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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Bedaquiline
(Proposed) Trade Name	Sirturo [®]
Therapeutic Class	Diarylquinoline
Applicant	Janssen Research and Development

Formulation(s)	100 mg uncoated tablet for oral administration
Dosing Regimen	400 mg PO Q Daily for 2 weeks followed by 200 mg PO

	thrice weekly for 22 weeks as part of a combination anti-tuberculous treatment regimen.
Indication(s)	Treatment of Pulmonary Tuberculosis Caused by Multi-Drug Resistant (MDR) Tuberculosis
Intended Population(s)	Adults (age \geq 18 years old)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Medical Officer recommends approval for bedaquiline as part of a multidrug treatment regimen for the treatment of pulmonary multidrug resistant tuberculosis (MDR-TB) under the Accelerated Approval pathway.

1.2 Risk Benefit Assessment

The global burden of tuberculosis is huge. The development of multidrug resistant isolates of *Mycobacterium tuberculosis* presents an urgent challenge for the development of new antimycobacterial drugs because of the paucity of antimycobacterial agents and the challenges of using very limited treatment options with poorly characterized risk-benefit properties to treat this deadly disease.

Bedaquiline is a bactericidal diarylquinoline antimycobacterial that primarily acts on the ATP synthase in the mycobacterial mitochondria. In vitro and in vivo microbiologic studies demonstrate the high affinity of bedaquiline to mycobacterial cells and the activity of bedaquiline against *M. tuberculosis*.

The efficacy of bedaquiline as part of a multidrug-regimen used for the treatment of pulmonary MDR-TB was evaluated in two Phase 2 trials using a surrogate endpoint of time to sputum culture conversion. In one randomized, double-blind, placebo with background regimen (BR)-controlled trial in sputum-positive pulmonary MDR-TB patients, the addition of a 24-week bedaquiline course to a recommended 5-drug treatment regimen significantly shortened the time to sputum conversion of patients compared to placebo-BR – treated patients. This was determined using a Kaplan-Meier survival curve analysis using data from the mITT population (66 patients in the bedaquiline group vs 66 patients in the placebo group) where the time to conversion for the bedaquiline-treated groups was shown to be significantly shorter than the time to conversion for the placebo treated group, with a logrank $p = 0.004$. At Week 24, the median time to conversion was 83 days (CI of 56, 97 days) for the bedaquiline group compared to 125 days for the placebo group (CI of 98, 168 days), with a log-rank test p -value of 0.0001.

Several sensitivity analyses of the primary endpoint using different methods of censoring yielded consistent findings of significantly shortening the time to sputum culture conversion in bedaquiline-treated patients compared to placebo-treated patients.

Two endpoints related to durability of response were examined. First, analysis of relapse as an endpoint showed that more patients relapsed in the placebo group

compared to the bedaquiline group. This difference in relapses between the two groups should be taken cautiously as there were very few patients who relapsed and the follow-up period is limited.

An additional endpoint reflecting durability of response was analyzed: time to culture conversion at Week 72. The findings of the analysis showed that when followed up to this timepoint, the statistically significant improvement in the time to culture conversion in bedaquiline-treated patients was still present but the difference between the two groups was less prominent. Again, this finding should be taken cautiously as endpoints reflecting durability of response could not be adequately evaluated in trials with limited follow-up such as Trials C208 and C209.

In all, data from the Phase 2 clinical trials indicate that bedaquiline, when added to a treatment regimen for pulmonary MDR-TB, significantly shortens the time for sputum culture conversion compared to an MDR-TB treatment regimen alone.

Nonclinical studies indicate the following potential human toxicities: the risk of QT prolongation, cardiac toxicity, pancreatic toxicity, hepatotoxicity, gastric necrosis, and phospholipidosis. Given that the animal exposures were multiple times higher the expected human exposure from the proposed dose, these organs of potential toxicities were monitored closely for safety during clinical trials.

The unique PK characteristics of bedaquiline increase its potential to cause toxicities, even after the termination of treatment with bedaquiline. Its highly protein bound (>99.9%) nature and high tissue retention are responsible for its long terminal half life of 4-5 months. Bedaquiline's main metabolite, M2, likewise has a prolonged terminal half life of 5.5 months. Because bedaquiline is metabolized by the cytochrome P450 isoenzymes, the evaluation of drug-drug interactions with CP450 inhibitors and inducers is essential in evaluating bedaquiline's potential to cause toxicities from elevated or decreased exposure. Among the drugs that can potentially interact with bedaquiline are antimicrobials that include antibacterial, antifungal, and antiviral agents

Analysis of safety data mainly from Trial C208 Stage 2 and augmented by data from Trial C209 has identified a number of potential risks that could be associated with the use of bedaquiline as treatment for pulmonary MDR-TB:

- Increased risk of death
- QT interval prolongation
- Hepatic-related adverse drug reactions.

In Trial C208 Stage 2, an increase risk of death was observed with the use of bedaquiline compared to placebo. Nine of 79 bedaquiline-treated patients (11.4%) died compared to 2 of 81 placebo-treated patients (2.5%), occurring during a follow-up period of 120 weeks from initiation of therapy. This is concerning, especially since an etiology of the imbalance could not be determined from the current safety database.

The most apparent trend that was observed was that tuberculosis was the cause of death in both placebo deaths and in five out of the nine (5/9) bedaquiline-treated deaths. Interestingly, seven of the nine (7/9) bedaquiline treated deaths converted and 3 of these 7 (3/7) patients relapsed early on during their clinical course and died from tuberculosis. Otherwise, no discernible pattern between death and conversion, relapse, microbiologic response, sensitivity to the background regimen, HIV status, severity of the disease, and the type of MDR-TB isolate, could be identified. The Medical Officer believes that given the limited number of patients in this placebo-controlled trial, the etiology of the imbalance would be difficult to detect and ascertain.

An increased risk of QT interval prolongation was observed in bedaquiline-treated patients compared to placebo-treated patients. In Trial C208 Stage 2, mean QTcF increases from reference were significantly larger in the bedaquiline group compared to the placebo group. After bedaquiline was stopped, the difference in the mean increase of QTcF from reference between the bedaquiline and placebo groups persisted, probably due to bedaquiline and M2's long terminal half lives. This was also seen in Trial C208 Stage 1.

Bedaquiline is an antimycobacterial drug given for a prolonged period of time in a multidrug regimen of other antimycobacterial drugs with their own toxicities. Given this, the potential for an additive effect on the QT interval prolongation with co-administration of drugs that have QT-prolonging potential exists. In particular, the antituberculous drug clofazimine was identified to additively increase the risk of QT prolongation. To minimize the risk of QT interval prolongation, the judicious choice and use of concomitant medications, with avoidance of drugs with QT-prolonging potential, if possible, should be done. If not, close monitoring of the QT interval is required.

Serum transaminase elevation occurred more frequently in bedaquiline-treated patients compared to the comparator. Hepatic-related serious adverse events, one of them resulting in death, occurred in the bedaquiline group. Three reasons preclude the assessment of definite causation of these events to bedaquiline. First, the safety database for bedaquiline in the controlled trial is acceptable but limited. Second, the cases of serum transaminase elevation and hepatic-related serious adverse events are confounded with chronic underlying medical illnesses such as alcohol use and concomitant hepatotoxic medication use. Lastly, the lack of information to rule out other potential etiologies of serum transaminase elevation such as the evaluation for viral hepatitis makes it difficult to determine association with bedaquiline. Despite these limitations, serum transaminase elevation occurred more often in the bedaquiline-treated patients, possibly indicative of an increased risk for the bedaquiline-treated patients. Risk factors that may worsen the transaminase elevation such as alcohol use and concomitant use of drugs with hepatotoxic potential should be avoided.

Several adverse drug reactions are discussed because of their seriousness. Acute pancreatitis, manifested by increased amylase and lipase, was seen rarely but more

frequently in the bedaquiline-treated patients. In one patient with a transient increase in pancreatic, hepatic, and gastric injury markers, phospholipidosis can be considered as an overall diagnosis but in the absence of pathological evidence and a negative dechallenge test, the diagnosis could not be verified. Similar to the other ADRs reported, causality assessment with bedaquiline is challenging because of the patient's multiple medications, chronic underlying illnesses, and the negative dechallenge.

The adverse reactions listed previously that occurred with bedaquiline use are serious and potentially life-threatening. However, the assessment of causality and association is challenging because of the following factors:

- The safety database and the follow-up period in the Phase 2 trials are acceptable but still limited so that a comparative analysis of the risks between treatment groups is difficult to do. This is especially true for ADRs that occur rarely. Because the safety database is limited, specific factors associated with these risks was difficult to assess (i.e. risk factors associated with the increased risk of death).
- Patients experiencing these adverse drug reactions are confounded with concomitant medications (non-antimycobacterial drugs), underlying disease, and concurrent diseases that, by themselves, may cause these purported drug reactions.
- Bedaquiline is given as part of a multidrug-regimen that could be modified during the course of treatment. Thus, any of the concomitant antituberculous medications could potentially cause the ADR, or contribute to the ADR's severity.

In addition, the PK characteristics of bedaquiline and the nature of treatment of tuberculosis (i.e. prolonged duration of treatment as part of a regimen) make causation assessment more complicated. Temporality between bedaquiline administration and the adverse even may not be present but association could still be possible because of the prolonged half-life.

The limitations of the current submitted clinical program of bedaquiline could be overcome by the completion of a confirmatory Phase 3 trial evaluating bedaquiline as treatment for pulmonary MDR-TB using traditional endpoints of long-term response, relapse, and mortality. This would increase the bedaquiline safety database to provide a more comprehensive set of safety data evaluating previously identified risks. Moreover, the proposed long-term follow-up of patients given a standardized regimen in the Phase 3 trial would clarify the role of bedaquiline in these identified risks.

The significant risks and limitations in ascribing causation must be taken in context with the urgent need for a new antimycobacterial, especially for patients with extremely limited therapeutic options (i.e. patients with pulmonary MDR-TB). It is because of this urgency that bedaquiline was submitted under the Accelerated Pathway. Given the safety risks potentially associated with bedaquiline and the urgent for an antimycobacterial for treatment of MDR-TB, the Medical Officer believes that

bedaquiline should only be reserved for use by patients who have very limited therapeutic options for treatment of their MDR-TB. Given the potential risk, patients should use bedaquiline only when the use of bedaquiline is needed to comprise a satisfactory effective regimen to treat their MDR-TB. Only with this restricted and reserved use can bedaquiline's risk-benefit profile be justified.

To ensure that only patients with the restricted the Medical Officer believes that The Medical Officer believes that marketing approval can be recommended in the premise of the following:

- Labeling and Medication Guide
This will ensure appropriate use of bedaquiline by patients and practitioners who are informed of the benefits and risks of bedaquiline. This would also foster safe use by both the patient and practitioner by providing guidance on appropriate monitoring for specific risks, adverse drug reactions, and drug-drug interactions.
- Adequate information for health care providers to educate practitioners on methods to successfully manage risks and optimize benefits with bedaquiline
- Patient Registry to monitor use by appropriate indication and to monitor safe use by active safety data monitoring.

The use of existing public health infrastructure involved with tuberculosis treatment and control is, in the Medical Officer's opinion, an optimal way to efficiently distribute bedaquiline to the intended patients who will benefit the most from bedaquiline and to manage and monitor the risks associated with bedaquiline use. Tuberculosis is, by law, a reportable disease both to the state health departments and the Centers for Disease Control and Prevention (CDC). Thus, there is an existing infrastructure being used to refer, diagnose, treat, educate, and monitor response and tolerability of patients with tuberculosis. The Medical Officer believes that the existing infrastructure could be optimized to facilitate safety monitoring and reporting of more granular safety data. This includes encouraging reporting of safety events in more standardized forms with information used to help attribute causality. Still, rather than establishing a new system, the public health system infrastructure already in place appears sufficient to streamline distribution to patients, improve safety monitoring, reporting, surveillance, and monitor the appropriate use by strict indication by public health providers who are already knowledgeable of tuberculosis control and treatment.

In addition to the public health system infrastructure, the CDC should be an integral component to ensure distribution of bedaquiline to appropriate patients with MDR-TB and to ensure sufficient monitoring of use and of safety. Most importantly, the CDC and its tuberculosis consultant group should act as a resource agency for public health providers seeking further guidance and assistance with the proper use of bedaquiline. As the expert agency, the CDC could provide consultations to providers and modify existing tuberculosis guidelines to include bedaquiline as a treatment option.

The public health providers (physicians, nurse practitioners, nurses and other allied medical professionals) involved with tuberculosis diagnosis and treatment are trained and adept in treating and monitoring patients with tuberculosis as they are knowledgeable of the anti-TB drug toxicities and the manner by which these toxicities are managed. Bedaquiline use should be accompanied by health provider education to inform and orient them of the benefits and the risks of the use of bedaquiline in select MDR-TB patients. These educational materials include materials from the Applicant, the SIRTURO Product Information (SIRTURO label), and the Medication Guide. Given these, the Medical Officer believes that public health providers dealing with tuberculosis should be adept in evaluating a patient's need for bedaquiline, in treating, and monitoring patients with bedaquiline.

The Applicant, to optimize the proper use of bedaquiline by public health practitioners involved with managing tuberculosis, (b) (4)

This could foster appropriate use in TB patients in great need for a new antimycobacterial drug.

In all, the Medical Officer believes that the use of the public health system infrastructure could direct appropriate use of bedaquiline by patients who need bedaquiline while ensuring safe use and adequate safety monitoring. This would ensure that by using the existing public health system infrastructure, providers who use bedaquiline would have the expertise in using medications with similar risk-benefit profiles as bedaquiline in treating patients with tuberculosis, while receiving guidance from the Applicant and the CDC.

In conclusion, the Medical Officer believes that the use of bedaquiline in select patients with MDR-TB involves the patient-specific evaluation of bedaquiline's risk-benefit profile. Specific components to ensure safe use in targeted patients with pulmonary MDR-TB are essential:

- The TB health care provider in the existing public health infrastructure
- The FDA in labeling, safety data collection and monitoring
- The CDC in expert consultation and guidance; and
- The Applicant in facilitating safety reporting and informing providers of the benefits and risks associated with the use of bedaquiline.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarketing Requirements (PMR)

1: Conduct a confirmatory randomized double blind placebo controlled multicenter phase 3 trial in subjects with sputum smear-positive pulmonary multi drug resistant tuberculosis (MDR-TB). This trial should assess long term outcomes of failure or relapse or death at least 6 months after all MDR-TB treatment is completed.

Final Protocol Submission: 06/2013

Trial Completion: 08/2021

Final Report Submission: 03/2022

2: Develop a patient registry for bedaquiline-treated patients to assess incidence rates of serious adverse events, including death. The registry should capture the information listed below:

- a. indication for use, including utilization of expert medical consultation
- b. Minimum Inhibitory Concentration (MIC) data for baseline and any subsequent isolate (in patients who have relapsed/at end of treatment) of multi drug resistant tuberculosis (MDR-TB)
- c. drug utilization data
- d. information on the drug distribution mechanisms used
- e. information on how the drug was actually distributed to patients
- f. patient outcomes (clinical and microbiologic)
- g. safety assessments in bedaquiline-treated patients, including deaths
- h. Concomitant medications

Final Protocol Submission: 06/2013

Interim Report Submission: 06/2014

06/2015

06/2016

06/2017

06/2018

Study Completion: 12/2018

Final Report Submission: 08/2019

3: In order to inform PMR 5, conduct a study to define the Quality Control ranges of bedaquiline for MDR-TB isolates using standard proportion methods.

Final Protocol Submission: 03/31/2013

Study Completion: 09/30/2014

Final Report Submission: 12/31/2014

4: In order to inform PMR 5, conduct a study to define the Quality Control ranges of bedaquiline for MDR-TB isolates using MIC methods.

Final Protocol Submission:	03/31/2013
Study Completion:	09/30/2014
Final Report Submission:	12/31/2014

5: Conduct a prospective in vitro study over a five-year period after introduction of SIRTURO (bedaquiline) to the market to determine minimum inhibitory concentrations (MICs) of multi drug resistant tuberculosis (MDR-TB) to bedaquiline for the first 5 years from marketing. Report interpretation of these MICs once additional quality control testing methods are developed as noted in the required postmarketing studies PMR 3 and PMR 4. Provide a detailed protocol describing the study to the Agency for review and comment before commencing the study.

Final Protocol Submission:	04/30/2015
Interim Report Submission:	12/31/2016
	12/31/2017
	12/31/2018
Study Completion:	09/30/2019
Final Report Submission:	12/31/2019

6: Conduct an in vitro study to characterize the potential of bedaquiline and M2 as a substrate, inhibitor or inducer of the OATP1B1 and OATP1B3 drug transporters.

Final Protocol Submission:	04/2013
Study Completion:	10/2013
Final Report Submission:	12/2013

7: Conduct a drug interaction trial of bedaquiline and efavirenz to determine a safe and effective dose regimen of both drugs when they are co-administered in HIV co-infected MDR-TB patients. Alternatively, adequate data from a previously conducted drug interaction trial may be submitted.

Final Protocol Submission:	03/30/2013
Trial Completion:	NA
Final Report Submission:	09/30/2013

Post-Marketing Commitments (PMC)

8: Submit final study report and electronic data for Study C208 Stage II

Final Protocol Submission:	N/A
Trial Completion:	N/A
Final Report Submission	11/2013

9: Submit final study report and electronic data for Study C209

Final Protocol Submission: N/A
Trial Completion: 01/2013
Final Report Submission: 11/2013

2 Introduction and Regulatory Background

About one third of the global population (2 billion) is infected with *Mycobacterium tuberculosis*, the etiologic cause of tuberculosis. Tuberculosis is the 8th leading cause of death in the world, based on data compiled by the World Health Organization (WHO) in 2008. In this reference year, 1.34 million deaths were caused by tuberculosis, accounting for around 2.4% of the total deaths that year.¹ Tuberculosis is a disease of poverty. A greater proportion of the deaths from tuberculosis, most of whom are young adults in their most productive years, occur in low-income countries. In fact, 95% of deaths from TB are in the developing world. In 2010, the number of people who fell ill with tuberculosis was 8.8 million, 1.1 million of whom were HIV infected. During this time, the estimated global incidence rate is 128 cases per 100,000 population and the number of people who died from tuberculosis was 1.4 million, including 350,000 people with HIV infection.²

According to the WHO, trends suggest that the estimated global incidence rate has been falling, albeit very slowly, since peaking in 2002 at 141 cases per 100,000 population. Similarly, the number of deaths attributable to tuberculosis has declined by 40% since 1990. Among other factors such as improved diagnostic capabilities available in low-income countries, the potential cause of this observed declining trend is the improvement with compliance with the therapeutic regimen ensured by the DOTS and the Stop TB Strategy. WHO data indicate that 46 million people have been successfully treated and up to 6.8 million lives were saved through these strategies.²

Treatment of drug-susceptible tuberculosis (DS-TB) typically involves the use of a regimen consisting of 4 antituberculous medications, given during the induction phase of treatment and 2 antituberculous medications, given during the remaining maintenance phase. Treatment usually takes 6 months. With good compliance, treatment of DS-TB results in cure rates of >90%.

However, new challenges in the control of tuberculosis have developed. One challenge is the TB/HIV Coinfection paradigm and the development of resistant tuberculous strains, specifically multidrug resistant tuberculosis (MDR-TB), pre-extensively drug resistant tuberculosis (pre-XDR-TB), and extensively drug resistant tuberculosis (XDR-TB).

MDR-TB is defined as an infection with a strain of *M. tuberculosis* resistant to at least isoniazid (INH or H) and rifampin (RMP or R). Treatment of MDR-TB is more complex and prolonged and typically has a favorable outcome rate (41-70%).³ Cases of MDR-TB are currently treated with at least 5 second-line anti-TB drugs for an extended period of time that may last up to 2 years. The 2 most important classes of second-line anti-TB drugs are the injectable drugs (capreomycin [CAP], amikacin [AMK], and kanamycin [KAN]) and the fluoroquinolones (FQs). The challenges of the treatment of MDR-TB include toxicities of the drugs, decreased potency, cost (50-200 times more expensive than treatment for DS-TB), and the need for possible hospitalization. Moreover, the individual drugs and the regimens have not been formally tested in randomized controlled trials, making it difficult to determine the benefit/risk profile of the individual drugs or regimens. The case fatality rate of patients with MDR-TB in HIV infected patients was estimated to be 26%,⁴ reflecting the challenges of poor diagnostic and treatment capacity for MDR-TB. Overall mortality still exceeds 10%, with a range of 8 to 21% for patients enrolled into good treatment programs.⁵

In 2008, around 390,000 to 510,000 cases of MDR-TB emerged globally, best estimate being 440,000 cases. Among all newly diagnosed tuberculosis cases in the world, 3.6% (CI 3.0, 4.4%) are estimated to be infected with MDR-TB. MDR-TB is estimated to be the etiology of 150,000 TB-related deaths. The incidence of MDR-TB also varies by region and country, with 50% of MDR-TB cases occurring in China and India. The highest proportions of MDR-TB documented in a subnational area occur in Russia where surveillance data from oblasts and republics reported proportions of 23.8%-28.3% MDR-TB among new TB cases. China reported 5.7% among new cases and 25.6% among those previously treated have documented MDR-TB strains.⁴ In the United States the total number of primary MDR-TB cases has fluctuated from 88 to 132 cases from 1993, with 88 cases reported in 2010.

Prior to this, in 2004, the WHO's Stop TB Department estimated that a total of 424,203 cases of MDR-TB have been diagnosed worldwide for all new and previously treated TB cases. The HIV-MDR-TB coinfection is reinforced by data stating that regions with the highest rates of MDR-TB coincide with the regions with the fastest growing HIV epidemics. Recent data demonstrate that in HIV-infected patients on antiretroviral therapy (ART), coinfection with MDR-TB could be a major predictor of imminent death. In this study, the median age of HIV-infected patients coinfecting with MDR-TB was 35 years, half with no history of prior TB treatment. Ninety-eight percent of these coinfecting patients died within a median of 16 days from sputum collection.

The WHO standard treatment regimen for MDR-TB is commonly divided into 2 phases. The first phase is the intensive treatment phase which is a 4 to 6 month phase in which an injectable drug is administered along with 3 or 4 other drugs that should typically include a fluoroquinolone (FQ). This is followed by a continuation phase without an injectable drug and often without pyrazinamide (PZA).

MDR-TB strains can become resistant to either at least one second-line injectable drug OR to any fluoroquinolone, strains classified as pre-extensively resistant TB (pre-XDR-TB). Lastly, MDR-TB strains can become resistant to both the second-line injectable drug AND any FQs, classified as extensively drug resistant TB (XDR-TB).

The WHO recently published a revised guideline for the management of drug-resistant tuberculosis.⁶ The guideline was issued to provide technical support to countries for the development and implementation of national frameworks of care (i.e. national and local guidelines) for patients with drug-resistant TB. The WHO issued the following recommendations:

- Use of rapid drug susceptibility tests (DST) of INH and rifampin or or rifampin alone at the time of diagnosis
- Use of sputum smear microscopy and culture rather than sputum microscopy alone to monitor patient during treatment
- Use of a fluoroquinolone, specifically a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone
- Use of ethionamide or prothionamide
- Use of four second-line anti-TB medications that includes the following in the intensive phase (the initial part of a course of treatment during which a parenteral agent is used):
 - A parenteral agent from among the second-line injectables kanamycin, amikacin, or capreomycin),
 - Pyrazinamide
- Regimens should include at least the following:
 - Pyrazinamide
 - Fluoroquinolone (levofloxacin [≥ 750 mg/day], moxifloxacin, gatifloxacin, sparfloxacin)
 - Parenteral agent (kanamycin, amikacin, or capreomycin)
 - Ethionamide (or prothionamide) (bacteriostatic)
 - Cycloserine or p-aminosalicylic acid (PAS) if cycloserine or other secondary TB medications could not be used (bacteriostatic)
- An intensive phase of ≥ 8 months duration
- Total treatment duration of ≥ 20 months is recommended for patients without any previous MDR-TB treatment.

While studies have shown that patients treated with Group 5 drugs such as clofazimine, linezolid, amoxicillin-clavulanate, thiocetazone, clarithromycin, and imipenem have generally worse outcomes, this observation could be due to confounding by indication. However, when the individual effects of amoxicillin/clavulanate, azithromycin, clarithromycin, clofazimine, roxithromycin, and thiocetazone were analyzed, no significant association with cure was observed.

Ultimately, the choice of drug regimen should depend on the DST of the strain isolated from the patient or from the contact (index patient), prior use of anti-TB drugs, and frequency of use of the drug or documented background resistance in the setting.

2.1 Product Information

Bedaquiline is a diarylquinoline with a novel mode of action. Bedaquiline acts by specific inhibition of mycobacterial adenosine 5'-triphosphate (ATP) synthase. Bedaquiline has been shown to be effective not only against multidrug-resistant (MDR) and drug-susceptible (DS) strains of *Mycobacterium tuberculosis* (*M. tuberculosis*)⁷, but also against dormant (nonreplicating) bacilli⁸. Bedaquiline has been demonstrated to have in vitro activity against *M. tuberculosis* strains that are monoresistant to INH, rifampin, streptomycin, ethambutol, pyrazinamide, or moxifloxacin and MDR-TB strains.⁹ Because intracellular ATP is low in hypoxic, nonreplicating *M. tuberculosis* organisms, the growth and survival of these particular bacterial populations are more sensitive to ATP depletion. This may have an impact on disease caused by mycobacterial strains that survive in the setting of appropriate therapy and need long treatment duration.

Bedaquiline was previously referred to as R207910 or JNJ-16175328-AAA (free base form), or R403323 or JNJ-16175328-AEP (fumarate salt). The international nonproprietary name (INN) and the United States adopted name (USAN) are both bedaquiline and the USAN modified is bedaquiline fumarate.

Largely metabolized by cytochrome P450 (CYP) 3A, bedaquiline has two metabolites. The major metabolite, M2, is identified as N-monodesmethyl-BEDAQUILINE and was measured in a number of in vivo and in vitro studies. The second metabolite, M3, is identified as N-didesmethyl-BEDAQUILINE.

2.2 Tables of Currently Available Treatments for Proposed Indications

The WHO guideline provides recommendations on the choice and duration of antimycobacterials used for the treatment of MDR-TB. The guideline also provides technical support to countries for the development and implementation of national frameworks of care (i.e. national and local guidelines) for patients with drug-resistant TB.

All drugs used to treat MDR-TB are used off label because clinical trials evaluating the risk-benefit profile are virtually nonexistent. The clinical evidence supportive of the use of the following drugs are based on low-quality evidence (i.e. case series and reports, anecdotal experience, and expert opinion). As such, the optimal use of individual drugs for MDR-TB is unknown and the contribution of individual agents to an individualized regimen is difficult to quantify.

The following medications are used to treat MDR-TB:

- Pyrazinamide
- Fluoroquinolone (levofloxacin [\geq 750 mg/day], moxifloxacin, gatifloxacin, sparfloracin)
- Parenteral agent (kanamycin, amikacin, or capreomycin)
- Ethionamide (or prothionamide) (bacteriostatic)
- Cycloserine or p-aminosalicylic acid (PAS) if cycloserine or other secondary TB medications could not be used (bacteriostatic)

Other medications are classified as Group 5 drugs and have been used to treat MDR-TB:

- Clofazimine,
- Linezolid,
- Amoxicillin-clavulanate,
- Thiocetazone,
- Clarithromycin, azithromycin, roxithromycin; and
- Imipenem

Ultimately, the drug regimen is chosen based on the drug susceptibility test of the strain isolated from the patient or from the patient contact, prior use of anti-TB drugs, and documented background resistance in the setting.

Medical Officer Comment:

The evaluation of the efficacy and safety of bedaquiline is challenging. This arises from a number of issues related to the drugs currently used to treat MDR-TB:

- *The limited number antimycobacterial drugs used to treat MDR-TB is used off-label, resulting from the lack of formal clinical evaluation of the individual drug's risk-benefit profile.*
- *Treatment of tuberculosis, including MDR-TB, requires a multi-drug regimen, with the contribution of each drug difficult to quantify.*

To be able to determine the contribution of bedaquiline in an MDR-TB drug regimen in evaluating bedaquiline's safety and efficacy, uniformity of the background regimen in enrolled patients should be attempted. The Medical Officer believes that this would minimize the confounding effects of individualized regimens. However, as the clinical trials should reflect actual clinical settings where drugs are stopped and used based on the isolate's susceptibilities and based on patient toxicities, the Medical Officer realizes that this would be challenging in a clinical trial setting.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

BEDAQUILINE is the only diarylquinoline evaluated in clinical trials. In these human clinical trials, BEDAQUILINE was co-administered with other antituberculous medications, most of which are second-line tuberculosis drugs. These anti-TB medications have been known to be associated with characteristic toxicities:

- fluoroquinolones (moxifloxacin in particular): increased risk for QT prolongation, dysglycemia, hepatotoxicity, and tendon rupture.
- pyrazinamide (PZA): hyperuricemia, gout, hepatotoxicity, and hematologic abnormalities such as thrombocytopenia and sideroblastic anemia
- ethambutol (EMB): retrobulbar neuritis
- aminoglycosides (ofloxacin, etc.): ototoxicity and nephrotoxicity
- ethionamide/protonamide: psychoses, depression, neuropathies, pellagra, blurred vision, hypersensitivity, hypoglycemia, postural hypotension
- protonamide: can additionally cause hepatotoxicity and convulsions
- cycloserine: neurologic events such as tremors, sudden onset congestive heart failure when given high dose
- Clofazimine: skin hyperpigmentation, QT prolongation
- Linezolid: myelosuppression, hypoglycemia, lactic acidosis, optic and peripheral neuropathy, convulsions, QT prolongation, and excess of deaths
- Azithromycin: severe allergy, severe cutaneous reaction, hepatotoxicity, cholestatic jaundice, QT prolongation

Overlapping toxicities from multiple anti-TB medications include gastrointestinal intolerance, hepatotoxicity, central nervous system effects, and/or skin reactions.

Medical Officer Comment:

The urgent need for a new anti-mycobacterial for MDR-TB is primarily a result of the nature of MDR-TB so that options to treat this disease are limited. More importantly, this urgent need is underscored by the lack of formal assessment of the efficacy and safety of not only the individual drugs used to treat MDR-TB, but also the regimens used. In addition, the toxicities enumerated above limit the use of these agents, especially when additive toxicity risks are considered from a multiple-drug regimen.

The evaluation of the efficacy and safety of bedaquiline as treatment for MDR-TB is fostered by an urgent need to develop and market new treatment options for this disease. Conducting clinical trials for bedaquiline for MDR-TB is challenging and prolonged as this would entail enrollment in sites outside the United States because of the low overall incidence of the disease both in the world and in the United States. This was foreseen by both the Applicant and Agency. In order to facilitate this, both the Agency and the Applicant concurred on evaluating evidence from Phase 2 clinical trials via the Accelerated Approval pathway.

The Accelerated Approval pathway utilized for the evaluation of bedaquiline as treatment for pulmonary MDR-TB will be discussed in the regulatory history that follows.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Bedaquiline, previously referred to as TMC 207, was developed by Tibotec, Inc. under the IND 69 600. IND 69,600 was submitted to the Division of Special Pathogens and Transplant Products on November 9, 2006. Other associated INDs for TMC 207 are IND (b) (4) with (b) (4) as the Sponsor, with (b) (4) as the Sponsor representative for submission of safety reports from several Phase 1 studies for bedaquiline. The Applicant and the Division met several times to discuss the bedaquiline development program. On December 22, 2011, the Agency was notified of the change of Sponsor from Tibotec, Inc. to Janssen Research and Development. LLC, which started on January 2, 2012.

On January 10, 2005, the FDA granted bedaquiline an orphan-drug designation for the treatment of tuberculosis. The FDA also subsequently granted bedaquiline a fast-track designation.

The following table summarizes major interactions between the FDA and the Applicant.

Table 1. Summary of Regulatory History of Bedaquiline

Date	Action/Issues
January 10, 2005	Orphan-drug designation was granted by the FDA for bedaquiline as treatment for MDR-TB.
July 11 2006	Face-to-face Pre-IND meeting between the Division of Special Pathogen and Transplant Products (DSPTP) and the Tibotec, Inc.
November 9, 2006	Submission of IND 69,600
September 28, 2008	Type C meeting between DSPTP and Tibotec, Inc to discuss results from Trial C208 Stage 1 and the bedaquiline treatment program to support an initial submission of a New Drug Application for bedaquiline for MDR-TB
June 3, 2009	Anti-Infective Drugs Advisory Committee meeting was held to discuss issues related to the development of MDR-TB treatment
February 9, 2011	EOP2 meeting to discuss the proposal for overall development program for bedaquiline, including the adequacy of the data from Trial C208 Stages 1 and 2 and the confirmatory Phase 3 Trial C210 study design to support an accelerated and traditional approval for bedaquiline as treatment for MDR-TB. The Sponsor agreed to modify the Phase 3 study design based on concerns about

	the lack of justification for the proposed noninferiority margin.
April 22, 2011	Bedaquiline was granted fast-track designation.
May 13, 2011	Teleconference on the two proposals for study design for the confirmatory Phase 3 trial. The use of a modified Bangladesh background regimen given 9 months with bedaquiline vs a Bangladesh background regimen with placebo could support traditional approval
October 7, 2011	Pre-NDA meeting
June 29, 2012	Submission of the New Drug Application for bedaquiline.

The Anti-Infective Drugs Advisory Committee meeting held in June 3, 2009 discussed pertinent issues on the conduct of clinical trials for drugs being developed to treat TB. The Advisory Committee voted 18 to 1, recommending that sputum culture conversion, with improvement/resolution of signs and symptoms could be used as a surrogate or clinically meaningful endpoint. The committee felt that the use of sputum conversion is reasonable and objective. The committee further recommended that 6 months is a reasonable timepoint to assess culture conversion. Therefore, the committee recommended that approval of an antimycobacterial drug could be done under Subpart H regulations (Accelerated Approval) using sputum culture conversion as a surrogate endpoint. Further, traditional endpoints used to evaluate treatment response such as relapse, failure, and mortality should still be used. These traditional endpoint should be used for traditional approval, with a recommended multiple timepoints in evaluating these endpoints.

Regarding safety, the Committee favored a modest database of 600, given the gravity of the disease. Risk-benefit analysis of the drug should consider the gravity of the disease and the benefits of the evaluated drug.

Bedaquiline is being considered for approval under the Subpart H regulations (Accelerated Approval) using the surrogate endpoint of time to sputum culture conversion evaluated in the Phase 2b clinical trials (Trials C208 Stages 1 and 2 and Trial C209). Findings of efficacy and safety using this endpoint will be verified by a confirmatory Phase 3 trial using traditional endpoints of relapse and durability of cure at a later timepoint.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Applicant states that all trials included in the NDA were conducted and reported in accordance with the ethical principles from the Declaration of Helsinki and in accordance with the ICH for Good Clinical Practice guidelines to comply with governmental regulatory requirements.

3.2 Compliance with Good Clinical Practices

The Applicant states that all clinical sites in the bedaquiline development program complied with principles of good clinical practice.

3.3 Financial Disclosures

The Applicant has submitted Certifications attesting to the absence of financial interests and financial arrangements of clinical investigators with the Applicant. The Applicant, Janssen Research and Development, LLC, has certified that none of the clinical investigators participating in the Phase 1 studies and Phase 2 trials for bedaquiline entered into any financial arrangements with them that would affect the outcome of the study. Moreover, the Applicant certified that all clinical investigators do not hold any disclosable financial arrangements with Johnson and Johnson, the parent company of Janssen Research and Development, LLC.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug product is an uncoated, immediate release tablet for oral administration. Each tablet contains 120.89 mg of bedaquiline fumarate drug substance that is equivalent to 100 mg of bedaquiline free base. The drug product is produced by (b) (4). The tablet appears white to almost white round biconvex tablet with a diameter of 11 mm and debossed with 'T' over '207' on one side and '100' on the other side. The formulation was assigned the formulation number F001, and referred to as bedaquiline 100-mg tablet (F001).

The container closure system, with each bottle containing 188 tablets, is an opaque, high-density, polyethylene bottle with polypropylene child-resistant closure and foil induction seal.

Table 2 summarizes the composition of the bedaquiline 100-mg tablet (including inactive ingredients):

Table 2. Composition of the bedaquiline tablet

Component	Quality Reference	Function	Weight per Tablet	
			(mg)	(%)
Bedaquiline Fumarate	Company specification	Active ingredient	120.89	26.28
Lactose Monohydrate	Ph. Eur./NF	(b) (4)		
(b) (4)	Ph. Eur./NF			
Hypromellose 2910 15 mPa.s	Ph. Eur./USP			
Polysorbate 20	Ph. Eur./NF			
Purified Water ^b	Ph. Eur./USP			
Microcrystalline Cellulose	Ph. Eur./NF			
Croscarmellose Sodium	Ph. Eur./NF			
Silica, Colloidal Anhydrous ^c	Ph. Eur./NF			
Magnesium Stearate	Ph. Eur./NF			
Total Tablet Weight:			460.00	100.00

^a NF monograph name: corn starch

^b Removed during processing.

^c NF monograph name: colloidal silicon dioxide

NA = Not applicable

4.2 Clinical Microbiology

Bedaquiline is bactericidal against both actively replicating and dormant bacilli of both drug-sensitive and multi-drug resistant strains of *M. tuberculosis*.⁸ The bactericidal activity of bedaquiline even in dormant, non-replicating bacteria is attributed to the sensitivity of ATP-depleted organisms to further ATP depletion caused by bedaquiline's inhibition of ATP synthesis.¹⁰

The activity of bedaquiline appears to be more selective towards the ATP synthase in mycobacterial mitochondria compared to the eukaryotic mitochondria. This is demonstrated by the finding that the bedaquiline IC₅₀ for mycobacterial organisms is 0.01 µM while the IC₅₀ for human cancer cells is >200 µM for human cancer cells, suggesting that bedaquiline's affinity for mycobacterial ATP synthase is >20,000-fold more than its affinity for human ATP synthase.

In vitro studies demonstrate that the inhibitory concentrations for the parent drug bedaquiline for 50% and 90% of preclinical isolates (MIC₅₀ and MIC₉₀) of *M. tuberculosis* were 0.03 µg/mL and 0.06 µg/mL, respectively for both drug-susceptible (DS-TB) and MDR-TB isolates. The table below shows the activity of bedaquiline against these isolates.

Table 3. In Vitro Activity of Bedaquiline against *M. tuberculosis* Isolates

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
MDR-TB	44	≤ 0.008 - 0.12	0.03	0.06	0.06

Source: Source: NDA 204384. Original Submission. Summary of Microbiology Studies. Table 1. p. 18. June 2012

The bactericidal activity of bedaquiline appears to be time-dependent, rather than concentration-dependent. A three-log unit reduction in bacterial load was noted after 12 days during the log-phase growth of *M. tuberculosis* isolates exposed to bedaquiline serum levels ten times (10x) the MIC. No further reductions in bacterial growth were noted with levels 100 times or greater of the MIC. A post-antibacterial effect of 9 hours was documented based on parallel in vitro studies that demonstrated 11 hours of post-antibacterial effect of 11 hours for INH.

Bedaquiline achieved effective intracellular concentrations against *M. tuberculosis*. This was demonstrated by studies using mouse peritoneal macrophages and J774A.1 cells. The studies demonstrated that the bactericidal effect of bedaquiline was rapid intracellularly and inhibited bacterial growth in a concentration-dependent manner.

The Applicant provided evidence from in vivo studies using murine models demonstrating the bactericidal and sterilizing activity of bedaquiline as monotherapy and in combination with first line anti-TB drugs. The murine studies demonstrated that the bactericidal activity from two months of treatment with the regimen RMP, INH, and PZA was similar to a month of a bedaquiline-containing regimen (i.e. bedaquiline + INH + PZA or bedaquiline + RMP + PZA). Another murine study demonstrated that 34 months of treatment with bedaquiline-containing regimens was as effective as a 6 month standard regimen, and more effective than 4 months of moxifloxacin + RMP + PZA. Bedaquiline was also shown to augment the sterilizing activity of second-line drug regimens, with lower relapse rates 3 months after a 6 month therapy with different drug combinations, as shown by the following table:

Table 4. Relapse Rates in a Murine TB Model After Second-Line Anti-TB Drugs

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

Bedaquiline's major metabolite, M2, is 4 to 6 times less active against *M. tuberculosis* than the parent compound. M2 is further metabolized to the bacteriologically inactive M3 metabolite.

Bedaquiline appears to have a narrow spectrum of activity specific for the *Mycobacterium* species. Bedaquiline, even at large doses, does not inhibit the growth of selected Gram positive and Gram negative bacteria. Limited information can be found regarding bedaquiline's activity on other relevant mycobacterial pathogens.

For a more detailed discussion, please refer to the review of the Clinical Microbiology reviewer, Dr. Lynette Berkeley.

4.3 Preclinical Pharmacology/Toxicology

The safety margin for bedaquiline was calculated based on the 9-month dog no observed adverse effect level (NOAEL) of 2 mg/kg/day and in the 6-month rat study at the 5 mg/kg/day dose. Both doses used in animal studies were used to calculate for a 6 month human dose regimen containing daily dosing of 400 mg q daily for 2 weeks, followed by 200 mg thrice in a week (TIW). The following table demonstrates the safety margin calculated from the exposure from the proposed dosing regimen when compared to the exposure in animal models.

Table 6: Animal/Human Exposure Ratio at NOAEL/LOAEL in Animals and Based on the Exposure Data in Human After 8 Weeks of Treatment

Species	Study	NOAEL (mg/kg/day)		TMC207				M2			
				AUC _{0-24h} (µg.h/mL)		Animal/Man Ratio		AUC _{0-24h} (µg.h/mL)		Animal/Man Ratio	
		M	F	M	F	M	F	M	F	M	F
Rat	26-weeks	5 ^b	5 ^b	6.6	16.8	0.30	0.77	5.1	8.9	0.85	1.48
Dog	39-weeks	2	2	27.9	21.3	1.27	0.97	11.7	13.3	1.95	2.22
Human	TMC207-C208 ^a			22				6			

^a Exposure data determined at the end of Stage 1 of trial TMC207-C208, in which subjects were treated with 400 mg TMC207 q.d. for 2 weeks followed by 200 mg t.i.w. for 6 weeks (AUC_{0-24h} were calculated by dividing AUC_{0-48h} by 2); ^b LOAEL
F = female; M = male

Table 7: Animal/Human Exposure Ratio at NOAEL/LOAEL in Animals and Based on the Exposure Data in Human After 24 Weeks of Treatment

Species	Study	NOAEL (mg/kg/day)		TMC207				M2			
				AUC _{0-24h} (µg.h/mL)		Animal/Man Ratio		AUC _{0-24h} (µg.h/mL)		Animal/Man Ratio	
		M	F	M	F	M	F	M	F	M	F
Rat	26-weeks	5 ^b	5 ^b	6.6	16.8	0.47	1.2	5.1	8.9	1.42	2.47
Dog	39-weeks	2	2	27.9	21.3	1.99	1.52	11.7	13.3	3.25	3.69
Human	TMC207-C208 ^a			14				3.6			

^a Exposure data determined at the end of Stage 2 of trial TMC207-C208, in which subjects were treated with 400 mg TMC207 q.d. for 2 weeks followed by 200 mg t.i.w. for 22 weeks (AUC_{0-24h} were calculated by dividing AUC_{0-48h} by 2); ^b LOAEL
F = female; M = male

Medical Officer Comment:

The proposed dosing regimen of 400 mg every day for two weeks and 200 mg thrice weekly for the succeeding 22 weeks appear to have adequate safety margins when compared to the NOAEL determined in the 9 month dog study after 8 weeks of treatment and after 24 weeks of treatment.

Results from nonclinical studies point to five organ systems and one pathological animal finding that could be seen in the clinical trials:

4.3.1. Cardiac Safety

The in vitro hERG assay demonstrates the potential of bedaquiline to cause QT prolongation because bedaquiline inhibited the K pump at an IC₅₀ of 0.2 mcg/mL. In the 6 month dog study, QT prolongation (12-16% from baseline) was noted at 2 months in dogs given a dose of 40 mg/kg/day, an exposure of AUC of ~ 150 mcg*h/mL. When the dose was reduced to 20 mg/kg/day and 140 mg/lg, no prolongation was noted.

In addition, cardiomyocyte degeneration and increased cardiac troponin and CPK was noted in the 6 month dog study at a dose of 20 mg/kg/day and 140 mg/kg twice weekly. These were not seen in dogs given lower doses.

4.3.2. Hepatic Safety

In animals (mice, rats, and dogs), centrilobular hypertrophy was seen. This change was partially reversible and was dose-related. Single-cell necrosis was also seen in mice, in addition to serum transaminase elevation. The NOAEL for rats was determined to be 5 mg/kg/day given for 6 months, similar to the 8 week human bedaquiline exposure. The

NOAEL in dogs was determined to be 18 mg/kg given for 9 months. This is eight times higher human exposures at 8 weeks.

4.3.3. Pancreas

Focal to multifocal pancreatitis with acinar cell atrophy was seen in mice and dogs given doses of 40 mg/kg/day for 13 weeks.

4.3.4. Skeletal Muscle

Degenerative and necrotic lesions in mice, dogs, and rats given bedaquiline doses of 24 mg/kg for 13 weeks were noted. These changes were reversible in rats.

4.3.5. Stomach

Necrosis of the gastric fundic mucosa was noted at dogs given 40 mg/kg/day at 13 weeks and 160 mg/kg/day. Recovery was noted at 20 to 40 weeks after exposure.

4.3.6. Phospholipidosis

The pathological change called phospholipidosis was noted in all species given all doses of bedaquiline. This change is characterized by the presence of intracellular lamellar inclusion bodies. These changes were observed to be most common in the cells of the monocytic phagocytic system (MPS) such as the lymph nodes and the spleen. Phospholipidotic changes were also seen in cells of the lungs, liver, stomach, skeletal muscle, pancreas, and the uterus. Phospholipidosis was reversible after bedaquiline dosing was stopped.

