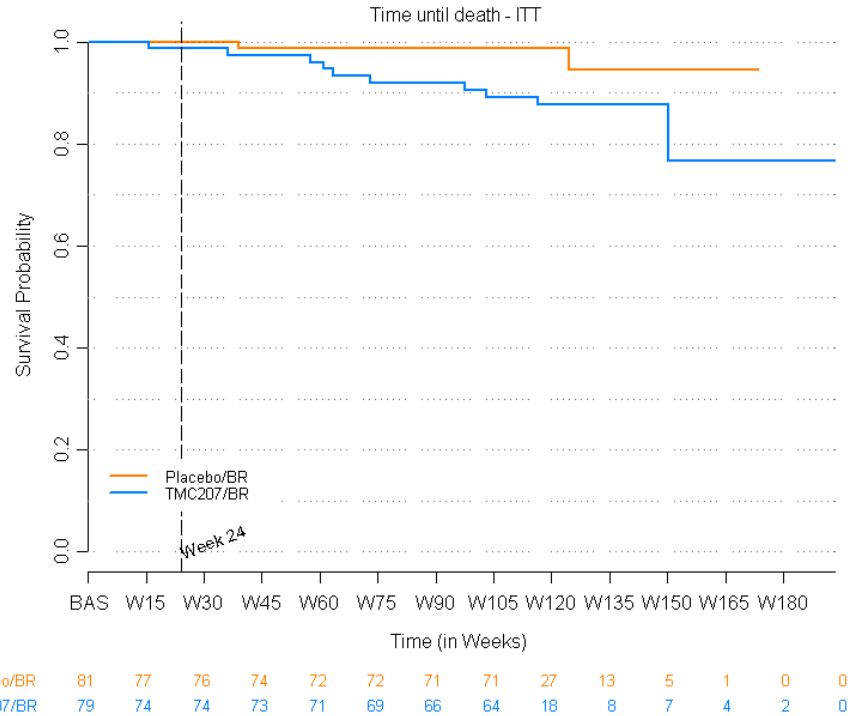
Source: Modified from NDA 204,384. Original Submission. Summary of Clinical Safety. p. 220.

At Week 24, laboratory criteria for Hy's Law (i.e., treatment-emergent ALT or AST levels of ≥ 3 x ULN with concurrent total bilirubin ≥ 2 x ULN) were met. The postdose bedaquiline plasma concentration was 2090 ng/mL, which is higher than the median concentration at the same time point in the overall population (i.e., 1245 ng/mL).

The patient completed the Investigational Treatment phase without further issues. However, on the 79th week, the subject was diagnosed with hepatitis, reported as a grade 3 AE unrelated to bedaquiline but probably related to the continuing BR (i.e., CS, ETH, and PAS-C) by the investigator. At follow-up at Week 84, the laboratory criteria for Hy's Law case were met. Three months later (Day (b) (6), 98th week), the subject died of peritonitis and septic shock. Peritonitis and septic shock were considered to be the cause of hospitalization and death by the investigator.

The Applicant submitted additional safety data (deaths, SAEs, AEs leading to treatment discontinuation, and pregnancies) on October 26, 2012 that is currently under review. Overall safety data from Trial C208 Stage II indicates that 10 bedaquiline-treated patients developed an SAE that led to death, compared to 2 placebo-treated patients. These include the fatalities reported in Table 29. The Kaplan-Meier survival curve below demonstrates the timing of the fatalities in both groups relative to the phase of the trial (i.e. investigational treatment phase vs. follow-up phase). Details of the additional cases of deaths are currently being reviewed.

Figure 7. Kaplan-Meier Survival Curve for Trial C208 Stage 2 ITT Population



Source: NDA 204,384. Overview of Deaths in the TMC207 Phase II Trials. p. 27. October 26, 2012

3.3.3 Nonfatal Serious Adverse Events

3.3.3.1 Trial C208 Stage 1

In the placebo group, the SAEs included one case each of Grade 3 drug intoxication to cycloserine, relapse of MDRTB, Grade 4 lobar pneumonia, symptomatic anemia, right leg deep vein thrombosis and Grade 4 pneumothorax. These events are anticipated in this patient population. In the bedaquiline group, SAEs included Grade 4 diabetic ketoacidosis on D42, and a traffic accident on D 293.

3.3.3.2 Trial C208 Stage II

During the investigational treatment phase (24 wk treatment with bedaquiline), six patients (7.6%) in the bedaquiline group and 1 (1.2%) in the placebo group developed one or more SAEs. One patient reported one SAE each in both groups. All SAEs, except for spontaneous abortion that was assessed as possibly related to the study drug, were assessed as not or doubtfully related to bedaquiline by the investigator. One SAE (alcohol poisoning) led to the death of a patient.

The SAE of spontaneous abortion was reported in a 24 year old Hispanic woman infected with an MDRTB strain randomized to placebo with a BR consisting of ciprofloxacin, EMB, ETH, KAN, and PZA. On D111, the patient had a positive serum pregnancy test, reported as a Grade 3 AE. On the same day, placebo was stopped and the BR was

temporarily stopped. On D (b) (6), the patient experienced uterine bleeding resulting in a spontaneous abortion, reported as Grade 4 SAE. The patient then had a uterine curettage. The AE was assessed to be possibly related to placebo.

During the overall treatment phase (investigational treatment phase and background treatment phase), 19 patients (24.1%) in the bedaquiline group and 15 patients (15.1%) in the placebo group developed one or more SAEs. Notably, most AEs were reported in the overall treatment phase.

Table 31. Overview of SAEs in Trial C208 Stage II Regardless of Severity and Causality

Body system or organ class Preferred Term n (%)	bedaquiline/BR			Placebo/BR		
	Investigational Treatment Phase N = 79	Overall Treatment Phase N = 79	Follow-up N = 30	Investigational Treatment Phase N = 81	Overall Treatment Phase N = 81	Follow-up N = 18
Any SAE	**6 (7.6)**	**19 (24.1)**	**2 (6.7)**	**1 (1.2)**	**15 (18.5)**	**1 (5.6)**
Blood and lymphatic system	**1 (1.3)**	**2 (2.5)**	**0**	**0**	**0**	**0**
Anemia	1 (1.3)	1 (1.3)	0	0	0	0
Lymphadenopathy mediastinal	0	1 (1.3)	0	0	0	0
Ear and labyrinth disorders	**1 (1 3)**	**1 (1.3)**	**0**	**0**	**0**	**0**
Conductive deafness	1 (1 3)	1 (1.3)	0	0	0	0
Gastrointestinal disorders	**0**	**2 (2.5)**	**0**	**0**	**0**	**0**
Abdominal pain	0	1 (1.3)	0	0	0	0
Pancreatitis acute	0	1 (1.3)	0	0	0	0
Hepatobiliary disorders	**0**	**0**	**1 (3.3)**	**0**	**0**	**0**
Hepatic cirrhosis	0	0	1 (3.3)	0	0	0
Hepatitis	0	0	1 (3.3)	0	0	0
Immune system disorders	**0**	**0**	**0**	**0**	**1 (1 2)**	**0**
Hypersensitivity	0	0	0	0	1 (1 2)	0
Infections and infestations	**1 (1 3)**	**6 (7.6)**	**0**	**0**	**4 (4.9)**	**0**
Bronchiectasis	1 (1.3)	1 (1.3)	0	0	0	0
Pneumonia	0	2 (2.5)	0	0	0	0
Pulmonary tuberculosis	0	2 (2.5)	0	0	1 (1.2)	0
Pyothorax	1 (1.3)	1 (1.3)	0	0	0	0
Tuberculosis	0	2 (2 5)	0	0	3 (3.7)	0
Injury, poisoning, procedure	**1 (1 3)**	**3 (3.8)**	**0**	**0**	**2 (2.5)**	**0**
Alcohol poisoninga	1 (1.3)	1 (1 3)	0	0	0	0
Drug toxicity	0	1 (1 3)	0	0	0	0
Humerus fracture	0	0	0	0	1 (1.2)	0
Pelvic fracture	0	0	0	0	1 (1.2)	0
Soft tissue injury	0	1 (1 3)	0	0	0	0
Nervous system disorders	**0**	**2 (2.5)**	**0**	**0**	**0**	**0**
Cerebrovascular accident	0	1 (1.3)	0	0	0	0
Hemiparesis	0	1 (1.3)	0	0	0	0
Pregnancy, puerperium ,	**0**	**0**	**1 (1.3)**	**1 (3.3)**	**0**	**1 (1.2)**
Abortion spontaneous	0	0	1 (1.3)	0	0	1 (1.2)
Intra-uterine death	0	0	0	1 (3.3)	0	0
Psychiatric disorders	**0**	**1 (1.3)**	**1 (1.3)**	**0**	**0**	**0**
Suicidal ideation	0	1 (1.3) b	1 (1.3) b	0	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**1 (1.3)**	**2 (2.5)**	**0**	**0**	**0**
Hemoptysisa	0	1 (1.3)	2 (2.5)	0	0	0
Pneumothorax	0	0	0	0	0	0
Pulmonary cavitation	0	0	0	0	0	0