Medical Officer Comment:

The findings of toxicities in the animal models could predict safety experience in clinical trials so close monitoring of toxicities in these organs was performed during clinical trials. For more details, please refer to the review of the Pharmacology/Toxicology reviewer, Dr. Owen McMaster.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Bedaquiline is a diarylquinoline with a specific mechanism of action: the inhibition of mycobacterial adenosine 5'-triphosphate (ATP) synthase, an enzyme integral for the generation of ATP in the mycobacterial organism. The inhibition of the mycobacterial ATP synthase is responsible for bedaquiline's bactericidal activity against both replicating and non-replicating *M. tuberculosis* bacteria.

More specifically, bedaquiline inhibits the proton pump of the ATP-synthase 3 molecule by binding to the enzyme's subunit C. This subunit C is responsible for the flow of protons (H⁺ and Na⁺) from the intercrisae region in the mitochondria and the periplasmic space of the bacteria to the mitochondrial matrix and the bacterial cytoplasm, respectively. The inhibition of the proton pump therefore results in inhibition of energy production specifically in the mycobacterial bacillus.

4.4.2. Pharmacokinetics

The following table describes the pertinent pharmacokinetic properties of bedaquiline.

The pharmacokinetics of bedaquiline is dose-proportional for doses between 10 mg and 700 mg. After oral administration, absorption is facilitated with food. After absorption, protein binding is > 99%. While its effective half-life is around 24 to 30 hours, bedaquiline's terminal half-life is around 4 to 5 months. Bedaquiline is metabolized by the cytochrome P450 enzyme CYP3A4 to its metabolite, M2, which is 4-6 fold less active and with a terminal half-life of 5.5 months. Bedaquiline is excreted through the feces.

Table 5. Summary of the Pharmacokinetic Properties of Bedaquiline

PK Property	PK Parameter	
Dose-proportionality	PK is dose-proportional for doses 10 – 700 mg	
Label dose at 8 weeks	TMC: 1.3 mcg/mL M2: 0.18 mcg/mL	
C _{max}	TMC: 14 mcg*h/mL M2: 3.64 mcg*h/mL	
AUC		
Absorption	T _{max} (median)	~5 hr
	Food Effect	2 fold increase in C _{max} & AUC w/ high fat meal
Distribution	Protein Binding	> 99%
	t _{1/2} effective	~24-30 hours
	t _{1/2} term	~ 4-5 months

Metabolism	Pathways	Metabolized to M2 (4-6-fold less active, t _{1/2} term of 5.5 months) and M3 by CYP3A4.
Excretion	Fecal excretion is the major route of elimination.	

Source: FDA Clinical Pharmacology Review

Medical Officer Comment:

Bedaquiline's pharmacokinetic properties result in clinically relevany consequences. First is the need to take bedaquiline with food to optimize oral absorption. Second is that both bedaquiline and its major metabolite, M2, have prolonged terminal half-lives (4 to 5.5 months), resulting in the persistence of its pharmacodynamic effects even after treatment duration. Therefore, monitoring for adverse drug reactions that could be attributed to bedaquiline should continue even after treatment duration. Lastly, since bedaquiline is metabolized by CYP3A4, serum levels are affected by cytochrome P450 substrate inhibitors and inducers. Thus, drug-drug interactions and their potential to increase or decrease bedaquiline levels, must be evaluated. While the metabolite M2 is less active than the parent compound, M2's pharmacodynamic effects, particularly in causing specific adverse reactions, should be evaluated.

The Clinical Pharmacology package appears to have evaluated salient issues associated with the pharmacokinetic and pharmacodynamic properties of bedaquiline. The Medical Officer refers the reader to the Clinical Pharmacology review of Dr. Dakshina Chilukuri.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 6. Summary of Phase 2 Clinical Trials

Trial (Status)	Design	Population	Treatment	Dose	Primary Efficacy Endpoint	N
TMC207-C202 (completed)	Randomized, open-label, active-controlled	DS-TB	TMC207 or RMP or INH followed by standard TB therapy	TMC207 25 mg q.d. TMC207 100 mg q.d. TMC207 400 mg q.d. RMP 600 mg q.d. INH 300 mg q.d. Duration: 7 days	Degree of reduction in the sputum viable count over a 7-day period (eEBA)	75 TMC207 25/100/400 mg; 15/16/14; RMP: 15; INH: 15
TMC207-C208 Stage 1 (completed)	Randomized, double-blind, placebo-controlled	newly diagnosed MDRH&R-TB/ pre-XDR-TB	TMC207 or placebo + preferred BR composed of: KAN, OFL, ETH, PZA, and CS/TRD	Week 1-2: TMC207 400 mg q.d. Week 3-8: TMC207 200 mg t.i.w. BR drugs: standard dose Duration 8 weeks	Time to culture conversion in MGIT during the 8-week investigational treatment period	47 (TMC207: 23; placebo: 24)

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Stage 2 (investigational treatment completed)	Randomized, double-blind, placebo-controlled	newly diagnosed MDRH&R-TB/ pre-XDR-TB	TMC207 or placebo + preferred BR composed of: KAN, OFL, ETH, PZA, and CS/TRD	Week 1-2: TMC207 400 mg q.d Week 3-24: TMC207 200 mg t.i.w. BR drugs: standard dose Duration: 24 weeks	Time to culture conversion in MGIT during the 24-week investigational treatment period	160 (TMC207: 79; placebo: 81)
TMC207-C209 (investigational treatment completed)	Open-label, uncontrolled	newly diagnosed or previously treated MDRH&R-TB/ pre-XDR-TB/ XDR-TB	TMC207 + individually optimized BR	Week 1-2: TMC207 400 mg q.d Week 3-24: TMC207 200 mg t.i.w. BR drugs: standard dose Duration: 24 weeks	Time to culture conversion in MGIT during the 24-week investigational treatment period	233

Source: Adapted from NDA 204,384. Initial submission. SD 1. June 29, 2012. Summary of Clinical Efficacy. p. 21.

5.2 Review Strategy

The Clinical Review is divided into two general parts: the review of efficacy and the review of safety. Both will be done by the Medical Reviewer.

The Review of Efficacy will center on the trial considered pivotal by both the Applicant and the Medical Officer, Trial C208 Stage 2, because this trial provides a comparative evaluation between the efficacy of bedaquiline on top of a BR and the BR by itself, using the proposed bedaquiline dosing regimen. Efficacy results from the smaller comparative trial with a shorter bedaquiline exposure, Trial C208 Stage 1, would be considered supportive.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1. Trial C208

This trial is a stratified, randomized, double-blind, placebo-controlled trial conducted in 2 consecutive stages: Stage 1 which is a completed exploratory stage, and Stage 2 which is an ongoing proof-of-efficacy stage. The trial was initiated on 5 June 2007 and ended on 4 December 2009. The two stages have similar designs, with the major difference being the length of bedaquiline exposure.

Objectives:

Stage 1 (Exploratory Stage)

- Primary: To evaluate the pharmacokinetics, antibacterial activity, safety, and tolerability of bedaquiline compared to placebo when added to an MDR-TB BR for 8 weeks in patients with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.

Stage 2

- Primary: To demonstrate the superiority in the antibacterial activity of bedaquiline compared to placebo when added to a BR for 24 weeks in patients with newly-diagnosed sputum smear-positive pulmonary MDR-TB infection.
- Primary Outcome Measure: time to sputum culture conversion during treatment with bedaquiline or placebo

Secondary Objectives for Both Stages:

- To evaluate and compare the safety and tolerability of a 24-week treatment with bedaquiline or placebo on top of the BR
- To investigate the pharmacokinetics (PK) of bedaquiline and M2 in plasma and sputum of patients receiving multiple doses of bedaquiline in combination with a BR during treatment and after discontinuation
- To explore drug-drug interactions between bedaquiline and the BR
- To explore PK/PD relationships for activity and tolerability/safety.

Objective of the Rollover Arm

- To offer open-label treatment with bedaquiline to Stage 2 patients who received placebo and are not sufficiently responding to their BR regimen (includes patients diagnosed with XDR-TB)
- To offer open-label treatment with bedaquiline to patients from whom there is evidence that they were infected with XDR-TB prior to randomization into the trial.

Patient Population

Patients with newly diagnosed pulmonary MDR-TB (confirmed resistance to at least both RMP and INH by susceptibility culture and/or repeated rapid screen tests [fast plaque and GenoType MTBDR line probe]) that was defined by the following were enrolled in the trial:

- Patients with MDR-TB who had never been treated for TB previously
- Patients with MDR-TB who had previously been treated with only first-line TB drugs (INH, RMP, EMB, PZA, or streptomycin (SM))

Pertinent Inclusion Criteria

- Male and female patients aged 18-65 years of age who are newly diagnosed with MDR-TB (never been treated for TB previously or who received treatment only with first-line TB drugs [INH, RMP, EMB, PZA, or SM])
- Patients with confirmed resistance to RMP and INH
- Patients able to produce sputum ≥ 10 mL nightly

- Patients willing to discontinue all TB medications 7 days before baseline assessments and initiation with treatment with BEDAQUILINE or placebo.

Pertinent Exclusion Criteria:

Patients with:

- Previous treatment for MDR-TB (received any second-line TB drug that includes aminoglycosides except SM, any fluoroquinolone, prothionamide or ETH, and cycloserine)
- Current or past history of alcohol and/or drug use that could compromise patient compliance
- Clinically active medical condition that may prevent appropriate participation in the trial
- Significant cardiac arrhythmia that required medication
- Complicated or severe extrapulmonary manifestations of TB or neurological manifestations of TB
- Concomitant severe illness or rapidly deteriorating health condition including immune deficiency or gastrointestinal disease that could interfere with BEDAQUILINE absorption.
- Required surgical procedure for TB within the 8 week treatment period.
- QT/QTc interval characteristics at screening:
 - Marked prolongation of QT/QTc interval (i.e. repeated demonstration of QTcF interval > 450 msec)
 - History of Torsade de Pointes, e.g. heart failure, hypokalemia, family history of Long QT Syndrome
 - Use of concomitant medications that prolong QT/QTc interval and are listed as disallowed medications in the protocol
- Potentially significant laboratory abnormalities at screening as defined by the enhanced Division of Microbiology and Infectious Diseases (DMID) adult toxicity table
- Chorioretinitis, optic neuritis, or uveitis
- Mycobacterial strain isolated is not susceptible to at least 3 of the 5 classes of TB drugs used to treat MDR-TB demonstrated by drug susceptibility test performed prior to screening

Criteria for Patient Withdrawal from the Trial

- Occurrence of an SAE
- Failure to comply with protocol requirements or to cooperate with the investigator
- Withdrawal of consent
- Safety reasons as determined by the investigator
- Broken randomization code
- Specific toxicities as described in the protocol
- Pregnancy
- False positive screening test for MDR-TB

- Documented XDR-TB

Background Regimen

According to the Applicant, the BR in the trial was standardized as much as possible. Similarly, the Applicant ensures that all subjects adhered as closely as possible to the preferred BR. These two measures would allow the optimal evaluation of the efficacy and safety of TB treatment regimen attributable to bedaquiline. Moreover, consistency and standardization of the background regimen is also important after the study drug administration period as long-term safety, cure, failure and relapse rates were also considered clinical outcomes.

The BR was specified prior to randomization. However, this BR could be modified according to susceptibility results of the documented *M. tuberculosis* strains. The modification should be consistent with standard clinical practice and after discussion with the medical leader. If the BR was modified because of toxicity or safety concerns, the modification would be reported as an AE.

The treatment regimen followed in the protocol is divided into 2 phases: a 6 month intensive treatment phase wherein an injectable aminoglycoside or capreomycin is administered along with 4 other drugs that are typically oral and that include a fluoroquinolone. This phase is followed by a continuation phase without an aminoglycoside or capreomycin or PZA.

The preferred BR regimen (Table 7) initiated at the intensive treatment phase is composed of the following: KAN, OFL, ETH, PZA, and cycloserine/terizidone. Substitutions were permitted in case of drug shortage or of patient intolerance to a component medication:

- AMK for KAN
- Prothionamide for ETH
- Ciprofloxacin for OFL
- EMB for cycloserine/terizidone, if resistance is not documented for EMB

To point out, modifications from the preferred BR were permitted depending on drug susceptibility test results or on patient tolerability of the BR

Treatment during the whole duration of the trial was administered by Directly Observed Therapy (DOT).

Table 7. Antituberculous drugs used in the Background Regimen

BR drugs	Formulation ^a	Daily dosage ^a (mg)		Phase (intensive/continuation)
		Minimum	Maximum	
Aminoglycosides				
- Kanamycin ^b	Vial, 1g	750	1000	Intensive
- Amikacin ^b	Vial, 1g	750	1000	Intensive
Thioamides				
- Ethionamide ^{c, d}	Tablet, 250 mg	500	750	Intensive/continuation
- Prothionamide ^c	Tablet, 250 mg	500	1000	Intensive/continuation
Pyrazinamide	Tablet, 400 or 500 mg	1200	1600	Intensive
Fluoroquinolones				
- Ofloxacin ^{e, f}	Tablet, 200 mg	600	800	Intensive/continuation
- Ciprofloxacin ^e	Tablet, 250 mg	1000	1500	Intensive/continuation
Ethambutol^g	Tablet, 400 mg	1000	1200	Intensive/continuation
Terizidone/Cycloserine^{g, h}	Capsule, 250 mg	500	750	Intensive/continuation

^a The formulations and daily dosage ranges mentioned are recommended formulations and doses (i.e., were to be used as guidance only)

^b in case of unavailability of kanamycin due to drug supply issues, amikacin could be used.

^c in case of unavailability of ethionamide due to drug supply issues, prothionamide could be used.

^d for reasons of intolerability (nausea), the dose could be split into 2 parts administered 10-12 hours apart, or the daily dose could be taken in the evening or could be taken with orange juice or milk or other liquid.

^e in case of unavailability of ofloxacin due to drug supply issues, ciprofloxacin could be used.

^f for reasons of intolerability, the dose could be reduced during the continuation phase.

^g in case of intolerance to terizidone/cycloserine and if there was no resistance to ethambutol as determined by drug susceptibility testing, ethambutol could be substituted for cycloserine/terizidone.

^h to reduce central nervous system effects, 150 mg/day of pyridoxine could be administered.

Analysis Populations

- ITT Population (Intent-to-Treat Population) – This population consists of all patients who were randomized and received at least one dose of bedaquiline or placebo. This population was used for safety analysis. As the Statistical Reviewer, Dr. Li, has pointed out in his review, an ITT population should consist of all randomized patients.
- mITT Population (Modified-Intent-to-Treat Population) – This population is a subset of the ITT population where patients with the following have been excluded:
 - Patients with DS-TB, XDR-TB, or MDR-TB for whom the MDR-TB status could not be confirmed based on susceptibility results taken prior to randomization;
 - Patients whose MGIT results did not allow for primary efficacy evaluation (no evidence of culture positivity prior to baseline or no results during the first 8 weeks after baseline)

Unless specified, the mITT population was used for all efficacy analyses. These analyses were conducted in the mITT population where 67 patients were randomized to bedaquiline and 66 patients were randomized to placebo.

5.3.2. Trial C209

Trial C209 is a Phase II, open-label, single-arm trial conducted to evaluate the safety, tolerability, and efficacy of bedaquiline in combination with an individualized background regimen to treat patients with sputum smear-positive pulmonary infection with MDR-TB. The open-label, single-arm trial was used to achieve the primary objective of the trial: to obtain supportive safety data for the use of bedaquiline.

Patients were enrolled based on inclusion and exclusion criteria similar to the inclusion and exclusion criteria utilized in Trial C208, except for some significant differences as discussed below.

The trial recruited patients with newly diagnosed and treatment-experienced MDR-TB using specific inclusion and exclusion criteria to reach the planned total sample size of 225 patients. Moreover, HIV-infected patients were allowed to enroll in the trial provided that they fulfill the inclusion and exclusion criteria, especially as it pertains to the use of antiretroviral therapy. HIV-infected patients were required to either switch to a triple NRTI regimen consisting of AZT/3TC/ABC or to discontinue all ARVs depending on their current virological status and treatment history.

Patients were treated with bedaquiline for 24 weeks together with an individualized BR selected by the investigator at the baseline visit guided by national TB program treatment guidelines. Standard treatment for MDR-TB is divided into 2 treatment phase: a 4 to 6 month intensive phase with an injectable aminoglycoside administered with 3 or 4 TB drugs that include a FQ. This is followed by a continuation phase without an aminoglycoside to achieve a total treatment duration of 18 to 24 months, or a minimum of 12 months after sputum conversion.

The trial is currently ongoing in Asia, South Africa, Eastern Europe, and South America. The Applicant provided the interim analysis of the ongoing trial performed when all patients had completed 24 weeks of treatment with bedaquiline or had discontinued earlier. Data provided were obtained from baseline to the patient's last visit before data cut-off last 29 March 2011. A total of 294 patients were screened, of whom 233 started treatment with bedaquiline with a BR. As in Trial C208 Stage II, the modified Intent-to-Treat (mITT) population excludes patients with DS-TB or whose MGIT results did not allow for primary efficacy evaluation. The mITT population consisted of 205 patients.

6 Review of Efficacy

Efficacy Summary

Bedaquiline is a diarylquinoline with activity against multidrug-resistant tuberculosis. The efficacy of bedaquiline as part of a multidrug TB treatment regimen is being

evaluated as treatment of pulmonary multidrug-resistant tuberculosis MDR-TB) in two Phase 2 clinical trials under the Accelerated Approval pathway. The proposed dose is 400 mg by mouth once daily for the first 2 weeks, followed by 200 mg by mouth three times in a week (TIW) for the next 22 weeks to complete 24 weeks.

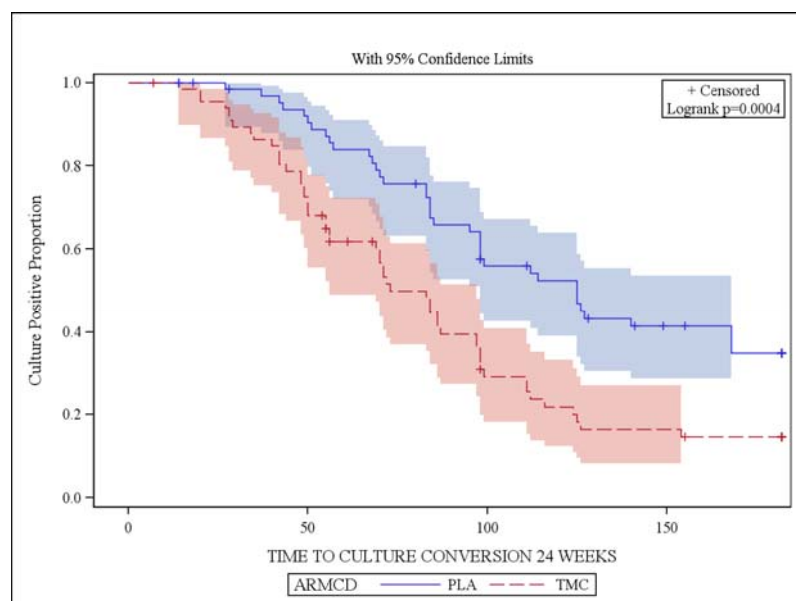
The first trial is Trial C208 Stages 1 and 2 which are two independent, randomized, double-blind, placebo/BR-controlled trials enrolling newly-diagnosed, treatment naive sputum-positive patients with pulmonary MDR-TB. Bedaquiline or placebo was given on top of a recommended background regimen of ETH, KAN, OFL, PZA, and TZD. The background regimen is given for 72-96 weeks. Stage 1 provides a bedaquiline or placebo exposure of 8 weeks and Stage 2 provides a bedaquiline or placebo exposure of 24 weeks (proposed regimen); after which the primary endpoint of time to sputum culture conversion is evaluated. Stage 1 is considered the exploratory stage while Stage 2 is considered the proof-of-efficacy and pivotal trial.

The second trial is Trial C209 which is an open-label, uncontrolled trial enrolling patients with sputum-positive, treatment-experienced pulmonary MDR-TB patients treated with the proposed 24 week bedaquiline regimen on top of an individualized background regimen. Trial C209 is considered a supportive trial with the objective of increasing both the databases for efficacy and safety.

The objective of the Trial C208 is to demonstrate the superiority of bedaquiline over placebo, given together with a recommended BR, in the time for patients to achieve sputum culture conversion.

A total of 160 patients (ITT population) were randomized to receive either bedaquiline (79 patients) or placebo (81 patients) for 24 weeks with a recommended background regimen in the pivotal trial, Trial C208 Stage 2. In the FDA efficacy analysis, 67 and 66 patients were included in the modified ITT population (mITT) in the bedaquiline and placebo group, respectively. When all patients completed week 24 or discontinued earlier, the primary efficacy analysis was performed. The analysis was performed with a prespecified primary endpoint of time to sputum culture conversion during the 24 week bedaquiline/placebo treatment period. Criteria for culture conversion were specified. Patients who prematurely discontinued, including deaths, were censored at the last culture visit.

The FDA analysis resulted in the following Kaplan-Meier survival curves:



The FDA analysis showed a significant shortening of the time to achieve sputum culture conversion for the bedaquiline group compared to the placebo group. The p-value from the log-rank test was 0.0004. The FDA analysis also utilized a Cox proportional hazards regression model that demonstrated that there was a statistically significant treatment effect with bedaquiline as measured by the relative risk between the two treatment groups (relative risk 2.15, CI [1.39, 3.31] with a p-value of 0.0005).

The FDA also performed analysis on a key secondary endpoint, culture conversion at Week 24. The analysis demonstrates that at Week 24, 78% of bedaquiline-treated patients (52/67) achieved culture conversion, compared to 58% of placebo-treated patients (38/66). The difference between the culture conversion rates of the two groups is 20%. This is statistically significant with a CI of 4.5%, 35.6% and a p-value of 0.014. Lastly, several FDA sensitivity analyses using different methods of handling missing culture results demonstrated consistency of findings. Lastly, culture conversion data after all patients completed 72 weeks in the study showed a statistically significant but diminishing improvement in the time to sputum culture conversion for bedaquiline-treated patients compared to placebo-treated patients.

An additional endpoint that was analyzed is relapse, defined as having a confirmed positive sputum culture during or after treatment after conversion. Analysis of data from the mITT population of Trial C208 Stage 2 showed that 4 (7.6%) bedaquiline-treated patients relapsed compared to 8 placebo-treated patients (12.1%). Data on relapses, however, is inconclusive as the number of patients that can be evaluated for relapses is extremely small in both treatment groups.

Analyses to identify specific subpopulations or risk factors that could predict efficacy or response revealed that at Week 24, Black patients had lower sputum culture conversion

rates than patients of other racial background. The etiology of this observation is unclear. It could be site-specific because placebo-treated Black patients in one South African clinical site was noted to have higher culture conversion trends than culture conversion trends of placebo-treated patients of other racial backgrounds. The other potential etiology is the documented higher clearance of bedaquiline in Black patients that has the potential to decrease effective bedaquiline levels. Currently, data from the pivotal trial is limited to make definitive conclusions on the effect of Black race on efficacy.

Efficacy results from Trial C208 Stage 1 are supportive of and consistent with a statistically significant improvement of the time for culture conversion for patients treated with bedaquiline for 8 weeks compared to patients treated with placebo, on top of a recommended background regimen

In summary, analysis of efficacy data from the pivotal trial C208 Stage 2 indicate that bedaquiline treatment with background regimen for 24 weeks significantly improves the time to sputum conversion compared to just treatment with background regimen alone. As sputum culture conversion has been identified as an acceptable marker for clinical response, when based on an Accelerated Approval pathway, these studies demonstrate the efficacy of bedaquiline as part of a multidrug regimen used for treatment of MDR pulmonary tuberculosis.

6.1 Indication

The indication evaluated in the Phase 2 clinical trials (Trials C208 Stages 1 and 2 and Trial C209) is the treatment of sputum smear-positive pulmonary tuberculosis caused by multi-drug resistant tuberculosis (MDR-TB)

6.1.1 Methods

Please refer to Section 7.1.

Briefly, Study C208 is a stratified, randomized, double-blind, multicenter, placebo-controlled Phase II trial in patients with newly diagnosed, treatment-naïve, sputum smear-positive pulmonary MDR-TB infection, with two consecutive but completely separate stages.

Stage 1, the exploratory stage, is to evaluate the efficacy and safety of 8-week TMC207 on top of a background regimen (72 – 96 weeks, or approximately 18 – 24 months).

Stage 2, the proof-of-efficacy stage, is to evaluate efficacy, safety, and tolerability of 24-week treatment of TMC207 on top of a background regimen (72 – 96 weeks, or approximately 18 – 24 months) to demonstrate the superiority of TMC207 over placebo in time to culture conversion.

6.1.2 Demographics

Please refer to Section 7.2 and the appropriate Sub-Sections.

The pertinent main exclusion criteria included:

- Prior treatments for MDR-TB, patients were defined as those having received any second-line TB drug.
- HIV-infected patients with
 - A CD4+ count < 300 cells/μL or
 - Received antiretroviral therapy and/or oral or intravenous antifungal medication within the last 90 days, or
 - Possibly needing to start ART during the investigational treatment period.
- Patients with complicated or severe extra-pulmonary manifestations of TB or neurological manifestations of TB.

Eligible patients were randomized 1:1 to receive either bedaquiline or placebo, on top of the BR for MDR-TB. Randomization was stratified by trial site and the 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), as determined by chest X-ray at screening. Randomization was performed using a central randomization system (the interactive voice response system). A minimization technique was used to ensure balance across the treatment groups in each stratum.

6.1.3 Subject Disposition

Please refer to Section 7.2 and the appropriate Sub-Sections.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was time to sputum culture conversion during treatment with bedaquiline or placebo, based on the qualitative assessment of culture growth in the mycobacterial growth indicator tubes (MGIT) using spot sputum samples. The following definitions were used to determine time to sputum culture conversion:

- Sputum culture conversion was defined as 2 consecutive negative cultures from sputa collected at least 25 days apart. All intermediate cultures have to be negative as well. A cut-off of 25 days was chosen as most visits are scheduled to be 28 days apart. 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 sputum culture conversion was calculated as the interval in days between the date of treatment initiation for MDR-TB and the date of the first of the 2 consecutive negative sputum cultures from sputa collected at least 25 days apart.

The 25-day requirement for two consecutive negative results (Criterion 2) was not part of the primary efficacy analysis for Trial C208 Stage 1 results in the week 8 primary efficacy analysis.

In Stage 2, for subjects who discontinued before the end of the analyzed time period, the following methods for the primary and sensitivity analyses were applied to calculate the time to culture conversion:

- They were considered treatment failures (i.e., no culture conversion event) and their time to culture conversion was censored at their last assessment with sputum culture (missing = censored; primary analysis).
- They were considered treatment failures (i.e., no culture conversion event) and were carried forward as not converting through the considered time period (missing = failure, end-censored). The subjects' time to culture conversion was censored on the last day of the analyzed time period.
- The discontinuation information was not taken into account (no overruling for discontinuation). For subjects whose microbiological status had converted before discontinuation, the actual time of conversion was used. For subjects with no sputum culture conversion before discontinuation, their time to culture conversion was censored at their last assessment with sputum culture

Medical Officer Comment:

For the first method, the Medical Officer concurs with the Statistical Reviewer, Dr. Xianbin Li, in pointing out that the Applicant referred to this analysis as missing = failure. However, both failure and missing value were censored in this definition. In a time-to-event analysis, subjects were excluded from the analysis after censoring time on and not considered as failure.

Efficacy Analyses and Statistical Method

The primary efficacy analysis in Stage 1 and Stage 2 was performed when all subjects completed 8 weeks and 24 weeks of treatment with TMC207 or placebo (or had discontinued earlier), respectively.

An additional statistical analysis of Stage 2 was conducted to support submission to Health Authorities, as planned per protocol, using cut-off dates of 10 May 2011 for efficacy data and of 10 June 2011 for safety data. At the time of these cut-off dates, all subjects had completed at least the Week 72 visit or had discontinued earlier.

Final analysis in Stage 1 was performed when all subjects completed 104 weeks (i.e. 8 weeks of TMC207 + 96 weeks of MDR-TB treatment and follow-up) or discontinued earlier. In Stage 2 final analysis will be performed when all subjects have completed 120 weeks (i.e. 24 weeks of TMC or placebo + 96 weeks of MDR-TB treatment and follow-up) or discontinued earlier.

The Applicant used a Cox proportional model was used with degree of lung cavitation and trial center as covariates to compare the time to sputum culture conversion between the two treatment groups. In the protocol, baseline log-CFU counts were to be included as a covariate, but this variable was not in the analysis. Treatment by center and treatment by cavitation interactions were explored with this model. A two-sided 5% significance level was used.

Interim Analysis Methods for Stage 2

Three interim analyses were conducted with different data selection dates: “Week 24 data selection”, “Week 72 data selection”, “All available data selection”.

Time to culture conversion was the primary efficacy endpoint for interim analyses at each data selection. Two sensitivity analyses for handling subjects who discontinued described in the primary endpoint section were also conducted. In addition, a binary outcome (treatment success/failure) was created to calculate culture conversion rates at these time points. The same statistical methods for the Stage 2 primary endpoint were used for time-to-culture-conversion endpoint analyses.

Culture Conversion Rate

The division considered the culture conversion rate is an important endpoint in accessing the effect of TMC207. The sponsor listed this endpoint under the Primary Efficacy Endpoint section.

The proportion of subjects with MGIT sputum culture conversion was determined according to the following definitions:

- Responder (missing = failure): sputum culture conversion had occurred, was not followed by a confirmed positive MGIT result, and the subject did not discontinue during the considered time frame.
- Non-responder (missing=failure): the last available microbiological status was 'not converted', or status was 'converted' but followed by a confirmed positive result, or the subject discontinued during the considered time frame regardless of the status at the last assessment.

Culture Conversion (Missing=Failure) were further subdivided in the following categories for non-response:

- Failure to culture convert (at any time point during the trial)
- Relapse: having a confirmed positive sputum culture (or a single positive sputum culture after which the subject discontinues) during or after treatment after having been defined converted with isolation of a *M. tuberculosis* strain with the same genotype compared to baseline or with unknown genotype as compared to baseline.
- Re-infection: having a confirmed positive sputum culture after having been defined converted with isolation of a *M. tuberculosis* strain with a different genotype compared to baseline.
- Discontinued with microbiological status 'converted'.
- Discontinued with microbiological status 'not converted'.

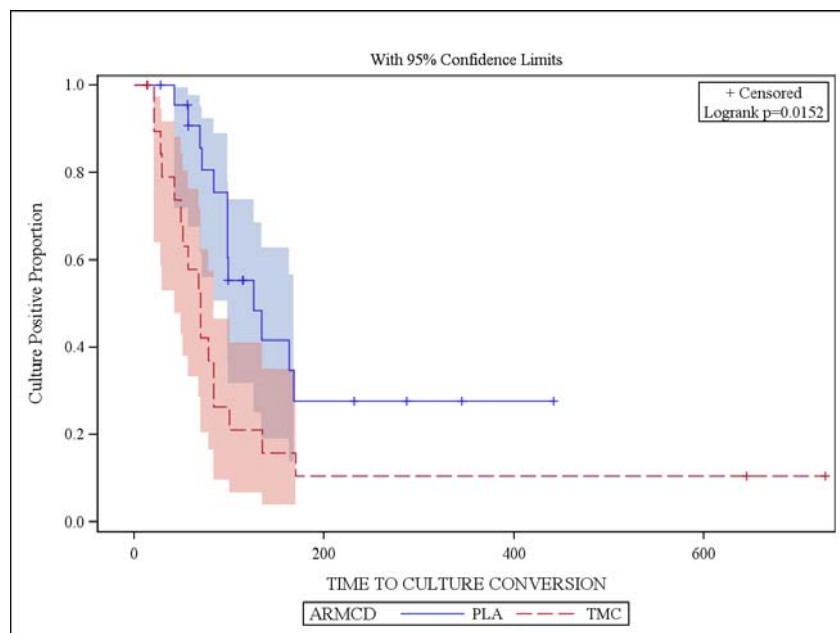
6.1.4.1. Results for Final analysis in the mITT Population

6.1.4.1.a. Trial C208 Stage 1

Time to Sputum Culture Conversion

Analysis of the primary efficacy data from Trial C208 Stage 1 showed that by Week 8, the time to sputum culture conversion was faster for the bedaquiline-treated group compared to the placebo group (Log-rank test p-value = 0.019). This significant improvement in time to sputum culture conversion persisted in the 24-week data analysis and in the analysis at follow-up at week 96 (Log-rank test p-value = 0.0152). The Cox proportional hazards model, with lung cavitation and pooled center sites as covariates, showed a significant treatment effect with a relative risk of 11.77 and a 95% CI (2.26, 61.23) with a p-value of 0.0034. The Kaplan-Meier curves for time to culture conversion for the final analysis are shown in the following figure.

Figure 1. Kaplan-Meier Survival Curves for Final Analysis (mITT Population)



Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Culture Conversion Rate

At Week 8, the culture conversion rate was statistically higher for the bedaquiline group than for the placebo group, with a difference of 38.9% at Week 8. However, at the later time points, the difference in culture conversion rates was no longer significant, indicating that the treatment effects were diminishing. This is probably a result of the fact that patients with culture conversion who discontinue or prematurely withdraw the trial were not considered successes on discontinuation. Note that the culture conversion rates in the table were lower than the survival curves.

Table 8: Culture conversion rates in the mITT population, Study C208 Stage 1

Microbiologic Status	TMC207 N=21	Placebo N=23	Difference [exact 95% CI] p-value
Week 8 Treatment success	10/21 (47.6%)	2/23 (8.7%)	38.9% [12.3%, 63.1%] 0.004
Week 24 Treatment success	17/21 (81.0%)	15/23 (65.2%)	14.8% [-11.9%, 41.9%] 0.29
Final Treatment success	11/21 (52.4%)	11/23 (47.8%)	4.6% [-25.5%, 34.1%] 0.76

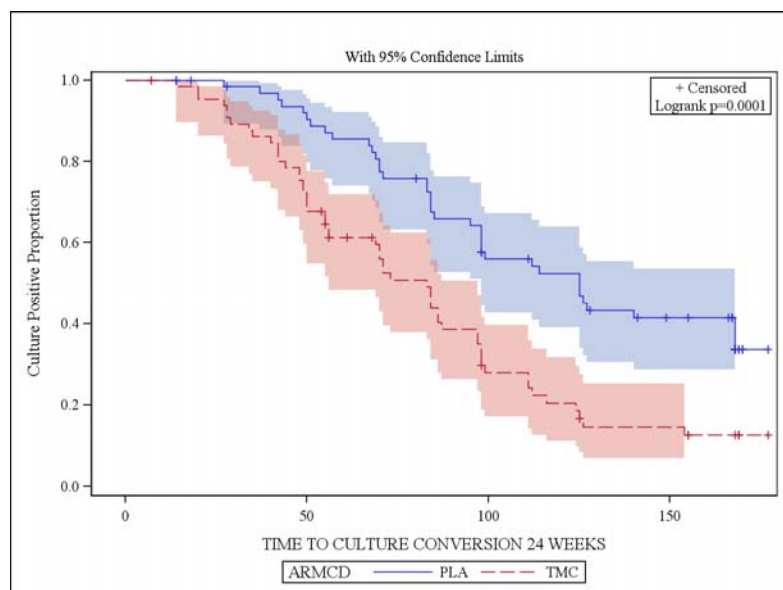
Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

6.1.4.1.b. Trial C208 Stage 2

In Stage 2, the primary efficacy analysis was conducted when all enrolled patients completed their 24-week treatment with either bedaquiline or placebo, or had discontinued earlier.

6.1.4.1.b.i. Primary Endpoint Analysis

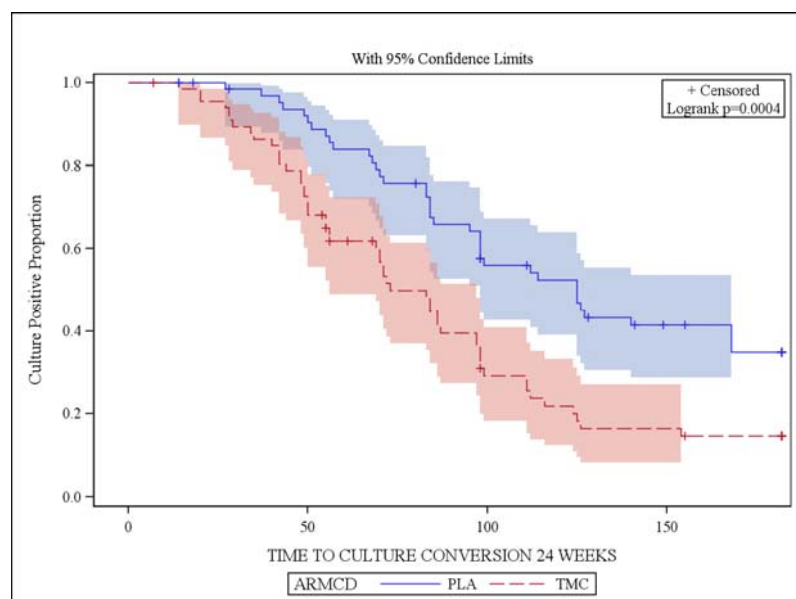
The Kaplan-Meier survival curves below demonstrate that the bedaquiline-exposed group achieved sputum culture conversion faster and in more patients than the placebo group. Four analyses were conducted using different methods of censoring as noted in the figures. All analyses demonstrate a significantly faster time for sputum culture conversion for patients treated with bedaquiline compared to placebo. Figure 2 represents the Applicant analysis. In this analysis, the median time to culture conversion was 83 days (95% CI: 56 to 97) in the bedaquiline group compared to 125 days (95% CI: 98, 168) in the placebo group. The log-rank test p value was 0.0001.



Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Figure 2. Applicant Analysis: Week 24 Primary Endpoint: censored at last MGIT assessment

The Statistical Reviewer conducted an analysis of the primary endpoint. The FDA analysis included a patient who was excluded from the mITT population by the Applicant because the patient (Patient 208-4135) did not have post-randomization MGIT results but had baseline culture results. The FDA analysis is seen in the following figure:



Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Figure 3. FDA Analysis: Kaplan-Meier survival curves for Trial C208 Stage 2: proportions of culture-positive patients over time up to Week 24 (mITT Population) censored at the last MGIT assessment

The FDA analysis showed a significant difference between the bedaquiline and placebo groups are seen. The p-value from the log-rank test was 0.0004, compared to the 0.0001 in the Applicant analysis.

The Applicant utilized a Cox proportional hazards model with treatment, lung cavitation, and pooled center as covariates to determine treatment effect. The primary endpoint analysis showed a statistically significant treatment effect in favor of bedaquiline (hazard ratio [95% CI] for bedaquiline = 2.44 [1.57, 3.80] as shown in the table below. When stratified according to the pooled center and the number of cavitations, the Cox proportional hazards estimates are also shown below.

Table 9. Estimates from Cox proportional hazards model for the primary endpoint (mITT population) with covariates of treatment, pooled center, and cavitation (Trial C208 Stage 2)

Parameter	Level	Estimate	SD	p-value	HR	HR 95% CI
Arm	TMC207	0.89	0.23	<0.0001	2.44	1.57, 3.80
Pooled Center (South America as reference)	Asia	0.53	0.40	0.1813	1.70	0.78, 3.70
	Europe	-0.61	0.49	0.2104	0.54	0.21, 1.42
	South Africa 1	-0.27	0.35	0.4469	0.77	0.39, 1.52
	South Africa 2	-0.09	0.34	0.7984	0.92	0.47, 1.79
	South Africa Other	-0.37	0.37	0.3070	0.69	0.34, 1.41
Cavitation (no as reference)	≥ 2cm in both lungs	-0.88	0.37	0.0159	0.42	0.20, 0.85
	≥ 2cm in one lung only	-1.17	0.30	0.0001	0.31	0.17, 0.56

Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

With stratification, the table above shows that compared with patients with no cavitations, patients with cavitations ≥ 2 cm in both or in one lung only were statistically significantly less likely to have culture conversion.

The FDA similarly performed the Cox proportional hazards model, including the patient excluded by the Applicant. The table below reflects that analysis. The hazard ratio for treatment was 2.15 with a 95% confidence interval of [1.39, 3.31] and a p-value of 0.0005. This is a slightly smaller treatment effect, compared with the Applicant's primary endpoint analysis. Compared with no cavitation or <2 cm category, the hazard for subjects with ≥ 2 cm cavitation was no longer statistically lower. Again, there were no significant interactions between treatment and other covariates in the model.

Table 10. FDA Analysis of treatment effects using the Cox proportional hazards model

Parameter	Level	Estimate	SD	p-value	HR	HR 95% CI
Arm	TMC207	0.77	0.22	0.0005	2.15	1.39, 3.31
Pooled Center (South America as reference)	Asia	0.41	0.39	0.2930	1.51	0.70, 3.25
	Europe	-0.75	0.48	0.1230	0.47	0.18, 1.22
	South Africa 1	-0.57	0.34	0.0890	0.57	0.29, 1.09
	South Africa 2	-0.19	0.34	0.5693	0.83	0.43, 1.60
	South Africa Other	-0.43	0.37	0.2378	0.65	0.32, 1.33
Cavitation (no as reference)	≥ 2 cm in both lungs	-0.57	0.35	0.1038	0.57	0.28, 1.12
	≥ 2 cm in one lung only	-0.88	0.29	0.0021	0.41	0.24, 0.73

Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

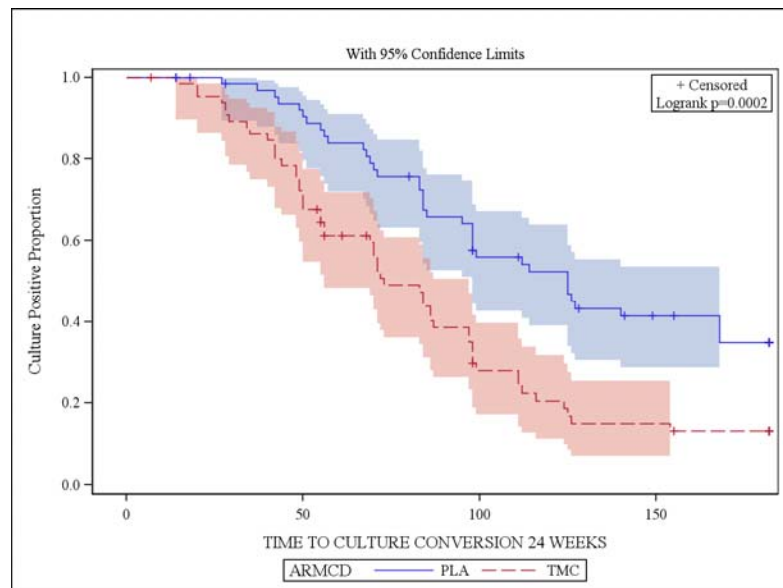
6.1.4.1.b.ii. Additional Primary Endpoint Analysis

The Statistical Reviewer, Dr. Xianbin Li, verified the Applicant-conducted additional analyses of the primary endpoint at Week 24. Figures 3 to 5 demonstrate that the time to sputum culture conversion in the bedaquiline group is faster than the placebo group using different methods of censoring.

Interim Week 24 Primary Endpoint (Time to Culture Conversion)

In this analysis, the primary endpoint, time to culture conversion, was defined similarly as before, except that censoring time for culture conversion was changed from last MGIT visit time (Day 170) to Day 182 in this analysis for some ongoing and discontinued subjects. The result of this analysis is seen below. Except for the change in censored time from Day 170 to Day 182 for some patients in both treatment groups,

no difference in the Kaplan-Meier (KM) curve in this analysis and the previous analysis could be seen.

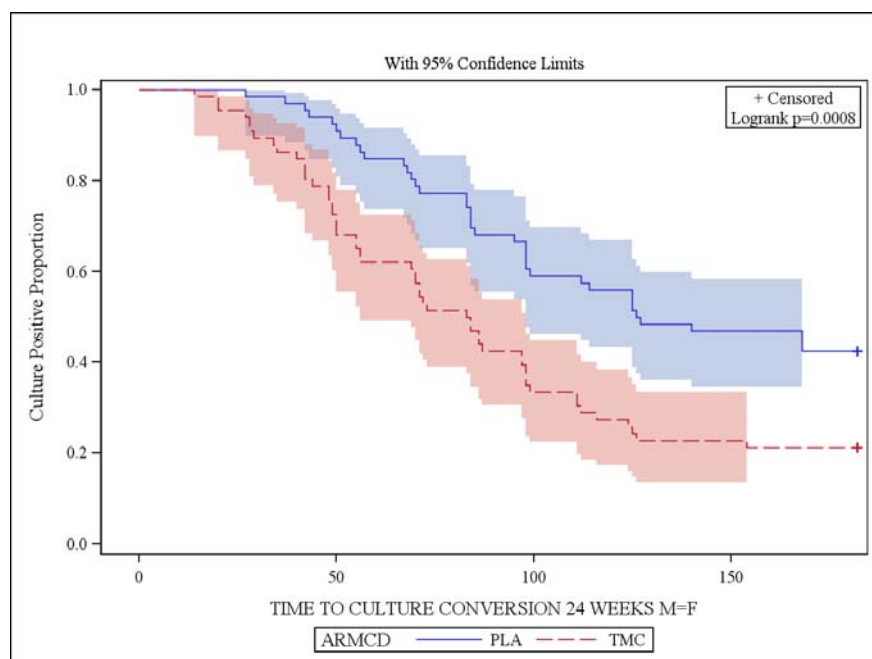


Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Figure 4. Interim Week 24 Primary Endpoint Analysis

Interim Week 24 Primary Endpoint (Time to Culture Conversion): Non-responder End-censored

All nonresponders were end-censored to Day 182. Dr. Li verified that compared to the original primary endpoint analysis, the conversion rates in this analysis were around 7-8% lower in each treatment group (87% versus 79% in the bedaquiline group; 66% versus 58% in the placebo group) because non-responders remained in the risk sets (i.e., a larger denominator for culture conversion rate calculation). However, a 21% difference between the bedaquiline and placebo groups is noted.