Body system or organ class Preferred Term n (%)	bedaquiline/BR			Placebo/BR		
	Investigational Treatment Phase N = 79	Overall Treatment Phase N = 79	Follow-up N = 30	Investigational Treatment Phase N = 81	Overall Treatment Phase N = 81	Follow-up N = 18
Social circumstances Pregnancy of partner	**0** 0	**0** 0	**1 (1.3)** 1 (1.3)	**0** 0	**0** 0	**0** 0
Surgical and medical procedures	**0**	**0**	**0**	**0**	**0**	**0**
Surgery	0	0	0	0	0	0

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 113

From the table above, the most common SOC to which the most number of SAEs are categorized is Infections and Infestations, reflective of the potential exacerbation of the underlying condition. There is a slight imbalance in the development of SAEs, i.e. more in the bedaquiline group compared to the placebo. However, the frequencies of SAEs in each treatment group are low so that the two treatment groups appear to be comparable in terms of the development and/or reporting of SAEs.

3.3.3.3 Trial C209

A total of 14 patients (6.0%) reported SAEs during the investigational treatment phase. All, except one of the SAEs, as summarized in the following table, was assessed as unrelated or doubtfully related to bedaquiline. The only SAE deemed likely related to bedaquiline is a case of ECG QT prolongation.

Table 32. Summary of SAEs reported in Trial C209

Body System or Organ Class Preferred Term, n (%)	TMC207/BR	
	Investigational Treatment Phase N = 233	Overall Treatment Phase N = 233
Any SAE	***14 (6.0)***	***27 (11.6)***
Gastrointestinal Disorders Vomiting	**1 (0.4)** 1 (0.4)	**2 (0.9)** 1 (0.4)
Hepatobiliary Disorders Cholelithiasis	**1 (0.4)** 1 (0.4)	**2 (0.9)** 1 (0.4)
Infections and Infestations	**3 (1.3)**	**7 (3.0)**
Lung infection	1 (0.4)	2 (0.9)
Pneumonia	1 (0.4)	2 (0.9)
Tuberculosis	1 (0.4)	2 (0.9)
Investigations ECG QT prolonged	**1 (0.4)** 1 (0.4)	**2 (0.9)** 1 (0.4)
Metabolism and Nutrition Disorders	**3 (1.3)**	**3 (1.3)**
Decreased appetite	1 (0.4)	1 (0.4)
Dehydration	1 (0.4)	1 (0.4)
Diabetes mellitus inadequate control	1 (0.4)	1 (0.4)
Hyponatremia	1 (0.4)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders Pain in extremity	**1 (0.4)** 1 (0.4)	**1 (0.4)** 1 (0.4)
Psychiatric Disorders Hallucination	**1 (0.4)** 1 (0.4)	**2 (0.9)** 1 (0.4)
Renal and Urinary Disorders Renal impairment	**1 (0.4)** 1 (0.4)	**2 (0.9)** 1 (0.4)

The patient who developed prolonged QT interval was a 32 year old male with an MDRTB strain who received bedaquiline with a BR consisting of PAS-C, CAP, clofazimine, CS, prothionamide, OFL, EMB, PZA, and thiacetazone. An ECG taken on D6 showed sinus tachycardia with inferior and lateral lead changes possibly from ischemia. QTcB was 486 ms (baseline of 481) and QTcF was 438 ms (baseline of 450). Cardiac enzymes (CPK, CPK-MB, and troponin I) were normal. On D8, an ECG showed tachycardia and QT prolongation with QTcF of 461 ms and QTcB of 519 ms, with T-wave negativity appearing before QT prolongation. An assessment of myocardial ischemia was made, though troponin I was within normal range. No signs of acute pericarditis or myocarditis were noted, except for the fever. The investigator reported QT prolongation with Grade 3 severity and assessed the SAE as very likely related to bedaquiline and unrelated to drugs in the BR. Bedaquiline was permanently stopped on Day 8. This patient will also be reported in Section 3.3.6. Cardiovascular Safety.

A total of 27 (11.6%) patients developed one or more SAEs during the overall treatment phase. The most frequent SAEs reported were pneumothorax (3 patients), lung infection, pneumonia, tuberculosis, and dyspnea (2 patients each).

3.3.4 Common Adverse Events

3.3.4.1 Trial C208 Stage 1

During the 8 week Investigational Treatment Phase, 21 of 23 (91.3%) and 23 of 24 (95.8%) patients presented with an AE in the bedaquiline-treated group and the placebo group, respectively. AEs were most frequently classified under the SOC Gastrointestinal Disorders (9/23 [39.3%] for the bedaquiline group and 9/24 [37.5%] for the placebo group). The most frequent AEs (rate > 10% of patients in the treatment groups) were nausea, arthralgia, hyperuricemia, unilateral deafness, hemoptysis, bilateral deafness, dizziness, and diarrhea. In particular, nausea was experienced more often in the bedaquiline group (6/23 [26.1%]) compared to the placebo group (1/24 [4/2%]). The table below summarizes the AE frequencies.

Table 33. Summary of AE Terms and SOCs reported in > 1 Patient in Trial C208 Stage 1 during the 8 week Investigational Treatment Phase

SOC Preferred Term, n (%)	**bedaquiline/BR N = 23**	**Placebo/BR N = 24**
Any AE During Investigational Treatment Phasea	***21 (91.3)***	***23 (95.8)***
Gastrointestinal Disorders	**9 (39.1)**	**9 (37.5)**
Nausea	6 (26.1)	1 (4.2)
Diarrhea	3 (13.0)	1 (4.2)
Vomiting	1 (4.3)	3 (12.5)
Abdominal pain	0	2 (8.3)
Ear and Labyrinth Disorders	**8 (34.8)**	**9 (37.5)**
Deafness unilateral	3 (13.0)	5 (20.8)
Deafness bilateral	3 (13.0)	3 (12.5)
Musculoskeletal and Connective	**6 (26.1)**	**7 (29.2)**

Tissue Disorders		
Arthralgia	4 (17.4)	3 (12.5)
Pain in extremity	2 (8.7)	4 (16.7)
Back pain	0	3 (12.5)
Respiratory, Thoracic, and Mediastinal Disorders	**6 (26.1)**	**7 (29.2)**
Hemoptysis	3 (13.0)	4 (16.7)
Pleuritic pain	2 (8.7)	0
Pharyngolaryngeal pain	1 (4.3)	2 (8.3)
Skin and Subcutaneous Tissue Disorders	**6 (26.1)**	**7 (29.2)**
Rash	2 (8.7)	4 (16.7)
Pruritus	2 (8.7)	2 (8.3)
Acne	1 (4.3)	2 (8.3)
Metabolism and Nutrition Disorders Hyperuricemia	**5 (21.7)** 4 (17.4)	**3 (12.5)** 3 (12.5)
Nervous System Disorders	**5 (21.7)**	**3 (12.5)**
Dizziness	3 (13.0)	2 (8.3)
Headache	2 (8.7)	2 (8.3)
Infections and Infestations	**3 (13.0)**	**4 (16.7)**
Eye Disorders	**3 (13.0)**	**1 (4.2)**
General Disorders and Administration Site Conditions	**2 (8.7)**	**5 (20.8)**
Chest pain	0	2 (8.3)
Non-cardiac chest pain	2 (8.7)	2 (8.3)
Investigations Blood uric acid increased	**2 (8.7)** 1 (4.3)	**4 (16.7)** 2 (8.3)
Reproductive System and Breast Disorders	**1 (4.3)**	**3 (12.5)**
Psychiatric Disorders	**1 (4.3)**	**2 (8.3)**

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 81. Module 5.3.5.1/bedaquiline-C208-Stage 1-Anal-SAF-AE/Display SAF.3

Except for the imbalance in the development of nausea in the bedaquiline group, the two treatment groups appear to be comparable in terms of the incidences of common AEs developing in > 1 patient during the investigational treatment phase (8 weeks). For the AE of nausea, the median onset of nausea from the initiation of treatment was 6.5 days (2-30 days for the six patients in the bedaquiline group. For the AE of hyperuricemia, the median onset of hyperuricemia from the start of treatment was 14.0 days (14-28 days) for the 4 patients in the bedaquiline group and 3 patients in the placebo group.

In terms of severity, the majority of AEs reported to start during the investigational and background treatment period was classified as Grade 1 or 2 in severity. The applicant summarized the incidence of AE preferred terms (PTs) occurring in both treatment phases (Investigational and Background Treatment Phases) stratified according to severity in the following table:

Table 34. Summary of AEs and SOCs of Grade 3 or 4 Severity during the Investigational and Background Treatment Phase for Trial C208 Stage 1

System Organ Class Preferred Term, n (%)	**Placebo N = 24**	**bedaquiline N = 23**
8-Week Investigational Treatment Period		

System Organ Class Preferred Term, n (%)	**Placebo N = 24**	**bedaquiline N = 23**
Any Grade 3 or 4 AE	***5 (20.8)***	***6 (26.1)***
Metabolism and Nutrition Disorders	**2 (8.3)**	**3 (13.0)**
Hyperuricemia	2 (8.3)	2 (8.7)
Diabetic ketoacidosis	0	1 (4.3)
Ear and Labyrinth Disorders	**1 (4.2)**	**3 (13.0)**
Deafness	1 (4.2)	1 (4.3)
Deafness bilateral	0	1 (4.3)
Deafness unilateral	0	1 (4.3)
Investigations	**1 (4.2)**	**1 (4.3)**
Blood uric acid increased	1 (4.2)	1 (4.3)
Prothrombin time prolonged	0	1 (4.3)
Gastrointestinal Disorders	**1 (4.2)**	**0**
Abdominal tenderness	1 (4.2)	0
Respiratory, Thoracic, and Mediastinal Disorders	**1 (4.2)**	**0**
Dyspnea	1 (4.2)	0
Pneumothorax	1 (4.2)	0
96-Week Background Treatment Period		
Any Grade 3 or 4 AE	***5 (20.8)***	***4 (17.4)***
Investigations	**4 (16.7)**	**1 (4.3)**
PT prolonged	0	1 (4.3)
ALT increased	1 (4.2)	0
Blood uric acid increased	1 (4.2)	0
Pancreatic enzymes increased	1 (4.2)	0
Transaminases increased	1 (4.2)	0
Metabolism and Nutrition Disorders	**1 (4.2)**	**1 (4.3)**
Hyperuricemia	1 (4.2)	0
Diabetic ketoacidosis	0	1 (4.3)
Injury, Poisoning, and Procedural Complications	**1 (4.2)**	**1 (4.3)**
Road traffic accident	0	1 (4.3)
Drug toxicity	1 (4.2)	0
Cardiac Disorders	**0**	**1 (4.3)**
Myocardial infarction	0	1 (4.3)
Infections and Infestations	**2 (8.3)**	**0**
Lobar pneumonia	1 (4.2)	0
Respiratory tract infection	1 (4.2)	0
Tuberculosis	1 (4.2)	0
Blood and Lymphatic System Disorders	**1 (4.2)**	**0**
Anemia	1 (4.2)	0
Vascular Disorders	**1 (4.2)**	**0**
Deep vein thrombosis	1 (4.2)	0

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 81. Display SAF.1, Display SAF.5, Listing SAF.4

3.3.4.2 Trial C208 Stage II

All AEs reported in > 5.0% of patients during the Overall Treatment phase are summarized in the Table 38 below.

During the 24 week investigational treatment phase, the most frequently coded AEs belong to the SOC gastrointestinal disorders that occurred in 63.3% of patients in the bedaquiline group and 61.7% of patients in the placebo group. The incidence of AEs classified within SOCs appears to be comparable between the two treatment groups, except for nervous system disorders (40.5% vs 25.9% of patients in the bedaquiline vs the placebo groups, respectively). This difference was impacted by the higher incidence of headache in the bedaquiline group.

During the overall treatment phase, AEs were most frequently coded to the SOC gastrointestinal disorders, reported in 67.1% of patients in the bedaquiline group and

65.4% of patients in the placebo group. Except for the SOC nervous system disorders (49.4% vs 39.5% of patients in the bedaquiline and placebo groups, respectively), the incidence of AEs classified under the remaining SOCs were comparable between the treatment groups.

Table 35. Incidence of AEs Reported in >5% of Patients in trial C208 Stage II

	TMC207/BR		Placebo/BR	
Body system or organ class Preferred Term n (%)	**Investigational Treatment Phase N = 79**	**Overall Treatment Phase N = 79**	**Investigational Treatment Phase N = 81**	**Overall Treatment Phase N = 81**
Any AE	**77 (97.5)**	**78 (98.7)**	**77 (95.1)**	**79 (97.5)**
Gastrointestinal disorders	**50 (63.3)**	**53 (67.1)**	**50 (61.7)**	**53 (65.4)**
Nausea	30 (38.0)	32 (40.5)	26 (32.1)	30 (37.0)
Vomiting	20 (25.3)	23 (29.1)	21 (25.9)	22 (27.2)
Abdominal pain upper	9 (11.4)	10 (12.7)	7 (8.6)	7 (8.6)
Gastritis	6 (7.6)	7 (8.9)	13 (16.0)	16 (19.8)
Constipation	3 (3.8)	4 (5.1)	0	0
Diarrhea	3 (3.8)	5 (6.3)	11 (13.6)	15 (18.5)
Abdominal pain	2 (2.5)	6 (7.6)	5 (6.2)	6 (7.4)
Dyspepsia	2 (2.5)	4 (5.1)	8 (9.9)	12 (14.8)
Musculoskeletal and connective tissue disorders	**35 (44.3)**	**39 (49.4)**	**32 (39.5)**	**40 (49.4)**
Arthralgia	26 (32.9)	29 (36.7)	18 (22.2)	22 (27.2)
Back pain	6 (7.6)	9 (11.4)	5 (6.2)	8 (9.9)
Myalgia	6 (7.6)	6 (7.6)	6 (7.4)	7 (8.6)
Musculoskeletal pain	4 (5.1)	4 (5.1)	1 (1.2)	4 (4.9)
Nervous system disorders	**32 (40.5)**	**39 (49.4)**	**21 (25.9)**	**32 (39.5)**
Headache	22 (27.8)	23 (29.1)	10 (12.3)	17 (21.0)
Dizziness	10 (12.7)	11 (13.9)	10 (12.3)	10 (12.3)
Paresthesia	3 (3.8)	4 (5.1)	3 (3.7)	4 (4.9)
Neuropathy peripheral	2 (2.5)	4 (5.1)	0	2 (2.5)
Metabolism and nutrition disorders	**30 (38.0)**	**33 (41.8)**	**31 (38.3)**	**35 (43.2)**
Hyperuricemia	19 (24.1)	20 (25.3)	26 (32.1)	27 (33.3)
Anorexia	7 (8.9)	8 (10.1)	3 (3.7)	6 (7.4)
Hypokalemia	3 (3.8)	4 (5.1)	3 (3.7)	3 (3.7)
Infections and infestations	**25 (31.6)**	**44 (55.7)**	**28 (34.6)**	**43 (53.1)**
Nasopharyngitis	4 (5.1)	12 (15.2)	1 (1.2)	4 (4.9)
Oral candidiasis	3 (3.8)	4 (5.1)	2 (2.5)	2 (2.5)
Urinary tract infection	3 (3.8)	5 (6.3)	2 (2.5)	2 (2.5)
Influenza	2 (2.5)	7 (8.9)	1 (1.2)	8 (9.9)
Pharyngitis	1 (1.3)	6 (7.6)	2 (2.5)	5 (6.2)
Upper respiratory tract infection	1 (1.3)	4 (5.1)	2 (2.5)	4 (4.9)
Tuberculosis	0	2 (2.5)	0	5 (6.2)
Respiratory, thoracic and mediastinal disorders	**25 (31.6)**	**29 (36.7)**	**23 (28.4)**	**35 (43.2)**
Hemoptysis	14 (17.7)	16 (20.3)	9 (11.1)	14 (17.3)
Cough	4 (5.1)	8 (10.1)	2 (2.5)	8 (9.9)
Rhinorrhea	4 (5.1)	4 (5.1)	0	0
Pleuritic pain	2 (2.5)	2 (2.5)	3 (3.7)	5 (6.2)
Dyspnea	1 (1.3)	3 (3.8)	5 (6.2)	6 (7.4)
Ear and labyrinth disorders	**24 (30.4)**	**26 (32.9)**	**26 (32.1)**	**29 (35.8)**
Deafness unilateral	9 (11.4)	9 (11.4)	6 (7.4)	7 (8.6)
Deafness	5 (6.3)	6 (7.6)	4 (4.9)	4 (4.9)
Deafness bilateral	4 (5.1)	5 (6.3)	6 (7.4)	7 (8.6)
Ear pain	2 (2.5)	4 (5.1)	2 (2.5)	3 (3.7)
Tinnitus	2 (2.5)	3 (3.8)	10 (12.3)	11 (13.6)