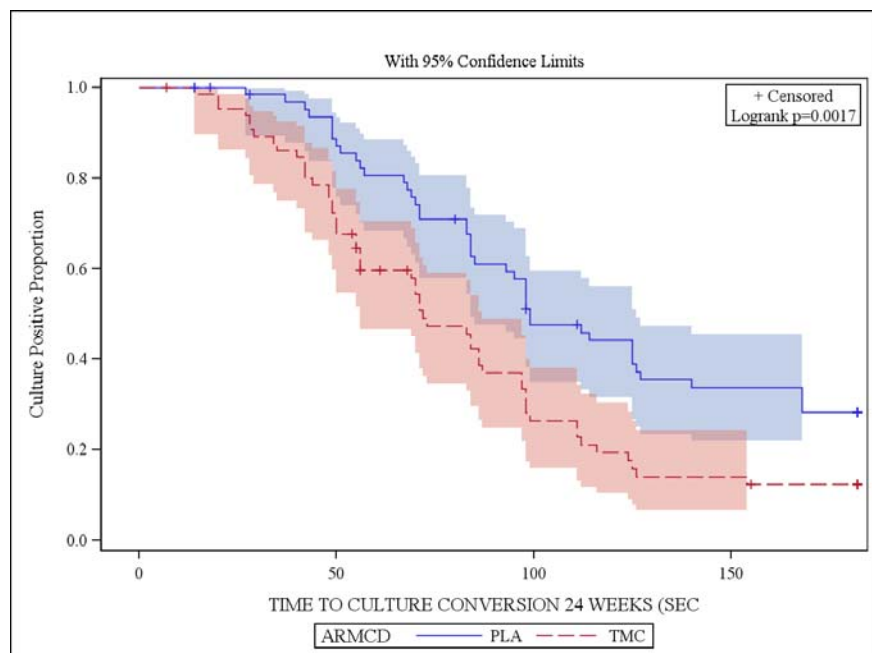


Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Figure 5. Week 24 Interim M=F (end-censored)

Interim Week 24 Primary Endpoint (Time to Culture Conversion): No Overruling by Discontinuation

In this analysis, the censoring status was based on the MGIT results, not on their discontinuation status. This analysis resulted in smaller conversion rates between the two treatment groups (15% vs 21%). The results from the Cox proportional hazards model also demonstrated the significant treatment effect, although the magnitude of effect was slightly reduced.



Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Figure 6. Week 24 Interim 2 (No overruling by discontinuation)

Based on these interim analyses using the three endpoints, bedaquiline was demonstrated to have a significant treatment effect compared with placebo on the time to culture conversion. The results of these interim analyses were consistent with the Week 24 primary endpoint, although the estimated treatment effects were slightly lower.

Table 11: Cox Proportional Hazards Model: Treatment Effect (Relative Risk to Culture Conversion) at week 24 of Trial C208 Stage 2 (mITT Population)

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: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

6.1.5 Analysis of Secondary Endpoints(s)

Time to Culture Conversion at Week 72

The NDA included 72 week data for all patients unless they prematurely discontinued from the study. The Statistical Reviewer conducted three analysis using Week 72 data. Only one analysis will be shown here.

Interim Week 72 Time to Culture Conversion

The figure below shows this analysis. The 72-week data shows that the largest difference between the two groups occurred around Day 150 (around 21 weeks); after which the difference became smaller in time.

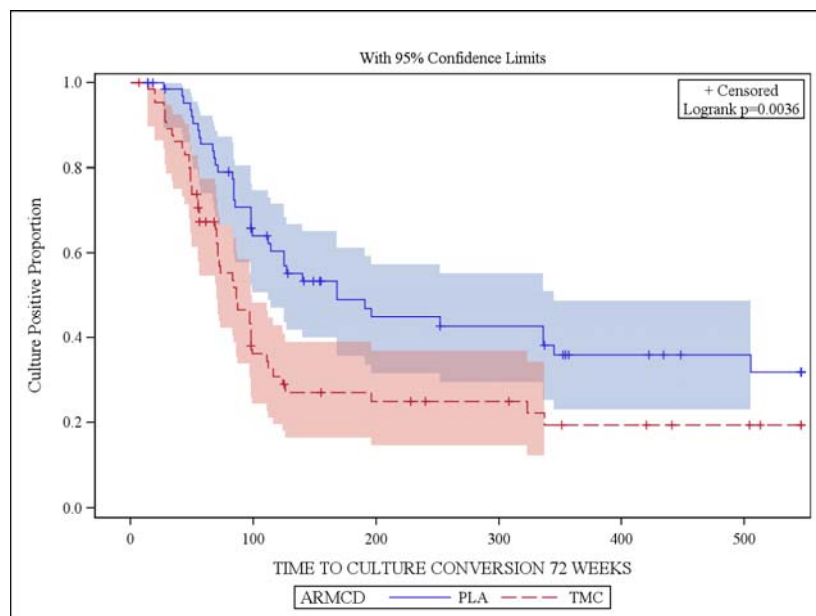


Figure 7. Week 72 Interim Primary Endpoint using Last MGIT or End-Censored

Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Medical Officer Comment:

The observation above could be due to two factors: one possibility is the lack of the durability of the response of bedaquiline-treated patients and the other possibility is the differential in follow-up between the two treatment groups. Given the limitations of the current efficacy data (i.e. limitation on follow-up and the size of the trial), the durability of bedaquiline response would only be determined during the Phase 3 confirmatory trial where durability of response is a primary endpoint.

Culture conversion rates at Week 24 and Week 72

Culture conversion rates based on the primary efficacy analysis at Week 24 are provided in the following table. There was a statistically significant difference in culture conversion rates between the two treatment groups. The reasons for failures were included in the table.

Table 12: Culture conversion rates at Week 24 in the mITT population, Study C208 Stage 2

Microbiologic Status at Week 24	Bedaquiline	Placebo	Diff [95% CI] p-value
Treatment success	52 (79%)	38 (58%)	

Treatment failure	14 (21%)	28 (42%)	21% [5.7%, 36.7%] p=0.008
Failure due to lack of conversion	5 (7.6%)	16 (24.2%)	
Failure due to discontinuation	9 (13.6%)	12 (18.1%)	

Adapted from Table 30, Study Report (page 144). The reported 95% CI was calculated by the reviewer.

Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

The table below shows the FDA analysis of the culture conversion rates at Week 24, including one patient. While still statistically significant, the difference between the two groups is slightly lower.

Table 13. Culture Conversion Rates at Week 24 in the mITT Population (FDA analysis)

Microbiologic Status at Week 24	Bedaquiline	Placebo	Difference [95% CI] p-value
Treatment success	52 (78%)	38 (58%)	20% [4.5%, 35.6%] p=0.0135
Treatment failure	15 (22%)	28 (42%)	

Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

The following table shows the culture conversion rates at Week 72 in the mITT population. Note that the difference in culture conversion rate at Week 72 between the treatment groups was no longer statistically significant.

Table 14: Culture conversion rates at Week 72 in the mITT population, Study C208 Stage 2

Microbiologic Status at Week 72	Bedaquiline	Placebo	Diff [95% CI] p-value
Treatment success	47 (71%)	37 (56%)	15% [-1.1%, 31.4%] 0.070
Treatment failure	19 (29%)	29 (44%)	
Failure due to lack of conversion	3 (4.5%)	7 (10.6%)	
Failure due to discontinuation	16 (24.2%)	22 (33.3%)	

Source: Dr. Xianbin Li. Statistical Review. NDA 2004384. Dec 4, 2012.

Medical Officer Comment:

The difference in culture conversion rates between the bedaquiline and placebo groups is statistically significant in the 24 week timepoint. While still present at Week 72, the difference is not statistically significant. While durability of response is an etiologic possibility that can only be determined in the Phase 3 confirmatory trial, the observation of greater failures in the placebo group because of more patients discontinuing the drug and not due to lack of conversion, as shown in Table 14, makes this less concerning. The increased failure rates from discontinuation may reflect reasons for discontinuation such as bedaquiline/regimen toxicities and compliance.

While this could be a valid observation, differences in follow-up and premature discontinuation/withdrawal in the two treatment groups could be the reason why the differences between the two Kaplan-Meier survival graphs started to disappear. Indeed, the uncertainty of findings that reflect durability of response is related to the fact that this Application is being evaluated under the Accelerated Pathway Program to hasten drug

development for diseases such as tuberculosis. The validation of this finding is therefore important in the Phase 3 confirmatory trial.

The primary endpoint of time to sputum culture conversion was deemed acceptable as an endpoint used for an antimycobacterial drug that will be evaluated under the Accelerated Pathway Program. The AIDAC meeting in June 2009 deemed that the use of sputum culture conversion as a surrogate to standard endpoints in tuberculosis clinical trials, such as relapse, long-term response, and durability of response, is acceptable. As said, this came from the urgent need to develop antibacterials to treat deadly diseases with very few therapeutic options.

6.1.6 Other Endpoints

Additional secondary analysis conducted by the Agency includes an analysis of relapses.

Relapse

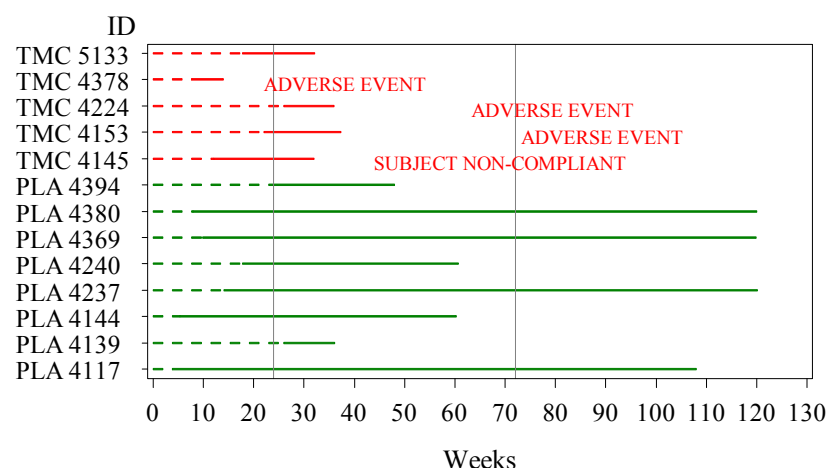
Relapse was defined as having a confirmed positive sputum culture (or a single positive sputum culture after which the subject discontinued) during or after treatment after conversion, with isolation of an *M. tuberculosis* strain with the same genotype compared to baseline or with unknown genotype as compared to baseline. Therefore, the definition of relapse does not require either week 24 culture conversion or week 72 culture conversion.

Relapse was considered as having occurred when not followed by a subsequent culture conversion. This was not captured in the definition but was used in analysis. However, because there were no genotype data provided in the NDA, differentiation between relapse versus re-infection could not be done.

In the mITT population, 5 subjects (7.6%) in the bedaquiline group and 8 subjects (12.1%) in the placebo group experienced relapse. There was one female (race: other) patient who relapsed in each group. In the ITT population, there was one additional relapse subject in the placebo group who was male, discontinued and relapsed at Day 172.

A graphical representation of the timing of the relapses in the mITT population is seen in the following figure. The time from onset of treatment to culture conversion is represented by a broken line while the time from culture conversion to relapse is represented by a solid line.

Figure 8: Time to culture conversion and time from culture conversion to relapse for subjects with relapse in the mITT population, Study C208 Stage 2



As can be seen from the figure, the subjects in the placebo group appear to take a longer time from culture conversion to relapse than those in the bedaquiline group.

Medical Officer Comment:

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 rather than two positive culture results. With the criteria of relapse defined as two positive cultures within a 25-day period, these patients could possibly be non-relapsers had subsequent cultures are obtained and these subsequent cultures are negative. However, since the time the sputum specimen for culture was obtained was the patient's last visit, then these patients were categorized as relapsers despite the fact that they only have one specimen becoming positive. If these four subjects were excluded, the two treatment arms become more comparable with respect to relapse with 5 relapses on bedaquiline and 4 on placebo.

Time on background regimen by treatment group for relapsed subjects is shown below. As more subjects in the bedaquiline group discontinued, the average time on background was much shorter.

Table 15: Time on background regimen in weeks for relapsed subjects by treatment group, Study C208 Stage 2

Time on Background Regimen	Bedaquiline	Placebo
N	5	8
Mean (SD)	53.7 (24.5)	79.3 (33.9)
[Range]	[20.1, 76.3]	[26.1, 115.7]

Medical Officer Comment:

From the table above, there appears to be no correlation between the time a treatment group was treated with the BR and the incidence of relapses. This analysis is confounded by the observation that more bedaquiline-treated patients discontinued.

6.1.7 Subpopulations

6.1.7.1. Gender, Race, Age, and Geographic Region

Gender

Subgroup analyses will be done for Study C208 Stage 2. The following table shows the culture conversion rates at Week 24 by gender. The trend was similar across the two subgroups with the males reaching statistical significance. The possible reason is that the sample size for female was small.

Table 16: Culture conversion rates at Week 24 by gender in the mITT Population, Study C208 Stage 2

	Bedaquiline	Placebo	Difference [95% CI] p-value
Male	35/45 (77.8%)	23/40 (57.5%)	20.3% [0.7%, 39.8%] 0.0450
Female	17/21 (81.0%)	15/26 (57.7%)	23.3% [-2.1%, 48.6%] 0.1208*

* Exact method.

Race

The following table shows the culture conversion rates at Week 24 by race. In all races, except Blacks, bedaquiline-treated groups demonstrated a consistently higher culture conversion rate than the placebo group, although the treatment effects varied among different races. Among Hispanic patients and patients with “Other” race, the difference in the treatment effect between the bedaquiline group and the placebo was statistically significant. In Black patients, the two treatment groups had similar conversion rates.

Table 17: Culture conversion rates at Week 24 by race in the mITT population, Study C208 Stage 2

Race	Bedaquiline	Placebo	Difference [95% CI] p-value
Black	17/24 (70.8%)	18/25 (72.0%)	-1.2% [-26.5%, 24.1%] 0.93
Caucasian/White	4/6 (66.7%)	4/8 (50.0%)	16.7% [-37.8%, 64.1%] 0.64*
Hispanic	12/12 (100%)	5/10 (50.0%)	50.0% [15.0%, 81.3%] 0.006*

Oriental/Asian	8/9 (88.9%)	5/6 (83.3%)	5.6% [-36.3%, 53.0%] 0.89*
Other	11/15 (73.3%)	6/17 (35.3%)	38.0% [2.1%, 67.7%] 0.037*

*Exact method

Medical Officer Comment:

Analysis by sites demonstrated that the lower conversion in Blacks is primarily due to results from one site (one investigator) in South Africa, with lower conversion rates at Week 24 in the bedaquiline group than in the placebo group. When rates of conversion in blacks are compared to the rates of conversion in other races, the Medical Officer believes that the placebo conversion rate is higher compared to the placebo conversion rates of other races. The bedaquiline conversion rate in blacks is similar to the bedaquiline conversion rate in other races.

As shown in the following table, Black patients from one clinical site in the South Africa-2 region had a lower culture conversion rate in the bedaquiline group than in the placebo group. This pattern is inconsistent with results from Black patients from the other regions. Except for the fact that only one investigator is responsible for this clinical site, the reason for this treatment effect discrepancy is unclear. Further investigations by demographic factors, HIV status, TB types, and lung cavitation did not provide any discernable patterns. In this particular site, the conversion rate of the bedaquiline group is similar to the conversion rate in groups with other ethnicities. The placebo group, however, appears to have a higher conversion rate compared to the other ethnic groups. Because the sample size in this site was small, the reason for the higher conversion rate in the placebo group could not be determined. The Medical Officer expects that the high conversion rate in the placebo group from this site would unlikely impact the overall treatment effects of the two treatment groups in the study. Nevertheless, the confirmatory Phase 3 trial could provide more insight to this observation.

Table 18: Conversion Rates at Week 24 in Black Subjects in the mITT population, Study C208 Stage 2

	Bedaquiline	Placebo
South-Africa 2	8/12 (66.7%)	11/12 (91.7%)
Black in other regions	9/12 (75.0%)	7/13 (53.8%)
One doctor from 'South Africa-2'		

The following table shows the culture conversion rates by region in the mITT population. Culture conversion rates in the bedaquiline arm were consistently higher than placebo. The only exceptions were in Asia, where culture conversion rate were 100% in both arms, and South Africa 2 regions, where the culture conversion rate was higher in the placebo compared to bedaquiline. In the South African site, twenty-four black patients (12 in each group) were enrolled.

Table 19: Culture conversion rate at Week 24 by pooled center in the mITT population, Study C208 Stage 2

TB type	TMC207	Placebo	Difference [exact 95% CI] exact p-value
Asia	8/8 (100%)	4/4 (100%)	
Eastern Europe	3/6 (50.0%)	3/7 (42.9%)	7.1% [-50.2%, 59.2%] 0.93
South Africa 1	11/14 (78.6%)	7/17 (41.2%)	37.4% [1.3%, 66.7%] 0.042
South Africa 2	9/13 (69.2%)	11/13 (84.6%)	-15.4% [-48.5%, 19.5%] 0.53
South Africa Other	7/10 (70.0%)	6/12 (50%)	20.0% [-23.4%, 58.4%] 0.46
South America	14/15 (93.3%)	7/13 (53.9%)	39.5% [6.6%, 69.0%] 0.019

One doctor from South Africa-1 and one doctor from South Africa-2

HIV status as a predictor of conversion was examined by region. All HIV infected patients were from South Africa. In the South African site in question, a higher proportion of HIV positive patients were randomized to the placebo group than in the bedaquiline group in this site. Given the challenge of culture conversion in HIV-infected patients, this imbalance in HIV-infected patients in the treatment groups in this center does not explain the observations.

Table 20: HIV status by region in mITT population, Study C208 Stage 2

Region	Bedaquiline	Placebo
South Africa 1	0/14	1/17 (6%)
South Africa 2	2/13 (15%)	8/13 (62%)
South Africa Other	3/10 (30%)	5/12 (42%)

Medical Officer Comment:

In all, the reason for the lower culture conversion rates in Blacks in this study is unknown. While the sample size was small, it appears that efficacy data from one South African site (one of the two sites enrolling Black patients where the culture conversion rate in the placebo group was higher in the placebo group compared to the bedaquiline group) could be responsible for this observation. The increased proportion of HIV-infected patients in the placebo group theoretically increases the risk of the placebo group NOT to convert.

One potential explanation for this observation is the higher bedaquiline clearance noted in Black patients compared to other races in a population PK analysis. PK studies have shown that the bedaquiline clearance for Blacks is 52% higher than patients of other races. However, the culture conversion rate for the bedaquiline group in this study appears to be similar to other races. It is the culture conversion rate for the placebo group that is higher than the placebo groups for other races. The increased bedaquiline clearance in blacks could explain the differences in culture conversion rate if a decrease in culture conversion was observed in the bedaquiline group relative to other races. This was not observed. Instead, it is the placebo group which seems to have a higher culture conversion

rate relative to the other placebo groups of other races. Thus, this imbalance in culture conversion rates is still unexplained.

The impact of the observed increased clearance in Black patients on culture conversion and time to sputum culture conversion is still under investigation. More PK studies to investigate the bedaquiline increased clearance and its effect on efficacy and safety are needed. Currently, in the absence of any definitive evidence of the impact of the PK differences based on race on the efficacy and safety of bedaquiline, the Applicant recommends no dosage adjustment is necessary based on race. The confirmatory trial, Trial C210, could probably clarify the observations noted in Black TB patients.

Age

The following table shows the culture conversion rates at Week 24 by age group. The culture conversion rates for the age group 30 to <50 years had a higher difference between the bedaquiline and placebo groups. In all age groups, bedaquiline showed consistently better culture conversion rates than the placebo.

Table 21: Culture conversion rate at Week 24 by pooled center in the mITT population, Study C208 Stage 2

Age group in yrs	Bedaquiline	Placebo	Difference [95% CI] p-value
18 to <30	22/29 (75.9%)	17/28 (60.7%)	15.1% [-8.7%, 39.0%] 0.22
30 to < 50	20/23 (87.0%)	16/30 (53.3%)	33.6% [11.1%, 56.2%] 0.009*
50 to 65	10/14 (71.4%)	5/8 (62.5%)	8.9% [-31.4%, 50.9%] 0.79
Sponsor's analysis			
≤45	39/47 (83.0%)	32/54 (59.3%)	
>45 to 65	13/19 (68.4%)	6/12 (50.0%)	

*Exact method.

Additional Analyses with Relapsed Subjects in Study C208 Stage 2

The following table shows the relapses by age and race. Eight relapses were in age group 30 to <50 years of age. Seven relapses were among Black subjects.

Table 22: Age and Race for subjects with relapse, Study C208 Stage 2

	TMC207	Placebo
Age		
<30	1	1
30 to <50	3	5
50 to 65	1	2
Race		
Black	2	5
Oriental/Asian	1	0
Other (non Caucasian/White or Hispanic)	2	3

Medical Officer Comment:

The Medical Officer does not observe any differences in culture conversion rate based on age. The observations stated here is most probably a reflection of the relative distribution of enrolled patients.

Lung Cavitation

The following table shows the culture conversion rates at Week 24 by cavitation type in the mITT population. The differences between the two treatment groups were not statistically different from each other for each lung cavitation type.

Table 23: Culture conversion rates at Week 24 by lung cavitation in the mITT population, Study C208 Stage 2

Lung cavitation	Bedaquiline	Placebo	Difference [95% CI] p-value
No cavitations or cavitations < 2 cm	12/12 (100%)	8/10 (80.0%)	20.0% [-10.8%, 55.6%] 0.17*
Cavitations >= 2 cm in one lung only	30/42 (71.4%)	21/41 (51.2%)	20.2% [-0.3%, 40.7%] 0.059
Cavitations >= 2 cm in both lungs	10/12 (83.3%)	9/15 (60%)	23.3% [-13.7%, 56.5%] 0.24*

*Exact method.

Medical Officer Comment:

The Medical Officer concurs that no apparent relationship between culture conversion and lung cavitation is noted.

Baseline Isolate Type

The following subgroup analysis shows the time to culture conversion by TB-type (MDR and pre-XDR TB) in the mITT population. The p-value from the Log-rank test was 0.0004 and 0.0097, respectively. TMC207 shows a consistent treatment effect in subjects with MDR-TB or pre-XDR-TB.

Sample sizes for DS-TB and Pre-XDR were too small for Kaplan-Meier plotting.

The following table shows the culture conversion rates at Week 24 by baseline TB type. Again, the difference in culture conversion rates was statistically significant in MDR or pre-XDR TB subjects.

Table 24: Culture conversion rates at Week 24 by baseline TB type in the mITT population, Study C208 Stage 2

TB type	Bedaquiline	Placebo	Difference [95% CI] p-value
MDR	32/39 (82.1%)	28/45 (62.2%)	19.8% [1.2%, 38.4%] 0.0448

Pre-XDR	11/15 (73.3%)	4/12 (33.3%)	40.0% [0.6%, 70.8%] 0.0467*
Missing values	9/12 (66.7%)	6/9 (66.7%)	

*Exact method. Missing values were considered as MDR-TB based on medical history.

Additionally, analyses by baseline TB type (DS, MDR, pre-XDR, XDR, missing) for the ITT population also showed consistent results; 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 25. Culture conversion rates at Week 24 by baseline TB type in the ITT population, Study C208 Stage 2

TB type	Bedaquiline	Placebo
DS	1/4 (25.0%)	1/4 (25.0%)
MDR	32/40 (80.1%)	29/46 (63.0%)
Pre-XDR	12/16 (75.0%)	4/12 (33.3%)
XDR	2/3 (66.6%)	3/4 (25.0%)
Missing values*	12/16 (75.0%)	9/15 (60.0%)
Total	59/79 (74.7%)	46/81 (56.8%)

Medical Officer Comment:

The trends observed appear to reassure the usefulness of bedaquiline as treatment for MDR-TB. The table above demonstrates that the patients with isolates with greater resistance (MDR-TB and Pre-XDR isolates) have greater culture conversion, compared to patients with DS-TB. While the number of patients here is limited, this trend is reassuring and should be explored in the Phase 3 confirmatory trial.

HIV Infection

There is a higher proportion of HIV negative subjects in the bedaquiline (61/66 or 92.4%) group, compared to the placebo group (52/66, 78.8%). The following graphs show the survival curves by HIV status at baseline. The number of HIV infected patients was too small to make a meaningful comparison. The p-value from the Log-rank test in HIV negative subjects in the mITT population was 0.0001.

The following table shows the culture conversion rates by HIV status at baseline. In the bedaquiline group, the conversion rates were similar regardless of HIV status, though the sample size for HIV infected patients was very limited. However, in the placebo

group, HIV uninfected patients had a lower conversion rate than HIV infected subjects. Therefore, the effect of the imbalance in the number of HIV-infected patients in the bedaquiline group is cancelled by the better culture conversion rates in HIV infected patients.

Among HIV negative patients, compared with the placebo group, the TMC207 group had a higher conversion rate. Among HIV positive, the conversion rates were similar.

Figure 9: Kaplan-Meier survival curves for culture conversion by Week 24 by baseline HIV status in the mITT population, Study C208 Stage 2

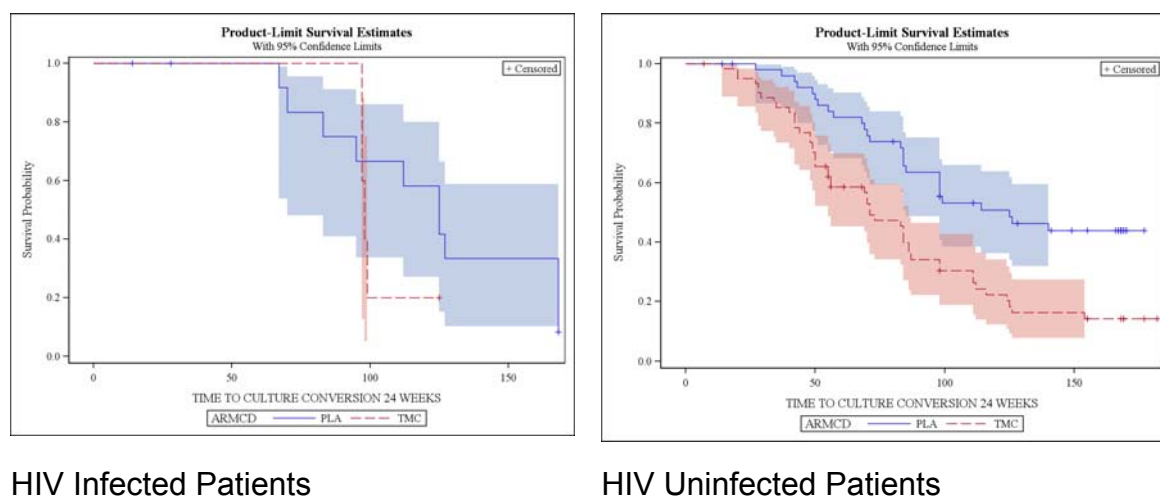


Table 26: Culture conversion rates at Week 24 by baseline HIV status in the mITT population, Study C208 Stage 2

HIV status	Bedaquiline	Placebo	Difference [95% CI] p-value
HIV negative	48/61 (78.7%)	27/52 (51.9%)	26.8% [9.7%, 43.8%] 0.0027
HIV positive	4/5 (80.0%)	11/14 (78.6%)	1.4% [-52.2%, 38.6%] 1*

*Exact method.

Based on the protocol subjects were expected not to take antiviral treatment for HIV/AIDS. Therefore no additional analyses on antiviral treatment among HIV positive subjects were conducted.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Culture Conversion Rate by Compliance

The following two tables show the conversion status at Week 24 by treatment compliance status in the investigational stage (first two weeks and Weeks 3-24). Compliance was defined by the percentage of number of doses taken during the actual

observation period for each subject (i.e. actual number of doses taken divided by planned number of doses during the observation period). Note compliance is not the same as the total number of doses taken, nor duration of treatment.

In the first two weeks, 61 and 62 subjects in the TMC207 and Placebo groups had 100% compliance and only a few subjects were in other compliance categories. Therefore, it is not possible to compare the effect of compliance in the first two weeks on culture conversion in each treatment group. Compliance seems not related with disposition type (completed, ongoing, discontinued, rollover).

In Weeks 3 to 24, only 7 and 10 subjects in the TMC207 and placebo took less than 95% of doses. When the compliance rates were higher than 80%, TMC207 showed a consistent treatment result. Discontinued subjects were less likely to have 100% or higher compliance. Since the sample size was small, it is not worthwhile to tabulate the conversion rates by compliance and disposition type.

Table 27: Culture conversion at Week 24 by compliance during Weeks 1 to 2 in the mITT population, Study C208 Stage 2

COMPLIANCE (Wk 1-2)	Bedaquiline	Placebo
100%	48/61 (78.69%)	37/62 (59.68%)
80% to 95%	4/4 (100%)	1/2 (50%)
50% to <80%	0/1	0/2
Total	52/66	38/66

Table 28: Culture conversion at Week 24 by compliance during Weeks 3 to 24 in the mITT population, Study C208 Stage 2

COMPLIANCE (Wks 3-24)	Bedaquiline	Placebo
<50%	0	0/2
50% to <80%	0/1	0/2
80% to <95%	4/6 (66.67%)	2/6 (33.33%)
95% to <100%	9/13 (69.23%)	2/6 (33.33%)
100%	15/17 (88.24%)	16/23 (69.57%)
>100% to 105%	22/25 (88.00%)	18/24 (75.00%)
> 105%	2/3 (66.67%)	0/1
Total	52/65	38/64

In this analysis, one TMC207 subject and two placebo subjects had missing compliance values.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The prolonged terminal half-life of bedaquiline (4-5 months) and its metabolite M2 (5.5 months) indicate that the bedaquiline effects (efficacy and toxicities) persist beyond bedaquiline's active interventional treatment phase.

7 Review of Safety

Safety Summary

The evaluation of safety for bedaquiline requires a synthesis of information from several disciplines. First, bedaquiline's mechanism of action, the inhibition of ATP synthase, is intracellular. Because the affinity of bedaquiline for mycobacterial ATP synthase is >20,000 fold greater than its affinity for eukaryotic ATP synthase, in vitro studies indicate that bedaquiline's action is specific to the mycobacterial organism.

Second, the unique pharmacokinetic properties of bedaquiline are closely tied to its safety profile. Bedaquiline's prolonged terminal half-life of 4 to 5 months is related to the fact that bedaquiline is extensively distributed and retained in tissues because it is more than 99% protein bound. Bedaquiline is metabolized by the CYP3A4 enzyme to its two metabolites: M2 which 4-6 fold less active, has a terminal half life of 5.5 months, and is thought to be responsible for the QT prolongation noted in clinical trials. Because bedaquiline is metabolized by the cytochrome P450 isoenzymes, the evaluation of drug-drug interactions with CP450 inhibitors and inducers is essential in evaluating bedaquiline's potential to cause toxicities from elevated or decreased exposure.

Nonclinical studies demonstrate the potential toxicities that could develop from the use of bedaquiline. Most of the observed toxicities were in animals given exposures that are significantly higher than human clinical exposures. The following toxicities were observed in animals given bedaquiline: QT prolongation, cardiac marker elevation (troponin, CPK), centrilobular hepatic hypertrophy, single cell hepatic necrosis, increased transaminases; phospholipidosis, and pancreatic, gastric, and skeletal muscle cellular changes with necrosis and atrophy.

The bedaquiline human safety clinical experience is informed by eleven Phase 1 studies and four Phase 2 trials. Phase 1 studies include single- and multiple-dose studies in healthy subjects and a hepatic impairment study, drug-drug interaction study, and the single-dose Thorough QT study. Phase 2 trials include a Phase 2a 7 day monotherapy early bactericidal activity study in patients with drug-susceptible tuberculosis, a Phase 2b trial in treatment naive MDR-TB patients with either an 8 week bedaquiline exposure

(Trial C208 Stage 1) or a 24 week bedaquiline exposure (Trial C208 Stage 2), on top of an optimized background regimen, and a Phase 2b trial (Trial C209) in treatment-experienced MDR, pre-XDR, and XDR-TB patients given a 24 week exposure of bedaquiline, on top of an individualized background regimen.

Given the indication of MDR-TB and the proposed dosing regimen of 400 mg once daily for the first two weeks, followed by 200 mg three times weekly for the next 22 weeks, the appropriate safety database for the clinical development program includes patients with similar indication and exposure: pulmonary sputum-positive MDR-TB patients treated with 24 weeks of bedaquiline on top of a background regimen. Of the 335 patients exposed to any dose of bedaquiline in the Phase 2b trials, 305 MDR-TB patients were exposed to the proposed 24 week dosing regiment of bedaquiline. This database appears limited but is sufficient for detection of ADRs that could potentially occur in 1% of the exposed population.

Of the Phase 2 clinical trials conducted, Trial C208 Stage 2 is considered the pivotal trial, noting the appropriate bedaquiline exposure of MDR-TB patients and its comparative nature. However, because of its limited enrollment (79 bedaquiline vs 81 placebo-exposed), safety data from the uncontrolled Trial C209 is used to augment the safety database.

Analysis of safety data mainly from Trial C208 Stage 2 and augmented by data from Trial C209 has identified a number of potential risks that could be associated with the use of bedaquiline as treatment for pulmonary MDR-TB:

- Increased risk of death
- QT interval prolongation
- Hepatic-related adverse drug reactions.

In Trial C208 Stage 2, an increase risk of death was observed with the use of bedaquiline compared to placebo. Using a 120 week cutoff from the initiation of treatment, nine of 79 bedaquiline-treated patients (11.4%) died compared to 2 of 81 placebo-treated patients (2.5%). While concerning, an etiology of the imbalance could not be determined from the current safety database. The most apparent trend that was observed was that tuberculosis was the cause of death in both placebo deaths and in five out of the nine (5/9) bedaquiline-treated deaths. Interestingly, seven of the nine (7/9) bedaquiline treated deaths converted and 3 of these 7 (3/7) patients relapsed early on during their clinical course and died from tuberculosis. Otherwise, no discernible pattern between death and conversion, relapse, microbiologic response, sensitivity to the background regimen, HIV status, severity of the disease, and the type of MDR-TB isolate, could be identified. The Medical Officer believes that given the limited number of patients in this placebo-controlled trial, the etiology of the imbalance would be difficult to detect and ascertain.

An increased risk of QT interval prolongation was observed in bedaquiline-treated patients compared to placebo-treated patients. In Trial C208 Stage 2, the largest mean increase from reference in QTcF during the 24 week bedaquiline treatment was 15.7 ms at Week 18, compared to 6.2 ms in the comparator group at the same timepoint. After bedaquiline was stopped, the difference in the mean increase of QTcF from reference between the bedaquiline and placebo groups persisted. This could be due to bedaquiline and M2's long terminal half lives. The prolongation of the QTcF interval in bedaquiline-treated patients was also observed in the smaller Trial C208 Stage 1.

The additive effect on QT interval prolongation of the co-administration of drugs with a QT-prolonging potential was observed in a posthoc analysis of bedaquiline-treated patients given another QT prolonging drug in Trial C208 Stage 2 and another posthoc analysis of patients in Trial C209. Analysis of the data from Trial C209 demonstrated that there is a positive relationship between the number of QT prolonging drugs added to the bedaquiline regimen and the greater severity of the QT prolongation. In particular, the antituberculous drug clofazimine was identified to additively increase the risk of QT prolongation. To minimize the risk of QT interval prolongation, the judicious choice and use of concomitant medications, with avoidance of drugs with QT-prolonging potential should be done.

Serum transaminase elevation occurred more frequently in bedaquiline-treated patients compared to the comparator. Hepatic-related serious adverse events, one of them resulting in death, occurred in the bedaquiline group. Three reasons preclude the assessment of definite causation of these events to bedaquiline. First, the safety database for bedaquiline in the controlled trial is limited. Second, the cases of serum transaminase elevation and hepatic-related serious adverse events are confounded with alcohol use and concomitant hepatotoxic medication use. Lastly, the absence of information to rule out other potential etiologies of the hepatic adverse event such as the evaluation for viral hepatitis makes it difficult to determine association with bedaquiline. Despite these limitations, current safety data from the controlled trial indicate a safety signal for hepatic-related adverse drug reactions, in particular, the elevation of serum transaminases. Risk factors that may worsen such adverse drug reactions such as alcohol use and concomitant use of drugs with hepatotoxic potential should be avoided.

Several adverse drug reactions are discussed because of their seriousness. Acute pancreatitis, manifested by increased amylase and lipase, was seen in greater frequency in three bedaquiline-treated patients. Two of these patients had mild isolated pancreatic enzyme elevation. Another patient with chronic pancreatitis and history of alcohol abuse developed a combined elevation of serum transaminase (AST), GGT and amylase. The fourth patient, whose death was attributed to alcohol poisoning, experienced transiently elevated levels of pancreatic (amylase, lipase), skeletal muscle (CK), and gastric (trypsin, gastrin) markers at Week 8 of the trial, with associated fever, abdominal pain, and protracted pruritus a few weeks later. Etiology could not be

determined but a spontaneously resolving drug idiosyncratic reaction is highly possible. Phospholipidosis can be considered but could not be verified in the absence of pathological evidence. Similar to the other ADRs reported, causality assessment with bedaquiline is challenging because of the patient's multiple medications and the negative dechallenge.

In all, while signals for QT prolongation and hepatic-related adverse events appear to be present in the pivotal and supportive trials, the risk for increased deaths in bedaquiline-treated patients compared to the comparator could be understood by the augmented safety database for bedaquiline coming from the confirmatory Phase 3 trial

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

7.1.1.1. Phase 1 Studies

The evaluation of safety of bedaquiline is based on safety data from 11 Phase 1 studies and 3 Phase 2 trials. Of the 11 Phase 1 bedaquiline studies, eight (8) studies in healthy subjects (5 single-dose studies and 3 multiple-dose studies) were included in a Phase 1 study pooled analysis. Table 29 summarizes the Phase 1 studies in healthy subjects included in the analysis.

Table 29. List of Phase 1 studies included in analysis

Trial	Design	N _{total} / N _{TMC207} ^a
<i>Single-dose trials</i>		
CDE-101	Part 1: Double-blind, randomized, placebo-controlled, single-ascending dose trial	54 / 36
	Part 2: Open-label, randomized, crossover, food interaction trial	12 / 12
BAC1003	Open-label, DDI trial with RMP	16 / 16
C108	Open-label, randomized, crossover, bioavailability trial	24 / 24
C110	Open-label, randomized, crossover, DDI trial with lopinavir/ritonavir	16 / 16
C111	Open-label, randomized, crossover, bioavailability trial	28 / 28
<i>Multiple-dose trials</i>		
CDE-102	Double-blind, randomized, placebo-controlled, multiple-ascending dose trial	27 / 18
C104	Open-label, crossover, DDI trial with INH and PZA	24 / 23
C109	Open-label, crossover, DDI trial with ketoconazole	16 / 16
Total number of subjects (8 trials):		217 / 189

^a number of subjects who received at least one dose of TMC207

Source: [Module 2.7.4/TMC207-C0000001-Anal-GEN/Display GEN.2](#)

Source: NDA 204384. Original Submission. Summary of Clinical Safety. p. 29. June 2012.

Three Phase 1 studies were excluded in the analysis. Two studies were not included because the studies did not enroll healthy subjects.

- Study C117 was an open-label, DDI trial with nevirapine in 16 HIV-1 infected patients without TB, all of whom received bedaquiline.
- Study C112 was an open-label, single-dose trial in 8 healthy subjects and 8 subjects with moderate hepatic impairment, all of whom received bedaquiline.

Another study, Study TBC1003 (Thorough QT Study), was a double-blind, single-dose trial in 88 healthy subjects to determine the effect on the QT/QTc interval of a single suprathreshold dose of bedaquiline (800 mg). Forty-four subjects received bedaquiline.

Appendix A summarizes the objectives, trial design, total number of patients in the trial, and dosing regimen for the Phase 1 studies conducted by Janssen Research and Development.

7.1.1.2. Phase 2 Trials

The Phase 2 trials conducted as part of the bedaquiline drug development program consist of 1 completed Phase IIa trial and 2 ongoing Phase IIb trials. This is summarized in tabular form.

Table 30. Overview of Phase 2 trials

Trial (Status)	Design	Population	Treatment	Dose (TMC207/control)	Duration	N _{total}	Refer to Module
TMC207-C202 (completed)	Randomized, open-label, active-controlled	DS-TB	TMC207 or RMP or INH followed by standard TB therapy	TMC207 25 mg q.d. TMC207 100 mg q.d. TMC207 400 mg q.d. RMP 600 mg q.d. INH 300 mg q.d.	TMC207/control treatment: 7 days	75	5.3.5.2
TMC207-C208 Stage 1 (completed)	Randomized, double-blind, placebo-controlled	newly diagnosed MDR-TB ^a	TMC207 or placebo + preferred BR composed of: KAN, OFL, ETH, PZA, and CS/TRD	Week 1-2: TMC207 400 mg q.d. Week 3-8: TMC207 200 mg t.i.w.	TMC207/control treatment: 8 weeks Follow-up ^b : 96 weeks	47	5.3.5.1
Stage 2 (ongoing)	Randomized, double-blind, placebo-controlled	newly diagnosed MDR-TB ^a	TMC207 or placebo + preferred BR composed of: KAN, OFL, ETH, PZA, and CS/TRD	Week 1-2: TMC207 400 mg q.d. Week 3-24: TMC207 200 mg t.i.w.	TMC207/control treatment: 24 weeks Follow-up ^b : 96 weeks	161 ^c	
	Open-label rollover arm	MDR-TB, XDR-TB ^d	TMC207 + individually optimized BR	Week 1-2: TMC207 400 mg q.d. Week 3-24: TMC207 200 mg t.i.w.	TMC207 treatment: 24 weeks Follow-up ^b : 96 weeks	1	
TMC207-C209 (ongoing)	Open-label, uncontrolled	MDR-TB ^e	TMC207 + individually optimized BR	Week 1-2: TMC207 400 mg q.d. Week 3-24: TMC207 200 mg t.i.w.	TMC207 treatment: 24 weeks Follow-up ^b : 96 weeks	233	5.3.5.2

N = number of subjects

^a Subjects found to have pre-XDR-TB after randomization were allowed to continue in both Stage 1 and Stage 2. Subjects found to have XDR-TB after randomization had to be withdrawn from the trial (in Stage 1, and in Stage 2 up to implementation Protocol Amendment IV, see also footnote d).

^b Follow-up consisted of a BR only treatment period and a treatment-free follow-up period.

^c A total of 161 subjects were randomized, of whom 160 were treated.

^d Subjects identified as XDR after randomization were given the option to either withdraw from the trial or immediately receive open-label treatment with TMC207 in the rollover arm after Protocol Amendment IV.

^e Subjects with XDR-TB were allowed to enter the trial.

Clinical Review
Ariel R. Porcalla, MD, MPH
NDA 204 384
BEDAQUILINE (bedaquiline)

Source: NDA 204384. Original Submission. Summary of Clinical Safety. p. 32. June 2012.

Specifically:

- Trial C202 was a proof-of-principle, open-label, active-controlled, randomized Phase IIa trial in patients with drug-susceptible tuberculosis (DS-TB). bedaquiline was given once daily (q Daily) in different doses for each group (25 mg, 100 mg, 400 mg). Comparative groups were given INH (300 mg q Daily) or rifampin (600 mg q Daily) as monotherapy. Of 75 subjects enrolled, 45 received bedaquiline.

In tabular form:

Table 31. Trial C202.

Trial Number (Status)	Trial Design and Trial Objectives	N ^a	Treatment	Formulation
<i>Phase IIa Multiple-Dose Trials in Infected, Treatment-Naïve Subjects</i>				
TMC207-C202 (C)	<p><u>Design</u></p> <p>Open-label, randomized trial</p> <p><u>Objective</u></p> <p>The primary objective of this trial was to assess the effects of 3 different multiple oral doses of TMC207 administered alone over a 7-day period on viable counts of <i>M. tuberculosis</i> in sputum in treatment-naïve subjects with pulmonary <i>M. tuberculosis</i> infection, compared to the effects of treatment with standard doses of rifampin or isoniazid, also administered over a 7-day period as monotherapy.</p>	75	<p>Treatment A: 25 mg TMC207 q.d. on Days 1-7</p> <p>Treatment B: 100 mg TMC207 q.d. on Days 1-7</p> <p>Treatment C: 400 mg TMC207 q.d. on Days 1-7</p> <p>Treatment D: 600 mg rifampin q.d. on Days 1-7</p> <p>Treatment E: 300 mg isoniazid q.d. on Days 1-7</p>	<p>TMC207 as F003^b</p> <p>TMC207 as F004^c</p> <p>TMC207 as F004^c</p> <p>Rifampin as commercially available capsules of 300 mg</p> <p>Isoniazid as commercially available tablets of 300 mg</p>

C = completed trial

^a actual number of subjects per trial

^b F003: oral solution containing 10 mg/mL TMC207 as the free base in 40% HP-β-CD + 1% polysorbate 20, pH 3

^c F004: oral solution containing 40 mg/mL TMC207 as the free base in 40% HP-β-CD + 1% polysorbate 20, pH 3

Source: NDA 204384. Original Submission. Summary of Clinical Safety. p. 332. June 2012.

- Trial C208 is a stratified, randomized, double-blind, multinational, placebo-controlled Phase IIb trial in newly diagnosed pulmonary MDR-TB patients (treatment naïve patients for second-line anti-TB drugs). The aim of the trial is to evaluate the antibacterial activity, safety, and tolerability of bedaquiline when added to a BR of MDR-TB therapy, compared to placebo plus BR. The primary outcome parameter was the time to sputum culture conversion during treatment with bedaquiline or placebo. The trial is divided into 2 stages that enrolled distinct subject populations:
 - Stage 1 is an exploratory study that consisted of an 8-week therapeutic period with bedaquiline, followed by a 96 week follow-up period that includes a Background Regimen (BR)-treatment period. A total of 47 patients were enrolled, 23 of whom received bedaquiline.
 - Stage 2 is a proof-of-efficacy study that consists of a 24-week therapeutic period with bedaquiline, followed by an additional 96 weeks of BR-only treatment and a treatment free follow-up period. This follow-up period is currently ongoing. Safety data from this Stage is included up to the cut-off

date of 10 June 2011, at which time all patients reached at least the Week 72 visit or discontinued earlier. Data reported from 11 June 2011 to the cutoff date of 15 March 2012 are included in the submission as an addendum. In this study, a total of 161 patients were enrolled, 79 of whom received bedaquiline.