Body system or organ class Preferred Term n (%)	TMC207/BR		Placebo/BR	
	Investigational Treatment Phase N = 79	Overall Treatment Phase N = 79	Investigational Treatment Phase N = 81	Overall Treatment Phase N = 81
General disorders and administration site conditions	**23 (29.1)**	**31 (39.2)**	**23 (28.4)**	**27 (33.3)**
Chest pain	9 (11.4)	11 (13.9)	6 (7.4)	8 (9.9)
Pyrexia	6 (7.6)	8 (10.1)	5 (6.2)	7 (8.6)
Fatigue	4 (5.1)	6 (7.6)	1 (1.2)	1 (1.2)
Injection site pain	4 (5.1)	7 (8.9)	10 (12.3)	10 (12.3)
Pain	2 (2.5)	2 (2.5)	2 (2.5)	6 (7.4)
Skin and subcutaneous tissue disorders	**19 (24.1)**	**25 (31.6)**	**21 (25.9)**	**28 (34.6)**
Pruritus	10 (12.7)	11 (13.9)	11 (13.6)	15 (18.5)
Rash	6 (7.6)	6 (7.6)	3 (3.7)	4 (4.9)
Investigations	**17 (21.5)**	**21 (26.6)**	**17 (21.0)**	**24 (29.6)**
Blood uric acid increased	5 (6.3)	5 (6.3)	3 (3.7)	3 (3.7)
Transaminases increased	4 (5.1)	5 (6.3)	0	0
AST increased	3 (3.8)	4 (5.1)	0	1 (1.2)
ECG QT corrected interval prolonged	3 (3.8)	3 (3.8)	4 (4.9)	5 (6.2)
ALT increased	2 (2.5)	4 (5.1)	1 (1.2)	1 (1.2)
Weight decreased	1 (1.3)	3 (3.8)	2 (2.5)	5 (6.2)
Psychiatric disorders	**15 (19.0)**	**17 (21.5)**	**11 (13.6)**	**17 (21.0)**
Insomnia	11 (13.9)	12 (15.2)	9 (11.1)	10 (12.3)
Depression	1 (1.3)	2 (2.5)	2 (2.5)	7 (8.6)
Eye disorders	**10 (12.7)**	**18 (22.8)**	**14 (17.3)**	**20 (24.7)**
Visual acuity reduced	1 (1.3)	5 (6.3)	2 (2.5)	2 (2.5)
Blood and lymphatic system disorders	**8 (10.1)**	**11 (13.9)**	**4 (4.9)**	**6 (7.4)**
Anemia	5 (6.3)	8 (10.1)	2 (2.5)	2 (2.5)
Reproductive system and breast disorders	**7 (8.9)**	**11 (13.9)**	**10 (12.3)**	**15 (18.5)**
Cardiac disorders	**5 (6.3)**	**6 (7.6)**	**8 (9.9)**	**13 (16.0)**
Injury, poisoning and procedural complications	**5 (6.3)**	**11 (13.9)**	**8 (9.9)**	**15 (18.5)**
Renal and urinary disorders	**2 (2.5)**	**5 (6.3)**	**2 (2.5)**	**3 (3.7)**
Vascular disorders	**2 (2.5)**	**5 (6.3)**	**3 (3.7)**	**6 (7.4)**
Immune system disorders	**1 (1.3)**	**1 (1.3)**	**3 (3.7)**	**5 (6.2)**

N = number of subjects; n = number of subjects with observation
Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 206-207

AEs considered related to TB were reported in 45.6% of patients in the bedaquiline group compared to 56.8 % of patients in the placebo group during the overall treatment phase.

AEs classified as Grade 3 or 4 are summarized in the table below. During the investigational treatment phase, Grade 3 or 4 AEs were reported in 27.8% of patients in the bedaquiline group and 23.5% in the placebo group. The most frequent AE reported was hyperuricemia (11.4% in the bedaquiline group and 14.8% in the placebo group). Grade 4 AEs developed in 6.3% of patients in the bedaquiline group and in 3.7% of patients in the placebo group. In the overall treatment phase, Grade 3 or 4 AEs were reported in 43% of patients in the bedaquiline group and in 35.8% in the placebo group, with the most frequently reported Grade 3 or 4 AE being hyperuricemia (12.7% and 16% in the bedaquiline group and placebo group, respectively).

Table 36. Incidence of Grade 3 or 4 AEs Reported in Trial C208 Stage II

Body system or organ class Preferred Term n (%)	TMC207/BR Investigational Treatment Phase N = 79	TMC207/BR Overall Treatment Phase N = 79	Placebo/BR Investigational Treatment Phase N = 81	Placebo/BR Overall Treatment Phase N = 81
Any AE of at least grade 3	**22 (27.8)**	**34 (43.0)**	**19 (23.5)**	**29 (35.8)**
Blood and lymphatic system disorders	**1 (1.3)**	**2 (2.5)**	**0**	**0**
Anemia	1 (1.3)	1 (1.3)	0	0
Leukocytosis	0	1 (1.3)	0	0
Ear and labyrinth disorders	**4 (5.1)**	**4 (5.1)**	**1 (1.2)**	**1 (1.2)**
Conductive deafness	1 (1.3)	1 (1.3)	0	0
Deafness	0	1 (1.3)	0	0
Deafness bilateral	2 (2.5)	2 (2.5)	0	0
Deafness unilateral	1 (1.3)	1 (1.3)	1 (1.2)	1 (1.2)
Endocrine disorders	**0**	**1 (1.3)**	**0**	**0**
Hyperthyroidism	0	1 (1.3)	0	0
Eye disorders	**0**	**1 (1.3)**	**0**	**0**
Ocular icterus	0	1 (1.3)	0	0
Gastrointestinal disorders	**0**	**3 (3.8)**	**0**	**0**
Abdominal pain	0	1 (1.3)	0	0
Gastritis	0	1 (1.3)	0	0
Pancreatitis acute	0	1 (1.3)	0	0
Hepatobiliary disorders	**0**	**1 (1.3)**	**0**	**0**
Hepatitis	0	1 (1.3)	0	0
Infections and infestations	**3 (3.8)**	**8 (10.1)**	**1 (1.2)**	**4 (4.9)**
Bronchiectasis	1 (1.3)	1 (1.3)	0	0
Hepatitis B	1 (1.3)	1 (1.3)	0	0
Lower respiratory tract infection	1 (1.3)	1 (1.3)	0	0
Pneumonia	0	1 (1.3)	1 (1.2)	1 (1.2)
Pulmonary tuberculosis	0	2 (2.5)	0	0
Pyothorax	1 (1.3)	1 (1.3)	0	0
Tuberculosis	0	2 (2.5)	0	3 (3.7)
Injury, poisoning and procedural complications	**1 (1.3)**	**3 (3.8)**	**1 (1.2)**	**3 (3.7)**
Alcohol poisoning	1 (1.3)	1 (1.3)	0	0
Drug exposure during pregnancy	0	0	1 (1.2)	1 (1.2)
Drug toxicity	0	1 (1.3)	0	0
Humerus fracture	0	0	0	1 (1.2)
Pelvic fracture	0	0	0	1 (1.2)
Soft tissue injury	0	1 (1.3)	0	0
Investigations	**5 (6.3)**	**7 (8.9)**	**3 (3.7)**	**3 (3.7)**
AST increased	0	1 (1.3)	0	0
Blood amylase increased	1 (1.3)	1 (1.3)	1 (1.2)	1 (1.2)
Blood creatine phosphokinase increased	0	0	1 (1.2)	1 (1.2)
Blood creatinine increased	1 (1.3)	1 (1.3)	0	0
Blood uric acid increased	1 (1.3)	1 (1.3)	1 (1.2)	1 (1.2)
GGT abnormal	1 (1.3)	1 (1.3)	0	0
GGT increased	0	1 (1.3)	0	0
Lipase increased	0	0	1 (1.2)	1 (1.2)
Transaminases increased	2 (2.5)	2 (2.5)	0	0

Body system or organ class Preferred Term n (%)	TMC207/BR		Placebo/BR	
	Investigational Treatment Phase N = 79	Overall Treatment Phase N = 79	Investigational Treatment Phase N = 81	Overall Treatment Phase N = 81
Metabolism and nutrition disorders	**10 (12.7)**	**11 (13.9)**	**12 (14.8)**	**13 (16.0)**
Gout	0	0	1 (1.2)	1 (1.2)
Hyperglycemia	1 (1.3)	1 (1.3)	0	0
Hyperuricemia	9 (11.4)	10 (12.7)	12 (14.8)	13 (16.0)
Musculoskeletal and connective tissue disorders	**2 (2.5)**	**2 (2.5)**	**0**	**0**
Arthralgia	2 (2.5)	2 (2.5)	0	0
Pain in extremity	1 (1.3)	1 (1.3)	0	0
Nervous system disorders	**1 (1.3)**	**3 (3.8)**	**0**	**1 (1.2)**
Cerebrovascular accident	0	1 (1.3)	0	0
Facial palsy	0	0	0	1 (1.2)
Headache	1 (1.3)	1 (1.3)	0	0
Hemiparesis	0	1 (1.3)	0	0
Pregnancy, puerperium and perinatal conditions	**0**	**1 (1.3)**	**2 (2.5)**	**2 (2.5)**
Abortion spontaneous	0	1 (1.3)	1 (1.2)	1 (1.2)
Pregnancy	0	0	2 (2.5)	2 (2.5)
Psychiatric disorders	**1 (1.3)**	**1 (1.3)**	**0**	**1 (1.2)**
Depression	0	0	0	1 (1.2)
Suicidal ideation	1 (1.3)	1 (1.3)	0	0
Respiratory, thoracic and mediastinal disorders	**1 (1.3)**	**3 (3.8)**	**1 (1.2)**	**4 (4.9)**
Dyspnea	0	1 (1.3)	1 (1.2)	1 (1.2)
Hemoptysis	1 (1.3)	2 (2.5)	0	1 (1.2)
Pneumothorax	0	0	0	1 (1.2)
Pulmonary cavitation	0	0	0	1 (1.2)
Surgical and medical procedures	**0**	**0**	**0**	**4 (4.9)**
Surgery	0	0	0	4 (4.9)
Vascular disorders	**0**	**1 (1.3)**	**0**	**0**
Hypertension	0	1 (1.3)	0	0

N = number of subjects; n = number of subjects with observation
Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 211

3.3.4.3 Trial C209

Summarized below are the most frequent AEs reported in > 5% of patients during the investigational treatment phase.

Table 37. Overall Summary of AEs

Safety (ITT population)	Investigational Treatment Phase	Overall Treatment Phase
Adverse Events	N = 233	N = 233
Most frequent AEs (reported in > 5% of subjects		
during Investigational Treatment phase), n (%)		
Hyperuricemia	32 (13.7)	32 (13.7)
Arthralgia	27 (11.6)	29 (12.4)
Nausea	25 (10.7)	26 (11.2)
Vomiting	20 (8.6)	21 (9.0)
Headache	20 (8.6)	22 (9.4)
Diarrhea	18 (7.7)	21 (9.0)
Blood uric acid increased	16 (6.9)	16 (6.9)
Hypokalemia	14 (6.0)	15 (6.4)
Pruritus	14 (6.0)	14 (6.0)
Injection site pain	13 (5.6)	15 (6.4)
Insomnia	13 (5.6)	13 (5.6)
Tinnitus	13 (5.6)	16 (6.9)
n (%) with at least 1 AE	207 (88.8)	211 (90.6)

Safety (ITT population)	Investigational Treatment Phase	Overall Treatment Phase
n (%) with at least 1 TB-related AE	43 (18.5)	51 (21.9)
n (%) with at least 1 grade 3-4 AE	44 (18.9)	62 (26.6)
n (%) with at least 1 serious AE (SAE)	14 (6.0)	27 (11.6)
n (%) with at least 1 AE leading to permanent discontinuation of TMC207	6 (2.6)	6 (2.6)

Source: Modified from NDA 204,384. Original Submission. Clinical Study Report – Study C209 Interim Analysis. Table 53, p. 166 and Table 54, p. 167.

3.3.5 Standardized MedDRA Query (SMQ) Events (except Torsade de Pointes/QT Prolongation SMQ) for Specific Safety Concerns

The safety database was queried for specific terminology representing co-occurring events (SMQ) that represent safety concerns associated with bedaquiline use.

3.3.5.1 Trial CT08

Acute Pancreatitis SMQ

During the investigational treatment phase, two patients in the bedaquiline group developed an acute pancreatitis SMQ event assessed as possibly related to bedaquiline, compared to 1 patient in the placebo group, assessed as probably related to placebo. Both patients in the bedaquiline group experienced increased blood amylase levels. None were reported as SAEs.

One additional patient experienced acute pancreatitis SMQ events in the bedaquiline group during the overall treatment phase. These events were assessed as possibly related to bedaquiline.

Rhabdomyolysis/Myopathy SMQ

No patient experienced this SMQ event during the trial.

Hepatic Disorders Sub-SMQs

During the investigational treatment phase, eight patients (10.1%) in the bedaquiline group and 2 patients (2.5%) in the placebo group experienced a hepatic disorder sub-SMQ event, the most frequently reported of which were transaminase increased (4 in the bedaquiline group), AST increased (3 in the bedaquiline group), and ALT increased (2 and 1 patient, respectively). None of these events were reported as SAEs. During the overall treatment phase, 3 additional patients in the bedaquiline group and 2 additional patients in the placebo group developed hepatic disorders. Of note, one patient who received bedaquiline died from an event considered Grade 4.

3.3.5.2 Trial CT09

Acute Pancreatitis

Three patients developed acute pancreatitis manifested by increased amylase in 2 patients and elevated bilirubin in one patient during the investigational treatment phase. All events were of Grade 2 severity and one was assessed as possibly related to bedaquiline. One patient developed hyperbilirubinemia during the overall treatment phase, classified as Grade 4 in severity and assessed as unrelated to bedaquiline.

Rhabdomyolysis/Myopathy
No patient developed this event during Trial C209.

Hepatic Disorders Sub-SMQ Events
Twenty-eight (12.0%) patients experienced a hepatic disorder event during the investigational treatment phase. The most common reported AEs were AST increased, heptic enzyme increased, ALT increased, transaminases increased, GGT increase, and hepatitis. None of these hepatic events were reported as SAEs during this phase. Two additional patients experienced hepatic disorder AEs during the overall treatment phase.

Table 38. Hepatic-Related Disorders SMQ Events.

Class of Event of Interest Preferred Term (event of interest), n (%)	TMC207/BR	
	Investigational Treatment Phase N = 233	Overall Treatment Phase N = 233
Hepatic Disorders (Selected sub-SMQs)	**28 (12.0)**	**30 (12.9)**
ALT increased	5 (2.1)	6 (2.6)
AST increased	9 (3.9)	10 (4.3)
Blood bilirubin increased	1 (0.4)	1 (0.4)
GGT increased	4 (1.7)	4 (1.7)
Hepatic enzyme increased	8 (3.4)	8 (3.4)
Hepatic function abnormal	1 (0.4)	2 (0.9)
Hepatitis	2 (0.9)	3 (1.3)
Hepatotoxicity	1 (0.4)	1 (0.4)
Hyperbilirubinemia	0	1 (0.4)
Liver disorder	0	1 (0.4)
Liver injury	1 (0.4)	1 (0.4)
PT prolonged	1 (0.4)	1 (0.4)
Transaminases increased	4 (1.7)	4 (1.7)

Source: Modified from NDA 204,384. Original Submission. Clinical Study Report – Study C209 Interim Analysis. p. 180.

3.3.6 Phase 2 Cardiovascular Safety Evaluation/Electrocardiograms (ECGs)

The cardiovascular safety of bedaquiline in the phase 2b program provides insight into the anticipated safety of the product when marketed. In each of these studies, cardiovascular safety assessment included vital sign and intensive ECG monitoring, during the interventional treatment phase, adverse event reporting and standard MedDRA queries. To evaluate the effect of bedaquiline on the changes from reference in QTcF in the controlled and uncontrolled trials during the Overall Treatment phase, triplicate ECGs were obtained at predose and 5h postdose.

Study C208 Stage 1 replicates the use of bedaquiline when used as part of an intensive induction phase with a standard background regimen, as exposure was limited to 8 weeks

and the concurrent use of interacting QT prolonging drugs were excluded. Note however that in both stage 1 and stage of C208, some patients in the placebo control group, but not the bedaquiline group were allowed use of moxifloxacin and clarithromycin.

Study C208 Stage 2 represents experience when bedaquiline is used with a standard background regimen for a full 24 weeks whereas Study C209 reflects a similar duration of exposure, but with individualized background regimen that may include drugs with individual QT prolonging potential.

3.3.6.1 Trial CT08 Stage 1

Vital signs: The mean heart rate was 81.9 bpm in the bedaquiline group and 86.7 bpm in the placebo group at baseline (D -1). Mean values decreased over time in both treatment groups with a slightly larger decrease in the placebo group (largest mean change was -19.8 ms at Week 60) compared to the bedaquiline group (largest mean change was -13.8 ms).