- After the interventional phase, patients are followed for safety, tolerability, pharmacokinetics, and efficacy for 96 weeks after the last dose of bedaquiline or placebo.
- Placebo-treated patients in Stage 2 were given the option to roll over to a bedaquiline treatment regimen for 24 weeks.

Table 32. Trial C208

Trial Number (Status)	Trial Design and Trial Objectives	N ^a	Treatment	Formulation	Refer to Module
<i>Phase IIb Multiple-Dose Trials in Infected, Treatment-Naïve Subjects</i>					
TMC207-C208 (O)	<p><u>Design</u> Placebo-controlled, double-blind, randomized trial</p> <p><u>Objective Stage 1</u> To evaluate the pharmacokinetics, antibacterial activity, safety, and tolerability of TMC207 compared to placebo when added to an MDR-TB BR for 8 weeks in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.</p> <p><u>Objective Stage 2</u> To demonstrate superiority in the antibacterial activity of TMC207 compared to placebo when added to a BR for 24 weeks in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection.</p>	<p>47</p> <p>160</p>	<p>Stage 1: <u>Investigational Treatment Period (8 weeks):</u> Weeks 1 and 2: 400 mg TMC207 or placebo q.d. + BR Weeks 3 to 8: 200 mg TMC207 or placebo t.i.w. + BR <u>Background Treatment Period (96 weeks):</u> MDR-TB treatment for 18-24 months, at least 12 months after the first documented negative culture</p> <p>Stage 2: <u>Investigational Treatment Period (24 weeks):</u> Weeks 1 and 2: 400 mg TMC207 or placebo q.d. + BR Weeks 3 to 24: 200 mg TMC207 or placebo t.i.w. + BR <u>Background Treatment Period (96 weeks):</u> MDR-TB treatment for 18-24 months, at least 12 months after the first documented negative culture</p>	TMC207 as F001 ^b	5.3.5.1

O = ongoing trial

^a actual number of subjects per stage of the trial TMC207-TIDP13-C208

^b F001: tablet containing eq. 100 mg TMC207 as the fumarate salt and the inactive ingredients lactose monohydrate, (b) (4) starch, hypromellose 2910 15mPa.s, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate

Source: NDA 204384. Original Submission. Summary of Clinical Safety. p. 333. June 2012.

- Trial C209 is an uncontrolled, single-arm Phase IIb trial enrolling newly diagnosed and treatment-experienced pulmonary MDR-TB. However, compared to Trial C208, patients with XDR-TB were also allowed to enter, provided that they had at least 3 drugs in their TB regimen the mycobacterial isolate is likely susceptible to. The 24 week investigational therapeutic period of trial C209 has already been completed but the 96 week follow-up period is still ongoing. Safety data for the ongoing part of the trial up to the cut-off date of 29 March 2011 are included in the safety data submitted in this submission. In addition, SAEs reported from 30 March 2011 to the cutoff date of 15 March 2012 are also included in this submission. Trial C209 enrolled 233 patients with pulmonary tuberculosis.

Table 33. Trial C209.

Trial Number (Status)	Trial Design and Trial Objectives	N ^a	Treatment	Formulation
<i>Phase IIb Multiple-Dose Trials in Infected, Treatment-Experienced Subjects</i>				
TMC207-C209 (O)	Design Open-label trial Objectives <ul style="list-style-type: none"> – To evaluate safety, tolerability, and efficacy of TMC207 as part of a multi-drug regimen in the treatment of subjects with MDR-TB. – To evaluate the pharmacokinetics of TMC207 and its primary metabolite M2, and pharmacokinetic/pharmacodynamic relationships for safety and efficacy. – To explore the effect of TMC207 on the experience of TB symptoms as measured by the Tuberculosis Symptoms Profile (TSP), and to explore the measurement properties of the TSP. 	233	Investigational Treatment Period (24 weeks): Weeks 1 and 2: 400 mg TMC207 or placebo q.d. + BR Weeks 3 to 24: 200 mg TMC207 or placebo t.i.w. + BR	TMC207 as F001 ^b

O = ongoing trial

^a actual number of subjects per trial

^b F001: tablet containing eq. 100 mg TMC207 as the fumarate salt and the inactive ingredients lactose monohydrate, (b) (4) starch, hypromellose 2910 151 polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate

Source: NDA 204384. Original Submission. Summary of Clinical Safety. p. 334. June 2012.

7.1.1.3. Duration of Treatment of Bedaquiline and Choice of Background Regimen

In both Trials C208 and C209 (Phase IIb trials), BEDAQUILINE was added to a background regimen (BR) for 8 weeks for Trial C208 Stage 1 and for 24 weeks for Trials C208 Stage 2 and Trial C209. After the BEDAQUILINE treatment duration, the BR was continued for a total of 72 to 96 weeks (18 to 24 months). The BR was continued for at least 48 weeks (12 months) after the first documented negative sputum culture.

The BEDAQUILINE treatment regimen used for Trials C208 and C209 consist of:

- Initiation Phase: 400 mg once daily for 2 weeks
- Maintenance Phase: 200 mg dosed three times in a week (TIW) for Weeks 3-8 for Trial C208 Stage 1 and for Weeks 3-24 for Trials C208 Stage 2 and C209.

The BR was chosen according to international guidelines and local health authority recommendations. In Trial C208, a BR consisting of the following was recommended:

- Kanamycin (KAN)
- Ofloxacin (OFL)
- Ethionamide (ETH)

- Pyrazinamide (PZA)
- Cycloserine (CS)/Terizidone (TRD)

In Trial C209, the BR was individually optimized by the investigator who considered the patient's prior TB treatment, drug susceptibility testing results, and national and international guidelines for the treatment of MDR-TB.

Medical Officer Comment:

The lack of standardization of the background regimen given to patients in these trials makes the analyses of efficacy and safety data from these trials challenging. Furthermore, the challenge is augmented by the potential that changes in the background regimen could be done either from a lack of susceptibility, toxicity, or patient intolerance. These result in an individualized treatment regimen for each patient enrolled in the study. Randomization might help mitigate the confounding effect of differing individualized regimen by balancing the differences in background regimen between treatment groups. However, the difficulty and challenge arise when looking at overall patterns of efficacy and safety.

For Trial C208 Stage 2, this is minimized by the protocol-recommended optimized background regimen. However, for Trial C209, no optimized background regimen is recommended.

7.1.2 Categorization of Adverse Events

Safety parameters were evaluated at specific timepoints: screening, at baseline, at predefined timepoints during treatment, end of dosing, and at follow-up. Typically, the last follow-up visits occurred 30 to 60 days after the last dose in all except the early Phase 1 trials where follow-up was between 4 and 12 days. Safety assessments include monitoring for adverse events (AEs), clinical laboratory parameters, electrocardiograms (ECGs), vital signs, and physical examinations that include skin (Trials C110, C111, and C117) and ophthalmological examinations (including fundoscopic examination for Trials C110, C111, C112, C117, and Phase II trials). Body weights and body mass index (BMI) were obtained.

Adverse event severity was evaluated and laboratory abnormalities were characterized and graded according to the Division of Microbiology and Infectious Disease (DMID) severity grading scales.

AEs and SAEs were defined according to the International Conference on Harmonization (ICH) E6 guidelines. Patient-reported AEs were recorded in case report forms (CRFs) in accordance with Good Clinical Practice (GCP) guidelines. Data on AEs were collected from the first trial-related procedure until the end of the follow-up period. The start and end dates and severity of AEs, causal relationship between the AE and

placebo/BEDAQUILINE as determined by the investigator or to the underlying TB, were recorded. Any abnormalities during routine procedures were reported as AEs. Several Standardized MedDRA queries (SMQs) were used to identify AEs that may represent specific toxicities.

Medical Officer Comment:

Aside from monitoring and comparisons of the reported Preferred Terms (PTs) between treatment groups, the Applicant's analysis included comparisons of Standardized MedDRA Queries (SMQs) using broad and narrow terms that could be attributed to an SMQ term. The Medical Officer concurs with the use of this analysis as it can capture all the preferred terms the investigator might have use to reflect a medical condition referred to as the SMQ term. Using this analysis, the possibility that the frequency of a medical condition

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

7.1.3.1. Phase 1 Trials

The Applicant conducted 11 Phase 1 studies to evaluate BEDAQUILINE. Eight studies enrolling healthy subjects (5 single-dose studies and 3 multiple-dose studies) were included in the pooled analysis.

The Applicant provided an analysis of Phase 1 pooled data from 8 Phase 1 studies consisting of 5 single-dose trials and 3 multiple dose studies. 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. Moreover, the 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 the evaluated BEDAQUILINE dose was higher (i.e. 800 mg suprathreshold dose for the QTc study. Lastly, the Applicant did not include two Phase 1 trials with placebo arms in their analysis because the Applicant deemed it inappropriate to present safety data from a placebo control study for comparison.

A total of 27 subjects received placebo (18 subjects in a single-dose study and 9 subjects in a multiple-dose study).

Table 34 summarizes the different Phase 1 studies included in the pooled analysis.

Table 34. List of Pooled Phase 1 Studies in Healthy Subjects

Trial	Design	N _{total} / N _{TMC207} ^a	Refer to Module
<i>Single-dose trials</i>			
CDE-101	Part 1: Double-blind, randomized, placebo-controlled, single-ascending dose trial Part 2: Open-label, randomized, crossover, food interaction trial	54 / 36 12 / 12	5.3.1.1
BAC1003	Open-label, DDI trial with RMP	16 / 16	5.3.3.4
C108	Open-label, randomized, crossover, bioavailability trial	24 / 24	5.3.1.1
C110	Open-label, randomized, crossover, DDI trial with lopinavir/ritonavir	16 / 16	5.3.3.4
C111	Open-label, randomized, crossover, bioavailability trial	28 / 28	5.3.1.2
<i>Multiple-dose trials</i>			
CDE-102	Double-blind, randomized, placebo-controlled, multiple-ascending dose trial	27 / 18	5.3.3.1
C104	Open-label, crossover, DDI trial with INH and PZA	24 / 23	5.3.3.4
C109	Open-label, crossover, DDI trial with ketoconazole	16 / 16	5.3.3.4
Total number of subjects (8 trials):		217 / 189	

^a number of subjects who received at least one dose of TMC207

Source: [Module 2.7.4/TMC207-C0000001-Anal-GEN/Display GEN.2](#)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 29

7.1.3.2. Phase 2 Trials

7.2 Adequacy of Safety Assessments

7.2.1. Phase 1 Trials

The total number of subjects participating in Phase 1 studies was 337 subjects, 265 of whom were exposed to BEDAQUILINE. The pooled analysis includes safety data from 217 healthy subjects, of whom 189 subjects received at least one dose of BEDAQUILINE. Table 35 presents the exposure to BEDAQUILINE in Phase 1 studies in non-TB infected subjects.

Table 35. Exposure Data in Non-TB Infected Subjects in Phase 1 Studies.

Exposure in non-TB infected subjects in the pooled Phase I trials	N_{TMC207}
Number of subjects exposed to TMC207 in 5 single-dose Phase I trials	132
Number of subjects exposed to TMC207 in 3 multiple-dose Phase I trials	57
<i>SUBTOTAL number of non-TB infected subjects exposed to TMC207 in the pooled Phase I trials</i>	189
Exposure in non-TB infected subjects in the non-pooled Phase I trials	
Number of subjects exposed to TMC207 in the single-dose trial C112 ^{a,b}	16
Number of subjects exposed to TMC207 in the single-dose trial C117 ^{a,c}	16
Number of subjects exposed to TMC207 in the single-dose trial TBC1003 ^{a,d}	44
<i>SUBTOTAL number of non-TB infected subjects exposed to TMC207 in the non-pooled Phase I trials</i>	76
<i>TOTAL number of non-TB infected subjects exposed to TMC207</i>	265

N_{TMC207} = number of subjects exposed to TMC207

^a Data for this trial are provided separately.

^b Subjects in C112 were either healthy (matched control subjects) or had moderate hepatic impairment.

^c Subjects in C117 were HIV-1 infected subjects.

^d Trial TBC1003 was a thorough QT trial.

Source: [Module 2.7.4/TMC207-C0000001-Anal-GEN/Display GEN.2, Module 5.3.3.3/TMC207-C112-CSR, Module 5.3.3.4/TMC207-C117-CRR, Module 5.3.5.4/TMC207TBC1003-CSR](#)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 49

In the single-dose studies included in the pooled analysis, 150 healthy subjects were enrolled and received the study medication. Of these, 132 received BEDAQUILINE at the following doses:

- 70 subjects: 100 mg or less
- 34 subjects: 300 mg
- 16 subjects: 400 mg
- 6 subjects: 450 mg and 700 mg.

In the 3 multiple-dose Phase 1 studies included in the pooled analysis, 67 healthy subjects were enrolled. Of these 67 subjects, 57 received BEDAQUILINE at the following dosage:

- 45 subjects: 400 mg q Daily
- 6 subjects: 150 mg q Daily
- 6 subjects: 50 mg q Daily

Of these 57 subjects, 37 subjects received BEDAQUILINE with other medication such as INH and PZA for 22 subjects and ketoconazole for 15 subjects. Of these 57 subjects, 54 received BEDAQUILINE for at least 14 days.

The following table provides the list of Phase 1 studies pooled in the Applicant's analysis. In all, there were 180 healthy subjects who were exposed to BEDAQUILINE. The following tables provide a summary of the BEDAQUILINE exposure.

Table 36. Descriptive Statistics of BEDAQUILINE Exposure in Multiple-Dose Trials

Duration of TMC207 exposure (days)	Multiple-Dose TMC207 Alone 400 mg	TMC207 Combined With Other Medications	Any TMC207 Alone	Any TMC207
N	45	37	57	57
Mean (SD)	10.6 (1.81)	4.2 (1.00)	11.2 (2.16)	13.9 (2.05)
Median (Range)	10.0 (4; 14)	5.0 (3; 5)	11.0 (4; 14)	14.0 (4; 15)

N = number of ITT subjects with data; SD = standard deviation

Source: [Module 2.7.4/TMC207-C0000001-Anal-GEN/Display GEN.4](#)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 49

Table 37. BEDAQUILINE Exposure Data (Days) in Multiple-Dose Trials

Duration of TMC207 exposure (days), n (%)	Multiple-Dose TMC207 Alone 400 mg N = 45	TMC207 Combined With Other Medications N = 37	Any TMC207 Alone N = 57	Any TMC207 N = 57
3	0	15 (40.5)	0	0
4	1 (2.2)	0	1 (1.8)	1 (1.8)
5	0	22 (59.5)	0	0
6	1 (2.2)	0	1 (1.8)	1 (1.8)
7	0	0	1 (1.8)	1 (1.8)
10	22 (48.9)	0	22 (38.6)	0
11	15 (33.3)	0	15 (26.3)	0
14	6 (13.3)	0	17 (29.8)	32 (56.1)
15	0	0	0	22 (38.6)

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

Source: [Module 2.7.4/TMC207-C0000001-Anal-GEN/Display GEN.5](#)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 50.

In all, 171 patients (90.5% [171/189]) completed the planned treatment duration for the Phase 1 trials. Eighteen subjects discontinued the Phase 1 studies prematurely after receiving bedaquiline. The most frequent reason for discontinuation was noncompliance (10 [5.3%]). These ten patients were withdrawn because they failed to comply with the pharmacokinetic sampling visits during the follow-up phase in Trial C104. During administration of bedaquiline alone, 3 (1.6%) subjects discontinued due to AEs.

The proportion of patients who completed dosing in single-dose and multiple-dose studies alone or in combination with other medications range between 85.5% to 96.2% (Table 38).

Table 38. Proportion of Patients who Completed Studies

n (%)	Single-Dose TMC207 Alone N = 132	Multiple-Dose TMC207 Alone 400 mg N = 45	TMC207 Combined With Other Medications N = 69	Any TMC207 Alone N = 189^a	Any TMC207 N = 189^a
Completed	127 (96.2)	43 (95.6)	59 (85.5)	181 (95.8)	171 (90.5)
Completed	127 (96.2)	43 (95.6)	59 (85.5)	181 (95.8)	171 (90.5)
Discontinued	5 (3.8)	2 (4.4)	10 (14.5)	8 (4.2)	18 (9.5)
AE	0	2 (4.4)	0	3 (1.6)	3 (1.6)
Subject Noncompliant	0	0	10 (14.5)	0	10 (5.3)
Subject Withdrew Consent	5 (3.8)	0	0	5 (2.6)	5 (2.6)

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

^a N in the last 2 columns is the same because all subjects who received TMC207 combined with other drugs in DDI trials also received TMC207 alone at some time during the trial.

Source: [Module 2.7.4/TMC207-C0000001-Anal-GEN/Display GEN.6](#)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 50.

The Applicant conducted Phase 1 studies in the United States and Europe. The majority of subjects exposed to BEDAQUILINE were white (83.1%) and male (98.4%), with a median age of 27 years of age (18 to 55 years) and median BMI of 24.8 kg/m² (range of 18-30.3 kg/m²). The demographic characteristics between subjects enrolled in the different pooled treatment groups were comparable. (Table 39)

Table 39. Demographic Information for Subjects Enrolled in Phase 1 Studies

Parameter	Single-Dose TMC207 Alone N = 132	Multiple-Dose TMC207 Alone 400 mg N = 45	TMC207 Combined With Other Medications N = 69	Any TMC207 Alone N = 189 ^a	Any TMC207 N = 189 ^a
Age (years)					
Mean (SD)	32.0 (10.78)	31.8 (12.20)	30.6 (10.93)	31.6 (10.94)	31.6 (10.94)
Median (Range)	28.0 (18; 55)	25.0 (18; 55)	26.0 (18; 55)	27.0 (18; 55)	27.0 (18; 55)
Weight (kg)					
Mean (SD)	79.3 (11.20)	80.2 (11.01)	80.6 (10.12)	79.5 (11.06)	79.5 (11.06)
Median (Range)	79.0 (56; 107)	80.1 (60; 101)	80.1 (61; 103)	79.0 (56; 107)	79.0 (56; 107)
Height (cm)					
Mean (SD)	178.2 (8.16)	179.1 (6.03)	179.3 (7.94)	178.7 (7.71)	178.7 (7.71)
Median (Range)	177.5 (151; 200)	179.0 (168; 190)	181.0 (151; 200)	179.0 (151; 200)	179.0 (151; 200)
BMI (kg/m²)					
Mean (SD)	24.91 (2.696)	24.94 (2.558)	25.04 (2.520)	24.84 (2.643)	24.84 (2.643)
Median (Range)	24.85 (18.2; 30.3)	24.80 (19.6; 29.5)	24.80 (19.6; 30.3)	24.80 (18.2; 30.3)	24.80 (18.2; 30.3)
Sex, n (%)					
Female	3 (2.3)	0	1 (1.4)	3 (1.6)	3 (1.6)
Male	129 (97.7)	45 (100)	68 (98.6)	186 (98.4)	186 (98.4)
Race, n (%)					
Asian	3 (2.3)	0	0	3 (1.6)	3 (1.6)
Black	25 (18.9)	0	6 (8.7)	26 (13.8)	26 (13.8)
Hispanic	0	1 (2.2)	1 (1.4)	1 (0.5)	1 (0.5)
Other	1 (0.8)	0	0	2 (1.1)	2 (1.1)
White	103 (78.0)	44 (97.8)	62 (89.9)	157 (83.1)	157 (83.1)
Country, n (%)					
Belgium	0	16 (35.6)	15 (21.7)	16 (8.5)	16 (8.5)
Netherlands	24 (18.2)	0	0	24 (12.7)	24 (12.7)
United Kingdom	64 (48.5)	29 (64.4)	38 (55.1)	105 (55.6)	105 (55.6)
United States	44 (33.3)	0	16 (23.2)	44 (23.3)	44 (23.3)

N= number of ITT subjects with data, n = number of ITT subjects with that observation, SD = standard deviation

^a N in the last 2 columns is the same because all subjects who received TMC207 combined with other drugs in DDI trials also received TMC207 alone at some time during the trial.

Source: Module 2.7.4/TMC207-C0000001-Anal-GEN/Display GEN.3

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 51.

Medical Officer Comment:

The Medical Officer believes that the exposure to bedaquiline of subjects in Phase 1 single-dose and multiple-dose studies is adequate. The proportion of subjects who completed dosing is between 85.5 to 96.2%. This appears sufficient, given the observation that the subjects included in the Phase 1 pooled analysis of safety are healthy and have similar baseline demographic characteristics. However, because of the variability in the frequency (single-dose and multiple doses) and of the doses themselves, the Medical Officer finds the analysis of safety data from Phase 1 studies limited. The Medical Officer believes that any safety data from the Phase 1 studies should be considered supportive to safety data with the exposure similar to the expected patient exposure in clinical use as these would more reliably reflect the potential safety risks from chronic bedaquiline use (i.e. 24 months). Safety data from these studies provide a general sense of initial human safety and tolerability for bedaquiline that could verify safety concerns from nonclinical studies.

7.2.2 Extent of Exposure in Phase IIa Trial

Trial C202 (Phase IIa Trial) was an open-label, randomized trial in treatment-naïve patients with sputum smear-positive pulmonary drug-susceptible tuberculosis (DS-TB)

conducted in South Africa. A total of 75 patients were randomized to 5 treatment groups for a 7-day treatment of the following:

- 15 patients: bedaquiline 25 mg q Daily
- 16 patients: bedaquiline 100 mg q Daily
- 14 patients: bedaquiline 400 mg q Daily
- 15 patients: RMP 600 mg q Daily
- 15 patients: INH 300 mg q Daily.

After the 7 day treatment duration, patients received standard anti-TB treatment, according to national guidelines.

Sixty seven out of the 75 patients (89.3%) completed the 7-day treatment period. The 8 patients who discontinued the treatment prior to the completion received at least one dose of the study drug. These patients discontinued treatment because of:

- AEs (hemoptysis in 2 patients)
- Grade 3 ALT and AST values at screening (1 patient)
- Cannabinoids in urine (4 patients)
- Cannabinoids in urine and intake of wrong study medication (1 patient).

Majority of the subjects in this trial were black (57%) and male (60%), with a median age of 34 years (18 to 61 years old) and median BMI of 19.3 kg/m² (15 to 33 kg/m²). The five groups were comparable in terms of their demographic characteristics. In terms of their disease, all patients had X-ray abnormalities consistent with TB, except for one patient given 100 mg bedaquiline whose X-ray findings were compatible with a lower respiratory tract infection. All patients had DS-TB isolates (susceptible to both RMP and INH confirmed by MGIT960 system). Thirty-five patients used concomitant medications, the most common of which were paracetamol and ibuprofen. After the last dose of study medication, all patients started anti-TB treatment for DS-TB.

Medical Officer Comment:

The main objective of this study is to determine and compare the early bactericidal activity of varying doses of bedaquiline compared to INH and RMP against DS M. tuberculosis. Considering that only a proportion of enrolled patients were exposed to the proposed dosage of bedaquiline (400 mg) and that the treatment duration is significantly shorter in this study compared to the proposed treatment regimen, the safety data from this study should be cautiously interpreted. However, safety data from this study is relevant as they demonstrate dose-response effects on safety parameters, with the three increasing bedaquiline doses used. Moreover, the study should reflect safety data from patients with exposure only to one drug. Since this are patients infected with DS-TB, safety data could reflect those from bedaquiline-exposed DS-TB patients.

7.2.3 Extent of Exposure in the Pooled Phase IIb Trials

The clinical safety database for the Phase IIb 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 40. Summary of BEDAQUILINE Exposure in MDR-TB Patients in Phase IIb Trials

Exposure in TB infected, treatment-naïve subjects in Phase IIb trials	N_{BEDAQUILINE}
Number of subjects treated with BEDAQUILINE in the Phase IIb trial C208 Stage 1	23
Number of subjects treated with BEDAQUILINE in the Phase IIb trial C208 Stage 2	79
<i>SUBTOTAL number of MDR-TB-infected subjects treated with BEDAQUILINE in placebo-controlled Phase II trials</i>	102
Exposure in TB infected, treatment-experienced subjects in Phase IIb trials	
Number of subjects treated with BEDAQUILINE in the Phase IIb 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 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/placebo 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).

Trial C208 is a Phase 2b, randomized, placebo-controlled, double-blind, multicenter trial in patients with newly diagnosed sputum smear-positive pulmonary MDR-TB infection. This trial has two consecutive but separate stages: Stage 1 (8 week bedaquiline exposure) and Stage 2 (24 week bedaquiline exposure) with different enrolled patient populations. In addition to their objectives of evaluating the efficacy, safety, and tolerability of bedaquiline, these studies also evaluate the PK of bedaquiline and M2 in plasma and sputum, PK/ PD relationships for safety and efficacy, and drug-drug interactions (DDIs) between bedaquiline and the background regimen.

7.2.3.1. 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 BR and 24 patients receiving placebo with the BR. The table below summarizes the exposure data for this trial in terms of the median number of exposure weeks and the comparability of treatment duration 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 41. Exposure in Trial C208 Stage 1

Total Duration (weeks)	Placebo N = 24	BEDAQUILINE N = 23
Investigational Treatment Perioda		
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. Summary of Clinical Safety. p. 79. Module 5.3.5.1/BEDAQUILINE-C208-Stage 1-Anal-GEN/Display GEN.19

In terms of patient disposition, out 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%). One patient discontinued due to a fatal AE and one patient in each group isolated XDR-TB at baseline and two patients in the placebo group developed XDR-TB during the trial. Other reasons for discontinuation is lost to follow-up and moving. No relevant differences were noted between the two groups in terms of the reasons for trial discontinuation.

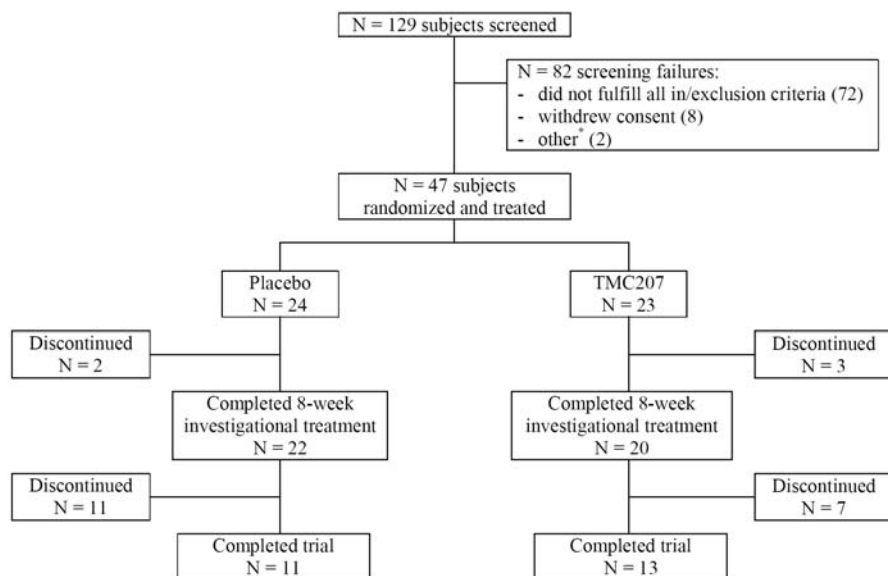
Table 42. Patient Disposition for Trial C208 Stage 1

Trial Termination Type	BEDAQUILINE/BR N = 23	Placebo/BR N = 24	All Subjects N = 47
Reason, n (%)			
Completed	13 (56.5)	11 (45.8)	24 (51.1)
Discontinued	10 (43.5)	13 (54.2)	23 (48.9)
Subject noncompliant	4 (17.4)	4 (16.7)	8 (17.0)
Subject withdrew consent	3 (13.0)	4 (16.7)	7 (14.9)
Subject lost to follow-up	1 (4.3)	1 (4.2)	2 (4.3)
Subject had XDR-TB at Baseline	1 (4.3)	1 (4.2)	2 (4.3)
Subject developed XDR-TB during trial	0	2 (8.3)	2 (4.3)
Subject transferred out	0	1 (4.2)	1 (2.1)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 78. Module 5.3.5.1/BEDAQUILINE-C208-Stage 1-Anal-GEN/Display GEN.12

The figure below illustrates patient disposition in this trial.

Figure 10. Patient Disposition in Trial C208 Stage 1



* One subject was ineligible to continue the trial; 1 subject wanted to start MDR treatment straight away

Source: Display GEN.4, Listing GEN.5, Display GEN.13, and Display GEN.12

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 90.

Baseline demographic characteristics were comparable between treatment groups. Thirty five (74.5%) patients were male and median age of the enrolled population was 33 years. Median BMI was 18.3 kg/m². In the ITT population, 55.3% were black. (Table 43)

Baseline disease characteristics were also comparable between the two groups. INH and RMP resistance was confirmed for all patients either by rapid screen tests and/or conventional local or central susceptibility testing. One patient in each treatment group had XDR-TB at baseline. Fourteen patients in the bedaquiline group and 13 in the placebo group (total 57.4% for both groups) had one or more lung cavities at least 2 cm in only one lung. Three patients in each group were HIV-infected with comparable CD4+ cell counts (bedaquiline group: 348 (310-445) x 10⁶ cells/L; placebo group: 375 (311-886) x 10⁶ cells/L. (Table 43)

Table 43. Demographic and Baseline Disease Characteristics for ITT Population for Trial C208 Stage 1

Parameter	Placebo N = 24	BEDAQUILINE N = 23	All Subjects N = 47
Age at screening, years Median (range)	33.0 (19-57)	33.0 (18-57)	33.0 (18-57)
Height, cm Median (range)	167.5 (153-182)	169.0 (144-191)	168.0 (144-191)
Weight, kg Median (range)	51.4 (36-83)	50.0 (37-75)	50.7 (36-83)
BMI, kg/m ²	18.46 (13.8-30.9)	18.31 (14.1-26.9)	18.31 (13.8-30.9)

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Median (range)			
Gender, n (%)			
Female	7 (29.2)	5 (21.7)	12 (25.5)
Male	17 (70.8)	18 (78.3)	35 (74.5)
Ethnic Origin, n (%)			
Black	13 (54.2)	13 (56.5)	26 (55.3)
Caucasian/White	1 (4.2)	0	1 (2.1)
Other	10 (41.7)	10 (43.5)	20 (42.6)
Lung cavity, n (%)			
Cavity ≥ 2 cm in both lungs	7 (29.2)	6 (26.1)	13 (27.7)
Cavity ≥ 2 cm in one lung only	13 (54.2)	14 (60.9)	27 (57.4)
No cavity ≥ 2 cm present	4 (16.7)	3 (13.0)	7 (14.9)
HIV status, n (%)			
Negative	21 (87.5)	20 (87.0)	41 (87.2)
Positive	3 (12.5)	3 (13.0)	6 (12.8)
CD4+ cell count at screening (x 10 ⁶ cells/L) All subjects ^c , median (range)			
HIV-positive subjects, median (range)	591.0 (299-1273) 375.0 (311-886)	674.5 (310-1567) 348.0 (310-445)	657.5 (299-1567) 361.5 (310-886)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 90. 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 (dapson, CAP, clarithromycin, and INH) were taken by patients in the placebo group, not in the bedaquiline group (2 patients per drug).

The background TB medications used in Trial C208 Stage 1 is summarized in the following table.

Table 44. Background Regimen Used During the Investigational Treatment Period in Trial C208 Stage 1

Background Regimen, 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	15 (62.5)	14 (60.9)	29 (61.7)

Background Regimen, n (%)	Placebo N=24	BEDAQUILINE N=23	All Subjects N=47
terizidone/cycloserine	16 (66.7)	12 (52.2)	28 (59.6)
dapsone	2 (8.3)	0	2 (4.3)
capreomycin	1 (4.2)	0	1 (2.1)
clarithromycin	1 (4.2)	0	1 (2.1)
isoniazidb	1 (4.2)	0	1 (2.1)
para-aminosalicylic acid	1 (4.2)	0	1 (2.1)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 98

Table 45. 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	(4.2)	0	1 (2.1)
Moxifloxacin	1 (4.2)	0	1 (2.1)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 98

Medical Officer Comment:

Trial C208 Stage 1 is an exploratory trial evaluating the safety and efficacy of an 8 week bedaquiline exposure. As a controlled study, the safety data from this study can be preliminarily informative of potential safety concerns but unless pooled with safety data from Stage 2 is insufficient in truly characterizing the clinical safety experience from the proposed exposure.

7.2.3.2 Trial C208 Stage II

The trial was conducted in Asia, South Africa, Eastern Europe, and South America, with 15 participating investigators. The trial was initiated on 23 April 2008 and the last patient contact was in 10 June 2011. Randomization was stratified by treatment center and extent of lung cavitation.

Two hundred eight 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 on top of a background regimen for MDR-TB (ITT population).

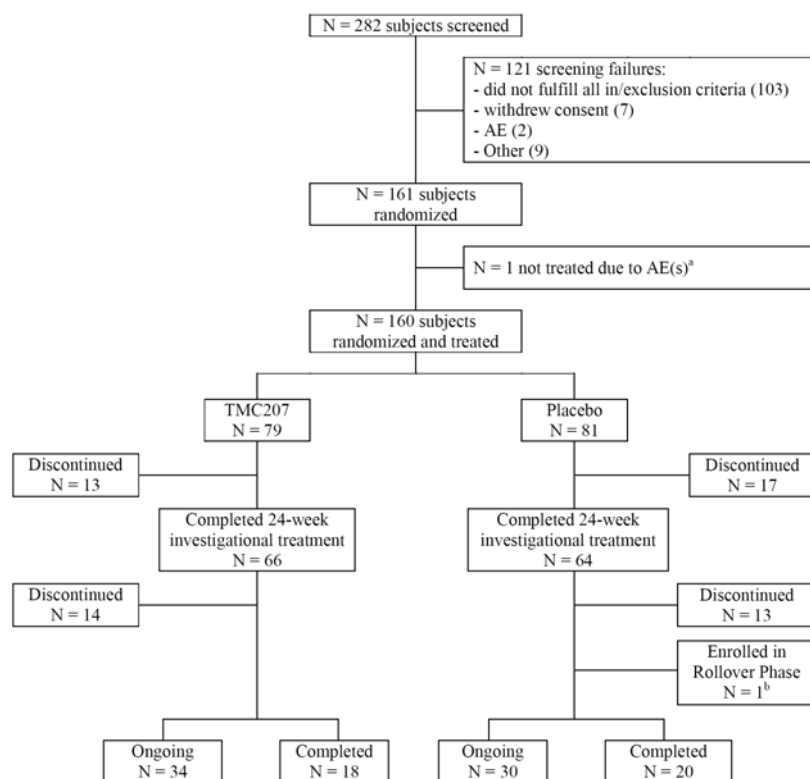
Patient Disposition

The mITT population excluded ITT patients because of the inability to confirm MDR-TB status based on susceptibility results taken prior to randomization or patients whose MGIT results did not allow for primary efficacy evaluation (no evidence of culture positivity prior to first intake or during first 8 weeks after first intake). The mITT population in this trial consisted of 132 patients (66 patients each in the BEDAQUILINE group and the placebo group). Of the 11 patients excluded from the ITT population because MGIT results did not allow for primary efficacy evaluation, 8 patients were MGIT negative at baseline and 3 patients had no MGIT results during the first 8 weeks of intake.

The Per Protocol (PP) population is a subset of the mITT population defined as having no major protocol violations. The PP population consisted of 95 patients, 52 in the BEDAQUILINE group and 43 in the placebo group.

The diagram below summarizes the disposition of patients screened and randomized in this trial.

Figure 11. Subject Disposition of Trial C208 Stage 2.



Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 105.

Of the patients in the ITT and mITT population, comparable proportion of patients discontinued prematurely from the trial, with slightly greater number in the placebo group. A greater 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 46. Disposition and Premature Discontinuation of Patients in Trial C208 Stage II

Population/Reason/ n (%)	ITT Population			mITT Population		
	BEDAQUILINE N = 79	Placebo N = 81	All N = 160	BEDAQUILINE N = 66	Placebo N = 66	All N = 132
Ongoing*	34 (43.0)	30 (37.0)	64 (40.0)	30 (45.5)	28 (42.4)	58 (43.9)
Completed*	18 (22.8)	20 (24.7)	38 (23.8)	15 (22.7)	14 (21.2)	29 (22.0)
Discontinued*	27 (34.2)	30 (37.0)	57 (35.6)	21 (31.8)	23 (34.8)	44 (33.3)
Adverse event	7 (8.9)	6 (7.4)	13 (8.1)	6 (9.1)	5 (7.6)	11 (8.3)
Subject ineligible to continue the trial	2 (2.5)	6 (7.4)	8 (5.0)	0	0	0
Subject is pregnant	3 (3.8)	2 (2.5)	5 (3.1)	3 (4.5)	2 (3.0)	5 (3.8)
Subject lost to follow-up	5 (6.3)	3 (3.7)	8 (5.0)	5 (7.6)	3 (4.5)	8 (6.1)
Subject non-compliant	3 (3.8)	6 (7.4)	9 (5.6)	2 (3.0)	6 (9.1)	8 (6.1)
Subject withdrew consent	6 (7.6)	7 (8.6)	13 (8.1)	5 (7.6)	7 (10.6)	12 (9.1)
Other	1 (1.3)	0	1 (0.6)	0	0	0
Rollover	0	1 (1.2)	1 (0.6)	0	1 (1.5)	1 (0.8)

*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.

The following table summarizes the final analysis of the data.

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/m².

Table 47. Demographic Characteristics of Patients Enrolled in Trial C208 Stage II

Demographic Characteristic n (%)	ITT			mITT		
	BEDAQUILINE N = 79	Placebo N = 81	All Subjects N = 160	BEDAQUILINE N = 66	Placebo N = 66	All Subjects N = 132
Age (years)						
Mean (SD)	36.0 (13.14)	35.8 (11.02)	35.9 (12.08)	35.8 (13.28)	34.7 (10.29)	35.3 (11.84)
Median (Range)	31.0 (18, 63)	35.0 (18,61)	34.0 (18, 63)	31.0 (18, 63)	34.0 (18, 57)	33.0 (18, 63)
Weight (kg)						
Mean (SD)	55.1 (10.57)	54.1 (8.74)	54.6 (9.67)	54.5 (10.24)	3.7 (8.87)	54.1 (9.55)
Height (cm)						
Mean (SD)	166.1 (9.63)	165.6 (9.45)	165.8 (9.51)	165.5 (9.49)	165.8 (9.69)	165.7 (9.55)
Body mass index						

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Demographic Characteristic n (%)	ITT			mITT		
	BEDAQUILINE N = 79	Placebo N = 81	All Subjects N = 160	BEDAQUILINE N = 66	Placebo N = 66	All Subjects N = 132
(kg/m ²) Mean (SD)	20.0 (3.43)	19.9 (3.70)	19.9 (3.56)	19.9 (3.39)	19.7 (3.70)	19.8 (3.53)
Body mass index (kg/m ²)						
< 18	26 (32.9)	32 (39.5)	58 (36.3)	24 (36.4)	29 (43.9)	53 (40.2)
18-<20	16 (20.3)	18 (22.2)	34 (21.3)	10 (15.2)	13 (19.7)	23 (17.4)
20-<25	31 (39.2)	22 (27.2)	53 (33.1)	28 (42.4)	18 (27.3)	46 (34.8)
25 and higher	6 (7.6)	9 (11.1)	15 (9.4)	4 (6.1)	6 (9.1)	10 (7.6)
Country						
Brazil	4 (5.1)	4 (4.9)	8 (5.0)	1 (1.5)	1 (1.5)	2 (1.5)
India	4 (5.1)	1 (1.2)	5 (3.1)	4 (6.1)	1 (1.5)	5 (3.8)
Latvia	5 (6.3)	4 (4.9)	9 (5.6)	5 (7.6)	1 (1.5)	6 (4.5)
Peru	16 (20.3)	17 (21.0)	33 (20.6)	14 (21.2)	12 (18.2)	26 (19.7)
Philippines	1 (1.3)	2 (2.5)	3 (1.9)	1 (1.5)	2 (3.0)	3 (2.3)
Russia	3 (3.8)	7 (8.6)	10 (6.3)	1 (1.5)	6 (9.1)	7 (5.3)
South Africa	43 (54.4)	45 (55.6)	88 (55.0)	37 (56.1)	42 (63.6)	79 (59.8)
Thailand	3 (3.8)	1 (1.2)	4 (2.5)	3 (4.5)	1 (1.5)	4 (3.0)
Ethnic origin						
Black	29 (36.7)	27 (33.3)	56 (35.0)	24 (36.4)	25 (37.9)	49 (37.1)
Caucasian/White	8 (10.1)	12 (14.8)	20 (12.5)	6 (9.1)	8 (12.1)	14 (10.6)
Hispanic	13 (16.5)	15 (18.5)	28 (17.5) 15	12 (18.2)	10 (15.2)	22 (16.7)
Oriental/Asian Other	9 (11.4)	6 (7.4)	(9.4) 41	9 (13.6)	6 (9.1)	15 (11.4)
	20 (25.3)	21 (25.9)	(25.6)	15 (22.7)	17 (25.8)	32 (24.2)
Sex						
Female	27 (34.2)	32 (39.5)	59 (36.9)	21 (31.8)	26 (39.4)	47 (35.6)
Male	52 (65.8)	49 (60.5)	101 (63.1)	45 (68.2)	40 (60.6)	85 (64.4)
HIV status						
Negative	71 (89.9)	65 (80.2)	136 (85.0)	61 (92.4)	52 (78.8)	113 (85.6)
Positive	8 (10.1)	16 (19.8)	24 (15.0)	5 (7.6)	14 (21.2)	19 (14.4)
Cavitations (as stratified)	79 (100)	81 (100)	160 (100)	66 (100)	66 (100)	132 (100)
Cavitations . ≥ 2 cm in both lungs	13 (16.5)	16 (19.8)	29 (18.1)	12 (18.2)	15 (22.7)	27 (20.5)
Cavitations . ≥ 2 cm in one lung only	50 (63.3)	49 (60.5)	99 (61.9)	42 (63.6)	41 (62.1)	83 (62.9)
No cavitations or cavitations < 2 cm	16 (20.3)	16 (19.8)	32 (20.0)	12 (18.2)	10 (15.2)	22 (16.7)
Extent of resistance of M. tuberculosis strain	79 (100)	77 (100)	156 (100)	66 (100)	66 (100)	132 (100)
DS-TB	4 (5.1)	4 (5.2)	8 (5.1)	0	0	0
MDR-TB	75 (94.9)	73 (94.8)	148 (94.9)	66 (100)	66 (100)	132 (100)
MDR _{H&R} -TB	40 (50.6)	46 (59.7)	86 (55.1)	39 (59.1)	45 (68.2)	84 (63.6)
Pre-XDR-TB	16 (20.3)	12 (15.6)	28 (17.9)	15 (22.7)	12 (18.2)	27 (20.5)
XDR-TB	3 (3.8)	4 (5.2)	7 (4.5)	0	0	0
Baseline albumin grade	79 (100)	81 (100)	160 (100)	66 (100)	66 (100)	132 (100)
Grade 0	47 (59.5)	36 (44.4)	83 (51.9)	38 (57.6)	24 (36.4)	62 (47.0)
Grade 1	12 (15.2)	15 (18.5)	27 (16.9)	11 (16.7)	14 (21.2)	25 (18.9)
Grade 2	16 (20.3)	29 (35.8)	45 (28.1)	14 (21.2)	27 (40.9)	41 (31.1)
Grade 3	4 (5.1)	1 (1.2)	5 (3.1)	3 (4.5)	1 (1.5)	4 (3.0)
Previous use of first-line TB drugs	79 (100)	81 (100)	160 (100)	66 (100)	66 (100)	132 (100)
No	7 (8.9)	11 (13.6)	18 (11.3)	6 (9.1)	8 (12.1)	14 (10.6)
Yes	72 (91.1)	70 (86.4)	142 (88.8)	60 (90.9)	58 (87.9)	118 (89.4)
CD4 cell count						
n	76	81	157	63	66	129

Demographic Characteristic n (%)	ITT			mITT		
	BEDAQUILINE N = 79	Placebo N = 81	All Subjects N = 160	BEDAQUILINE N = 66	Placebo N = 66	All Subjects N = 132
Mean (SD)	689.4	681.6	685.4	691.6	656.3	673.6
	-312.57	-290.09	-300.23	-317.16	-248.9	-283.72
Median (range)	642	621	634	635	596	621
	(127, 1711)	(291, 1655)	(127, 1711)	(127, 1711)	(310, 1369)	(127, 1711)
CD4 cell count (HIV negative)						
n	68	65	133	58	52	110
Mean (SD)	712.3	737.4	724.5	712	712.2	712.1
	-320.1	-292.38	-305.96	-321.85	-246.06	-287.23
Median (range)	661.5	682	673	661.5	678.5	670
	(127, 1711)	(291, 1655)	(127, 1711)	(127, 1711)	(344, 1369)	(127, 1711)
CD4 cell count (HIV positive)						
n	8	16	24	5	14	19
Mean (SD)	494.6	455.1	468.3	455.2	448.9	450.6
	-132.66	-125.91	-126.72	-84.74	-115.83	-106.27
Median (range)	487	432.5	454.5	463	432.5	446
	(340, 692)	(310, 670)	(310, 692)	(352, 559)	(310, 667)	(310, 667)

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

Medical Officer Comment:

From the summary table, the demographic characteristics of the population enrolled in each group are similar and that the treatment groups are comparable. Moreover, baseline severity information between treatment groups are comparable. An exception is the number of HIV-infected patients enrolled where more HIV infected patients were enrolled in the placebo group (16/81, 19.8%) compared to the bedaquiline group (8/79, 10.1%). On the strain isolated, more MDR_{H&R}-TB patients were enrolled in the placebo group compared to the bedaquiline group (59.7% vs 50.6%, respectively). Interestingly, pre-XDR TB and XDR-TB isolates were enrolled in the study, considered a major protocol violation. More pre-XDR TB isolates were noted in the bedaquiline group vs the placebo group. Overall, the two treatment groups appear to be comparable.

Prior Tuberculosis Treatment

Patients with previous TB treatment was still able to be included in the trial provided they did not receive previous treatment for MDR-TB. Prior treatment for MDR-TB is defined as receiving treatment with any second-line TB drug such as: any aminoglycoside except streptomycin (SM), any fluoroquinolone, the thioamides protionamide or ETH, and CS.

A total of 88.8% (142/160) of patients in the ITT population received prior treatment for TB. A large proportion of randomized patients received first line anti-TB medications, notably INH (86.1%) and RMP (88.1%) which are the most frequently administered prior TB medications in the trial. Others include PZA (91.3%), EMB (80.0%), and streptomycin (29.4%). No significant difference with use of prior TB medications between the BEDAQUILINE and placebo groups were noted.

Table 48. Prior anti-TB drug treatment for Trial C208 Stage II

Previous TB treatment Class Treatment n (%)	ITT			mITT		
	BEDAQUIL INE/ N = 79	Placebo N = 81	All subjects N = 160	BEDAQUI LINE N = 66	Placebo N = 66	All subjects N = 132
No previous use of TB drug treatment	7 (8.9)	11 (13.6)	18 (11.3)	6 (9.1)	8 (12.1)	14 (10.6)
Any previous use of TB drug treatment	72 (91.1)	70 (86.4)	142 (88.8)	60 (90.9)	58 (87.9)	118 (89.4)
Aminoglycosides	29 (36.7)	18 (22.2)	47 (29.4)	27 (40.9)	15 (22.7)	42 (31.8)
Streptomycin	29 (36.7)	18 (22.2)	47 (29.4)	27 (40.9)	15 (22.7)	42 (31.8)
First-line anti-TB drugs	71 (89.9)	70 (86.4)	141 (88.1)	59 (89.4)	58 (87.9)	117 (88.6)
Ethambutol	66 (83.5)	62 (76.5)	128 (80.0)	56 (84.8)	51 (77.3)	107 (81.1)
Isoniazid	70 (88.6)	69 (85.2)	139 (86.9)	59 (89.4)	57 (86.4)	116 (87.9)
Pyrazinamide	67 (84.8)	63 (77.8)	130 (81.3)	56 (84.8)	52 (78.8)	108 (81.8)
Rifampicin	71 (89.9)	70 (86.4)	141 (88.1)	59 (89.4)	58 (87.9)	117 (88.6)

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

Medical Officer Comment: As described in the inclusion criteria, most patients have had exposure to first line anti-tuberculosis drugs. A minority of patients did not have prior use of any TB drug treatment (8.9% in the bedaquiline group vs 13.6% in the placebo group. The 9 to 14% prevalence of treatment-naïve MDR-TB patients is slightly higher than the expected prevalence, based on the epidemiology of the global prevalence of MDR-TB in TB treatment-naïve patients (3.4%). This probably reflects the endemicity of tuberculosis in the trial sites.

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, substitutions are 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).

As can be seen in Table 49, the most frequently used TB drugs in the BT were FQs (99.4%), aminoglycosides (95.6%), PZA (93.1%), ETH (84.4%), and EMB (65.0%). 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. In terms of background regimen, the Applicant claims that the treatment groups were comparable. There were no clinically significant differences between the two groups with their BR. (Table 49)

Table 49. Baseline Background Regimen in the ITT and mITT Populations of Trial C208 Stage II.

Background regimen Class Treatment n (%)	ITT			mITT		
	BEDAQU ILINE /BR N = 79	Placebo /BR N = 81	All Subjects N = 160	BEDAQU ILINE /BR N = 66	Placebo /BR N = 66	All Subjects N = 132
<i>Any use of background TB treatment</i>	79 (100)	81 (100)	160 (100)	66 (100)	66 (100)	132 (100)
Aminoglycosides	76 (96.2)	77 (95.1)	153 (95.6)	64 (97.0)	63 (95.5)	127 (96.2)
Amikacin sulfate	19 (24.1)	24 (29.6)	43 (26.9)	12 (18.2)	17 (25.8)	29 (22.0)
Aminoglycoside antibacterialsb	10 (12.7)	5 (6.2)	15 (9.4)	9 (13.6)	4 (6.1)	13 (9.8)
Kanamycin	51 (64.6)	49 (60.5)	100 (62.5)	47 (71.2)	44 (66.7)	91 (68.9)
Streptomycin	0	1 (1.2)	1 (0.6)	0	0	0
Fluoroquinolones	79 (100)	80 (98.8)	159 (99.4)	66 (100)	65 (98.5)	131 (99.2)
Ciprofloxacin	17 (21.5)	17 (21.0)	34 (21.3)	15 (22.7)	12 (18.2)	27 (20.5)
Levofloxacin	2 (2.5)	2 (2.5)	4 (2.5)	1 (1.5)	2 (3.0)	3 (2.3)
Moxifloxacin	1 (1.3)	1 (1.2)	2 (1.3)	0	0	0
Ofloxacin	59 (74.7)	60 (74.1)	119 (74.4)	50 (75.8)	51 (77.3)	101 (76.5)
Miscellaneous anti-TB drugs	79 (100)	80 (98.8)	159 (99.4)	66 (100)	65 (98.5)	131 (99.2)
Amoxicillin + clavulanic acid	1 (1.3)	0	1 (0.6)	0	0	0
Capreomycin	3 (3.8)	5 (6.2)	8 (5.0)	2 (3.0)	4 (6.1)	6 (4.5)
Cycloserine	18 (22.8)	20 (24.7)	38 (23.8)	15 (22.7)	17 (25.8)	32 (24.2)
Ethambutol	53 (67.1)	51 (63.0)	104 (65.0)	46 (69.7)	46 (69.7)	92 (69.7)
Ethionamide	70 (88.6)	65 (80.2)	135 (84.4)	59 (89.4)	55 (83.3)	114 (86.4)
Pas-C	4 (5.1)	8 (9.9)	12 (7.5)	3 (4.5)	6 (9.1)	9 (6.8)
Protionamide	8 (10.1)	13 (16.0)	21 (13.1)	6 (9.1)	9 (13.6)	15 (11.4)
Pyrazinamide	75 (94.9)	74 (91.4)	149 (93.1)	65 (98.5)	61 (92.4)	126 (95.5)
Terizidone	13 (16.5)	16 (19.8)	29 (18.1)	10 (15.2)	9 (13.6)	19 (14.4)

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

A number of TB 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.

Disallowed medications were also used as part of the BR:

- 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.

Medical Officer Comment:

Another important factor that may impact the efficacy and safety data in this trial is the frequency patients modify their BR. According to the Applicant, more than half of all patients did not alter their BR during the investigational treatment phase. Specifically, 59.5% of patients in the BEDAQUILINE group and 54.3% in the placebo group did not modify their baseline BR. One new drug was added in 21.3% of patient's BR during the investigational treatment phase. Two new drugs were added in 10.0% and three new drugs were added to the BR of 8.1% of patients. The modifications of the BR, while

7.2.3.2. Trial C209

Trial C209 is a Phase II, open-label, single-arm trial conducted to evaluate the safety, tolerability, and efficacy of bedaquiline in combination with an individualized background regimen to treat patients with sputum smear-positive pulmonary infection with MDR-TB. The open-label, single-arm trial was used to achieve the primary objective of the trial: to obtain supportive safety data for the use of bedaquiline.

The trial recruited patients with newly diagnosed and treatment-experienced MDR-TB using specific inclusion and exclusion criteria to reach the planned total sample size of 225 patients. Moreover, HIV-infected patients were allowed to enroll in the trial provided that they fulfill the inclusion and exclusion criteria, especially as it pertains to the use of antiretroviral therapy. HIV-infected patients were required to either switch to a triple NRTI regimen consisting of AZT/3TC/ABC or to discontinue all ARVs depending on their current virological status and treatment history.

Patients were treated with bedaquiline for 24 weeks together with an individualized BR selected by the investigator at the baseline visit guided by national TB program treatment guidelines. Standard treatment for MDR-TB is divided into 2 treatment phase: a 4 to 6 month intensive phase with an injectable aminoglycoside administered with 3 or 4 TB drugs that include a FQ. This is followed by a continuation phase without an aminoglycoside to achieve a total treatment duration of 18 to 24 months, or a minimum of 12 months after sputum conversion.

The trial is currently ongoing in Asia, South Africa, Eastern Europe, and South America. The Applicant provided interim analysis of the ongoing trial performed when all patients had completed 24 weeks of treatment with bedaquiline or had discontinued earlier. Data provided were obtained from baseline to the patient's last visit before data cut-off last 29 March 2011. A total of 294 patients were screened, of whom 233 started treatment with bedaquiline with a BR. As in Trial C208 Stage II, the modified Intent-to-Treat (mITT)

population excludes patients with DS-TB or whose MGIT results did not allow for primary efficacy evaluation. The mITT population consisted of 205 patients.

The following table represents the subject disposition during the course of the trial. While all patients are still being followed for safety monitoring, 203/233 (87.1%) are still ongoing.

Table 50. Patient Disposition and Reason for Discontinuation.

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

Source: NDA 204,384. June 29, 2012. SD 1. Clinical Summary of Safety. p. 124

The extent of bedaquiline exposure in the trial can be seen in the following table.

Table 51. Extent of Exposure in Trial C209

Extent of Exposure -Phase Duration	ITT	mITT
	N = 233	N = 205
Investigational Treatment phase		
Mean (SD), weeks	23.8 (4.56)	23.8 (4.54)
Median (range), weeks	25.0 (1.1; 28.3)	25.0 (1.1; 28.3)
Overall Treatment phaseb		
Mean (SD), weeks	39.2 (14.90)	40.0 (15.10)
Median (range), weeks	37.9 (1.1; 81.1)	38.1 (1.1; 81.1)

Source: NDA 204,384. June 29, 2012. SD 1. Clinical Summary of Safety. p. 124.

The following table summarizes the demographic and baseline disease characteristics of the ITT and mITT population in C209.

Table 52. Baseline patient demographic and disease characteristics

Parameter Value	TMC207/BR	
	ITT N = 233	mITT N = 205
Gender, n (%)		
Female	83 (35.6)	73 (35.6)
Male	150 (64.4)	132 (64.4)
Age at screening, years		
Median (Range)	32.0 (18-68)	32.0 (18-68)
Ethnic origin, n (%)		

American-Indian or Alaska Native	8 (3.4)	6 (2.9)
Asian	90 (38.6)	84 (41.0)
Black or African-American	75 (32.2)	67 (32.7)
Caucasian/White	60 (25.8)	48 (23.4)
Lung cavitationa, n (%)		
Cavitation in both lungs	27 (11.6)	26 (12.7)
Cavitation in one lung only	121 (51.9)	109 (53.2)
No cavitation	85 (36.5)	70 (34.1)
HIV status at screeningb, n (%)	N = 225	N = 198
Negative	214 (95.1)	188 (94.9)
Positive	11 (4.9)	10 (5.1)
Extent of resistance of <i>M. tuberculosis</i> strain, n (%)		
DS-TB	3 (1.3)	0
MDR-TBc	230 (98.7)	205 (100)
<i>MDRH&R-TB</i>	93 (39.9)	93 (45.4)
<i>pre-XDR-TB</i>	44 (18.9)	44 (21.5)
<i>XDR-TB</i>	37 (15.9)	36 (17.6)
Albumin grade at baseline, n (%)		
Grade 0	190 (81.5)	167 (81.5)
Grade 1	19 (8.2)	15 (7.3)
Grade 2	23 (9.9)	22 (10.7)
Grade 3	1 (0.4)	1 (0.5)

Source: NDA 204,384. June 29, 2012. SD 1. Clinical Summary of Efficacy. p. 87

Medical Officer Comment:

Trial C209 is an open-label uncontrolled trial conducted to increase the safety database of patients exposed to the proposed dosing regimen of bedaquiline. This supportive trial enrolled patients who are MDR-TB treatment-experienced. As such, the trial enrolled patients who have pre-XDR and XDR TB isolates. The enrolled patient population in C209 would therefore be more reflective of the global clinical setting where bedaquiline could be used for MDR-TB treatment when no other alternative antimycobacterial is available.

The patient demographic and baseline disease characteristics appear to be consistent with those noted in Trial C208 Stage 2.

Prior Tuberculosis Treatment and Baseline Susceptibility

Ninety-three patients (40%) were infected with an MDRH&R-TB strain, 44 patients (19%) with a pre-XDR strain, and 37 patients (16%) with an XDR strain. Baseline susceptibilities of the patients to the secondary antimycobacterial drugs used to treat MDR-TB relative to the extent of strain resistance are shown in the following table:

Table 53. Baseline Susceptibility to Secondary Drugs in the mITT population

n (%) of isolates susceptiblea to	TMC207/BR							
	MDRH&R-TB		pre-XDR-TB		XDR-TB		All Subjects	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
EMB	90	27 (30.0)	43	8 (18.6)	34	2 (5.9)	167	37 (22.2)

SM	89	24 (27.0)	43	6 (14.0)	34	3 (8.8)	166	33 (19.9)
PZA	92	26 (28.3)	44	8 (18.2)	36	3 (8.3)	172	37 (21.5)
ETH	90	79 (87.8)	43	35 (81.4)	34	24 (70.6)	167	138 (82.6)
OFL	89	89 (100)	43	13 (30.2)	34	0	166	102 (61.4)
KAN	89	89 (100)	43	32 (74.4)	34	0	166	121 (72.9)
CAP	89	89 (100)	43	34 (79.1)	34	18 (52.9)	166	141 (84.9)

Source: NDA 204,384. June 29, 2012. SD 1. Clinical Summary of Efficacy. p. 88

As provided by the the inclusion criteria, 87.1% of patients had previously used second-line antimycobacterial drugs and most patients (86%) received anti-TB treatment during screening. Median previous treatment duration at screening was 36 days. Using the agar proportion method, more than 82% of the patients in the mITT population were susceptible capreomycin (CAP) and ethionamide (ETH) while 73% and 61% of patients were susceptible to kanamycin (KAN) and ofloxacin (OFL). Only 20% were susceptible to streptomycin (SM), 21% to PZA, and 22% to ethambutol, all first line antimycobacterial drugs. In all, only 29.1% of patients in the mITT population were infected with a strain that is susceptible to at least 5 drugs.

In this trial, patients received bedaquiline treatment for 24 weeks together with an individualized background regimen of antibacterial drugs chosen by investigators according to the national tuberculosis program (NTP) treatment guidelines.

Medical Officer Comment:

Trial C209 enrolled newly-diagnosed and treatment-experienced MDR-TB patients for a 24-week bedaquiline treatment period with an individualized background regimen. The demographic characteristics, disease severity characteristics, baseline isolate susceptibility data, and prior use of second-line tuberculosis drugs of patients in C209 represent characteristics of patients that would potentially use bedaquiline in the clinical setting. Safety findings from this trial will therefore provide the potential safety experience of patients who would actually use bedaquiline.

Overall Medical Officer Comment on the Adequacy of Safety Assessments:

The following table describes the safety database of bedaquiline in the Phase 2 studies. While the indication being evaluated is pulmonary MDR-TB, the number of patients exposed to bedaquiline includes a few patients with DS-TB. Moreover, while the proposed treatment duration is 24 weeks, the exposure provided in these trials vary, from an 8-week to a 24-week exposure duration.

Table 54. Phase 2 Safety Database

<i>Trial/Phase/Description</i>	<i>Number of Patients</i>
<i>Phase 2a (7-day monotherapy EBA in DS-TB)</i>	<i>(45)</i>
<i>Phase 2b (Controlled Trial in Treatment-naïve patients with BR)</i>	

C208 Stage 1 (8-wk bedaquiline exposure w/ 96 week BR)	23
C208 Stage 2 (24-wk bedaquiline exposure w/ 96 wk BR)	79
Phase 2b C209 (uncontrolled trial in treatment-experienced patients with BR)	
C209 (24-wk bedaquiline exposure w/ 96 wk BR)	233
24 week exposure	312
Total number of tuberculosis patients	335
Total number of MDR-TB patients in Phase 2b	328
Total number of MDR-TB patients w/ a 24-week bedaquiline exposure	305

The safety database of the Phase 2 bedaquiline trials is limited, especially if considering the placebo controlled trial where exposure is the same as the proposed exposure (79 patients). However, when patients included in Trial C209 is included, the safety database appear adequate. With 305 MDR-TB patients exposed to a 24-week bedaquiline dosing regimen, the combined trials would be able to detect ADRs that could occur in 1% of the exposed population, based on the Rule of 3s principle.

The reliance on safety data obtained from the safety database of the Phase 2 trials consisting of patients with MDR-TB exposed to the 24 week dosing regimen for bedaquiline should be taken in context with the fact that bedaquiline is evaluated via the Accelerated Approval regulations. The impetus for the Accelerated Approval Pathway are twofold. First, the last drug to treat TB was formally evaluated decades ago. There is therefore a great need for a new drug to MDR-TB exists. Second, the incidence of MDR-TB is low, especially in the United States. Therefore, traditional approval would entail at least a 5-year duration of formal clinical evaluation prior to filing of an NDA. Because of these and based on the recommendations from the AIDAC meeting in 2009, the safety database in this application for bedaquiline should be sufficient.

7.2.4 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant proposes to use bedaquiline in patients with pulmonary MDR-TB patients who are either treatment-naïve or treatment-experienced. Please see the above discussion.

7.2.5 Explorations for Dose Response (Trial C202)

The Applicant conducted Trial C202 that could be considered a dose-response study. The objective of this study is to determine the early bactericidal activity of 3 different doses of bedaquiline given for 7 days as monotherapy compared to INH monotherapy and rifampin monotherapy. The outcome measure was the viable counts of M. tuberculosis in sputum. This is an open-label, randomized trial in treatment-naïve patients with pulmonary DS-TB in South Africa. Seventy-five patients were randomized to five treatment groups: 15 patients treated with 25 mg of bedaquiline, 16 patients

treated with 100 mg of bedaquiline, 14 patients treated with 400 mg of bedaquiline, 15 patients treated with 600 mg of RMP, and 15 patients treated with 300 mg of INH, all for 7 days; after which patients received standard anti-TB multidrug therapy.

The study showed that the group treated with INH showed early bactericidal response from Day 1 onwards, similar to the group treated with rifampin. A delay in the onset of response for the 400 mg bedaquiline treatment group was noted in terms of change in log₁₀ CFU counts that started from Day 4 onwards. The lower doses (25 and 100 mg) did not show statistically relevant changes during the 7 day treatment regimen.

This is shown in the following table:

Table 55. Change in viable sputum counts of M. tuberculosis after 7 day treatment of bedaquiline, INH, rifampin

Activity	Bedaquiline						Rifampin		INH	
	25 mg		100 mg		400 mg		600 mg		300 mg	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
EBA (log ₁₀ CFU/day)										
Day 2	13	0.01(0.137)	14	-0.10(0.341)	13	0.02(0.300)	13	-0.44 (0.523)	11	-0.28(0.606)
Day 7	14	-0.01(0.066)	14	-0.04(0.091)	12	-0.11(0.083)	13	-0.24 (0.102)	11	-0.27(0.105)
Changes From Baseline in log ₁₀ sputum CFU count										
Day 2	13	0.02(0.274)	14	-0.20(0.681)	13	0.04(0.599)	13	-0.88 (1.046)	11	-0.57(1.212)
Day 7	14	-0.04(0.459)	14	-0.26(0.638)	12	-0.77(0.578)	13	-1.70 (0.713)	11	-1.88(0.736)

Source: NDA 204,384, June 29, 2012. SD 1. Clinical Study Report C202. p. 13.

In terms of exposure-response relationships for safety, the Clinical Pharmacology reviewer concluded in his analysis that “no clear and consistent relationship between exposure and adverse event (AE) incidence was identified for the most frequently observed adverse events”. Dr. Fang Li, the Pharmacometrics reviewer provided an analysis to determine a dose-response relationship between exposure and the most frequently reported AEs in Trial C208 Stage 2. He observed that the most frequently reported AEs (nausea [38%], arthralgia [32.9%], headache [27.8%], and hemoptysis [17.7%]) occurred consistently more frequently in the bedaquiline arm. Except for a small trend for arthralgia, no significant relationship between the AE incidence and bedaquiline exposure could be identified, as shown in the following figures.

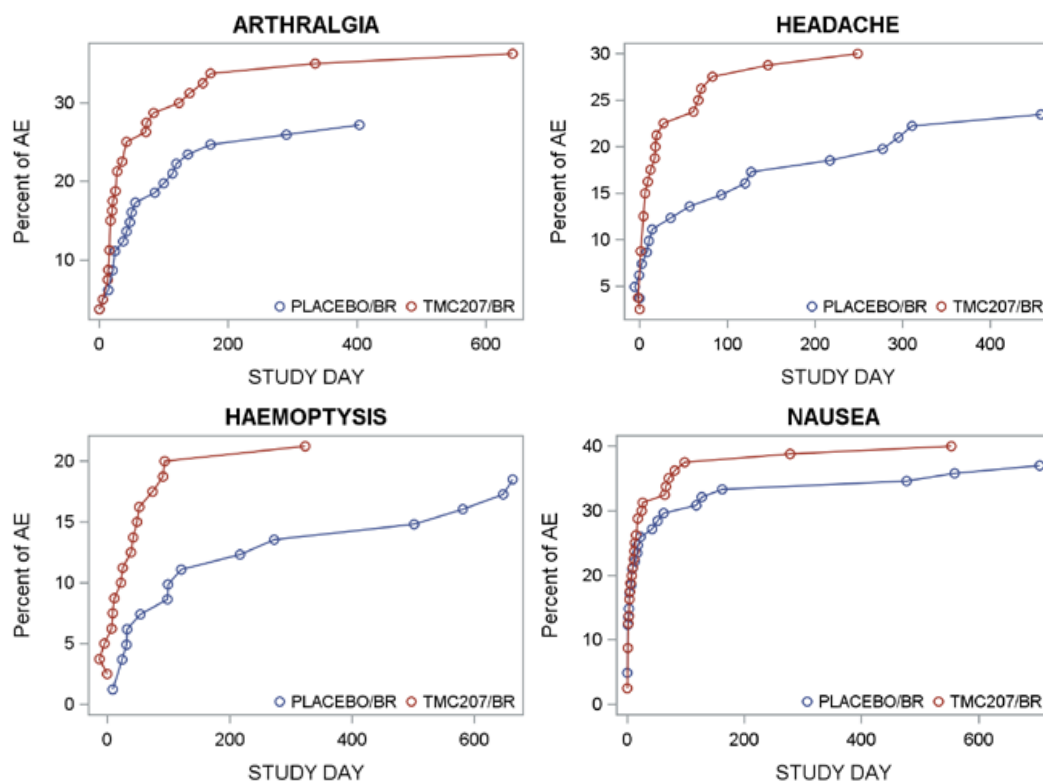


Figure 12. Relationship between AE incidence and AUC24h

Dr. Li cautions that because of the limited safety database and PK profiles in a limited number of patients, undetected significant exposure-response relationships could still be present.

Medical Officer Comment:

I concur with Dr. Li's conclusion. Moreover, while the AE hemoptysis occurred more frequently in the bedaquiline group, its association with bedaquiline is unlikely. Hemoptysis is more probably associated with the patient's underlying condition.

At this point, it is noteworthy to mention that 2 patients in the 400 mg bedaquiline arm died. One died 25 days post-bedaquiline treatment from tuberculosis and retroviral infection and another died 13 days post-bedaquiline treatment from tuberculosis and hemoptysis. These deaths will be further discussed in a subsequent section.

Study C202 also demonstrated a suggestion of a greater QTcF prolongation in the group given 400 mg of bedaquiline for 7 days.

7.2.6 Special Animal and/or In Vitro Testing

Please see Section 4.3. Preclinical Pharmacology/Toxicology

7.2.7 Routine Clinical Testing

None

7.2.8 Metabolic, Clearance, and Interaction Workup

The Medical Officer refers the reader to the review of the Clinical Pharmacology review team, led by Dr. Dakshina Chilukuri.

7.2.9 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

7.3 Major Safety Results

7.3.1 Deaths

A total of 36 deaths were reported during the entire clinical development program of BEDAQUILINE. The deaths occurred in the four Phase 2 trials (Trial C202 [Phase IIa], Trial C208 [Phase IIb Stage I, Phase IIb Stage II], and Trial C209. The last two deaths were reported in a Communication submitted by the Applicant on December 4, 2012.

The number of deaths in the clinical program is summarized in the following table:

Table 56. Tabular summary of mortalities in the bedaquiline program.

	Type of Study	Bedaquiline	Placebo
Phase 1		0	0
Phase 2			
Study C202	Randomized, open-label, dose-ranging EBA study	N=45	N=30 (INH, RMP)
Deaths		2 (4.4%)	0
Trial C208 Stage 1	Randomized, placebo-controlled, 8-week exposure	N=23	N=24
Deaths		2 (8.7%)	2 (8.3%)
Trial C208 Stage 2	Randomized, placebo-controlled, 24 week exposure	N=79	N=81
Deaths		10 (12.6%)	4 (4.9%)
Trial C209	Open-label, uncontrolled, 24-week exposure	N=233	
Deaths		16 (6.9%)	

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The following table summarizes the clinical courses of the deaths that occurred in the bedaquiline clinical development program. In this table, mortalities from the C202 study, Trial C208 Stage 1, and Trial C208 Stage 2 reported to the Agency on December 4, 2012 in the Applicant's 4 month safety update report are included. However, only the 5 mortalities from Trial C209 reported to the Agency on initial submission of the NDA (June 29, 2012) are included. The rest of the mortalities in Trial C209 are described in the text that follows.

Table 57. 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/ Treatment	Conversion/Response
CONTROLLED TRIALS							
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	D (b) (6) ~4 mos. post bedaquiline	Post-treatment	Myocardial Infarction, complete occlusion of LAD	None	Conversion (Wk 14). Outcome: Non-responder (death)
	208-3100 (withdrawn)	25 yo F; treated for 6 days but withdrawn from trial on D13 because of isolation of XDR-TB. Withdrawn for clarithromycin concomitant antibacterial	D (b) (6) post bedaquiline	Late Post-treatment	Pulmonary tuberculosis	None	Non-converter. Outcome: Non-responder (no conversion and death)
Trial C208 Stage 1 (8-week course) Placebo Group	208-3010 (withdrawn)	19 yo M. Baseline isolate was an w/ MDR _{H&R} -TB strain. Completed 56d of bedaquiline. Patient developed XDR-TB after 9 months	(b) (6) post-placebo	Late Post-treatment	Tuberculosis-related illness	None	Non-converter. Outcome: Non-responder (no conversion and death)
	208-3049 (withdrawn)	20 yo M with XDR-TB at baseline. Treated for 6d with bedaquiline. Patient was withdrawn on D13 after XDR-TB identified	(b) (6) post placebo	Late Post-treatment	Pulmonary tuberculosis	None	Non-converter. Outcome: nonresponder (no conversion with 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) (6) post-bedaquiline	Immediate post-treatment phase	Alcohol Poisoning (Grade 4) high alcohol blood concentration(3.73%) unwitnessed death	None	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) (6) post-bedaquiline	Post-treatment (Follow-up)	D228: Hepatitis (Grade 3) and Hepatic Cirrhosis (Grade 4); On (b) (6) admitted for a alcoholic liver cirrhosis with ascites, volume depletion, malnutrition	Background regimen or bedaquiline could be contributory	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 every other week	(b) (6) post-bedaquiline	Post-treatment	Tuberculosis AE-Tuberculosis (Grade 3); readmitted to hospital 10 mos after bedaquiline for TB worsening and noncompliance w/	None	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; (b) (6) Px relapsed	D (b) (6) post-bedaquiline	Post-treatment	Tuberculosis AE- Dyspnea (Grade 3), TB relapse (Grade 4); readmitted to hospital 8 ½ mon hs after last intake dose of bedaquiline and died 3 weeks later	None	Conversion (Wk 28) but with recurrence (Wk 60). Outcome: Non-responder (relapse)
Late Follow-Up (reported between 10 June 2011 and 15 March 2012)	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).	D (b) (6) post-bedaquiline	Late Post-treatment	Cerebrovascular Accident (CVA) (Grade 4) probably from hypertension (Grade 3)	None	Conversion (Wk 28). Outcome: death but converted

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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/ Treatment	Conversion/Response
bedaquiline Group		Completed 168d of bedaquiline;					
	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.	(b) (6) post-bedaquiline)	Late Post-treatment	AE-Infectious Peritonitis; Septic Shock (Grade 4)	None	Conversion (Wk 14). Outcome: death but converted
Prematurely Withdrawn	208-4127	51 yo F with unilateral cavitations from an MDR _{H&R} -TB strain. Received 29d of bedaquiline but was withdrawn because of noncompliance, BR: EMB, PZA, ETH, OFL, and KAN. Readmitted 16 mos later for MDR-TB and was diagnosed with XDR-TB; Absconded from the hospital	(b) (6) post-bedaquiline intake	Late, late post-treatment	TB-related illness (unknown details)	None	No documented conversion; XDR-TB
	208-4145	36 yo M with bilateral cavitations from an MDR _{H&R} -TB strain. BR: EMB, PZA, ETH, OFL, KAN. Completed 24 wks (168d) of bedaquiline; withdrawn on Wk 36 because of noncompliance; readmitted for worsening MDR-TB	(b) (6) post-bedaquiline intake	Late, late post-treatment	TB-related illness (unknown details)	None	Conversion on D84 but relapsed on D308
	208-4378	36 yo black M with unilateral cavitation from an MDR _{H&R} -TB strain. BR: AMK, OFL, ETH, EMB, PZA. Treated with bedaquiline for 142d. Withdrawn because of increased transaminase (Grade 3/4)	(b) (6) post-bedaquiline intake	Late, late post-treatment	Motor-vehicle accident	None	Conversion on D54 but relapsed on D98. Outcome: relapse
	208-4464	30 yo M without cavitations; infected with an XDR-TB strain. BR: KAN, ETH, PAS-C, PZA, EMB, MOX, AMK, CS, ciprofloxacin, and amox/clav; Received 90d of bedaquiline; withdrawn because of isolation of XDR and receipt of moxifloxacin	(b) (6) post-bedaquiline intake	Late, late post-treatment	TB-related illness Complications from XDR-TB	None	No conversion: Outcome: nonresponder
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) (6) post-placebo)	Post-treatment	Tuberculosis AE-Hemoptysis (Grade 3)	None	No conversion. Outcome: nonresponder
	208-4155	36 yo F with bilateral cavitations from an MDR _{H&R} -TB strain. BR: EMB, PZA, ETH, OFL, KAN. Received 165d of placebo. Withdrawn because of noncompliance (interruption > 14d); Readmitted 2 mos prior to death for MDR-TB treatment and treated for XDR-TB (unknown if with documented isolate) 3 wks prior to death	(b) (6) post-placebo	Late, late post-treatment	Tuberculosis-related illness	None	No conversion; Outcome: nonresponder (failure to convert)
	208-4453	Isolated MDR-TB and given 128d of placebo	(b) (6) post-placebo	Late, late post-treatment	MDR-TB	None	Discontinued/ but converted
	208-4154	Isolated MDR-TB; completed placebo treatment	(b) (6) post-placebo	Late, late post-treatment	Pneumothorax/empyema	None	No conversion
UNCONTROLLED TRIALS							
Phase IIa (7-day	202-	25 yo, HIV (+) black F; treated for	D (b) (6)	Post-	Tuberculosis	None	

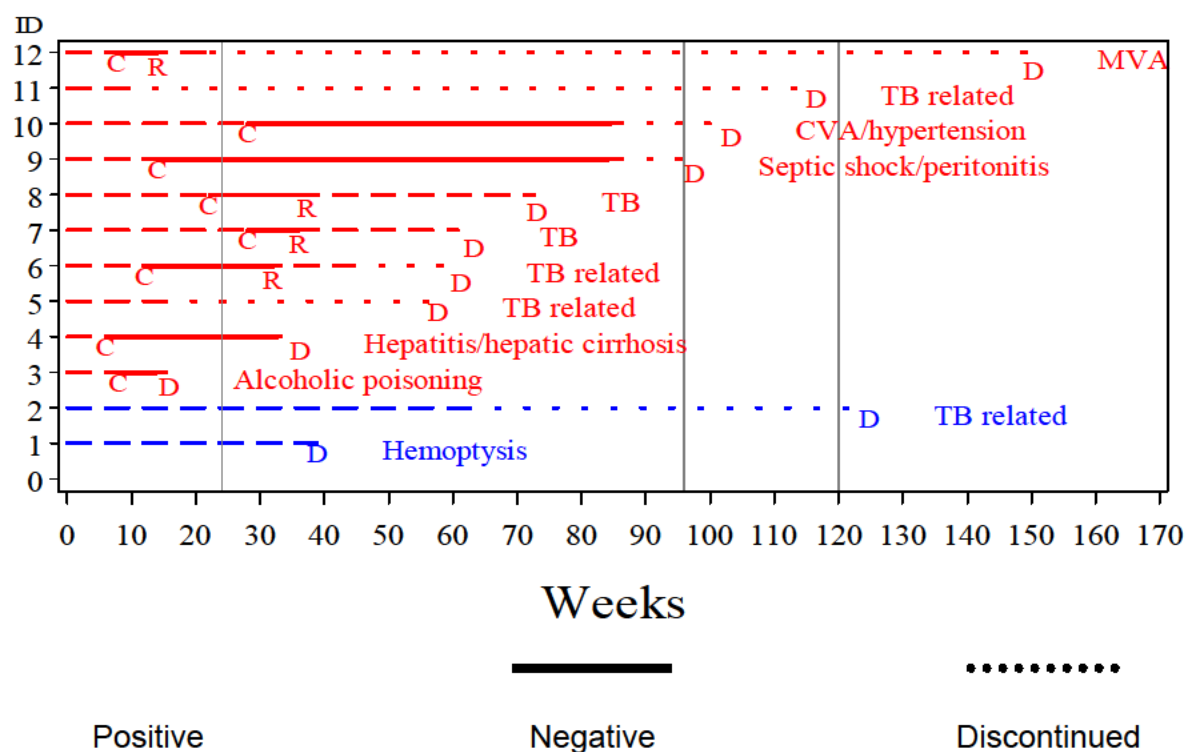
Clinical Review
Ariel R. Porcalla, MD, MPH
NDA 204 384
BEDAQUILINE (bedaquiline)

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/ Treatment	Conversion/Response
treatment) (Trial C202) Bedaquiline Group 400 mg qDaily	0109	7d; CD4 count 80; completed 7d of bedaquiline BR: RMP, INH, PZA, and EMB	(b) (6) post-bedaquiline)	treatment	AE -Pulmonary TB Retroviral Infection (D41)		
	202-0036	41 yo M, treated for 3d; d/c'ed study bec. of cannabinoids; finished 3d of bedaquiline but discontinued; BR: RMP, INH, PZA, and EMB	D (b) (6) post-bedaquiline)	Post-treatment	Tuberculosis AE- Hemoptysis (Grade 3) (D13)	None	
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; D (b) (6) B treatment DCed	(b) (6) 52d post-bedaquiline)	Investigational Treatment Phase	Tuberculosis AE- Tuberculosis (Gr 4)	None	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	(b) (6)	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; D (b) (6) death	Possibly related Investigator: doubtfully related	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; Completed 44d bedaquiline	(b) (6) post-bedaquiline)	Overall Treatment Phase; post-bedaquiline	Tuberculosis AE-Tuberculosis (Gr 4) Organic Hallucinations (Gr 3) likely due to combination of drugs;	None	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 replaced with clarithromycin and clofazimine; improved but on D228, readmission for lung infection.	D (b) (6) post-bedaquiline)	Overall Treatment Phase;	Lung Infection (Gr 4) starting D201; patient converted	None	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) (6) post-bedaquiline)	Overall Treatment Phase;	D (b) (6) Gr 3 right-sided congestive cardiac failure ECG: QTcB 450-480ms. QTcF w/ normal (418 ms) Shortness of breath	Possibly related	Conversion (Wk 36). Outcome: Non-responder (discontinuation)

#: The mortalities included in the table are the mortalities adequately described in the Applicant's initial NDA submission (June 29, 2012). The remaining mortalities are described in the text that follows.

A graphical representation of the timing of the deaths, in relation to their conversion, relapse, discontinuation, and treatment exposure to bedaquiline follows. The graph demonstrates the observations noted by both the Applicant and Medical Officer.

Figure 13. Graphical Representation of Timeline of Deaths in Trial C208 Stage 2 (reported as of the original NDA submission date)



Select Case Narratives of Deaths (cutoff date of June 10, 2011 for the initial NDA submission)

7.3.1.1. Phase IIa (Trial C202)

This is an open-label, randomized trial in treatment-naïve patients with sputum smear (+) pulmonary DS-TB in South Africa. No deaths occurred during the treatment period but 2 deaths occurred during the follow-up period. As noted in the tabular summary of deaths, these 2 patients were both in the bedaquiline 400 mg qD group died during the immediate follow-up period when these patients were receiving standard TB treatment for their DS-TB. These mortalities will be discussed in Section 7.4.5.2.

7.3.1.2. Phase IIb (Trial C208 and Trial C209)

7.3.1.2.a. Controlled Trials (Trial C208)

7.3.1.2.a.i. Stage 1

This is an exploratory trial using an 8 week course of bedaquiline with background regimen. No deaths occurred during the 8-week Investigational Treatment phase. During the treatment period with BR (post 8-week investigational treatment phase with bedaquiline), two patients in the bedaquiline group died while two patients in the placebo group died. Details of these deaths are found in the tabular summary above.

Medical Officer Comment:

Among the four deaths in this trial, the mortality from a fatal acute myocardial infarction occurred during the treatment period for the BR. While cardiac in etiology, this mortality is unlikely to be from cardiotoxicity secondary to bedaquiline. The pathological evidence of the myocardial infarction was noted by autopsy findings of an occlusion of the L anterior descending coronary artery and the presence of a negative T wave on baseline ECG.

The rest of the mortalities (one in the bedaquiline group and two in the placebo group) are tuberculosis-related. These patients failed to convert so the Medical Officer concurs that these deaths are probably from the exacerbation of the underlying tuberculosis.

7.3.1.2.a.ii. Stage 2

This is the pivotal, proof-of-efficacy trial enrolling treatment-naive patients with sputum-smear positive pulmonary MDR-TB who were treated with 24 weeks of bedaquiline or placebo on top of a 5-drug optimized background regimen consisting of KAN, ETH, OFL, PZA, and TRD. The following are the subject narratives reported by the Applicant for the deaths reported in the trial.

Bedaquiline Group

Subject 208-4041

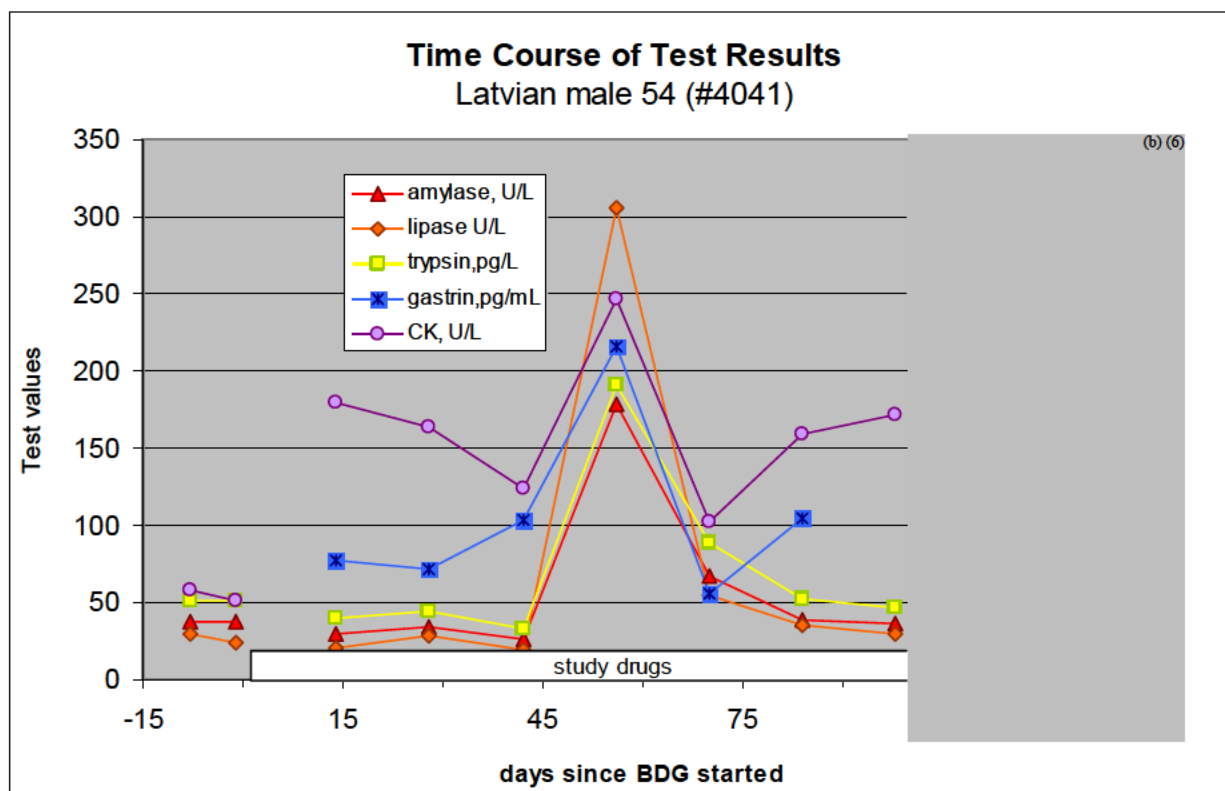
- This is a 54 year old white man with MDR_{H&R}-TB strain at baseline randomized to receive bedaquiline. Patient had no relevant past medical history with no history of drug allergy or hypersensitivity. He presented with cough, fever, and night sweats

- Started 31 March 2009 with a BR of KAN, OFL, protionamide, PZA, terizidone (TRD).
- Stopped bedaquiline (b) (6). He converted his sputum to negative at Week 8 and Week 14 of therapy.
- Left hospital voluntarily on (b) (6) and did not return.
- Site was contacted by the police who found subject dead at the roadside.
- Autopsy showed a high alcohol blood concentration of 3.73%.
- Alcohol intoxication was diagnosed as cause of death. Screening for other drugs was negative.
- Grade 4 SAE/Cause of death: Alcohol Poisoning (b) (6); not related to bedaquiline and not related to the BR

Medical Officer Comment:

This is the only death that occurred during the interventional treatment period with bedaquiline. This death was an unwitnessed death that presumably occurred on Day (b) (6). Several aspects of this death need to be further discussed:

- *The cause of death of this patient was presumably from an elevated alcohol level of 3.73%, determined from a postmortem blood sample. While alcohol intoxication is plausible as a cause of death given the elevated blood alcohol level, this was still basically an unwitnessed death.*
- *The Applicant reported that an autopsy was performed. Yet, no other autopsy findings for this patient was presented.*
- *The Applicant failed to report in this patient's narrative that this patient had concurrent abnormalities in laboratory parameters related to the pancreas, muscle, and stomach.*
- *During the course of his treatment, the patient developed upper abdominal pain from Days 52 for 5 days, followed by fever on Day 55 for 23 days. On Day (b) (6), the patient developed pruritus which persisted for 26 days. The pruritus resolved 5 days prior to the day he discontinued bedaquiline and the patient absconded from the hospital.*
- *Around the time the patient developed upper abdominal pain and fever, on Week 8 of the trial, the patient developed abnormalities in the following laboratory parameters:*
 - *creatinine kinase= 247 (Normal (N)=18-198)*
 - *lipase = 306 (N=0-100)*
 - *amylase = 178 (1-46)*
 - *gastrin=216 (N=25-111 pg/mL)*
 - *trypsin= 190.8 (N=20.5-132.6 ng/mL)**The laboratory values returned back to normal at Week 10, except for amylase which decreased to 67 U/L. At the same time, fever and abdominal pain resolved.*
- *The following is a graphical representation of the laboratory abnormalities of the patient during his clinical course:*



Source: Preliminary consultation by Dr. John Senior and Dr. Leonard Seeff on the potential for DILI of selected deaths. December 17, 2012.

- The patient had other concomitant medications: pentoxifylline, omeprazole, ranitidine, and the antihistamine clemastine.
- The following are the patient's transaminases and liver function tests, all of which are within normal limits:

Table 58. Summary of transaminases and bilirubin for Patient 208-4041.