ECG monitoring: During the 8-week investigational treatment period, QTcB and QTcF intervals increased in duration in the bedaquiline group from Week 2 onwards, with mean increases of > 10 ms observed from Week 6 onwards (largest mean changes of 16.8 ms for QTcB and 17.6 ms for QTcF). In the placebo group, less pronounced mean QTcB and QTcF increases were also observed from Week 6 onwards (largest mean change were 5.9 ms for QTcB and 8.6 ms for QTcF) compared to the bedaquiline group. (Figure 8)

This increase in the bedaquiline treated arm persisted beyond the 8 week investigational treatment period. During the 96-week background treatment period, mean QTcB and QTcF absolute values were higher in the bedaquiline group compared to the placebo group. Maximum difference between the two treatment groups were at Week 60 (difference of the means: 18.8 ms for QTcB and 22.5 ms for QTcF). (Figure 8).

No consistent or relevant changes for QRS segment or PR interval were observed.

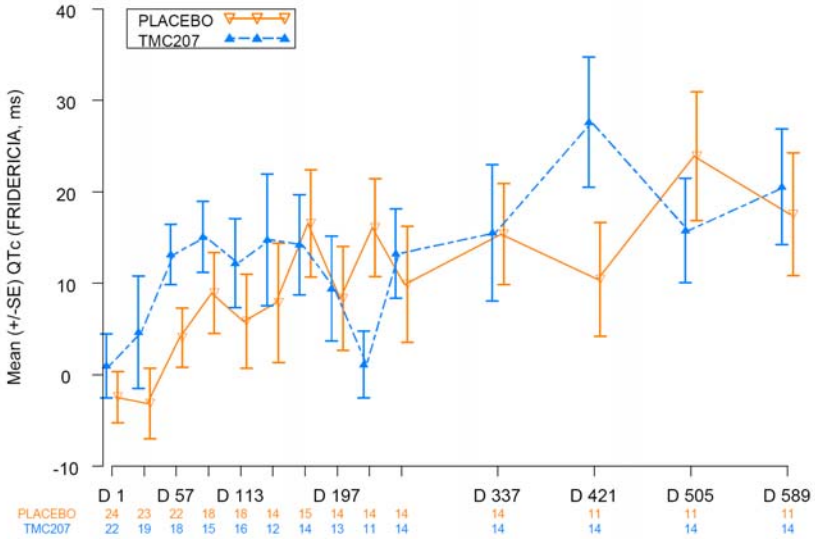
Similar proportions of patients developed postbaseline changes in their EKGs in the investigational and background treatment period [20 (87%) and 17 (70.8%) in the bedaquiline and placebo group, respectively, when any individual ECG abnormalities are considered.

No absolute values of > 500 ms in QTcF were observed. A postbaseline increase of > 60 ms (91 and 123 ms) from reference developed in two patients in the bedaquiline group: patient 208-3092 (91 ms at Wk 5 predose, with a QTcF of 485 ms), and Patient 208-3137 (123 ms increase at Wk 7 predose with a QTcF of 500ms).
More modest QTc interval increases of 30 to 60 ms in QTcF and QTcB were more frequent in the bedaquiline group compared to placebo during the investigational treatment period. No consistent differences between the treatment groups were observed in terms of 30-60 ms increases in QTcF during the background treatment period.

AEs related to ECG parameters were not reported in any patient during the investigational treatment group. However, 4 patients (2 in each treatment group) developed AEs related to ECG parameters during the background treatment period.

- Bedaquiline group:
  - One patient developed Grade 4 myocardial infarction 16 weeks after the last dose of bedaquiline.
  - One patient was reported as "ECG QT interval prolonged" 52 wks after last intake of bedaquiline. Increases from reference QTcB and QTcF (52 and 26 ms, respectively) corresponded to values between 450 and 480 ms. The patient recovered at Wk 96.
- Placebo Group
  - One patient reported Grade 1 "ECG signs of ventricular hypertrophy" but ECG interpretation was P terminally negative in V1 left atrial abnormality.
  - One patient developed Grade 2 sinus tachycardia at Wk 84, with ECG findings of minor ST depression, nonspecific ST abnormality, depressed ST, sinus tachycardia, and slightly negative T waves. QTcB increase was between 30 to 60 ms.

Figure 8. Mean Changes from Reference for QTcF



Source: Display SAF.22

Source: NDA 204,384. Original Submission. Updated Clinical Research Report – Trial C208 Stage 1. p. 181.

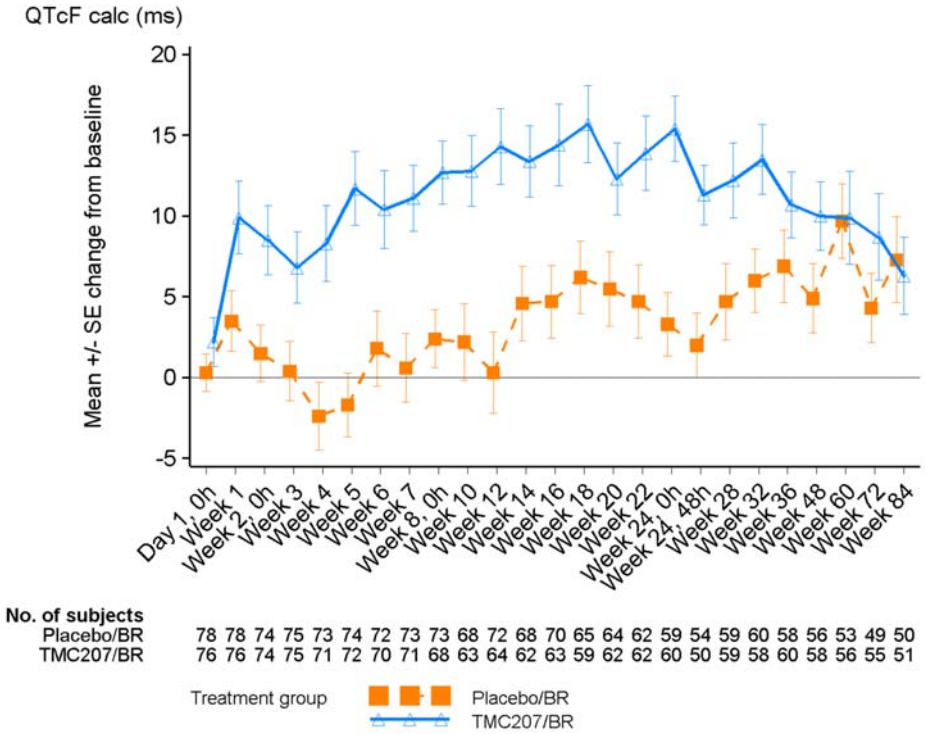
3.3.6.2 Trial C208 Stage II

ECG Changes Over Time

QTcF segment prolongation developed during the Investigational Treatment phase in the bedaquiline-treated group. Relative to the Week1 visit changes, the mean increases were > 10 ms from Week 5 onwards and decreased after Week 24. The largest mean change from reference was 16.2 ms at Week 24, 5 hours postdose. It is notable that at steady state, in both treatment groups, mean changes from reference for QTcF at the 5-hour

assessment time points were comparable to those at predose timepoints, suggestive of the absence of a direct relationship between Cmax of bedaquiline and QTcF prolongation. This does not exclude a delayed effect.

Figure 9. Mean Changes from Reference in QTcF Over Time



Source: NDA 204,384. Original Submission. Clinical Study Report – Trial C208 Stage II. Interim Analysis. p. 251.

Individual Abnormalities in ECG

The following ECG abnormalities occurred most frequently: tachycardia (defined as sinus rhythm > 100 bpm) that occurred in 45.6% and 49.4% of patients in the bedaquiline and placebo group, respectively; prolonged QT interval (57.0% and 33.3% respectively); and low T waves – nonspecific T wave abnormalities (27.8% and 22.2%, respectively).

During the trial, reports describing treatment emergent hemiblock abnormalities were received after Week 24 of treatment prior to database lock. A posthoc analysis was conducted that showed no differences between the treatment groups in the incidence of the abnormalities, as can be seen in the table below.

Table 39. Incidence of Reported Treatment-Emergent Hemiblock Abnormalities

n (%)	Bedaquiline/BR		Placebo/BR	
	Investigational Treatment Phase	Overall Treatment Phase	Investigational Treatment Phase	Overall Treatment Phase
	N = 79	N = 79	N = 81	N = 81
Broad QRS intraventricular block	5 (6.3)	5 (6.3)	4 (4.9)	4 (4.9)

n (%)	Bedaquiline/BR		Placebo/BR	
	Investigational Treatment Phase	Overall Treatment Phase	Investigational Treatment Phase	Overall Treatment Phase
	N = 79	N = 79	N = 81	N = 81
Broad QRS, terminal QRS rightward and anterior incomplete right bundle branch block	1 (1.3)	1 (1.3)	1 (1.2)	1 (1.2)
QRS -45 to -90, initial axis inferior and rightward consistent with left anterior hemiblock	3 (3.8)	4 (5.1)	1 (1.2)	3 (3.7)
QRS axis range 120 to 194 left posterior hemiblock	3 (3.8)	3 (3.8)	2 (2.5)	2 (2.5)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 254

During the Investigational Treatment Phase, one (1.3%) patient in the bedaquiline group had a QTcF value of > 500 ms, compared to none in the placebo group. This patient developed a QTcF value of 505 ms in Week 16, corresponding to an increase from baseline of 88 ms. One patient each from the bedaquiline and placebo groups developed QTcF values between 480 and 500 ms. Lastly, QTcF values between 450 and 480 ms were observed in 26.6% and 8.6% of patients in the bedaquiline and placebo group, respectively.

In terms of increase from reference in QTcF, seven (9.1%) patients in the bedaquiline group developed a >60 ms increase from reference in QTcF compared to two (2.5%) patients in the placebo group. One of the patients in the bedaquiline group was the same patient who had a QTcF of 505 ms. Fifty-six percent of patients in the bedaquiline group vs. 31.6% of patients in the placebo group experienced increases in QTcF between 30 to 60 ms.

Table 40 Change in QTc by method in the investigational and overall treatment phases

N (%)	bedaquiline		Placebo	
	Investigational Treatment Phase	Overall Treatment Phase	Investigational Treatment Phase	Overall Treatment Phase
QTcB calc (ms), N	**79**	**79**	**81**	**81**
]450 ms, 480 ms]	36 (45.6)	37 (46.8)	30 (37.0)	32 (39.5)
]480 ms, 500 ms]	8 (10.1)	9 (11.4)	3 (3.7)	6 (7.4)
More than 500 ms	2 (2.5)	2 (2.5)	0	0
QTcF calc (ms), N	**79**	**79**	**81**	**81**
]450 ms, 480 ms]	21 (26.6)	23 (29.1)	7 (8.6)	10 (12.3)
]480 ms, 500 ms]	1 (1.3)	1 (1.3)	1 (1.2)	1 (1.2)
More than 500 ms	1 (1.3)	1 (1.3)	0	0
QTcB calc (ms), N	**77**	**77**	**79**	**79**
Normal	34 (44.2)	31 (40.3)	49 (62.0)	46 (58.2)
Increase by 30-60 ms	37 (48.1)	40 (51.9)	30 (38.0)	33 (41.8)
Increase by > 60 ms	6 (7.8)	6 (7.8)	0	0
QTcF calc (ms), N	**77**	**77**	**79**	**79**
Normal	27 (35.1)	22 (28.6)	52 (65.8)	48 (60.8)
Increase by 30-60 ms	43 (55.8)	45 (58.4)	25 (31.6)	29 (36.7)

Increase by > 60 ms	7 (9.1)	10 (13.0)	2 (2.5)	2 (2.5)

Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 256

Standardized MedDRA Query

Torsade des Pointes/QT Prolongation SMQ

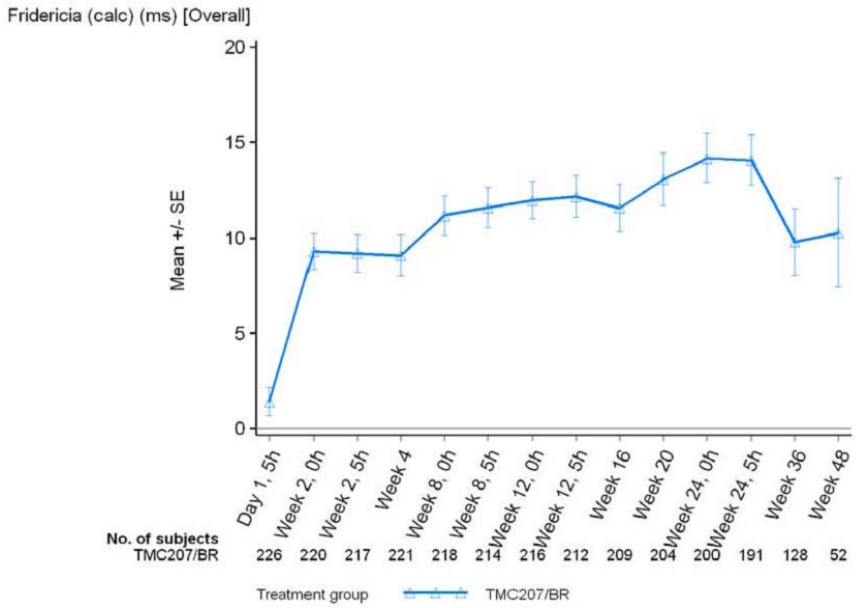
Four patients (5.1%) in the bedaquiline group and 4 patients (4.9%) in the placebo group experienced one or more SMQ events related to Torsade/QT Prolongation during the investigational treatment phase. In the bedaquiline group, three patients experienced ECG QTc prolonged events and one patient experienced syncope. All events of prolonged QTc were Grade 1 in severity. No patient developed an AE with a preferred term of Torsade des Pointes. During the overall treatment phase, one additional patient in the placebo group experienced a Grade 1 AE of ECG QTc prolonged (464 ms, change of 53 ms) considered not related to the study drug.

3.3.6.3 Trial C209

Mean Changes of QTcF from Reference Over Time

Mean absolute values in QTcF increased during the investigational treatment phase by Week 2, with mean increases from reference of > 10 ms observed from Week 8 onwards. Note that in this trial, the largest mean change from reference was 14.2 ms at Week 24 (at the end of bedaquiline treatment) as shown in the figure below. As in the other clinical trials, mean changes from reference for QTcF at the 5 hour assessment time points were comparable to those at predose time points. Data on mean changes in patients with 0, 1, 2, or 3 or more QT prolonging drugs concurrently administered with bedaquiline is subject of a pending information request, not available for presentation in this backgrounder document.

Figure 10. Mean QTcF Changes from Reference over Time in the ITT Population



Source: NDA 204,384. Original Submission. Clinical Study Report – Study C209 Interim Analysis. p. 193.

Individual Abnormalities in ECG reported as AEs

A total of nine (3.9%) patients developed an increase from reference of > 60 ms, whereas more modest increases of 30-60 ms in QTcF were observed in a larger proportion of patients (36.7%). No significant differences were noted between males and females. Of these 9 patients with an increase of > 60 ms, one developed a QTcF value of > 500 ms. An abnormal QTcF value between 450 and 480 ms during the investigational treatment phase developed in 11.6% of patients with one patient (ID No. 209-0111) having a QTcF value of > 500 ms (514 ms). During the overall treatment phase, another patient (ID No. 209-0167) developed a QTcF value > 500 ms.

Table 41. Relevant ECG Abnormalities (QTcF Changes)

ECG Parameter Abnormality	Bedaquiline/BR			
	Investigational Treatment Phase		Overall Treatment Phase	
	N	n (%)	N	n (%)
QTcB (calculated)				
]450 ms, 480 ms]	232	98 (42.2)	232	100 (43.1)
]480 ms, 500 ms]	232	11 (4.7)	232	11 (4.7)
> 500 ms	232	4 (1.7)	232	6 (2.6)
Increase by 30-60 ms	229	101 (44.1)	229	100 (43.7)
Increase by > 60 ms	229	5 (2.2)	229	7 (3.1)
QTcF (calculated)				
]450 ms, 480 ms]	232	27 (11.6)	232	30 (12.9)
]480 ms, 500 ms]	232	3 (1.3)	232	4 (1.7)
> 500 ms	232	1 (0.4)	232	2 (0.9)
Increase by 30-60 ms	229	84 (36.7)	229	86 (37.6)
Increase by > 60 ms	229	9 (3.9)	229	10 (4.4)

Source: Modified from NDA 204,384. Original Submission. Clinical Study Report – Study C209 Interim Analysis. Table 68. p. 195.

Posthoc analyses that evaluated the effect of the co-administration of clofazimine and bedaquiline on the QTcF interval reveal that 17 patients who, at Week 24, were using clofazimine had mean increases in QTcF that were larger (mean change of 31.94 ms at 0h) compared to the 170 patients who did not receiving concomitant clofazimine at Week 24 (mean change of 12.28 ms at 0h).