Timepoint	Alkaline Phosphatase (N=35-131) U/L	ALT (N=6-43) U/L	AST (N=11-36) U/L	Timepoint	Direct Bilirubin Result (0-7) umol/L
SCREENING	67	10	17	SCREENING	<2
SCREENING	69	13	18	SCREENING	<2
BASELINE	67	10	17	BASELINE	<2
WEEK 2	73	11	22	WEEK 4	<2
WEEK 4	73	6	23	WEEK 6	2
WEEK 6	74	8	22	WEEK 8	2
WEEK 8	74	8	35	(b) (6)	<2
(b) (6)		6	14	(b) (6)	
		<4	19		

(b) (6)	6	21		
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- *From the table above, no hepatic laboratory abnormalities developed. Hepatotoxicity did not develop in this patient.*
- *The elevation of gastric, skeletal, and pancreatic analytes at Week 8 with abdominal pain and fever are indicative of an unidentified acute event that occurred during this time.*
- *Both bedaquiline and the background regimen were not held or discontinued when these abnormalities developed. The negative dechallenge test may indicate that these transient laboratory abnormalities may not be related at all to the BR or to bedaquiline. However, a negative dechallenge test, by itself, could not rule out association with a culprit drug in instances when the host was able to recover from the initial drug-induced injury either spontaneously or with treatment.*
- *Because of the pancreatitis with concomitant gastric and skeletal muscle involvement, phospholipidosis as the etiology of these transient abnormalities is considered. Phospholipidosis is a pathological diagnosis noted in animal studies for bedaquiline. As such, pathological verification is needed to clinch the diagnosis, in addition to nonspecific clinical manifestations in the affected organs. In this patient, the transient increase in markers for the stomach, skeletal muscle, and pancreas could be from phospholipidosis. The diagnosis needs to be verified by pathological findings in the involved organs and clinical and laboratory evaluation such as bicarbonate, anion gap, etc.*
- *Another drug reaction that can be considered as etiology is the Drug Reaction, Eosinophilia, and Systemic Symptoms (DRESS) Syndrome. The narrative did not provide information to rule this out: presence of a rash, eosinophilia and thrombocytopenia, and renal impairment.*
- *An idiosyncratic reaction to any of the medications that spontaneously resolved could also have caused the transient increase in organ-specific pathological markers.*
- *In all, more information regarding this patient's clinical course is needed to identify the etiology of his transient laboratory abnormalities and to have, if possible, an alternative cause of death.*

Subject 208-4153

- 33 year old HIV negative woman of race designated as "other" with MDR_{H&R}-TB strain at baseline randomized to receive bedaquiline
- Started 27 August 2009 in combination with a BR of EMB, ETH, KAN, OFL, PZA. DST shows patient's isolate was susceptible to 5 drugs in her baseline BR
- Completed treatment period as planned but with interruption of the BR every other week
- Last intake of bedaquiline was (b) (6)

- May 2010: patient experienced worsening of TB (unknown symptoms)
- (b) (6): Because of TB worsening and noncompliance with the BR, patient was admitted to the hospital and restarted on her MDR TB treatment
- SAE reported as: Tuberculosis (Grade 3)
- (b) (6): Death from worsening TB

Subject 208-4224

- 18 year old black HIV-negative male with cavitations in one lung from an MDR_{H&R}-TB strain
- Received bedaquiline with a BR consisting of aminoglycosides, CIP, CS, EMB, ETH, and PZA. The isolate was susceptible to 2 drugs in his BR.
- Completed treatment as planned with clinically significant interruption of the BR (>14 days).
- Last bedaquiline intake: (b) (6)
- D252 (28 April 2009): The patient relapsed after 89 days from last bedaquiline intake.
- Grade 4 SAE: tuberculosis as cause of death
- Tuberculosis assessed as not related to bedaquiline and BR as per the investigator.
- (b) (6): admitted to the hospital and found to have extensive bilateral disease
- October 2009: SAE of Grade 3 dyspnea considered unrelated to bedaquiline and BR as per investigator
- Initially experienced improvement of symptoms.
- (b) (6): Dyspnea worsened
- (b) (6): Death due to respiratory failure due to extensive bilateral TB

Subject 208-5069

- 63 year old HIV negative Asian male with unilateral pulmonary cavitation due to an *M. tuberculosis* strain at least resistant to INH and RMP.
- No full DST results available
- BR: CS, ETH, KAN, OFL, PZA
- Completed the treatment period as planned
- Day (b) (6): Admitted to the hospital for a 2 month history of fatigue and a 1 week history of epigastric pain.
- (b) (6) Diagnosed with Grade 3 hepatitis and Grade 4 hepatic cirrhosis SAEs
- Considered not related to bedaquiline or to the BR
- (b) (6) death due to hepatitis and hepatic cirrhosis
- Hospital Records indicate patient died from alcoholic liver cirrhosis. Comorbidities include ascites, volume depletion, and malnutrition.

Medical Officer Comment:

This death will be discussed in greater detail in the Hepatic-Related Adverse Drug Reactions section.

Subject 208-4399

- 55 year old male who died of a cerebrovascular accident
- Fatal SAE (CVA) occurred (b) (6) days after last dose of bedaquiline
- Not related to bedaquiline as per Investigator

Subject 208-5067

- 43 year old Asian male who died from peritonitis and septic shock
- SAE 1: Infectious peritonitis (b) (6) days after last dose of bedaquiline) – not related according to the investigator
- SAE 2: Septic shock (b) (6) days after last dose of bedaquiline) – not related to bedaquiline as per investigator
- The following table describes the trends in this patient's serum transaminases and liver function tests. This patient developed peak AST values ≥ 3 x the ULN and total bilirubin ≥ 2 x the ULN around the end of the interventional treatment period with bedaquiline (Week 24). This patient was subsequently diagnosed with alcoholic hepatitis. He later on developed infectious peritonitis and sepsis from which he subsequently died. This patient's clinical course will be discussed in the Hepatic-Related Adverse Drug Reactions section.

Table 59. Laboratory evaluation of serum transaminases of Patient 208-5067 (SAE: Infectious Peritonitis and Septic Shock)

Phase Analysis time point	ALT (U/L)	AST (U/L)	Total bilirubin (μmol/L)	Indirect bilirubin (μmol/L)	Direct bilirubin (μmol/L)	ALP (U/L)	GGT (U/L)	Albumin (U/L)
	6-43	11-36 3xULN: ≥ 108	3-21 2xULN: ≥ 42		0-7	31-129	10-61	33-49
Overall treatment								
Baseline	10	18	4	3	1	65	52	35
Week 2	9	26	4	3	1	76	50	
Week 4	7	24	4	3	1	80	65	
Week 6	8	24	7	6	1	90	53	
Week 8	7	43	12	9	3	97	91	
Week 10	11	40	5	4	1	100	101	
Week 12	9	35	10	7	3	84	89	
Week 14	11	30	6	5	1	95	125	

Week 16	11	40	5	3	2	100	161	
Week 18	35	119	9	6	3	120	232	
Week 20	32	134	13	9	4	157	473	
Week 22	21	94	11	6	5	150	621	
Week 24	118	501	52	23	29	189	939	31
Week 28	35	226	14	9	5	173	879	
Week 32	13	78	9	6	3	147	879	
Week 48	8	47	18	14	4	95	511	
Week 60	29	122	15	11	4	86	793	
Week 72	14	41	8	6	2	79	509	
Week 84	41	148	129	49	80	243	1240	30

Placebo Group

Subject 208-4120

- 24 year old HIV negative female with bilateral cavitations > 2 cm from a pre-XDR TB strain at baseline
- BR therapy included EMB, ETH, KAN, OFL, PZA. Isolate was susceptible to 2 drugs in the BR
- Day (b) (6): 2 episodes of hemoptysis, reported as Grade 3 SAE resulting to death
- SAE considered doubtfully related to placebo and possibly related to the BR as per investigator

Medical Officer Comment for Trial C208 Stage 2 Mortalities:

The placebo-controlled, randomized, double-blinded nature of Trial C208 Stage 2 is informative when evaluating safety. Throughout the course of the NDA evaluation, the number of deaths reported in each treatment group varied according to the reporting cut-off time set, applicable for patients who are prematurely withdrawn from the trial. According to the protocol, patients who are prematurely withdrawn are followed up every six months for survival until the last patient in the trial is in his last visit. While the Applicant's analysis of the deaths indicate that none of the deaths were related to bedaquiline, including deaths that occur remotely from exposure may be problematic when comparing the total number of deaths in each arm.

While useful to a degree especially for drugs with long half-life such as bedaquiline, this method of monitoring deaths could inflate the number of deaths in each arm, even if the timing of death is so remote from the last drug intake that association is impossible. Deaths that occur so late and so remote from exposure may not be relevant. Thus, setting a reasonable cutoff time (for example, twice or thrice the terminal half-life of bedaquiline) after which deaths are not followed up may be more logical.

We therefore set a cutoff time of 120 weeks; afterwhich, deaths will not be counted. With this cutoff, it appears that there are 9 bedaquiline deaths vs 2 placebo deaths. The following table summarizes the results of the analysis.

Table 60. Number of Deaths per Arm with 120 wks as follow-up cutoff date

Trial Phase	Deaths (%)		RD	P-Value (Fisher's)
	Bedaquiline (N=79)	Placebo (N=81)		
Total for Trial C208 Stage 2	9 (11.4%)	2 (2.5%)	8.9%	0.031 (-1.1%, 18.2%)

A statistically significant imbalance in mortality is noted in the bedaquiline group. This mortality imbalance is concerning. To understand the reason behind this observation, deaths were examined in detail to look for trends that could explain this imbalance.

The following table describes pertinent information from each death that could be helpful.

Table 61. Information on Deaths Occurring During the Trial

Group/ Patient	Cause of Death (SAE)	Days since intake of drug	Exposure to study drug	Microbiologic Conversion	Risk Factor for SAE
Bedaquiline					
4041	Alcoholic poisoning	(b) (6)	109	Responder	Intoxication at autopsy; 4 active drugs
4153	Tuberculosis		168	Relapse	Interruption, noncomp, cavitations; susceptible to all 5 BR drugs
4224	Tuberculosis		163	Relapse	< 3 active drugs, susc. to 2 BR, interruption, cavitations
5069	Hepatitis/hepatic cirrhosis		168	Responder	liver cirrhosis; Recorded principal diagnosis: alcoholic liver cirrhosis; unknown susceptibility
5067	Septic shock/peritonitis		170	Responder	Heavy alcohol consumption and hepatitis (initial normal LFTs); Pre-XDR (R to FQ)
4399	CVA		168	Responder	Hypertension; unknown susceptibility
Placebo					
4120	Hemoptysis		168	Nonconv	Pre-XDR; < 3 active drugs, 2 active drugs; cavitation

Table 62. Information on Patients who were prematurely withdrawn and died.

Follow-up of Withdrawn Patients	Cause of Death (SAE)	Days since intake of drug	Exposure to study drug	Microbiologic Conversion	Risk Factor for SAE	Reason for withdrawal
Bedaquiline						
4127	TB-related	(b) (6)	29	Nonconvert	Cavitations	Noncomp
4145	TB-related		168	Relapse	Cavitations; noncompliance	Noncomp
4464	TB-related		90	Nonconvert	XDR	XDR at baseline
Placebo						
4155	TB-related		165	Nonconvert	Cavitations	Noncomp

The following observations can be made.

- *Of the 9 deaths in the bedaquiline group, 7 patients converted.*
- *Of these seven patients, 3 relapsed early and died of tuberculosis-related illnesses.*
- *Of the four patients who did not relapse, all died of non-TB-related diseases.*
- *Lastly, interestingly, tuberculosis was the cause of death in two placebo deaths who failed to convert and in 5 out of 9 bedaquiline deaths. Of the 5 TB-related deaths, two patients failed to convert and as stated above, three converted but relapsed.*

No discernible pattern between death and conversion, relapse, microbiologic response, sensitivity to the BR, HIV status, severity of the disease, and the type of TB isolation, could be observed. The most

In all, the reason for the imbalance of deaths in Trial C208 Stage 1 is unknown.

7.3.1.2. b. Uncontrolled Trials (Trial C209)

Five patients (2.1%) died during Trial C209 due to SAEs. Two patients died due to an AE that started during the Investigational Treatment Phase of the trial (TB and renal impairment). Three patients occurred after the Investigational Treatment Phase (TB, lung infection, cardiac failure congestive. All deaths in this uncontrolled trial were determined as not related to bedaquiline by the investigator. The only exception is renal impairment from vomiting and dehydration, which was considered doubtfully related.

Investigational Treatment Phase (Select Case Narratives with (cutoff date of June 10, 2011 for the initial NDA submission)

Patient 209-0024

- 52 year old black HIV-negative woman with > 2 cm unilateral cavitations due to an XDR-TB strain. The strain was susceptible to 1 drug used in the BR, which consisted of KAN, OFL, EMB, ETH, and PZA.
- On D55, TRD was added to the BR.
- On D62, patient discontinued bedaquiline and discontinued from the trial because of worsening of her condition.
- On D62, the SAE Tuberculosis (XDR-TB) was reported as Grade 4 SAE
- This was assessed as not related to the bedaquiline or the BR
- On D86, all drugs in the BR were permanently discontinued.
- On D (b) (6) the patient died with the cause of death determined to be tuberculosis.

Patient 209-0044

- 63 yo black female with > 2 cm unilateral cavitations due to an MDR_{H&R}-TB strain.
- BR consisted of ETH, KAN, OFL, PZA, and TRD.
- On D (b) (6) n SAE of vomiting was reported as Grade 3. Patient was hospitalized for this SAE.
- SAE was evaluated as doubtfully related to bedaquiline and probably related to the BR
- On D22, bedaquiline was discontinued.
- Despite initiating medical treatment, vomiting persisted and caused dehydration and renal impairment on D26.
- On D (b) (6) the patient died from Grade 4 renal impairment from vomiting and dehydration.
- The three SAEs leading to the patient's death were considered doubtfully related to bedaquiline and possibly related to the BR.

Overall Treatment Phase

Three patients died during the overall treatment phase.

Patient 209-0001

- 59 yo white HIV negative male with cavitations of at most 2 cm due to an XDR-TB strain.

- BR: amoxicillin/clavulanate, CAP, prothionamide, TRD. The isolate was susceptible to 1 drug in the BR.
- On D (b) (6) the patient experienced organic hallucinations (Grade 3) and was hospitalized. The most likely cause was a combination of drugs, not further specified.
- bedaquiline was permanently discontinued and the BR was temporarily discontinued but was restarted on D61.
- On D (b) (6) the patient's condition worsened and on the same day, the patient died.
- The cause of death was determined to be worsening of the TB infection leading to pulmonary failure.
- Tuberculosis, categorized as a Grade 4 SAE, was considered as the cause of death.
- The investigator determined that the SAE was not related to bedaquiline or the BR.

Patient 209-0327

- 31 yo Asian HIV negative male with unilateral, >2 cm cavitations due to a pre-XDR-TB
- BR: AMK, EMB, levofloxacin, prothionamide, and PZA
- The isolate was susceptible to 2 drugs used in the BR
- Patient completed bedaquiline as planned
- On D (b) (6), the patient developed an SAE of Lung Infection (Grade 4) for which he was hospitalized.
- On D (b) (6), the patient was re-hospitalized due to the lung infection (Grade 4).
- On D (b) (6) the patient died at home due to a lung infection. This SAE was determined as not related to either bedaquiline or the BR.

Patient 209-0025

- 57 yo black female with unilateral cavitations > 2 cm due to MDR_{H&R}-TB strain.
- BR: KAN, OFL, EMB. ETH, and PZA.
- The patient competed therapy with bedaquiline.
- On D407, the patient experienced symptoms of shortness of breath
- On D (b) (6), the patient was diagnosed with the SAE right-sided cardiac failure (cor pulmonale) classified as a Grade 3 SAE
- BR was continued.
- On D (b) (6) ECG revealed a QTcB value between 450 and 480 msec (461 msec). QTcF was within normal limits (418 msec).
- On D (b) (6) patient experienced Grade 3 congestive cardiac failure that was considered unrelated to bedaquiline or the BR. All BR medications were discontinued.
- On D (b) (6) the patient died due to cardiac congestive failure.

During the period from the cutoff date for safety data for the initial safety data analysis to the 4 month safety update report, 11 more deaths were reported to the Applicant.

These additional deaths are as follows:

Uncontrolled Trial (Trial C209):

During Trial C209:

Tuberculosis (3)

Pyopneumothorax/Respiratory failure

Cardiac Arrest (underlying cause pneumonia)

Hemoptysis

Hypertension

Follow-up of Prematurely Withdrawn Patients (4 patients)

3 TB-related Illness

TB-related Illness (hemoptysis)

7.3.1.2. b.1. Summary of Deaths in Trial C209

Uncontrolled Trials (Trial C209)

Up to the cut-off date of 15 July 2012 for the 4 month safety update report, the Applicant has reported that 16 patients have died in Trial C209. Of the 16 patients who died, 12 patients died during the trial and 4 patients were withdrawn prematurely and reported during follow-up.

The causes of death for the 12 deaths occurring during the trial were varied but the most common cause of death was tuberculosis (5 patients). Other deaths were from renal impairment, lung infection, congestive cardiac failure, pyopneumothorax/respiratory failure, cardiac arrest (with pneumonia as the underlying cause), hemoptysis, and hypertension. Three of the patients died during the Investigational Bedaquiline Treatment period while the rest occurred after. None of the deaths were from AEs of interest (prolonged QTcF of liver AE) except for one patient who had elevated GGT. Of the twelve deaths, only the death from renal impairment was evaluated as doubtfully related to bedaquiline.

The following table summarizes the 12 deaths that occurred during the trial.

Table 63. Summary of Deaths in Trial 209 Occurring During the Trial

Subject	Microbiologic Response	Cause of Death	Days Since Last Study Drug Intake	Investigator causality	QTcF \geq 500 ms/ Grade 3 or 4 LFT abnormalities/ liver-related AEs
209-0024	Non-converter	Tuberculosis	27	Not related	-/-/-
209-0044	Non-converter	Renal impairment	12	Doubtful	-/-/-

209-0001	Non-converter	Tuberculosis	45	Not related	-/-/-
209-0327	Converter	Lung infection	71	Not related	-/-/-
209-0025	Converter	Congestive cardiac failure	262	Not related	-/-/-
209-0021	Non-converter	Pyopneumothorax/ Respiratory failure	476	Not related	-/-/-
209-0038	Non-converter	Tuberculosis	463	Not related	-/-/-
209-0077	Relapse	Tuberculosis	288	Not related	-/-/-
209-0046	Converter	Tuberculosis	632	Not related	-/-/-
209-0156	Non-converter	Cardiac arrest (underlying cause pneumonia)	685	Not related	-/-/-
209-0552	Converter	Hemoptysis	479	Not related	-/-/+
209-0225	Non-converter	Hypertension	473	Not related	-/-/-

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The remaining 4 patients who were prematurely withdrawn were all reported to have died from TB-related illnesses (3 TB and 1 hemoptysis). All four deaths were microbiological failures as 3 did not convert and 1 relapsed. The four patients died around 30 to 244 days after their last bedaquiline intake. The investigators assessed that only one patient's death was doubtfully related to bedaquiline.

Medical Officer Comment:

In all, the 16 deaths reported in Trial C209 constitute a death rate of 6.9%, lower than the reported mortality rate for MDR-TB of around 10% despite optimal therapy. The noncomparative and open label nature of the trial makes interpretation of this data challenging. However, the mortality experience in this trial appear to support findings in Trial C208 Stage 2. Ten, or potentially 11, of the 16 reported deaths were from tuberculosis-related illnesses. The underlying reason for this observation is unknown. No recognizable association between predictive factors such as HIV infection, susceptibility to the BR, cavitations, and death was observed.

The Medical Officer concurs that death from renal impairment secondary to vomiting and dehydration may be attributed to bedaquiline. In addition, while association between bedaquiline and cardiac failure is unlikely because of the temporal dissociation, bedaquiline's role could not be ruled out. The evaluation of association between a drug such as bedaquiline is confounded by different factors: chronic nature of cardiac failure, presence of underlying conditions such as DM, hypertension, concomitant medications, and tuberculosis. Therefore, the current safety data do not indicate a signal for cardiac failure and bedaquiline.

7.3.1.3. Summary and Overall Medical Officer Comment on Deaths

In summary, as of 6 December 2012, the Applicant has reported 36 deaths in the bedaquiline clinical trials. These trials include the EBA Study C202, the two controlled Phase 2 C208 Stages 1 and 2 trials, and the uncontrolled Phase C209

trial. Excluding the 16 bedaquiline-exposed deaths reported in the uncontrolled C209 trial and the 2 bedaquiline deaths in the C202 trial, there were 12 deaths reported in the bedaquiline group and 6 deaths reported in the placebo group. In Trial C208 Stage 2 where patients were exposed to the proposed dosing regimen for bedaquiline, ten deaths were reported in the bedaquiline group compared to four deaths in the placebo group.

The Medical Officer focuses on the imbalance of deaths noted in controlled Trial C208 Stage 2 with the same proposed 24 week exposure to bedaquiline. Deaths occurring beyond the 120 week trial duration period could be excluded from the analysis since death attribution to bedaquiline is increasingly unlikely the more removed the time of death is from bedaquiline exposure. Even if the later deaths are included, the Medical Officer observes a concerning greater number of deaths in the bedaquiline group compared to the placebo group (10 deaths vs 4 deaths, respectively). When deaths occurring after 120 weeks are excluded, the imbalance in mortality becomes statistically significant (9 deaths vs 2 deaths, respectively). This is seen in the following table:

Table 64. Deaths Included in the Final Analysis (excluding deaths after 120 weeks).

	Bedaquiline group (N=79) (%)	Placebo group (N=81) (%)	p-value (Fisher's) (Confidence Interval)
Number of Deaths	9 (11.4)	2 (2.5)	P=0.031 (1.1%, 18.2%)

Only 1 death in the bedaquiline group (alcohol poisoning) occurred during the bedaquiline treatment phase. The rest of the nine deaths occurred after the bedaquiline treatment period. However, because of bedaquiline's long terminal half-life, deaths occurring relatively close to the termination of bedaquiline treatment (i.e. 2-3 terminal half-lives from termination) could still be related to bedaquiline.

The Medical Officer has the following observations:

- Of the 9 deaths in the bedaquiline group, seven converted. The other two patients did not convert and succumbed to tuberculosis-related illnesses
- Of the 7 patients who converted, 3 relapsed and died from TB-related causes (1 from hemoptysis).
- The other patients who converted but did not relapse died from non-TB-related causes (alcoholic poisoning, hepatitis/hepatic cirrhosis, CVA/hypertension, septic shock/peritonitis).
- Both deaths from the placebo group did not convert and died of tuberculosis-related illnesses.

The baseline patient characteristics and some disease severity parameters are summarized comparatively between the two treatment groups.

Table 65. Patient Demographics and Disease Severity Characteristics

Clinical Parameter	No. of Patients with Parameter in Bedaquiline (N=9)	No. of Patients with Parameter in Placebo (N=2)
History of Alcohol Abuse	2 or 3	0
HIV Infection	0	0
Cavitations	9	2
MDR-TB strain	9	2
MDRH&RTB	6 (60%)	1 (50%)
Pre-XDR	1 (10%)	1 (50%)
XDR-TB	1 (10%)	0

It is notable that none of the patients who died were HIV infected. All patients had pulmonary cavitations and all patients have an MDR-TB strain isolated with one, pre-XDR in both groups and 1 XDR in the bedaquiline group.

Tuberculosis was the cause of death in the 2 placebo mortalities and in 5/9 bedaquiline mortalities. From the analysis above, no discernible pattern between death and conversion, relapse, microbiologic response, sensitivity to the BR, HIV status, severity of the disease, and the type of MDR-TB isolate, could be observed. The Medical Officer could not identify specific epidemiologic patterns that could explain the higher incidence of TB-related deaths in the bedaquiline group compared to the placebo group in the controlled trial. Perhaps, the significance of this imbalance is difficult to determine because of the low incidence of deaths due to TB-related deaths in the controlled trial.

All in all, the reason for the increased mortalities in the bedaquiline group compared to the placebo group is unknown.

While none of the SAEs that caused deaths in the Phase IIb trials were determined to be related to bedaquiline, the Medical Officer believes that the role of bedaquiline with the BR could not be ruled out in three deaths, one in Trial C208 Stage 2 and two in the uncontrolled Trial C209.

- Patient 208-5069 died on D (b) (6) with diagnoses of hepatitis and hepatic cirrhosis on D (b) (6). 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. The Medical Officer could not rule out the possibility that either bedaquiline and/or the BR could have exacerbated the hepatic pathology that caused the patient's demise.
- Patient 209-0044 died on D (b) (6) during the investigational treatment phase from vomiting and dehydration that caused renal impairment. The Medical

Officer believes that either bedaquiline and/or the BR could possibly 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. The Medical Officer could not rule out the possible association between the slightly prolonged QTcB interval and bedaquiline, given the potential of bedaquiline to cause QT prolongation. This persistent prolongation may have caused the congestive heart failure that caused this patient's demise.

One patient who died from infectious peritonitis and septic shock developed severe elevation of his serum transaminases and bilirubin. The degree of elevation was consistent only with the laboratory criteria for Hy's Law. With the initial increase developing towards the end of his bedaquiline treatment, the role of bedaquiline in the patient's elevation of serum transaminases could not be ruled out. His concomitant alcohol use, concomitant use of medications that are hepatotoxic, and the absence of serology for infectious hepatitides confound the determination of bedaquiline-induced liver injury. Thus, because other etiologies for the elevation of his serum transaminases are present and other etiologies for the elevation of his transaminases and bilirubin could not be ruled out, this patient does not fulfill Hy's Law criteria for drug-induced liver injury from bedaquiline.

In all, the Medical Officer could not determine any definite etiology for the imbalance of deaths in the bedaquiline group, especially as noted in the pivotal Phase 2 controlled trial, Trial C208 Stage 2. The challenge results from the nature of the disease and the treatment for MDR-TB. The complexity of the management of MDR-TB with the limited treatment options, toxicities of the treatment, treatment compliance, chronic medical conditions, prolonged treatment duration, and the bedaquiline PK characteristics make the identification of trends that could explain the imbalance of mortalities in the bedaquiline group very challenging.

The most common COD was TB-related. The Medical Officer likewise could not determine any epidemiologic patterns or differences in patient demographics and baseline disease characteristics (HIV infection, infection with pre-XDR/XDR strains, susceptibility to baseline regimen, and radiologic manifestations of TB disease) that could be responsible for the increased frequency of tuberculosis-related deaths in the bedaquiline group in Trial C208 Stage 2. While concerning, the limited safety database for the Stage 2 trial makes it difficult to rely on the potential safety concerns that could otherwise be an incidental finding in a study with a larger safety database. Analysis of SAEs that caused deaths in the Trial C208 Stage 2 does not identify any definite safety signal. Among the SAEs, the

role of either bedaquiline or BR in the development of 3 SAEs could not be ruled out: hepatitis, vomiting, congestive heart failure.

While the current safety data preclude the determination of the etiology of the imbalance of mortalities in the bedaquiline arm, the Medical Officer believes that this concerning observation would be further clarified from safety data from the proposed Phase 3 confirmatory trial and from the postmarketing safety data that will be collected with the use of the drug. The Medical Officer believes that data on serious adverse events, some of which may lead to death, should be closely captured and monitored. Reports of serious adverse events should be expeditiously sent to the Agency for review. Therefore, if bedaquiline was to be approved under the Accelerated Approval regulations, close safety monitoring and reporting for serious adverse events, including deaths, and for ADRs of concern should be required.

7.3.2 Nonfatal Serious Adverse Events

Trial C208 Stage 1

In this exploratory trial, in addition to the bedaquiline-treated patient who died on D (b) (6) ((b) (6)) days after the last bedaquiline dose) from an SAE of Acute Myocardial Infarction, five additional patients experienced one or more SAEs during the trial. Two of these eight patients experienced SAEs during the 8 week investigational treatment with bedaquiline.

Placebo Group

1. Patient 3076 – black female who experienced **Grade 3 drug intoxication** (cycloserine intoxication) manifested as Grade 2 on D250 of the trial while on BR. SAE duration was 81 days. Investigator evaluated SAE as not related to bedaquiline, unrelated to TB, but related to BR. SAE resolved after stopping cycloserine.
2. Patient 3095 – black female who experienced **Grade 4 relapse of MDR-TB** on D419 of the trial, **Grade 4 lobar pneumonia** on D503 of trial for 7 days and Grade 4 **symptomatic anaemia** for 31 days, and 2 episodes **Grade 4 right leg deep vein thrombosis** on D615. Pneumonia resolved and patient improved after treatment. Pneumonia was evaluated as NOT RELATED to bedaquiline, to TB, or to the BR. Anaemia resolved after initiation of treatment after 31 days and was evaluated as NOT RELATED to bedaquiline and to TB, but DOUBTFULLY RELATED to the BR. Relapse of TB was still ongoing and was evaluated as RELATED to the TB. Deep vein thrombosis resolved and evaluated as NOT RELATED to bedaquiline, TB, and BR.
3. Patient 3113 – white male who experienced **Grade 4 pneumothorax** on D11, during the Investigational Treatment Phase (8 week bedaquiline Treatment).

Pneumothorax resolved after 163 days. SAE evaluated as RELATED to TB, not to bedaquiline or BR. No action on the study drug was made. A chest tube was placed to treat the SAE, with pain control.

Bedaquiline

1. Patient 3079 – female of unknown ethnicity who experienced **Grade 4 myocardial infarction** On D (b) (6). The SAE resulted in death. SAE was evaluated as NOT RELATED to bedaquiline, BR, or TB.
2. Patient 3125 – male of unknown ethnicity who experienced **Grade 4 diabetic ketoacidosis** on D42 during the Investigational Treatment Phase (8 week bedaquiline treatment). The patient was known to have diabetes mellitus and was treated with insulin at screening. The SAE was treated with human insulin, sodium chloride, and potassium chloride and initially resolved after 4 days. SAE was evaluated as NOT RELATED to bedaquiline, TB, or to the BR. Patient's SAE recurred on D85-D88 and D118-122, during which times the SAE resolved after treatment.
3. Patient 3137 – black male who experienced Grade 3 SAE described as **Road Traffic Accident** on D (b) (6). Patient recovered. SAE evaluated as NOT RELATED to bedaquiline, TB, or BR.

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, was 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 MDRH&R_TB 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 D117, 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 the the 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.

A summary of SAEs reported during the trial can be found in the table below.

Table 66. 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 disorders	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 0	0 0 0	1 (3.3)	0	0	0
Hepatic cirrhosis			1 (3.3)	0	0	0
Hepatitis			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 and procedural complications	1 (1.3)	3 (3.8)	0	0	2 (2.5)	0
Alcohol poisoning	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 and perinatal conditions	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
Hemoptysis	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
Social circumstances	0	0	1 (1.3)	0	0	0
Pregnancy of partner	0	0	1 (1.3)	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

Medical Officer Comment:

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

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 prolonged.

Table 67. 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	1 (0.4)	2 (0.9)
Vomiting	1 (0.4)	1 (0.4)
Hepatobiliary Disorders	1 (0.4)	2 (0.9)
Cholelithiasis	1 (0.4)	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	1 (0.4)	2 (0.9)
ECG QT prolonged	1 (0.4)	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	1 (0.4)	1 (0.4)
Pain in extremity	1 (0.4)	1 (0.4)
Psychiatric Disorders	1 (0.4)	2 (0.9)
Hallucination	1 (0.4)	1 (0.4)
Renal and Urinary Disorders	1 (0.4)	2 (0.9)
Renal impairment	1 (0.4)	1 (0.4)

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).

The patient who developed prolonged QT interval was a 32 year old male with an MDRH&R-TB 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.

Medical Officer Comment:

The Medical Officer could not identify a trend in the SAEs reported for Trial C209. The most common SOC to which SAEs were categorized are Infections and Infestations and Metabolism and Nutrition Disorders. One significant SAE was the QT prolongation noted in a patient with a diagnosis of myocardial ischemia (normal troponin). The Medical Officer concurs with the assessment of causality of the investigator for the QT prolongation.

7.3.3 Dropouts and/or Discontinuations

Trial C208 Stage 1

In Trial C208 Stage 1, no adverse events were reported for which bedaquiline or placebo was permanently discontinued.

Trial C208 Stage 2

In Trial C208 Stage 2, one of more AEs led to the permanent discontinuation of the study drug in 4 bedaquiline-treated patients (5.1%) and in 5 placebo-treated patients (6.2%); and to the temporary discontinuation of 2 bedaquiline-treated patients and 3 placebo-treated patients.

By preferred term, none of the AEs leading to discontinuation occurred in more than 1 patient, except for transaminases increased in 3 patients (3.8%) in the bedaquiline group and 2 patients who became pregnant in the placebo group.

AEs leading to the permanent discontinuation of one or more of the BR drugs occurred in 9 bedaquiline-exposed patients (11.4%) and 10 placebo-exposed patients (12.3%). In the bedaquiline group, three patients (3.8%) discontinued their BR because of arthralgia and 2 patients (2.5%) discontinued their BR because of unilateral deafness. In the placebo group, 3 patients discontinued their BR because of nausea and vomiting and 2 patients discontinued because of hyperuricemia.

The following table summarizes the incidence of AEs leading to permanent discontinuation of either bedaquiline or placebo.

Table 68. Incidence of AEs Leading to Permanent Discontinuation of Bedaquiline or Placebo

Body system or organ class		
Preferred Term	TMC207/BR	Placebo/BR
n (%)	N = 79	N = 81
Overall	4 (5.1)	5 (6.2)
Any event leading to permanent discontinuation	4 (5.1)	5 (6.2)
Injury, poisoning and procedural complications	1 (1.3)	1 (1.2)
Alcohol poisoninga	1 (1.3)	0
Drug exposure during pregnancy	0	1 (1.2)
Investigations	3 (3.8)	1 (1.2)
Blood amylase increased	0	1 (1.2)
Lipase increased	0	1 (1.2)
Transaminases increased	3 (3.8)	0
Pregnancy, puerperium and perinatal conditions	0	2 (2.5)
Pregnancy	0	2 (2.5)
Skin and subcutaneous tissue disorders	0	1 (1.2)
Urticaria	0	1 (1.2)

Source: NDA 204384, SD 1, June 29, 2012. Clinical Study Report (Interim Analysis), Trial C208 Stage 2. p. 227.

Medical Officer Comment:

Similar proportion of bedaquiline- and placebo-controlled patients discontinued the study drug because of AEs. Only one AE resulted in more discontinuations in the bedaquiline group: transaminases increased.

Trial C209

Six patients (2.6%) developed one or more AEs that led to permanent discontinuation of bedaquiline while four patients (1.7%) developed one or more AEs that led to the temporary discontinuation of bedaquiline. The AEs leading to the permanent discontinuation of bedaquiline were vomiting, tuberculosis, drug exposure during pregnancy, ECG QT prolonged, diabetes mellitus, inadequate control, and hallucination.

7.3.4 Significant Adverse Events

7.3.4.1. Electrocardiograms (ECGs)

The evaluation of cardiovascular safety of bedaquiline in the phase 2b program provides insight into the anticipated safety of the product. 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.

7.3.4.1.a. Trial CT08 Stage 1

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).

During the 8-week investigational treatment period, mean absolute values in QTcB and QTcF increased in the bedaquiline group from Week 2 onwards, with mean increases from reference of > 10 ms observed from Week 6 onwards (largest mean changes from reference at predose were 16.8 ms for QTcB and 17.6 ms for QTcF). In the placebo group, mean QTcB and QTcF increases during the investigational treatment period were also observed from Week 6 onwards, but these changes were less pronounced (largest mean change from reference at predose were 5.9 ms for QTcB and 8.6 ms for QTcF) compared to the bedaquiline group. (Table 69 and Figure 14)

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). (Table 69 and Figure 14).

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

When individual abnormalities in ECG were considered, during the investigational treatment period, postbaseline abnormalities developed in 20 patients (87%) in the bedaquiline group compared to 17 (70.8%) patients in the placebo group. During the background treatment period, any abnormality in ECG parameters occurred in 17 (81%) and 19 (82.6%) patients in the bedaquiline and placebo group, respectively.

For QTcF specifically, no absolute values of > 500 ms were observed. Two patients in the bedaquiline group developed a QTcF value between 480 and 500 ms which corresponded to an increase of > 60 ms from reference. These are Patient 208-3092 (485 ms at Wk 5 predose, with an increase of 91 ms, and Patient 208-3137 (500 ms at Wk 7 predose with increase of 123 ms). QTcF increases by 30 to 60 ms were more frequent in the bedaquiline group compared to placebo during the investigational treatment period, similar to what was observed with 30 to 60 ms increases in QTcB (26.3 % in the bedaquiline group vs 4.9 % in the placebo group at Wk 6 predose). No consistent differences between the treatment groups were observed in terms of 30-60 ms increases in QTcF during the background treatment period.

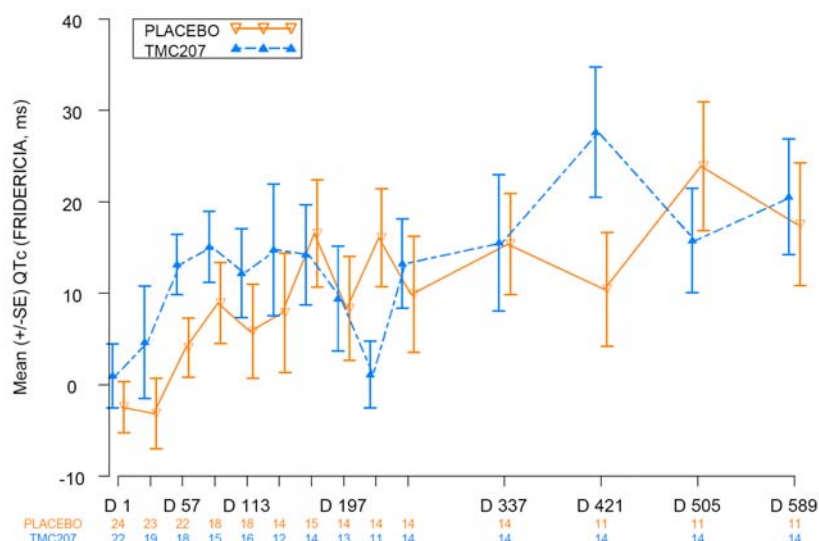
AEs related to ECG parameters were not reported in any patient during the investigational treatment group. However, 4 patients (2 in each treatment group) developed AEs related to ECG parameters during the background treatment period.

- Bedaquiline group:
 - One patient developed Grade 4 myocardial infarction 16 weeks after the last dose of bedaquiline.
 - One patient reported an “ECG QT corrected interval prolonged of Grade 1 at 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.

Medical Officer Comment:

Safety data related to ECG parameters from Trial C208 Stage 1 indicate that with an 8 week exposure to bedaquiline, bedaquiline-exposed patients developed a greater mean increase from reference compared to placebo-exposed patients (maximum change from reference: 17.6 ms for bedaquiline patients vs 8.6 ms for placebo patients). Together with nonclinical studies that demonstrate the potential of bedaquiline to prolong the QT interval, findings that clinically show a difference between the mean increase from reference in bedaquiline- vs placebo-treated patients is significant.

Figure 14. 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.

Table 69. Mean Changes from Reference for QT Intervals Over Time

Parameter Analysis time pointa	Placebo			BEDAQUILINE		
	N	Mean	SE	N	Mean	SE
QTcB (ms)						
Day 1, predose	24	-3.6	2.23	22	-0.7	3.75
Week 8, predose	22	-0.9	3.16	18	11.4	3.23
Week 16, predose	18	-0.6	6.34	16	10.4	4.22
Week 24, predose	15	1.5	5.27	14	8.9	4.87
Week 36, predose	14	-3.3	7.02	14	9	4.79
Week 48, predose	14	2.2	3.86	14	6.1	5.64
Week 60, predose	11	-4.1	7.43	14	16.7	6.99
Week 72, predose	11	8.7	8.02	14	5.2	4.49
Week 84, predose	11	7.5	6.45	14	11.3	6.91
QTcF (ms)						
Day 1, predose	24	-2.4	2.78	22	1	3.51
Week 8, predose	22	4.1	3.25	18	13.1	3.29
Week 16, predose	18	5.8	5.14	16	12.2	4.86
Week 24, predose	15	16.6	5.86	14	14.2	5.46
Week 36, predose	14	9.9	6.34	14	13.2	4.88
Week 48, predose	14	15.4	5.53	14	15.5	7.48
Week 60, predose	11	10.4	6.2	14	27.6	7.1
Week 72, predose	11	23.9	7.03	14	15.8	5.72
Week 84, predose	11	17.5	6.71	14	20.5	6.33
Uncorrected QT (ms)						
Day 1, predose	24	-0.3	4.39	22	3.6	5.91
Week 8, predose	22	12.6	5.71	18	15.7	5.78
Week 16, predose	18	16.6	7.01	16	15.2	10.44
Week 24, predose	15	42.4	8.73	14	23.5	9.99

Week 36, predose	14	32.3	10.13	14	20.5	10.42
Week 48, predose	14	38	13.16	14	33.1	13.35
Week 60, predose	11	35.1	12.68	14	46.5	9.89
Week 72, predose	11	50.5	12.51	14	34.5	11.61
Week 84, predose	11	33.9	14.21	14	37.7	9.45

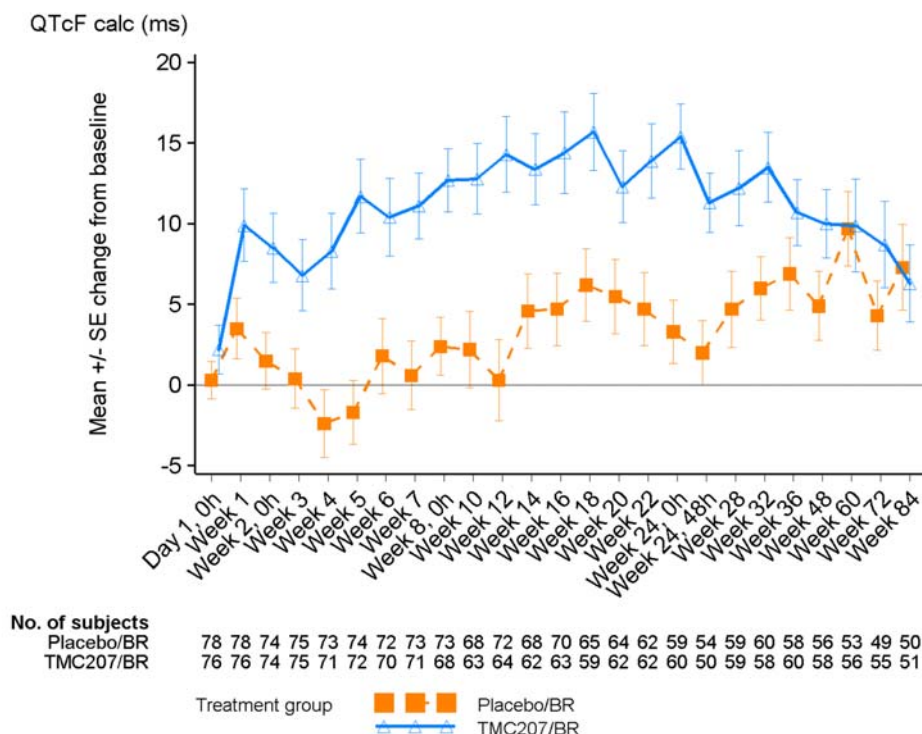
Source: Modified from NDA 204,384. Original Submission. Updated Clinical Research Report – Trial C208 Stage 1. Table 59. p. 182.

7.3.4.1.b. Trial C208 Stage II

ECG Changes Over Time

Mean absolute values in QTcF increased compared to reference during the Investigational Treatment phase in the bedaquiline-treated group. Seen by the Week 1 visit, the mean increases were > 10 ms from Week 5 onwards and decreased after Week 24. The largest mean increase in QTcF for the bedaquiline group during the first 24 weeks was 15.7 ms at Week 18, compared to 6.2 ms for the placebo group at Week 18. The maximum mean increase in QTcF for the bedaquiline group was 16.2 ms at Week 24, 5 hours postdose, compared to 15.6 ms in the placebo group also at Week 24. It is notable that, 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 C_{max} and QTcF prolongation. This does not exclude a delayed effect.

Figure 15. Mean Changes from Reference in QTcF Over Time



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

Medical Officer Comment:

Given that Trial C208 Stage 2 is the pivotal study with patients given the same exposures as the proposed dose, the findings demonstrated in the figure above indicate a clear signal that bedaquiline has the potential to prolong the QT interval. Two observations from this figure allow us to understand the trend of QT prolongation that could be expected from bedaquiline use.

First, a week after bedaquiline was initiated, the mean change from baseline observed in bedaquiline-exposed patients was significantly greater than the mean change observed in placebo exposed group. The difference between the two groups become more significant so that by Week 18, the largest mean increase in QTcF for the bedaquiline group during the first 24 weeks was 15.7 ms, compared to 6.2 ms for the placebo group, probably due to the prolonged terminal half-life of bedaquiline and its metabolite M2. In time, the differences between the two groups became less pronounced.

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 70. Incidence of Reported Treatment-Emergent Hemiblock Abnormalities

n (%)	BEDAQUILINE/BR		Placebo/BR	
	Investigational	Overall	Investigational	Overall
	Treatment Phase	Treatment Phase	Treatment Phase	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)
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, 7 (9.1%) patients in the bedaquiline group developed a > 60 ms increase from reference in QTcF compared to 2 (2.5%) of patients in the placebo group. One of the patients in the bedaquiline group was the same patient who had a QTcF of 505 ms. 55.8% 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 71. Frequencies of patients with QTcF value ranges and QTcF increases

N (%)	Bedaquiline		Placebo	
	Investigational Treatment Phase	Overall Treatment Phase	Investigational Treatment Phase	Overall Treatment Phase
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
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

Medical Officer Comment:

The table above provides more evidence that a greater proportion of bedaquiline-exposed patients develop QTcF increases compared to placebo. Within a treatment group, there are less bedaquiline patients who develop increases of > 60 ms compared to increases between 30 to 60 ms. This data verifies the QT prolonging potential of bedaquiline.

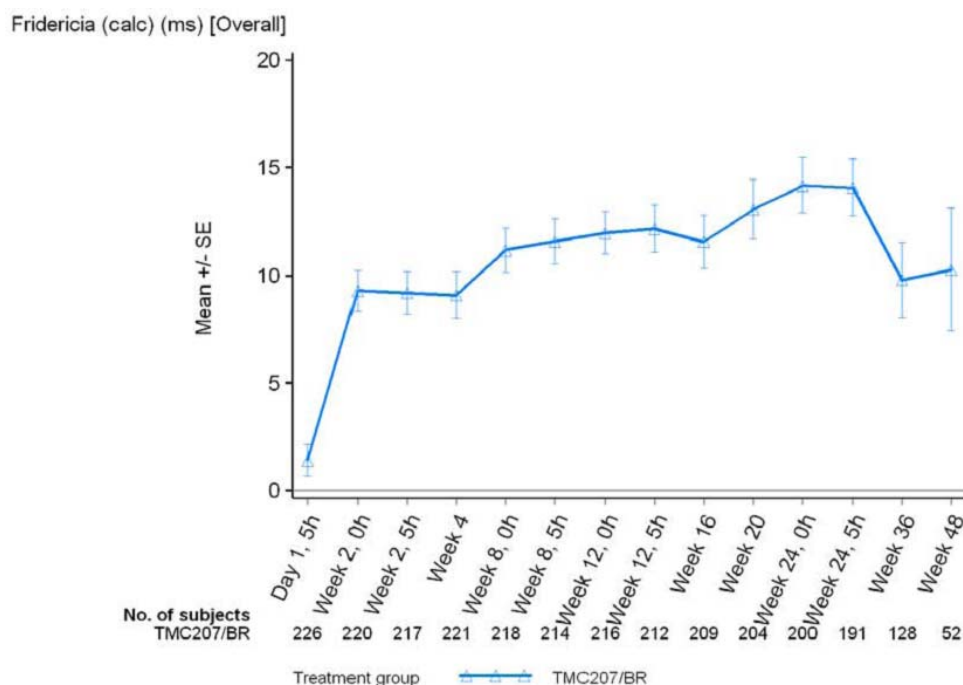
7.3.4.1.c. Trial C209

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 as indicated 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.

Figure 16. Mean QTcF Changes from Reference over Time in the ITT Population



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

Analysis of mean changes from reference for QTcF by sex did not demonstrate any significant differences between males and females.

Medical Officer Comment:

The trend seen in the figure above is consistent with the trend seen in Trial C208 Stage 2. Changes in QTcF started on Week 2 and persisted even after Week 24 when treatment with bedaquiline was stopped.

Individual Abnormalities in ECG

Treatment-emergent abnormalities for QTcF was common: 11.6% of patients developed an abnormal value between 450 and 480 ms during the investigational treatment phase, with one patient (ID No. 209-0111) having a QTcF value of > 500 ms (514 ms). An increase from reference of 30-60 ms in QTcF was observed in 36.7% of patients and 9 (3.9%) patients developed an increase from reference of > 60 ms. Of these 9 patients with an increase of > 60 ms, one developed the QTcF value of > 500 ms. No significant differences were noted between males and females.

During the overall treatment phase, another patient (ID No. 209-0167) developed a QTcF value > 500 ms.

Table 72. Relevant ECG Abnormalities (QTcF Changes)

ECG Parameter Abnormality	TMC207/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 69. p. 195.

Medical Officer Comment:

The analyses shown above verify the QTcF prolonging potential of bedaquiline shown in Trials C208 Stages 1 and 2.

QTcF Prolongation In Patients Coadministrered with Other QT Prolonging Drugs

To determine the effect on the QT interval of the adding other QT prolonging drugs to bedaquiline, the Division requested the Applicant to conduct a posthoc analysis comparing QTcF intervals when other drugs with QT prolonging potential are given with bedaquiline in Trials C208 Stage 2 and Trial C209.

The results of the posthoc analysis are summarized in the following tables.

Table 73. QTcF with the Addition of 1 QT Prolonging Medication (Trial C208 Stage 2)

QT Correction; Number of QT Prol. Drugs	Bedaquiline					Placebo				
	n	Mean	1st Quart	Median	3rd Quart	n	Mean	1st Quart	Median	3rd Quart
QTcF (calculated)										
0	76	436.2	420.5	437.5	451.5	76	424.2	414.5	423.5	435.0
1	2	460.0	458.1	460.0	462.0	5	431.2	416.0	421.0	438.0

Applicant-provided analysis.

Table 74. QTcF with the Addition of One to Three QT Prolonging Drugs (Trial C209)

Table 3: TMC207-C209 - ECG - descriptive statistics of the maximum measured QT by number of QT prolonging drugs during the investigational treatment phase

QT Correction Number of QT Prolonging Drugs	TMC207/BR							
	n	Mean	SE	Min	1st Quartile	Median	3rd Quartile	Max
QTC BAZETT (calculated) (ms)								
0	132	443.2	1.94	384	428.0	444.0	457.5	510*
1	65	447.5	2.82	403	431.0	445.0	462.0	519^
2	25	458.3	4.38	417	447.0	461.0	465.0	519#
3	7	462.4	5.78	436	456.0	460.0	479.0	480
QTC FRIDERICIA (calculated) (ms)								
0	130	427.4	1.66	386	413.0	427.5	442.0	480
1	67	429.1	2.42	390	414.0	429.0	439.0	496
2	25	441.6	4.69	393	433.0	438.0	445.0	516#
3	7	442.1	4.34	428	430.0	443.0	450.0	461

Note: not all safety subjects had a post baseline QTc assessment

Applicant-provided Analysis

Medical Officer Comment:

The data from the two tables above indicate that the use of another QT prolonging drug with bedaquiline could cause an additive risk of QT prolongation. The table above shows the positive relationship between the number of QT prolonging drugs coadministered with bedaquiline and the QTcF interval so that the more QT prolonging drugs you add, the longer the QT interval becomes. The conclusion from these analyses is that the use of bedaquiline with other QT prolonging medications could cause additive risks of QT prolongation.

In relation to the additive risks of QT prolongation when bedaquiline is used with other QT prolonging drugs, the Applicant provided the results of posthoc analyses that evaluated the effect of the co-administration of clofazimine and bedaquiline on the QTcF interval. The first analysis included patients who, at Week 24, were using clofazimine and had an ECG assessment at Day -1 and Week 24. The analysis of this subset of patients revealed that mean increases in QTcF at Week 24 were larger in the 17 patients using clofazimine at Week 24 (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). Patients with duration of < 3 days of concomitant bedaquiline and clofazimine administration were excluded. The post-hoc analysis is summarized in the table below.

Table 75. Changes from Reference for QTcB and QTcF in Patients with Concomitant Use of Clofazimine at Week 24.

	Clofazimine Use At Week 24
--	----------------------------

Clinical Review
Ariel R. Porcalla, MD, MPH
NDA 204 384
BEDAQUILINE (bedaquiline)

ECG Parameter	NO ^a							YES ^b						
	N	Mean	SE	SD	Median	Min	Max	N	Mean	SE	SD	Median	Min	Max
Change in QTcF (calc) (ms)														
WEEK 24, 0 h	177	12.28	1.229	16.353	13.00	-34.0	67.0	17	31.94	5.735	23.644	27.00	6.0	82.0
WEEK 24, 5 h	170	12.36	1.258	16.406	11.50	-49.0	60.0	16	28.81	5.672	22.687	29.00	-11.0	82.0

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 Applicant conducted another posthoc analysis evaluating the mean changes from baseline in QTcF and QTcB for patients with paired data with and without clofazimine (patients with ECGs performed during the period patients were taking bedaquiline plus BR without clofazimine and during the period the same patients were taking bedaquiline plus BR with clofazimine. Mean increases in QTcF were larger during administration of bedaquiline plus BR with clofazimine (mean change at 0h of 40.5 ms) than during administration of bedaquiline plus BR without clofazimine (mean change at 0h of 12.9 ms). The applicant, however, states that the greater change observed during co-administration of bedaquiline with a clofazimine-containing BR may be overestimated as clofazimine was added later during the course of treatment, not at baseline. Typically, increases in QTcF occur gradually over the course of treatment.

The results of the second posthoc analysis are summarized in the table below.

Table 76. Descriptive Statistics for Changes from Reference at Last Assessments in QT Intervals in Patients with Paired Observations

ECG Parameter Timepoint	Endpoint TMC207a							Endpoint TMC207+Clofazimineb						
	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.

Medical Officer Comment: The analyses above confirm the additive effects of using clofazimine, an anti-TB drug used for MDR-TB, with bedaquiline. Not previously identified as a QT prolonging medication, clofazimine should not be used with

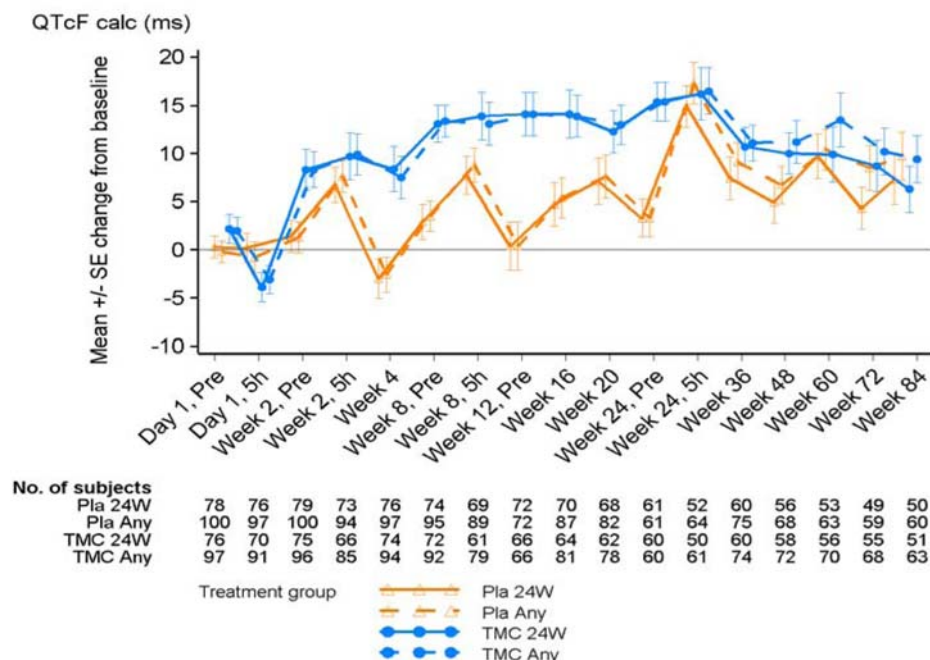
bedaquiline. If use with bedaquiline could not be avoided, then cautious monitoring of the QT interval is warranted.

7.4.4.3. 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 1, 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 17. QTcF Changes from Reference Over Time in the Controlled Trials (including Trial C208 Stage 2 and Trial C209)



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

Medical Officer Comment:

While pooling of QTcF changes from reference over time from Phase C208 Stage 2 and C209 appear to demonstrate that the difference between the bedaquiline treated group and the placebo-treated group is not as marked, the figure above still demonstrate the differences between the two. In conclusion, increases in QTcF from reference appear to be greater for patients treated with bedaquiline compared to patients treated with placebo.

7.3.4.2. Hepatic Adverse Events

Analysis of safety data from Trial C208 Stage 2 indicate that there is an increased incidence of serum aminotransferase elevation in bedaquiline-treated patients compared to placebo-treated patients.

Specifically, the Applicant reported that during the interventional treatment period with bedaquiline, increased transaminase occurred in 4 bedaquiline-treated patients (5.1%) compared to none in the placebo-treated patients.

Similar to an analysis conducted by the Applicant, an exploratory analysis of Standardized MedDRA Queries for different Preferred Terms (PTs) that reflect medical conditions of hepatic-related disorders indicate a safety signal towards a greater incidence in the bedaquiline-treated group. This is summarized in the following table.

Table 77. FDA Analysis of Hepatic-related SMQ Adverse Events

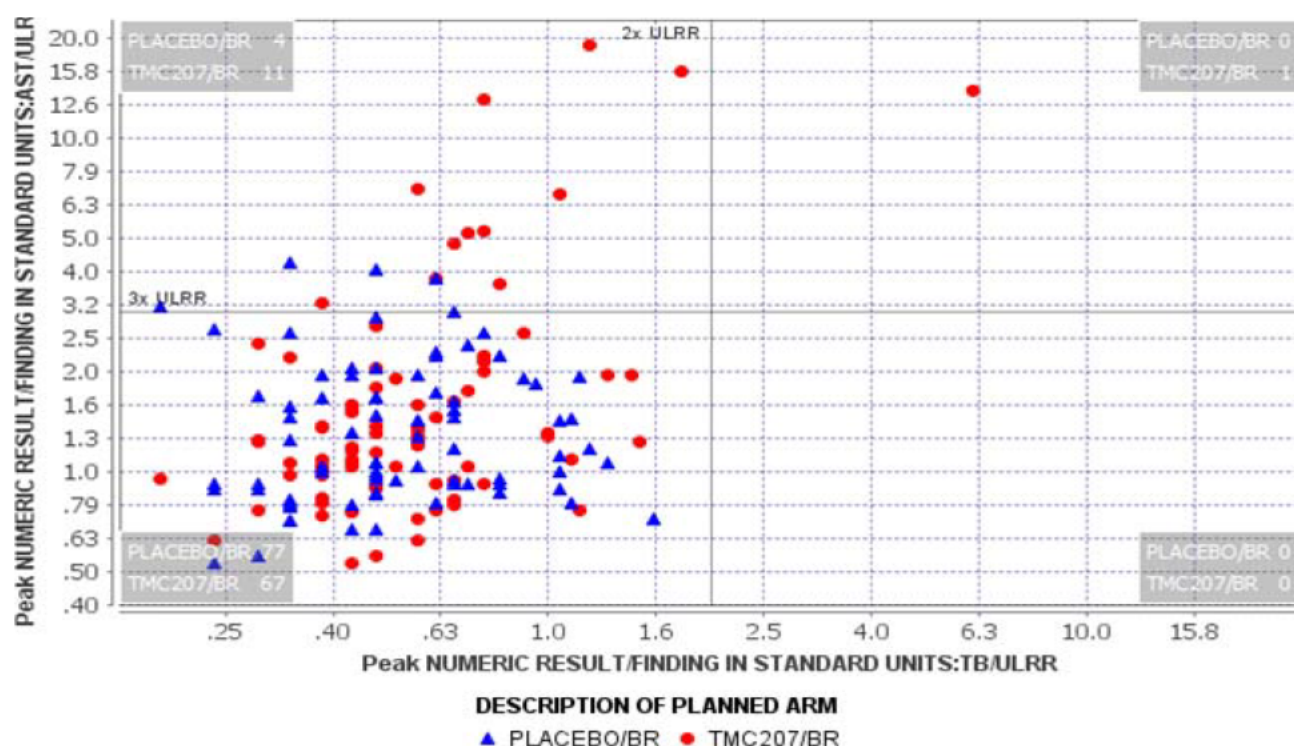
Investigator Reported Events	Bedaquiline 24 wks (N=79)	Placebo 24 wks (N=81)
Liver-related signs and symptoms	8 (10)	3 (3.7)
Hepatic disorders	10 (12.5)	5 (6.7)
Poss. Drug related hepatic d/o (comp)	10 (12.5)	5 (6.7)
Hepatitis (non-infectious)	2 (2.5)	1 (1.23)
Hepatic failure, fibrosis, cirrhosis, liver damage related conditions	1 (1.25)	0

The FDA also conducted an exploratory analysis of SMQ searches for hepatobiliary disorders. The analysis demonstrated that bedaquiline exposure has a relative risk of 2.856 for hepatic-related adverse drug reactions compared to placebo exposure as seen in the following table.

Table 78. Exploratory Analysis of Hepatic-Related ADRs

SOC	Relative Risk (all 24 wk bedaquiline-treated patients [N=312] vs 24 wk placebo [N=81])
Hepatobiliary Disorders	2.856

Figure 18. Peak AST and Total Bilirubin Values for Patients In Trial C208 Stage 2.



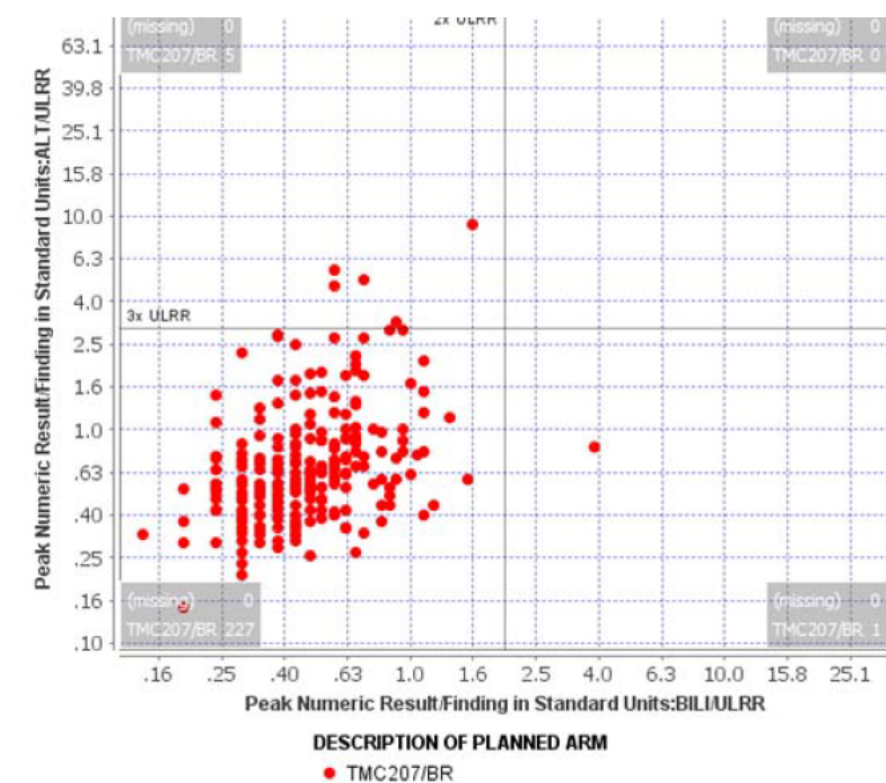
208 Stage ii : T.BILI 2xULN vs AST 3xULN Upper Limit Normal Range Plot

To further explore where the signal for increased hepatic events is coming from, an analysis of the peak transaminases for each patient were graphed against the peak total bilirubin of the patient (Figure 5). The figure above has bilirubin in standard units in the X-axis and the peak AST in the Y-axis. A horizontal line denotes the AST cutoff value for 3x the ULN for AST and a vertical line denotes the total bilirubin cutoff value for the 2x the ULN of the total bilirubin. The red dots are bedaquiline-treated patients and the blue dots are placebo-treated patients. As you can see from the figure below, there are more bedaquiline-treated patients who have AST peak values that are more than the 3x the ULN for AST. One bedaquiline-treated patient, previously discussed in the Mortality

Section, developed a > 3x the ULN elevation of his peak AST and a > 2x the ULN of his total bilirubin.

In Trial C209, patients were more homogenous in terms of their peak AST and bilirubin levels, with most developing only mild to modest increases. There were less outlying patients who developed peak AST values > 3x the ULN and only 1 patient developed a peak total bilirubin level of > 2x ULN. This can be seen in the following figure.

Figure 19. Peak AST and Bilirubin Levels in Trial C209 Patients



NDA204384: tmc207-tidp13-209 : No Patients in the upper right quadrant of Hy's Law Plot

The proportion of patients with both serum transaminase and bilirubin elevation in both treatment arms in the mITT population can be seen in the following table.

Table 79. Proportion of Patients with both Serum Transaminase and Bilirubin Elevation in Trial C208 Stage 2 (mITT Population)

	Bedaquiline Group	Placebo Group
Elevated Serum Transaminase and Bilirubin	11	4

Hepatic Serious Adverse Events

Two serious adverse events were reported in the bedaquiline group. Both patients died.

Patient 208-5067

This is a 43 year old Asian male with a history of heavy alcohol use who converted during the bedaquiline treatment period. He completed 24 weeks of bedaquiline during which the patient developed progressive increases of AST, GGT and bilirubin. On Week 24, his AST reached 501 (>3x ULN) and bilirubin of 52 U/L (>2xULN). After finishing bedaquiline treatment, both AST and bilirubin levels improved. A few weeks later, the patient became symptomatic with vomiting and jaundice. On Week 84, his bilirubin and AST levels reached the threshold of > 3x ULN for his AST and > 2x ULN for his bilirubin. This prompted investigation of possible causes for his elevated AST and total bilirubin. He was diagnosed at this time with alcoholic hepatitis. On Week 96, he developed fever, abdominal pain, nausea, and vomiting and was diagnosed with peritonitis, suspicious for an intra-abdominal organ perforation. He was admitted for surgery but expired prior to having surgery on Week (b) (6). The Investigator attributed his death to Peritonitis and Septic Shock.

The table below shows the trend of his AST and bilirubin levels.

Table 80. Laboratory evaluation of serum transaminases of Patient 208-5067 (SAE: Infectious Peritonitis and Septic Shock)

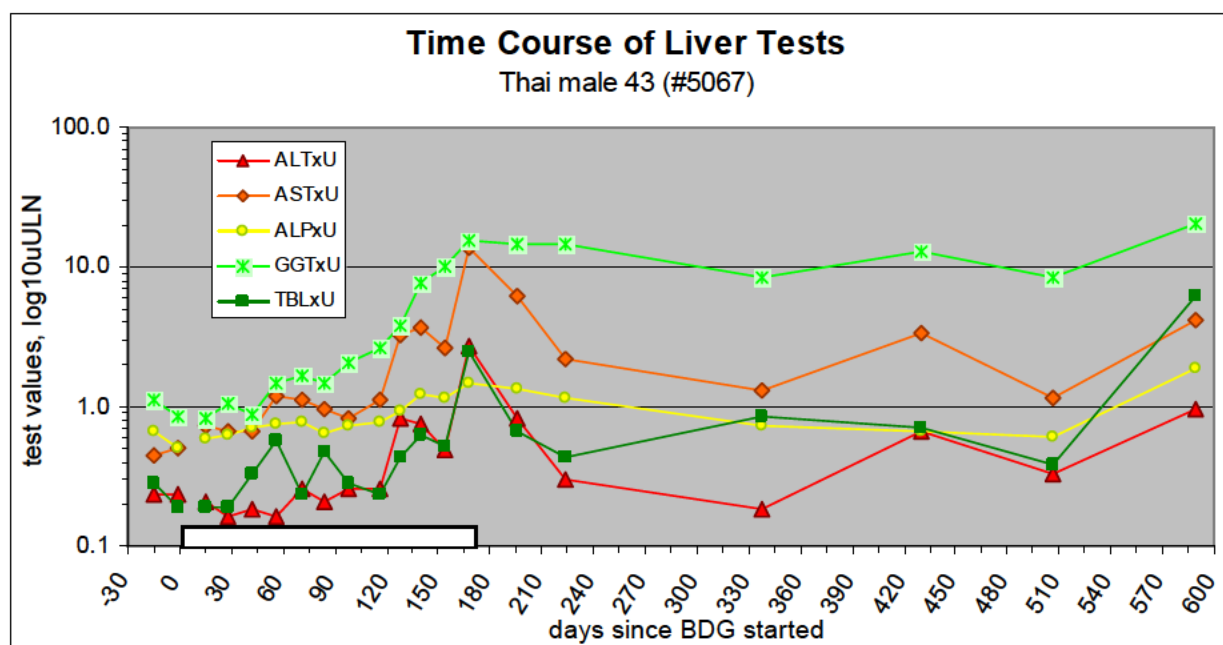
Phase Analysis time point	ALT (U/L)	AST (U/L)	Total bilirubin (μmol/L)	Indirect bilirubin (μmol/L)	Direct bilirubin (μmol/L)	ALP (U/L)	GGT (U/L)	Album in (U/L)
	6-43	11-36 3xULN: ≥108	3-21 2xULN: ≥42		0-7	31-129	10-61	33-49
Overall treatment								
Baseline	10	18	4	3	1	65	52	35
Week 2	9	26	4	3	1	76	50	
Week 4	7	24	4	3	1	80	65	
Week 6	8	24	7	6	1	90	53	
Week 8	7	43	12	9	3	97	91	
Week 10	11	40	5	4	1	100	101	
Week 12	9	35	10	7	3	84	89	
Week 14	11	30	6	5	1	95	125	
Week 16	11	40	5	3	2	100	161	
Week 18	35	119	9	6	3	120	232	
Week 20	32	134	13	9	4	157	473	
Week 22	21	94	11	6	5	150	621	
Week 24	118	501	52	23	29	189	939	31

Week 28	35	226	14	9	5	173	879	
Week 32	13	78	9	6	3	147	879	
Week 48	8	47	18	14	4	95	511	
Week 60	29	122	15	11	4	86	793	
Week 72	14	41	8	6	2	79	509	
Week 84	41	148	129	49	80	243	1240	30

Modified from NDA 204,384 Initial submission. Clinical Summary of Safety

This is the graphical representation of the patient's course.

Figure 20. Serum Transaminase Profile of Patient 208-5067



Because the increase in AST and bilirubin started during the bedaquiline treatment period and because of bedaquiline's prolonged half life, the role of bedaquiline on the elevated transaminase and bilirubin could not be ruled out. However, causality assessment is confounded in this case by the patient's alcohol use, use of hepatotoxic medications, and the absence of serology for infectious viral hepatitis.

Patient 208-5069

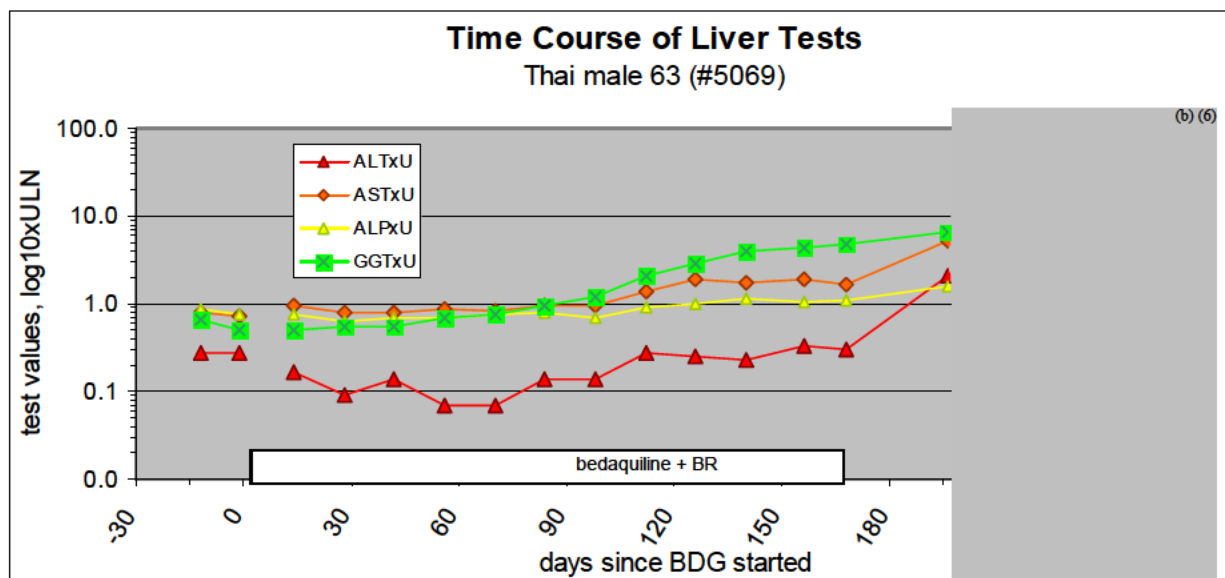
This is a 63 year old Asian male with a history of alcohol use. He developed elevated serum transaminase 4 weeks after his last bedaquiline intake (Week 28). four weeks later, he developed signs and symptoms of hepatic disease likely to be chronic: fatigue, epigastric pain, ascites, volume depletion, and elevated serum transaminase. He was diagnosed with alcoholic liver cirrhosis. Four weeks later, at Wk 36, and (b) (6) days post bedaquiline intake, the patient died from hepatitis and hepatic cirrhosis.

Table 81. Serum Transaminase for Patient C208-5069

Phase Analysis time point	ALT (U/L)	AST (U/L)	Total bilirubin ($\mu\text{mol/L}$)	Alkaline Phosphatase
	6-43	11-36 3xULN: ≥ 108	3-21 2xULN: ≥ 42	
Screening	12	29	5	110
Week 2	12	26	4	95
Week 4	4	29	6	78
Week 6	6	29	8	85
Week 8	3	31	7	96
Week 10	3	30	8	95
Week 12	6	34	8	99
Week 14	6	34	7	27
Week 16	12	50	9	114
Week 18	11	70	9	127
Week 20	10	64	8	142
Week 22	14	68	12	132
Week 24	13	61	12	136

Below is the graphical representation of the serum transaminase trends for this patient, 208-5069.

Figure 21. Serum Transaminase Profile of Patient 208-5069



Based on the provided data, the contributory role of bedaquiline in this patient's hepatitis and hepatic cirrhosis could not be ruled out. Note that the mild elevation of this patient's AST developed towards the end of therapy. Both bilirubin levels and ALT were

normal throughout the bedaquiline treatment course. The presence of ascites suggests hepatic cirrhosis that results from longstanding hepatic disease. Therefore, this patient probably has undetected hepatic disease even prior to bedaquiline exposure. Bedaquiline and/or his BR could have exacerbated his liver disease. In all, similar to the previous case, the contributory role of bedaquiline and/or his BR could not be ruled out from this patient. Confounding factors that complicate evaluation of causality include his BR, alcohol use, and the absence of serology for infectious hepatitis.

Medical Officer Comment:

The potential of bedaquiline to cause hepatic injury could not be supported by the current safety data, as more information to rule out other etiologies of hepatic injury is needed. For example, etiologies such as infectious viral hepatitis, especially in endemic areas of the world such as Asia, should be ruled out. The two patients presented with SAEs from hepatic-related disorders both are complicated by alcohol use and concomitant use of other medications. Thus, causality could not be assessed.

Nevertheless, the higher proportion of patients reporting hepatic-related ADRs such as elevated transaminases indicate that bedaquiline could affect the liver. This potential observed in Trial C208 Stage 2 needs to be verified in the confirmatory Phase 3 trial. The risk of liver injury is increased if the patient also has concomitant long-standing liver disease, alcohol use, and use of known hepatotoxic drugs. Thus, alcohol use and concomitant use of hepatotoxic drugs should be avoided with bedaquiline intake, specially in the presence of underlying hepatic disease.

Overall Medical Officer Comment on Hepatic-Related ADRs

The Medical Officer concludes that a concern for hepatic-related ADRs is demonstrated from the safety data from the placebo-controlled Trial C208 Stage 2. In particular, bedaquiline-exposed patients have an increased potential to develop elevated liver transaminases. The evaluation of causality for these hepatic-related events may be difficult, as cases are confounded by the use of concomitant medications with hepatotoxic potential and the underlying conditions that can cause elevated transaminases and liver function tests.

Two patients who died developed hepatic-related serious adverse events. One patient developed hepatitis and hepatic cirrhosis, most likely alcohol induced, from which he died of. Another patient developed severe elevation of AST and bilirubin. The latter patient died from peritonitis and sepsis. These two cases demonstrate the challenge in determining whether these two cases are drug-induced liver injury from bedaquiline. Clearly, the information to rule out other causes of hepatotoxicity is lacking (absence of serology for infectious hepatitis). Moreover, factors such as use of concomitant hepatotoxic medications and alcohol abuse confound evaluation of causality. Lastly, the types of serum transaminase elevation and the clinical course of these two patients both point to

diagnoses other than drug-induced liver injury from bedaquiline. The isolated elevation of AST, rather than ALT, is less specific for hepatocellular injury caused by a drug but more likely points to alcoholic hepatitis. The presence of cirrhosis and portal hypertension that caused ascites indicates a more chronic disease process, not from a subacute exposure to the study drug.

The Office of Safety and Epidemiology has been consulted to assist the Division determine the role of bedaquiline in these cases of hepatic-related SAEs.

Based on the safety data presented, the Medical Officer concludes that a concern for hepatic-related adverse drug reactions (i.e. increased serum transaminases and liver function tests) exists in bedaquiline-exposed patients. Because of this potential and because of the observation from the trials that the use of other concomitant hepatotoxic drugs and alcohol use increase the risk for these events, alcohol and concomitant hepatotoxic drug use should be avoided when taking bedaquiline. If the use of other hepatotoxic drugs could not be avoided, serum transaminases and liver function tests should be more frequently monitored as clinically appropriate.

7.3.4.3. Standardized MedDra Query (SMQ) Events

The frequencies of certain adverse events of specific interest whose potential relevance were identified by nonclinical and clinical data were monitored. The following Standardized MedDRA Queries (SMQs) were used to identify the frequencies of similar medical concepts coded under different preferred terms (PTs), from the same or different SOC. Each patient with an event within an SMQ category was counted but counted only once.

Trial C208 Stage 2

Acute Pancreatitis SMQ

During the investigational treatment phase, two patients (2.5%) in the bedaquiline group developed an acute pancreatitis SMQ event of increase in blood amylase, classified as Grade 1 and Grade 3 (this patient discontinued treatment), respectively, assessed as possibly related to bedaquiline. These two reports of pancreatitis had isolated elevations (Grade 1 to 3) of amylase that resolved (Patients 208-4076 and 208-6008). In comparison, 1 patient (1.25%) in the placebo group who developed a Grade 3 increase in blood amylase and lipase, assessed as probably related to placebo and discontinued treatment. None were reported as SAEs.

Patient 208-4076, a 38 year old male with pre-XDR-TB strain treated with bedaquiline with KAN, CIP, EMB, ETH, and PZA, experienced a Grade 1 increase in blood amylase (48 U/L) which resolved at the next visit without discontinuing bedaquiline (amylase 41). Lipase levels remained normal.

Patient 208-6008, a 61 yo male with pre-XDR TB strain treated with bedaquiline with AMD, ETH, OFL, PZA, and TRD, developed multiple episodes of isolated Grade 1-3 increase in blood amylase levels between Week 12 to Week 28. Bedaquiline and the background regimen were not discontinued.

One additional patient experienced acute pancreatitis SMQ events in the bedaquiline group during the overall treatment phase (Patient 208-6000). This patient developed 3 episodes of pancreatitis (on D 278, D376, and D579) reported as Grade 3 in severity and related to bedaquiline and 1 episode of increased blood amylase (D424). The first 2 events of pancreatitis in this patient were assessed as possibly related to bedaquiline.

Patient 208-6000 was a 47 yo male with no DST results available who received bedaquiline with a BR of AMK, ETH, OFL, PZA, and TRD. He has a past medical history of alcoholism and chronic pancreatitis. He had baseline elevations of alkaline phosphatase, GGT, amylase, and lipase. He completed 24 weeks of bedaquiline but at week 40 was noted to have a more pronounced GGT elevation. On Wk (b) (6) the patient experienced abdominal pain and was hospitalized. A CT scan revealed reoccurrence of the pancreatitis. Grade 3 elevation of amylase was noted. This improved but recurred on D579 (Wk 83) following alcohol consumption. GGT was elevated between Wks 40-96 (Max at Wk 96 with value of 2202 U/L [N=10-61]). Amylase was intermittently high but maximal at Wk 60 (129 U/L [N=1-46]) and Wk 96 (122). Lipase was also elevated at baseline but was normal during the bedaquiline treatment, and increased at Wk 60 (370 [N=0-100]) and Wk 96 (247). He completed bedaquiline treatment. Aminotransferase elevations developed at the late timepoint, Gr 2 ALT increase at Wk 96 (374 N=31-129), ASt increase Gr 3 Wk 96 (244 N=11-36). He also reported myalgia, arthralgia but the timing is not clear. This case of pancreatitis, with concurrent elevation of AST and GGT with mild elevation of ALT, was confounded by alcohol use and prior history of chronic pancreatitis.

Medical Officer Comment:

Patient 208-6000 was discussed in great detail above because of concurrent elevations of pancreatic and hepatic markers. One of the toxicities noted in animal studies is phospholipidosis which was observed in all animal species given all doses of bedaquiline. The disease could manifest clinically from the organs of involvement (skeletal muscle, liver, pancreas, stomach, organs of the reticuloendothelial system). This patient experienced concurrent elevations of hepatic and pancreatic markers, which could remotely be from phospholipidosis. However, this could only be verified by pathological examination of the organs, which was not done. Most importantly, evaluation of this patient is highly confounded by this patient's history of chronic pancreatitis and alcoholism.

Rhabdomyolysis/Myopathy SMQ

No patient experienced this SMQ event during the trial.

Torsade de Pointes/QT Prolongation SMQ

Four patients (5.1%) in the bedaquiline group and 4 patients (4.9%) in the placebo group experienced 1 or more SMQ events related to Torsade/QT Prolongation during the investigational treatment phase. In the bedaquiline group, 3 patients experienced ECG QTc prolonged events and 1 patient experienced syncope. All events of prolonged QTc were Grade 1 in severity. No patient developed an AE with a preferred term of Torsade de 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.

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.

Medical Officer Comment:

Analysis of the frequencies of the SMQ category searches reveal safety findings consistent with other methodologies used in comparing the two treatment groups. Both QTc prolongation and elevation of hepatic transaminase remain safety signals. Increases in amylase and lipase that reflect acute pancreatitis is becoming prominent as this is an adverse event with serious complications. The absence of cases of rhabdomyolysis, myopathy, and Torsade de Pointes are reassuring but should be interpreted with caution given the limited safety database of this controlled trial.

7.3.5 Submission Specific Primary Safety Concerns

See previous Section.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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 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 82. Summary of AE Terms and SOC 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 Phase^a	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 Tissue Disorders	6 (26.1)	7 (29.2)
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	5 (21.7) 4 (17.4)	3 (12.5) 3 (12.5)

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

Table 83. Summary of AEs and SOC 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		
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

System Organ Class Preferred Term, n (%)	Placebo N = 24	Bedaquiline N = 23
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

Medical Officer Comment:

The incidences of Grade 3 and 4 AEs were similar in both groups during the Investigational Treatment and Background Treatment group. During the first 8 weeks (bedaquiline treatment period), a higher incidence of otologic-related AEs were reported in the bedaquiline group while a higher incidence of respiratory-related AEs were reported in the placebo group. The latter may be related to worsening of the underlying condition (i.e. tuberculosis). During the background treatment period, AEs related to laboratory abnormalities (ALT and transaminases increased, pancreatic enzymes increased, uric acid increased) and related to infections and infestations (pneumonia, respiratory tract infection, tuberculosis) were reported more frequently in the placebo group compared to the bedaquiline group.

Trial C208 Stage II

All AEs reported in > 5.0% of patients during the Overall Treatment phase are summarized in the table below. (Table 83)

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. These data are summarized in the table below.

Table 84. Most Frequently Reported AEs in the Overall Treatment Phase (Except Acute Pancreatitis)

SOC Preferred Term	Bedaquiline/BR N=79 (%)	Placebo/BR N=81 (%)
Musculoskeletal and Connective Tissue	39 (49.4)	40 (49.4)
Myalgia	6 (7.6)	7 (8.6)
Musculoskeletal Pain	4 (5.1)	4 (4.9)
Gastrointestinal Disorders	53 (67.1)	53 (65.4)
Pancreatitis Acute (SAE)	1 (1.3)	0
Nausea	32 (40.5)	30 (37.0)
Vomiting	23 (29.1)	22 (27.2)
Abdominal pain upper	10 (12.7)	7 (8.6)
Gastritis	7 (8.9)	16 (19.8)

Table 85. Incidence of AEs Reported in >5% of Patients in trial C208 Stage II

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
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. 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. (Table 85)

Table 86. Incidence of AEs Assessed as TB-Related for Trial C208 Stage II

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
Any AE related to TB	32 (40.5)	36 (45.6)	34 (42.0)	46 (56.8)
Blood and lymphatic system disorders	3 (3.8)	4 (5.1)	2 (2.5)	2 (2.5)
Anemia	3 (3.8)	3 (3.8)	1 (1.2)	1 (1.2)
Leukocytosis	0	0	1 (1.2)	1 (1.2)
Leukopenia	0	0	1 (1.2)	1 (1.2)
Lymphadenopathy mediastinal	0	1 (1.3)	0	0
Lymphopenia	0	0	1 (1.2)	1 (1.2)
Neutrophilia	0	0	1 (1.2)	1 (1.2)
Cardiac disorders	0	0	0	1 (1.2)
Bradycardia	0	0	0	1 (1.2)
Gastrointestinal disorders	1 (1.3)	1 (1.3)	1 (1.2)	1 (1.2)
Dyspepsia	0	0	1 (1.2)	1 (1.2)
Vomiting	1 (1.3)	1 (1.3)	0	0
General disorders and administration site conditions	13 (16.5)	14 (17.7)	11 (13.6)	11 (13.6)
Asthenia	0	0	1 (1.2)	1 (1.2)
Chest discomfort	0	0	1 (1.2)	1 (1.2)
Chest pain	6 (7.6)	6 (7.6)	4 (4.9)	4 (4.9)
Fatigue	1 (1.3)	1 (1.3)	0	0
Injection site pain	1 (1.3)	1 (1.3)	0	0
Malaise	1 (1.3)	2 (2.5)	1 (1.2)	2 (2.5)
Non-cardiac chest pain	0	1 (1.3)	0	0
Pain	0	0	1 (1.2)	1 (1.2)
Pyrexia	5 (6.3)	6 (7.6)	5 (6.2)	6 (7.4)
Infections and infestations	3 (3.8)	8 (10.1)	3 (3.7)	9 (11.1)
Bronchiectasis	1 (1.3)	1 (1.3)	0	0
Bronchitis	0	1 (1.3)	0	0
Lower respiratory tract infection	1 (1.3)	1 (1.3)	0	0
Oral candidiasis	0	0	2 (2.5)	2 (2.5)
Pulmonary tuberculosis	0	2 (2.5)	0	1 (1.2)
Pyothorax	1 (1.3)	1 (1.3)	0	0
Respiratory tract infection	1 (1.3)	1 (1.3)	1 (1.2)	1 (1.2)
Tuberculosis	0	2 (2.5)	0	5 (6.2)
Investigations	1 (1.3)	2 (2.5)	1 (1.2)	4 (4.9)
GGT abnormal	1 (1.3)	1 (1.3)	0	0
Neutrophil count increased	0	0	1 (1.2)	1 (1.2)
Weight decreased	0	1 (1.3)	1 (1.2)	4 (4.9)
Metabolism and nutrition disorders	1 (1.3)	2 (2.5)	3 (3.7)	4 (4.9)
Anorexia	1 (1.3)	1 (1.3)	2 (2.5)	3 (3.7)
Decreased appetite	0	1 (1.3)	0	0
Diabetes mellitus	0	0	1 (1.2)	1 (1.2)
Hypokalemia	0	0	1 (1.2)	1 (1.2)
Musculoskeletal and connective tissue disorders	1 (1.3)	1 (1.3)	1 (1.2)	2 (2.5)
Arthralgia	0	0	0	1 (1.2)
Back pain	0	0	1 (1.2)	1 (1.2)
Costochondritis	1 (1.3)	1 (1.3)	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
Nervous system disorders	0	0	1 (1.2)	1 (1.2)
Headache	0	0	1 (1.2)	1 (1.2)
Reproductive system and breast disorders	2 (2.5)	2 (2.5)	0	0
Erectile dysfunction	1 (1.3)	1 (1.3)	0	0
Menorrhagia	1 (1.3)	1 (1.3)	0	0
Respiratory, thoracic and mediastinal disorders	17 (21.5)	19 (24.1)	18 (22.2)	28 (34.6)
Asthma	0	0	0	1 (1.2)
Chronic obstructive pulmonary disease	1 (1.3)	1 (1.3)	0	0
Cough	4 (5.1)	6 (7.6)	2 (2.5)	6 (7.4)
Dyspnea	1 (1.3)	2 (2.5)	4 (4.9)	4 (4.9)
Dyspnea exertional	1 (1.3)	2 (2.5)	0	0
Hemoptysis	14 (17.7)	16 (20.3)	9 (11.1)	14 (17.3)
Pleuritic pain	2 (2.5)	2 (2.5)	3 (3.7)	5 (6.2)
Pneumothorax	0	0	0	1 (1.2)
Pulmonary cavitation	0	0	0	1 (1.2)
Rales	0	0	1 (1.2)	1 (1.2)
Rhinitis allergic	0	0	1 (1.2)	1 (1.2)
Rhonchi	0	0	2 (2.5)	2 (2.5)
Surgical and medical procedures	0	0	0	4 (4.9)
Surgery	0	0	0	4 (4.9)

N = number of subjects; n = number of subjects with observation
Source: NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 208

Medical Officer Comment:

The Medical Officer has reviewed the AEs reported in the table above and selected AEs that can be considered to be adverse drug reactions from the study treatment. These adverse drug reactions are enumerated in the table below:

Table 87. List of Adverse Drug Reactions from the Table of AEs Reported for Trial C208 Stage 2

Adverse Drug Reactions	Sirturo With other TB drugs N=79 n(%)	Other TB drugs Alone N=81 n (%)
Nervous system disorders Headache	22 (27.8)	10 (12.3)
Gastrointestinal disorders Pancreatitis and increased amylase Nausea Abdominal Pain Upper	3 (3.8) 30 (38.0) 9 (11.4)	1 (1.2) 26 (32.1) 7 (8.6)
Hepatobiliary disorders Transaminases Increased	4 (5.1)	0
Musculoskeletal and connective tissue disorders Arthralgia	26 (32.9)	18 (22.2)

Several adverse events were reported more in the bedaquiline-treated group compared to the placebo group. However, the Medical Officer could not establish the relationship of these AEs to bedaquiline. These AEs are listed in the following table:

Table 88. Adverse Events Observed More in the Bedaquiline Group With Questionable Association with Study Drug

Adverse Events	Bedaquiline N=79 n(%)	Placebo N=81 n (%)
Hemoptysis	14 (17.7%)	9 (11.1%)
Chest Pain	9 (11.4%)	6 (7.4%)
Anorexia	7 (8.9%)	3 (3.7%)
Rash	6 (7.6%)	3 (3.7%)

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

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
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

7.4.1.2. Adverse Drug Reactions from Pooled Safety Population

The table below lists the adverse events the Applicant considered as adverse drug reactions reported in the pooled safety population, consisting of patients from Trial C208 Stage 2 and Trial C209.

Table 90. Analysis of Pooled Data from Trials C208 Stage 2 and C209

SOC ADR (Grouped term), n (%)	Investigational Treatment Phase					
	Controlled Trials				Controlled + Uncontrolled Trials	
	TMC207		Placebo		TMC207	
	24 Weeks N = 79	Any N = 102	24 Weeks N = 81	Any N = 105	24 Weeks N = 312	Any N = 335
ADR	58 (73.4)	70 (68.6)	49 (60.5)	60 (57.1)	154 (49.4)	166 (49.6)
Nervous system disorders	27 (34.2)	32 (31.4)	18 (22.2)	21 (20.0)	55 (17.6)	60 (17.9)
Headache	22 (27.8)	24 (23.5)	10 (12.3)	12 (11.4)	42 (13.5)	44 (13.1)
Dizziness	10 (12.7)	13 (12.7)	10 (12.3)	12 (11.4)	20 (6.4)	23 (6.9)
Cardiac disorders	3 (3.8)	3 (2.9)	4 (4.9)	4 (3.8)	9 (2.9)	9 (2.7)
ECG QT prolonged	3 (3.8)	3 (2.9)	4 (4.9)	4 (3.8)	9 (2.9)	9 (2.7)
Gastrointestinal disorders	39 (49.4)	46 (45.1)	36 (44.4)	41 (39.0)	87 (27.9)	94 (28.1)
Nausea	30 (38.0)	36 (35.3)	26 (32.1)	27 (25.7)	55 (17.6)	61 (18.2)
Vomiting	20 (25.3)	21 (20.6)	21 (25.9)	24 (22.9)	40 (12.8)	41 (12.2)
Diarrhea	3 (3.8)	6 (5.9)	11 (13.6)	12 (11.4)	21 (6.7)	24 (7.2)
Hepatobiliary disorders	7 (8.9)	7 (6.9)	1 (1.2)	1 (1.0)	29 (9.3)	29 (8.7)
Transaminases increased ^a	7 (8.9)	7 (6.9)	1 (1.2)	1 (1.0)	29 (9.3)	29 (8.7)

Musculoskeletal and connective tissue disorders	26 (32.9)	30 (29.4)	20 (24.7)	24 (22.9)	58 (18.6)	62 (18.5)
Arthralgia	26 (32.9)	30 (29.4)	18 (22.2)	21 (20.0)	53 (17.0)	57 (17.0)
Myalgia	6 (7.6)	6 (5.9)	6 (7.4)	7 (6.7)	14 (4.5)	14 (4.2)

7.4.2 Laboratory Findings

7.4.2.1. Trial C208 Stage 1

To determine any safety signals from abnormalities in clinical laboratory evaluation, laboratory values were visually inspected for trends over time.