Table 42. Changes from Reference for QTcB and QTcF in Patients with Concomitant Use of Clofazimine at Week 24.

ECG Parameter	Clofazimine Use At Week 24													
	NO[a]							YES[b]						
Timepoint	N	Mean	SE	SD	Median	Min	Max	N	Mean	SE	SD	Median	Min	Max
Change in QTcB (calc) (ms)														
WEEK 24, 0 h	177	8.70	1.430	19.027	10.00	-52.0	58.0	17	28.18	3.983	16.421	25.00	0.0	56.0
WEEK 24, 5 h	170	9.80	1.443	18.809	11.00	-51.0	57.0	16	28.31	3.860	15.439	29.50	2.0	59.0
Change in QTcF (calc) (ms)														
WEEK 24, 0 h	177	12.3	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	12.4	1.258	16.406	11.50	-49.0	60.0	16	28.81	5.672	22.687	29.00	-11.0	82.0

a – Subgroup included patients who did not use clofazimine at Week 24 and had an ECG assessment at Day -1 (reference) and at Week 24
b - Subgroup included patients who used clofazimine at Week 24 and had an ECG assessment at Day -1 (reference) and at Week 24
Source: Modified from NDA 204,384. Original Submission. Clinical Study Report – Study C209 Interim Analysis. Table 69. p. 197.

The mean changes from baseline in QTcF and QTcB for patients with paired data with and without clofazimine showed that mean increases in QTcF were larger during administration of bedaquiline+ BR with clofazimine (mean change at 0h of 40.5 ms) than during bedaquiline + BR without clofazimine (mean change at 0h of 12.9 ms).

Table 43. Descriptive Statistics for Changes from Reference at Last Assessments in QT Intervals

Parameter	Endpoint TMC207a							Endpoint TMC207+Clofazimineb						
Timepoint	n	Mean	SE	SD	Median	Min	Max	n	Mean	SE	SD	Median	Min	Max
QTcB (calculated) (ms)														
0 h	10	10.30	4.899	15.492	15.00	-22.0	25.0	10	34.50	5.334	16.867	30.50	4.0	56.0
5 h	8	12.38	5.261	14.880	14.00	-15.0	31.0	8	34.13	3.409	9.643	35.00	16.0	48.0
QTcF (calculated) (ms)														
0 h	10	12.90	4.132	13.068	15.00	-12.0	30.0	10	40.50	8.371	26.471	31.50	11.0	82.0
5 h	8	14.50	4.347	12.294	17.50	-6.0	30.0	8	34.88	4.797	13.569	36.00	14.0	51.0

Source: Modified from NDA 204,384. Original Submission. Clinical Study Report – Study C209 Interim Analysis. Table 70. p. 197.

Torsade des Pointes/QT Prolongation

Six patients were reported to have AE ECG QT prolonged while on bedaquiline; none developed torsade des pointes. The events varied in severity (1 Grade 3, 1 Grade 2, and 4 Grade 1). The patient who developed the Grade 3 prolongation of QT interval was reported as an SAE and led to the permanent discontinuation of the drug. None of the remaining events were serious (SAEs) or led to permanent discontinuation of bedaquiline. Five of these AEs were assessed as possibly related to bedaquiline.

Table 44. SMQ Events Related to Torsade des Pointes/QT Prolongation

Class of Event Of Interest	Investigational Treatment Phase	Overall Treatment Phase
Preferred Term (event of interest), n (%)	**N = 233**	**N = 233**
Torsade de Pointes/QT Prolongation (SMQ)	6 (2.6)	7 (3.0)
ECG QT prolonged	6 (2.6)	6 (2.6)
Syncope	0	1 (0.4)

Source: Modified from NDA 204,384. Original Submission. Clinical Study Report – Study C209 Interim Analysis. Table 62. p. 179

During the overall treatment phase, two patients developed one of each AEs: Grade 3 syncope and prolonged QT interval. One patient developed Grade 1 syncope on D197, assessed to be unrelated to bedaquiline and doubtfully related to the BR.

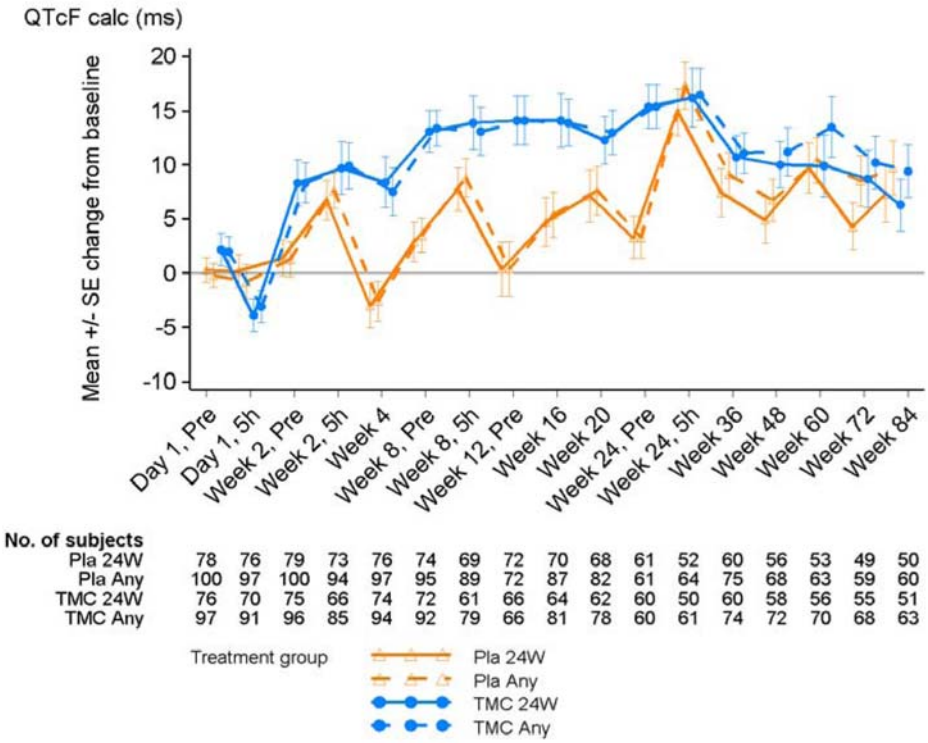
Cardiac failure was reported as a Grade 3 AE that occurred on D204 of the study. A 46 year old white male with diabetes mellitus developed pretibial edema on D199. At this time, the patient's QTcF was between 450-480 ms (481 ms at predose level and 464 ms at 5h postdose), within normal range from reference values (<30 ms). On D206, the patient developed atrial gallop rhythm, pulmonary hypertension, and ventricular ejection fraction of 30%, diagnosed as congestive heart failure. No ECG results were available during this time. BR, consisting of AMK, CS, EMB, OFL, and CS, was continued. The AE, cardiac failure was classified as a Grade 3 SAE and assessed as doubtfully related to bedaquiline and the BR. The investigator attributed the cardiac failure to the patient's pulmonary hypertension.

Analysis of QT interval Changes Over Time Using Pooled Data from the Controlled Trials (Trial C208 Stages 1 and 2)

In the Any Bedaquiline group in the controlled trials, the mean changes from reference in QTcF were comparable between the 5h postdose assessments and the respective predose assessments. However, as shown in Figure 11, the changes were greater than the respective predose assessments in the Any Placebo group in the controlled trials. The Applicant states that these results suggest the absence of a direct relationship between Cmax and the risk of QTcF prolongation.

To determine any QTcF effects over time, the Applicant noted that a mean increase in QTcF from reference was observed from the first predose assessment (8.3 ms at Week 2). Such an increase grew larger over the first 8 weeks of bedaquiline and remained stable until Week 24. In the Any Bedaquiline group, the largest mean increase in QTcF at a predose timepoint in the first 24 weeks was 15.4 ms, compared to the placebo group where mean changes from reference were generally <10 ms. After Week 24, the QTcF increases in the bedaquiline group became less pronounced.

Figure 11. QTcF Changes from Reference Over Time in the Controlled Trial



Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 226.

4 POINTS FOR ADVISORY COMMITTEE DISCUSSION

1. Do the data provided by the applicant provide substantial evidence of the efficacy of bedaquiline for the proposed indication of treatment of pulmonary tuberculosis

due to MDR *M. tuberculosis* as part of combination therapy in adults (≥ 18 years)?

a. If not, what additional data are required?
b. If so, please discuss any recommendations for labeling and use of bedaquiline.

2. Do the data provided by the applicant provide substantial evidence of the safety of bedaquiline for the proposed indication of treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* as part of combination therapy in adults (≥ 18 years)?

   a. If not, what additional data are required?
   b. If so, please discuss any recommendations for labeling and risk management.