To summarize, the following patterns of laboratory value abnormalities were observed:

- Mean values for creatinine initially increased in both treatment and placebo groups, to a greater degree in the bedaquiline group.
- Mean uric acid also increased in both groups to levels twice the reference value within the first two weeks.
- Mean total cholesterol values decreased for both groups during the investigational treatment period.
- Hematology parameters that include neutrophil and platelet counts decreased in both groups while the proportion of lymphocytes increased over time in both groups
- Mean values for the hepatic parameters, ALT, alkaline phosphatase, and GGT decreased in both groups during the investigational treatment period with bedaquiline or placebo, while AST mean value increased in both groups during the same period. After this period, the mean values fluctuated around similar values at the end of the investigational treatment period or recovered.
- Other laboratory parameters did not demonstrate consistent relevant changes over time or did not demonstrate differences between groups.

Medical Officer Comment:

In Trial C208 Stage 1, increases in the ALT, alkaline phosphatase, and GGT values over time reflecting hepatotoxicity were not reported. In fact, decreases in these laboratory parameters were noted during the investigational treatment phase. With AST, increases in both groups were noted. This is interesting given the potential concern over hepatotoxicity with bedaquiline use from the nonclinical studies. Only one AE of increased prothrombin time that could reflect hepatotoxicity was reported in the BEDAQUILINE group. Analysis of treatment-emergent laboratory abnormalities during the 96 week background treatment period showed that increases in hepatic function parameters (i.e. ALT, alkaline phosphatase, AST, GGT) were more frequent in the placebo group than in the BEDAQUILINE group. (Table 90)

The potential for pancreatitis associated with bedaquiline use was not demonstrated by Trial C208 Stage 1 as there was only one case of the AE pancreatic enzyme increased reported in the placebo group. Moreover, analysis of treatment-emergent laboratory abnormalities during the 96 week background treatment period showed that increases in lipase and pancreatic amylase were more frequently noted in the placebo group. (Table 90)

Table 91. Select Frequencies of Laboratory Abnormalities

Laboratory Parameter, n (%)	Worst Grade	Placebo N = 24	BEDAQUILINE N=23
Pancreatic function			
Lipase	Grade 1	1 (4.5)	0
	Grade 3	1 (4.5)	0
Pancreatic amylase	Grade 1	4 (18.2)	3 (13.6)
	Grade 2	0	1 (4.5)
	Grade 3	2 (9.1)	0
Liver Function			
ALT	Grade 1	2 (9.1)	3 (13.6)
	Grade 2	1 (4.5)	0
	Grade 3	1 (4.5)	0
	Grade 4	1 (4.5)	0
ALP	Grade 1	2 (9.1)	4 (18.2)
	Grade 2	0	1 (4.5)
	Grade 3	1 (4.5)	0
AST	Grade 1	9 (40.9)	7 (31.8)
	Grade 2	3 (13.6)	3 (13.6)
	Grade 3	2 (9.1)	0
GGT	Grade 1	2 (9.1)	1 (4.5)
PT	Grade 1	5 (22.7)	1 (4.8)
	Grade 2	0	1 (4.8)
	Grade 3	1 (4.5)	2 (9.5)
	Grade 4	2 (9.1)	1 (4.8)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 170.

7.4.2.2. Trial C208 Stage 2

Laboratory evaluation of laboratory parameters were examined by patient and over time. All tests were analyzed by a central laboratory. The following general laboratory evaluations were done:

- Hematology (hemoglobin, hematocrite, RBC count, WBC count with differential, platelet count and prothrombin time.
- Biochemistry (total protein, GGT, alkaline phosphatase, ALP, AST, ALT, LDH, total cholesterol, triglycerides, direct, indirect, and total bilirubin, blood urea

nitrogen (BUN), uric acid, creatinine, creatine phosphokinase (CPK), CPK-muscle-brain isoenzyme (CPK-MB0, cardiac troponin I, electrolytes, glucose, pancreatic amylase, lipase, human serum albumin, trypsin-like immunoreactivity, gastrin, pepsinogen and glycosylated hemoglobin were assessed.

- HIV Serology
- Urinalysis
- ECG.

Overall, mean values for CPK, creatinine, uric acid, albumin, hemoglobin, lymphocytes, and total bilirubin increased for both the bedaquiline and placebo group during the study drug treatment phase. Mean values for gastrin, platelet count, WBC count, % of neutrophils, and total neutrophil count decreased over time for both groups.

The most frequently observed treatment-emergent graded laboratory toxicity of Grade 3 or 4 during the study treatment phase was hyperuricemia (35.9% [28/79 bedaquiline] vs 35.0% [28/81 placebo]). All these patients received concomitant pyrazinamide, an antibacterial known to increase uric acid.

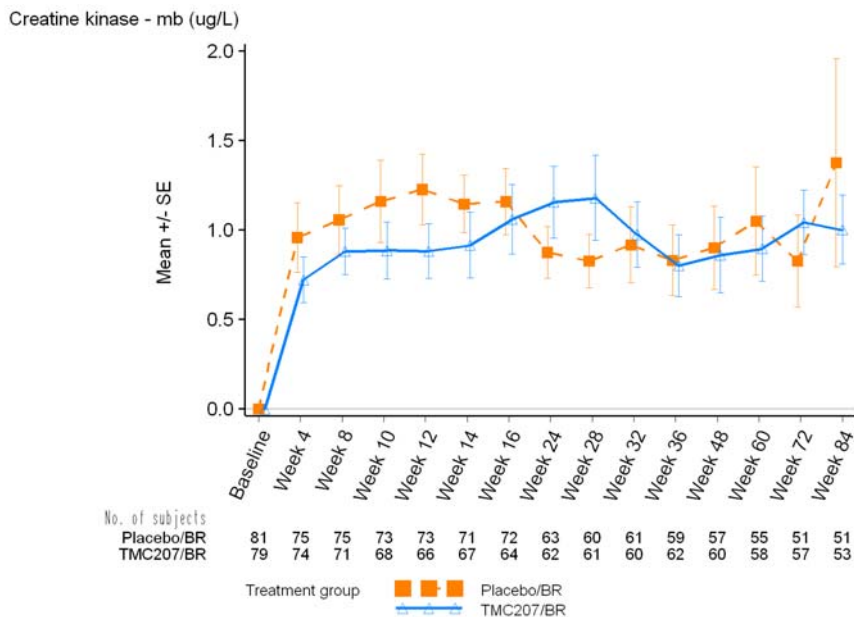
Treatment-emergent Grade 3 or 4 laboratory abnormalities observed in > 5.0% of patients during the study drug treatment that were more frequently reported in the bedaquiline group were: increased WBC, increased AST, and increased ALT. The most frequently observed treatment-emergent graded laboratory abnormalities during the study drug treatment period in > 20% of patients and that were more frequently observed in the bedaquiline group were:

- above normal CPK (66.7% bedaquiline vs 57.5% placebo)
- above normal LDH (20.5% bedaquiline vs 7.5% placebo)

The following bullets summarize the trends over time for the laboratory values.

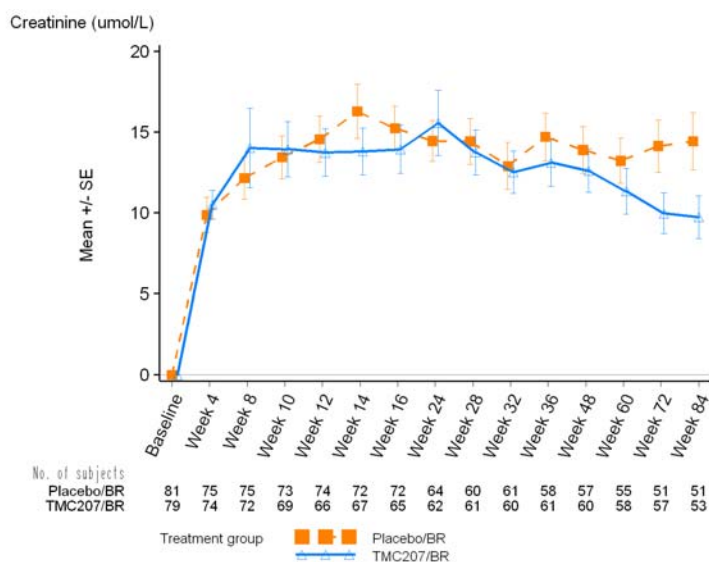
- Uric acid increased at Week 2, stabilized by Week 12 and decreased thereafter for both groups.
- Albumin increased for both treatment groups until Week 84.
- Mean troponin I and trypsin-like factor levels did not change over time.
- Mean and median gastrin levels decreased for both treatment groups.
- Mean values of CK-MB and CK increased for both bedaquiline and the placebo group, which the Applicant attributes to the use of injectable aminoglycosides in almost all subjects. The figure belows shows the trends:

Figure 22. Trend over time of CPK-MB between placebo and bedaquiline-treated patients



Source: NDA 204,384. Clinical Study Report Stage 2. Interim analysis, p. 238

Figure 23. Trend over time of CPK between placebo and bedaquiline-treated patients



Source: NDA 204,384. Clinical Study Report Stage 2. Interim analysis, p. 238

Medical Officer Comment: These two graphs demonstrate that CPK and CPK-MB increased similarly in both the placebo and bedaquiline groups during the bedaquiline treatment group, indicative that the increasing trends were probably not due to bedaquiline but could come from the background regimen.

Lactate and bicarbonate levels, and other blood gas parameters were not monitored in the trials so comparative frequencies of abnormalities reflecting changes in blood pH could not be done.

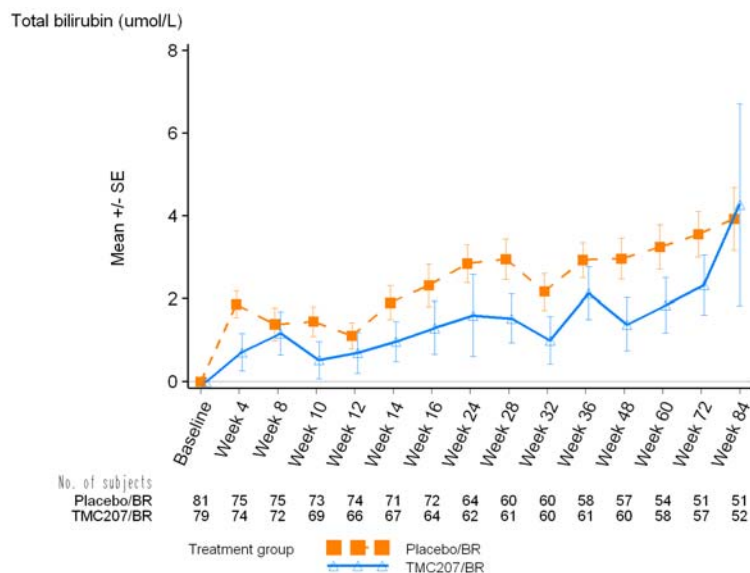
Other laboratory parameters included hematology values:

- Hemoglobin values slightly increased over time
- Mean platelet and WBC counts decreased over time for both groups.

Laboratory parameters pertaining to liver function showed the following trends over time:

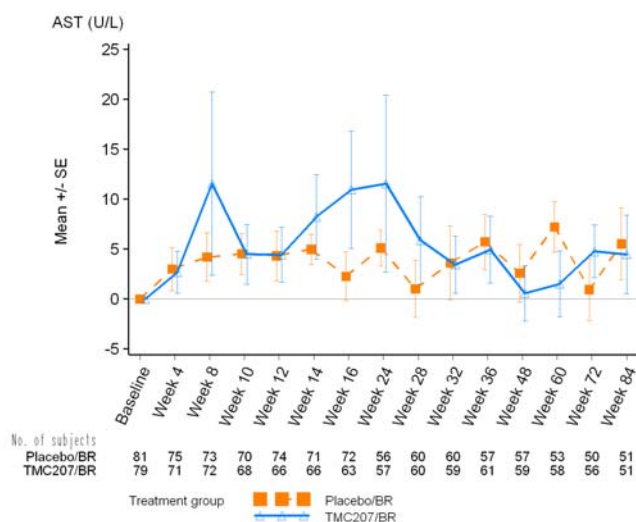
- Mean values for total bilirubin increased over time, due to increases in both direct and indirect bilirubin for both groups. (Figure 24)
- AST values abnormally increased in at least 50% of patients in the bedaquiline group.
- Overall, no consistent change over time in mean AST levels was observed over time. Median values increased over time during the study drug treatment period that remained elevated even after Week 24. (Figure 25)

Figure 24. Trend over time of total bilirubin between placebo and bedaquiline-treated patients



Source: NDA 204,384. Clinical Study Report Stage 2. Interim analysis, p. 241

Figure 25. Trend over time of AST between placebo and bedaquiline-treated patients



Source: NDA 204,384. Clinical Study Report Stage 2. Interim analysis, p. 241

Medical Officer Comment:

The trend in AST where AST levels in the bedaquiline group were greater than the placebo group is noted. However, it is difficult to determine the etiology of the observed increase in AST. As stated previously, elevations of AST is not a sensitive indicator for hepatocellular damage caused by a drug.

Overall, the following clinically significant laboratory evaluation changes were noted:

- Increases in CPK-MB and CPK levels during overall treatment phase with bedaquiline and background regimen. These increases were similar in degree in both the placebo and bedaquiline arm, suggesting that these changes could be attributed to the background regimen.
- Total bilirubin increased similarly in both groups.
- Mean AST values were higher in patients treated with bedaquiline, reiterating the potential of bedaquiline to cause liver injury.
- Trends over time with other laboratory values appear to be similar between the bedaquiline and placebo groups and appear not to be clinically significant.

Therefore, laboratory evaluation results in Trial C208 Stage 2 support the signal for hepatotoxicity noted with the increased frequencies of ADRs reflecting hepatotoxicity observed in the bedaquiline group.

7.4.3. Vital Signs

7.4.3.1 Trial CT08 Stage 1

To determine effects on vital signs, descriptive statistics of actual values and changes from reference in vital sign parameters were done, together with graphical presentations. Supine systolic blood pressure (sBP), supine diastolic blood pressure (dBP), supine pulse rate, and respiratory rate were measured and recorded. The reference value to calculate descriptive statistics on changes was the Day 1 value. Body temperature was not captured in this trial.

During the investigational treatment period, a small increase in mean supine systolic BP (sBP) in the bedaquiline group and a small decrease in the placebo group were observed. During the background treatment period, mean supine sBP increased further in the bedaquiline group with the largest mean change from reference of 17.5 mmHg (4.17) at Week 96. Mean supine sBP remained the same until Week 72, after which it increased at the last three evaluations. No consistent changes or relevant differences between the treatment groups were observed for supine dBP.

Over time, supine pulse decreased through the investigational and background treatment period in both bedaquiline and placebo groups. Mean respiratory rate slightly decreased in both treatment groups near the end of the trial (Week 60), with the decrease larger in the bedaquiline group compared to the placebo group.

According to the Applicant, none of the changes in vital sign parameters were considered to be clinically relevant.

Abnormalities in vital sign parameters were monitored and analyzed. As with changes in vital signs, the reference value to calculate abnormalities was the Day 1 value. Any treatment-emergent abnormality in vital sign parameters was observed in 2 patients in each group (9.1% in the bedaquiline group and 8.7% in the placebo group) during the investigational treatment period and in 5 patients in each group (22.7% and 21.7% in the bedaquiline and placebo groups, respectively). Abnormalities in supine dBP, sBP, or pulse occurred in 1 patient (7.7%) in the bedaquiline group and in 2 patients (18.2%) in the placebo group.

The Applicant concluded that no treatment-emergent AEs related to vital sign abnormalities were reported in Trial C208 Stage 1.

7.4.5 Special Safety Studies/Clinical Trials

7.4.5.1. Phase 1 Trial Safety Results

No deaths or serious adverse events were reported in any of the Phase 1 studies. The Applicant, as previously described, focused the safety analysis on safety data from the group of enrollees who received bedaquiline alone (total number = 189 subjects) as these patients would have safety data that could be more readily attributed to bedaquiline. (Table 91)

Table 92. Summary of Adverse Events in Pooled Phase 1 Studies

n (%)	Single-Dose TMC207 Alone N = 132	Multiple-Dose TMC207 Alone 400 mg N = 45	TMC207 Combined With Other Medications N = 69	Any TMC207 Alone N = 189 ^a	Any TMC207 N = 189 ^a
Number of subjects with at least one					
AE	80 (60.6)	25 (55.6)	48 (69.6)	114 (60.3)	138 (73.0)
SAE	0	0	0	0	0
AE leading to death	0	0	0	0	0
AE of at least grade 3	2 (1.5)	2 (4.4)	9 (13.0)	4 (2.1)	13 (6.9)
AE leading to permanent stop of TMC207	0	2 (4.4)	0	3 (1.6)	3 (1.6)
AE leading to temporary stop of TMC207	0	0	0	0	0
AE at least possibly related to TMC207	38 (28.8)	24 (53.3)	35 (50.7)	69 (36.5)	86 (45.5)

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

^a N in the last 2 columns is the same because all subjects who received TMC207 combined with other drugs in DDI trials also received TMC207 alone at some time during the trial.

Source: [Module 2.7.4/TMC207-C0000001-Anal-SAF-AE/Display AE.1](#)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 52.

Treatment Discontinuations

Among enrollees who received bedaquiline alone, there were 3 subjects (1.6%) who discontinued treatment from AEs and there were 4 subjects (2.1%) who reported Grade 3 AEs. The AEs that led to permanent discontinuation of treatment are: Grade 2 symptomatic urinary tract infection in 1 subject, Grade 1 pharyngolaryngeal pain and Grade 3 pyrexia in 1 subject, and Grade 3 lipase increased in 1 subject.

Adverse Event Frequencies (Overall)

In the pooled treatment group where subjects received any dose of bedaquiline alone, reported AEs were most frequently related to the SOC nervous system disorders (d/o) (24.3%) and gastrointestinal d/o (16.9%). By preferred term (PT), the most frequent AE in the bedaquiline Alone group was headache that was reported in 34/189 subjects

(18.0%). This was followed by dizziness postural reported in 10/189 subjects (5.3%). All other AEs were reported in < 5% of subjects. This information is found in the following table.

In the Multiple Dose bedaquiline Alone group, AEs most commonly reported (>15%) were classified in the SOC's gastrointestinal d/o (28.9%), nervous system d/o (17.8%), and general disorders and administration site conditions (15.6%). The most frequently reported AEs were headache (15.6%) and dry mouth (11.1%), followed by fatigue and diarrhea (both reported in 8.9%) and dizziness postural (6.7%). All other AEs were reported in <5% of subjects.

In the Single dose Bedaquiline Alone group, AEs were most frequently classified in the SOC's nervous system d/o (25.0%), followed by gastrointestinal d/o (12.1%) and infections and infestations (11.4%). The most frequently reported AE was headache (18.9%) and nasal congestion and nasopharyngitis (5.3%), other AEs were reported < 5%.

Table 93. Summary of Adverse Events Reported in at least 5 Subjects in Phase 1 Trials (bedaquiline alone Group)

SOC, Preferred term, n (%)	Single-Dose TMC207 Alone N = 132	Multiple- Dose TMC207 Alone 400 mg N = 45	TMC207 Combined With Other Medications N = 69	Any TMC207 Alone N = 189 ^a	Any TMC207 N = 189 ^a
Any AE	80 (60.6)	25 (55.6)	48 (69.6)	114 (60.3)	138 (73.0)
Nervous system disorders	33 (25.0)	8 (17.8)	13 (18.8)	46 (24.3)	57 (30.2)
Headache	25 (18.9)	7 (15.6)	13 (18.8)	34 (18.0)	45 (23.8)
Dizziness postural	5 (3.8)	3 (6.7)	0	10 (5.3)	10 (5.3)
Gastrointestinal disorders	16 (12.1)	13 (28.9)	11 (15.9)	32 (16.9)	40 (21.2)
Diarrhea	5 (3.8)	4 (8.9)	3 (4.3)	9 (4.8)	11 (5.8)
Dry mouth	0	5 (11.1)	0	6 (3.2)	6 (3.2)
Nausea	3 (2.3)	2 (4.4)	1 (1.4)	5 (2.6)	5 (2.6)
General disorders and administration site conditions	14 (10.6)	7 (15.6)	3 (4.3)	25 (13.2)	26 (13.8)
Application site vesicles	4 (3.0)	0	0	7 (3.7)	7 (3.7)
Fatigue	3 (2.3)	4 (8.9)	1 (1.4)	7 (3.7)	7 (3.7)
Respiratory, thoracic and mediastinal disorders	13 (9.8)	5 (11.1)	6 (8.7)	19 (10.1)	25 (13.2)
Nasal congestion	7 (5.3)	1 (2.2)	0	8 (4.2)	8 (4.2)
Oropharyngeal pain	3 (2.3)	2 (4.4)	4 (5.8)	5 (2.6)	9 (4.8)
Infections and infestations	15 (11.4)	0	4 (5.8)	16 (8.5)	19 (10.1)
Nasopharyngitis	7 (5.3)	0	0	7 (3.7)	7 (3.7)
Musculoskeletal and connective tissue disorders	11 (8.3)	1 (2.2)	0	14 (7.4)	14 (7.4)
Injury, poisoning and procedural complications	11 (8.3)	0	3 (4.3)	12 (6.3)	15 (7.9)
Investigations	6 (4.5)	3 (6.7)	8 (11.6)	9 (4.8)	14 (7.4)
Skin and subcutaneous tissue disorders	8 (6.1)	1 (2.2)	8 (11.6)	9 (4.8)	17 (9.0)
Eye disorders	7 (5.3)	0	4 (5.8)	7 (3.7)	11 (5.8)
Psychiatric disorders	2 (1.5)	2 (4.4)	0	6 (3.2)	6 (3.2)

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

^a N in the last 2 columns is the same because all subjects who received TMC207 combined with other drugs in DDI trials also received TMC207 alone at some time during the trial.

Source: Module 2.7.4/TMC207-C0000001-Anal-SAF-AE/Display AE.2

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 54.

AEs By Severity

By severity, AEs at least Grade 2 in severity classified under nervous system d/o (headache [4.2%]) were reported most frequently (10/189=5.3%), followed by infections and infestations (influenza [1.6%]) reported in 2.6% (5/189). The other AEs most frequently reported were lipase increased (3=1.6%), and laceration (2=1.1%). It is noteworthy that hyperuricemia was reported in 13/69 subjects (13.0%) in the treatment group Bedaquiline Combined with Other Medications.

In the Phase 1 trials (189 total number of patients), the only AEs reported to have at least Grade 3 severity were hyperuricemia in 4.8% (9/189) and lipase increased in 1.6% (3/189), followed by pyrexia in 1 patient (0.5%).

Table 94. Summary of AEs at Least Grade 2 in Severity

SOC, Preferred term, n (%)	Single-Dose TMC207 Alone N = 132	Multiple-Dose TMC207 Alone 400 mg N = 45	TMC207 Combined With Other Medications N = 69	Any TMC207 Alone N = 189 ^a	Any TMC207 N = 189 ^a
Any AE at Least Grade 2	18 (13.6)	6 (13.3)	16 (23.2)	26 (13.8)	41 (21.7)
Nervous system disorders	7 (5.3)	2 (4.4)	1 (1.4)	10 (5.3)	11 (5.8)
Headache	5 (3.8)	2 (4.4)	1 (1.4)	8 (4.2)	9 (4.8)
Dizziness	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Syncope	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Infections and infestations	4 (3.0)	0	2 (2.9)	5 (2.6)	7 (3.7)
Influenza	3 (2.3)	0	0	3 (1.6)	3 (1.6)
Gastroenteritis	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Urinary tract infection	0	0	0	1 (0.5)	1 (0.5)
Furuncle	0	0	1 (1.4)	0	1 (0.5)
Upper respiratory tract infection	0	0	1 (1.4)	0	1 (0.5)
Investigations	2 (1.5)	2 (4.4)	2 (2.9)	4 (2.1)	5 (2.6)
Lipase increased	2 (1.5)	1 (2.2)	0	3 (1.6)	3 (1.6)
GGT increased	0	1 (2.2)	1 (1.4)	1 (0.5)	1 (0.5)
Transaminases increased	0	0	1 (1.4)	0	1 (0.5)
Gastrointestinal disorders	2 (1.5)	0	0	2 (1.1)	2 (1.1)
Diarrhea	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Nausea	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Toothache	1 (0.8)	0	0	1 (0.5)	1 (0.5)
General disorders and administration site conditions	1 (0.8)	1 (2.2)	1 (1.4)	2 (1.1)	3 (1.6)
Influenza like illness	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Pyrexia	0	1 (2.2)	0	1 (0.5)	1 (0.5)
Fatigue	0	0	1 (1.4)	0	1 (0.5)
Injury, poisoning and procedural complications	2 (1.5)	0	0	2 (1.1)	2 (1.1)
Laceration	2 (1.5)	0	0	2 (1.1)	2 (1.1)
Musculoskeletal and connective tissue disorders	2 (1.5)	0	0	2 (1.1)	2 (1.1)
Arthralgia	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Back pain	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Hepatobiliary disorders	0	1 (2.2)	0	1 (0.5)	1 (0.5)
Hyperbilirubinemia	0	1 (2.2)	0	1 (0.5)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Skin papilloma	1 (0.8)	0	0	1 (0.5)	1 (0.5)
Immune system disorders	0	0	1 (1.4)	0	1 (0.5)
Seasonal allergy	0	0	1 (1.4)	0	1 (0.5)
Metabolism and nutrition disorders	0	0	9 (13.0)	0	9 (4.8)
Hyperuricemia	0	0	9 (13.0)	0	9 (4.8)

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

^a N in the last 2 columns is the same because all subjects who received TMC207 combined with other drugs in DDI trials also received TMC207 alone at some time during the trial.

Source: [Module 2.7.4/TMC207-C0000001-Anal-SAF-AE/Display AE.4](#) and [Display AE.1](#)

Source: NDA 204,384. Original Submission. Summary of Clinical Safety. p. 57.

In terms of AEs that may be possibly be related to bedaquiline during treatment alone in at least two subjects, AEs were most frequently classified under the SOC nervous system disorders (18.0%) and gastrointestinal disorders (12.2%). The most frequent AE that may be possibly related to bedaquiline were headache (12.2%) and dizziness postural (5.3%) in the Bedaquiline Alone group. Other AEs reported in > 5% of the pooled treatment group were dry mouth (11.1%), diarrhea (8.9%), fatigue (8.9%), hyperuricemia (13.0%) and erythema (7.2%). It is noteworthy that all the subjects with hyperuricemia were in Study C104 where INH and PZA were part of the treatment regimen either alone or in combination with bedaquiline. All subjects reporting erythema occurred after administration of bedaquiline with INH and PZA in Study C104, except one patient in Study C109 (treated with bedaquiline + ketoconazole).

In particular, aside from hyperuricemia, the only Grade 3 AE reported in Phase 1 studies is lipase increased that occurred after bedaquiline administration alone in 3 subjects. This may reflect pancreatic injury so increased pancreatic amylase levels were monitored in these 3 subjects. One subject also developed a Grade 2 increased pancreatic amylase levels that was not reported as an AE while another subject reported as a Grade 1 AE a Grade 1 increase in pancreatic amylase levels. The last patient did not develop an increase in amylase levels. The Applicant did not report any development of acute pancreatitis during the Investigational Treatment phase for the pooled Phase 1 studies.

Cardiovascular Safety

To evaluate for cardiovascular safety in Phase 1 studies, a resting 12-lead ECG was recorded pre- and postbaseline in all pooled Phase 1 studies. For Studies C110 (Open-label, randomized, crossover, DDI study with lopinavir/ritonavir) and C111 (Open-label, randomized, crossover, bioavailability study), triplicate ECGs were taken. In single-dose CDE-101 study (single-ascending dose study with a component of food interaction study), a continuous 12-lead ECG was obtained for the first 4 hours postdose. The table below shows the frequencies of cardiac-related AEs reported in Phase 1 studies.

Table 95. Incidence of Cardiac-related AEs in Phase 1 Studies

SOC, Preferred term, n (%)	Single-Dose Bedaquiline Alone N=132	Multiple-Dose Bedaquiline Alone 400 mg N=45	Bedaquiline Combined with Other medications N=69	Any Bedaquiline Alone N=189	Any Bedaquiline N=189
Cardiac disorders	0	0	1 (1.4)	0	1(0.5)
ECG QT prolonged	0	0	3 (4.3)	0	3(1.6)

Pooling of safety data for cardiovascular safety from Phase 1 studies was not done because of the limited number of multiple-dose trials.

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 Study C109 (DDI study between bedaquiline and ketoconazole), the AE - ECG QT prolonged – was reported in 3 subjects exposed to bedaquiline in Phase 1 studies. These ECG-related AEs were classified as Grade 1 events. A greater effect on QTc was noted after repeated dosing with bedaquiline and ketoconazole combined than after repeated dosing of individual drugs. In these cases, the absolute QTcF were all below 450 msec. To summarize,

Table 96 summarizes the ECG findings in these patients. The ECG findings resolved after one day and were considered to be possibly related to both bedaquiline and ketoconazole.

Table 96. ECG findings for 3 Patients with Prolonged QT in Phase 1 Trials

	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](#)

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.

In this trial, prolonged QTcF, as defined by QTcF > 450 ms) was noted in 1 (6.7%) subject in the bedaquiline group and no subject in the bedaquiline + ketoconazole group.

In addition to the three subjects discussed above, 4 more subjects were noted to have a prolonged QTcF interval (QTcF > 450 ms) after bedaquiline administration in other Phase 1 studies:

- Two subjects (QTcF: 453 and 457 ms) after receiving a single dose of bedaquiline in Study C108 (Open-label, randomized, crossover, bioavailability trial)
- One subject (QTcF: 452 ms) after receiving multiple doses of 400 mg of bedaquiline alone in Study C104 (DDI study with INH and PZA)
- One subject (QTcF: 481 ms) after receiving bedaquiline with other medications (INH and PZA) in 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.).

Medical Officer Comment:

Analysis of pooled safety data from 8 Phase 1 studies enrolling 189 healthy adult subjects, receiving at least 1 dose of bedaquiline support the safety and tolerability of bedaquiline alone or together with other medications. No deaths or SAEs were reported. While AEs were reported by 60.3% of subjects who received bedaquiline alone and by 55.6% of subjects who received multiple doses of 400 mg bedaquiline alone, the majority of the reported AEs were Grade 1 or 2 in severity. The most frequently reported AE in subjects given bedaquiline alone was headache (18.0%) while the most frequently reported AE in subjects given multiple doses of 400 mg of bedaquiline alone were headache (15.6%) and dry mouth (11.1%).

The Medical Officer thinks that the Phase 1 study provided supportive safety data that verified the need for monitoring for the AEs of interest for bedaquiline. Four patients were observed to have prolonged QTcF interval (defined as >450 ms) that did not cause symptomatology (Torsade, cardiac signs and symptoms, etc). The QT prolongation of these subjects was not reported as AEs. Two of these patients were given other concomitant medications (INH, PZA), resulting in the challenge in attributing the prolongation solely to bedaquiline. No subject developed prolonged QTcF greater than 500 ms.

In the study evaluating bedaquiline -ketoconazole coadministration, three patients reported increases in their QTcF from baseline (24 to 58 ms from baseline) as AEs. However, none of the QTcF intervals from these patients were > 450 ms. The Medical officer believes that this study and the reported AEs related to increases in the QTcF in these patients demonstrate two important features of the QT prolongation associated with bedaquiline. First, ketoconazole also have the potential to cause QT prolongation. The observation that greater increases in QTcF were observed in multiple doses of bedaquiline and ketoconazole in combination that when these drugs are given independently demonstrate the potential for drugs with QT prolonging effects to have an additive effect on QTcF when given together. Secondly, the ability for ketoconazole to increase bedaquiline systemic exposure could result in greater increase in QTcF. Therefore, the Medical Officer believes that an important part of evaluating the risk of QTcF prolongation is looking at drug-drug interactions and the individual drug's ability to cause increases in QTcF.

7.4.5.2 Phase IIa Trial (Trial C202)

No deaths occurred from an AE that started during the treatment period. As seen in Table 14, two patients died during the follow-up period. A summary of the deaths follows.

CRF ID 202-0109

- 25 year old black female received bedaquiline 400 mg qD for 7 days (7/15 to 7/21/2005) and Kombipak II for tx of TB (3 tablets qD)
- No known medical history.
- PE: slight wheeze in the LLL
- No follow-up for 1 month because she moved.
- Patient admitted to the hospital on (b) (6) and diagnosed with pulmonary TB and retroviral infection (reported as SAEs) after she presented with a 1 month history of hemoptysis, general body pains and night sweats
- PE: wasted and dyspneic, afebrile, increased JVP, loud second pulmonic sound, widespread chest crackles, tenderness in the R side of her abdomen, hepatomegaly
- M. TB sputum viable counts (+)
- (+) serology for HIV with CD4 count of 80
- Treatment initiated on 7/22/2005 with RMP, INH, PZA, and EMB.
- No improvement despite TB meds.
- Abnormal Hgb, lymphocytes, % lymphocytes, plt. ct. neutrophils (%), monocytes (%) and RBC count
- Died on (b) (6) due to the SAEs
- Both SAEs assessed as doubtfully related to bedaquiline but related to tuberculosis.
- Medical Officer agrees with this assessment.

CRF ID 202-0036

- 41 year old male received bedaquiline 400 mg qD for 3 days (from 13 Sept 2005 to 15 Sept 2005).
- Prematurely withdrawn on D3 because of (+) UA test for cannabinoids
- CXR on enrollment showed extensive pathology of the L lung (cavities, dense infiltration, pleural reaction. R lung had mild alveolar infiltration and cavitation.
- M. TB viable sputum counts (+)
- Treatment initiated on 16 Sept 2005 with RMP, INH, PZA, and EMB
- On (b) (6) readmitted to a TB hospital for social reasons.
- (b) (6): mild hemoptysis and referred to tertiary hospital
- Hemoptysis reported as an SAE, Grade 3.
- Hemoptysis doubtfully related to bedaquiline and related to TB
- (b) (6): bronchial arterial embolization treatment for hemoptysis
- (b) (6): death due to massive hemoptysis
- Death assessed as doubtfully related to bedaquiline
- Medical Officer agrees with assessment.

The AEs causing the mortalities were classified by the Investigators as doubtfully related to bedaquiline.

Two patients who received INH reported Grade 3 hemoptysis. One patient experienced the AE while in treatment which was discontinued and another experienced the AE during follow-up.

7.4.5.2.a. Adverse Events

AEs starting during treatment were reported in 2 patients (13%) treated with 25 mg of bedaquiline, in 6 patients (38%) treated with 100 mg of bedaquiline, and in 9 (64%) patients treated with 400 mg of bedaquiline. Seven patients (47%) receiving RMP and 3 (20%) receiving INH reported AEs.

During bedaquiline treatment, AEs from the SOC nervous system disorders and respiratory, thoracic, and mediastinal disorders (5 [11.1%] patients each) were most frequently reported. The AE hemoptysis was reported in 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 a Grade 4 hemoptysis that led to premature discontinuation of INH.

In the 100 mg bedaquiline group, diarrhea and rash were reported to be at least possibly related to bedaquiline. Somnolence was reported in the 400 mg bedaquiline group. Hemoptysis and pleuritic chest pain were considered related to TB by the investigator.

No clinically relevant changes over time in laboratory parameters, including Grade 4 treatment-emergent laboratory abnormality, were observed. The most frequent treatment-emergent graded abnormalities were hemoglobin decreased, ALT increased, GGT increased, and hypercalcemia. Hyperglycemia was reported in the RMP group.

To evaluate for cardiovascular safety, ECGs were done at screening, Day -1 (reference), and Day 7 (predose and 5 h postdose)

In this trial, average increases of > 10 ms in median QTcF value were seen on D7 for the bedaquiline 400 mg group and both control groups. No increases were observed in the median QTcF value in the bedaquiline 25 mg and 100 mg groups. On Day 7, the increases in QTcF observed in the bedaquiline 400 mg group were larger than those in both control groups at the predose (i.e. bedaquiline 400 mg: 24.5 ms; RMP: 10.7 ms, and INH: 8.4 ms) and 5 hours postdose assessment timepoints (bedaquiline 400 mg: 24.5 ms; RMP: 13.1 mg; and INH: 15.8%).

No QTcF values of more than 500 ms were observed in this trial.

Relating the above information to the PK/PD relationships for safety parameters, no clear PK/PD relationship was observed for either bedaquiline or M2. There was, however, a tendency towards greater QTcF prolongation with bedaquiline 400 mg dosage.

Medical Officer Comment:

The Medical Officer observes that the notable safety data in this trial is that 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.

7.4.6 Immunogenicity

None

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dr. Fang Li, the Clinical Pharmacometric Reviewer, has conducted an analysis of dose-response effects on safety parameters. Please refer to Section 7.2.5. Explorations for Dose Response (Trial C208 Stage 2).

In essence, the Clinical Pharmacology Review team concludes that there is no clear relationship between bedaquiline exposure and efficacy in MDR-TB patients given the range of exposures observed with the proposed regimen. Similarly, no strong relationship between exposure and incidence of the most frequently reported adverse events such as nausea, headache, chest pain, and arthralgia, was seen.

7.5.2 Time Dependency for Adverse Events

Dr. Fang Li, the Clinical Pharmacometric Reviewer, has conducted an analysis of dose-response effects on safety parameters. Please refer to Section 7.2.5. Explorations for Dose Response (Trial C208 Stage 2).

7.5.3 Drug-Demographic Interactions

Please see Section 6. Review of Efficacy.

7.5.4 Drug-Disease Interactions

The Lead Clinical Pharmacology reviewer, Dr. Dakshina Chilukuri, and the Clinical Pharmacology review team have adequately reviewed the potential drug-disease interactions, such as the impact of hepatic impairment and renal impairment, with the metabolism and the PK properties of bedaquiline.

The renal excretion of bedaquiline appears to be negligible. Therefore, the Applicant does not recommend any dose modification with mild or moderate renal impairment. Bedaquiline should be used with caution by patients with severe or end-stage renal disease.

Similarly, no dose adjustment for bedaquiline is needed in patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment was not evaluated. Because bedaquiline is metabolized by hepatic enzymes, this has to be evaluated in the confirmatory trial C210. Please see the Clinical Pharmacology review.

7.5.5 Drug-Drug Interactions

Because bedaquiline is metabolized by the CYP3A4 system, the potential for drug-drug interaction exists with drugs that either inhibit or induce this enzyme. Bedaquiline has either no potential, or only a weak potential, to induce or inhibit CYP isoenzyme activity.

CYP3A4 inducers such as rifampin was shown to decrease bedaquiline exposure. Therefore, coadministration of bedaquiline with CYP3A4 inducers such as rifampin is not recommended.

Drug-drug interaction studies showed that coadministration of bedaquiline with CYP3A4 inhibitors such as ketoconazole and lopinavir with low-dose ritonavir (LPV/r) increased bedaquiline exposure. Therefore, the Applicant and the Clinical Pharmacology reviewers do not recommend coadministration of bedaquiline with moderate or strong CYP3A4 inhibitors for more than 2 weeks.

Lastly, both the Applicant and the Clinical Pharmacology reviewers conclude that there was no considerable effect of bedaquiline on the exposure of background regimen drugs for tuberculosis such as EMB, KAN, PZA, OFL, and Cycloserine/terizidone.

While the Applicant has addressed some of the potential drug-drug interactions that can occur with bedaquiline, more studies are needed to characterize drug-drug interactions with bedaquiline. In particular, the interaction between bedaquiline and efavirenz and the effect of severe hepatic impairment need to be characterized.

The Clinical Reviewer refers the reader to the Clinical Pharmacology Review Team review.

7.6 Additional Safety Evaluations

None

7.6.1 Human Carcinogenicity

Please see Dr. Owen McMaster's Pharmacology-Toxicology review

7.6.2 Human Reproduction and Pregnancy Data

Please see Dr. Owen McMaster's Pharmacology-Toxicology review.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies were conducted to evaluate the efficacy and safety of bedaquiline in pediatric patients. In addition, the requirements of the Pediatric Research Equity Act (PREA) do not apply to bedaquiline as this drug was granted orphan designation. The Applicant has therefore not provided a pediatric assessment for bedaquiline.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Bedaquiline does not appear to have any drug abuse potential so studies evaluating bedaquiline's overdose, drug abuse potential, withdrawal, and rebound have not been conducted.

7.7 Additional Submissions / Safety Issues

7.7.1. Bedaquiline Experience in HIV-Infected Patients

In Trial C208 Stage 2 and Trial C209, the evaluation of the efficacy and safety of bedaquiline in patients with co-infection of HIV and MDR-TB was not addressed. Patients with HIV infection and tuberculosis was included only if they did not fulfill the following exclusionary criteria:

- HIV-infected patients with
 - A CD4+ count < 300 cells/μL or
 - Received antiretroviral therapy and/or oral or intravenous antifungal medication within the last 90 days, or
 - Possibly needing to start ART during the investigational treatment period.

With these exclusionary criteria, Trials C208 Stage 2 and C209 enrolled the following number of patients with co-infection with HIV and MDR-TB.

Table 97. Enrollment of Patients Co-Infected with HIV and MDR-TB in Trials C208 Stage 2 and C209

Trial/HIV Status	Bedaquiline group	Placebo group
Trial C208 Stage 2	(N=79) (%)	(N=81) (%)
HIV negative	71 (89.9)	65 (80.2)
HIV infected	8 (10)	16 (19.8)
Trial C209	(N=225)	
HIV negative	214 (95.1)	N/A
HIV infected	11 (4.9%)	N/A

Medical Officer Comment:

The bedaquiline experience in HIV-infected patients with MDR-TB from these trials is limited. Any observations regarding safety and efficacy should be interpreted cautiously with such a limited enrollment. In Trial C208 Stage 2, more HIV infected patients were randomized to the placebo group. This did not appear to impact the efficacy results in this trial.

More importantly, enrolled HIV infected patients in these trials do not represent the immunosuppressed HIV infected patients needing antiretroviral medications and who are at greater risk for worse outcomes when coinfecting with MDR-TB. Therefore, Trials C208 Stage 2 and C209 could not optimally evaluate the efficacy and safety of bedaquiline in the subpopulation of HIV infected patients who are immunosuppressed and at risk for worse outcomes. Lastly, the two trials could not evaluate important drug-drug interactions between bedaquiline and antiretrovirals.

To address the issue of the need to evaluate bedaquiline in the more vulnerable population of patients coinfecting with HIV, the Applicant will be enrolling HIV infected patients on specific antiretroviral regimens in the confirmatory trial C210. In addition, as a postmarketing requirement, the Agency requires the Applicant to evaluate the effect of bedaquiline on the PK properties of efavirenz.

8 Postmarket Experience

Bedaquiline has not received marketing approval in any country so there is no postmarketing experience associated with bedaquiline use. However, the Applicant has

9 Appendices

9.1 Literature Review/References

Please refer to references below.

9.2 Labeling Recommendations

Please refer to the Labeling recommendations in the Action Package.

9.3 Advisory Committee Meeting

Appendix A. Overview of Phase 1 Studies

Trial Number (Status)	Trial Design and Trial Objectives	N ^a	Treatment	Formulation	Refer to Module
Phase 1 Single-Dose Trials in Healthy Subjects					
R207910-CDE-101 (C)	<p>Part 1</p> <p><u>Design</u> Double-blind, randomized, placebo-controlled, single ascending dose trial</p> <p><u>Objective</u> To assess the safety, tolerability, and pharmacokinetics of single ascending oral doses of TMC207 in healthy male subjects.</p> <p>Part 2</p> <p><u>Design</u> Open-label, randomized, 2-way crossover, food interaction trial</p> <p><u>Objective</u> To evaluate the effect of food on the safety, tolerability, and pharmacokinetics of a single oral dose of TMC207 in healthy male subjects.</p>	54	<p>All Panels: single dose of TMC207 (oral solution) after a meal</p> <p>Panel 1: 10 mg TMC207</p> <p>Panel 2: 30 mg TMC207</p> <p>Panel 3: 100 mg TMC207</p> <p>Panel 4: 300 mg TMC207</p> <p>Panel 5: 450 mg TMC207</p> <p>Panel 6: 700 mg TMC207</p> <p>(per dose level: n = 6 TMC207, n = 3 placebo)</p>	TMC207 as F003 ^b TMC207 as F004 ^c	5.3.1.1
		12	<p>Single oral dose of 300 mg TMC207 (oral solution):</p> <ul style="list-style-type: none"> - fasted/fed (n = 6) - fed/fasted (n = 6) 	TMC207 as F003 ^b TMC207 as F004 ^c	

C = completed trial

^a actual number of subjects per trial

^b F003: oral solution containing

(b) (4)

^c F004: oral solution containing

Trial Number (Status)	Trial Design and Trial Objectives	N ^a	Treatment	Formulation	Refer to Module
Phase 1 Single-Dose Trials in Healthy Subjects, Cont'd					
R207910BAC1003 (C)	<p><u>Design</u> Open-label, single-dose interaction trial (TMC207/rifampin)</p> <p><u>Objectives</u></p> <ul style="list-style-type: none"> - To evaluate the effect of repeated doses of rifampin on the pharmacokinetics of a single oral dose of TMC207 in healthy male subjects. - To assess the safety and tolerability of TMC207 when given as a single dose in combination with rifampin. 	16	<p>All subjects:</p> <ul style="list-style-type: none"> - single oral dose of 300 mg TMC207 alone on Day 1 - 600 mg q.d. rifampin alone on Day 15-20 - single combined dosing of 300 mg TMC207 and 600 mg rifampin on Day 21 	TMC207 as F004 ^b Rifampin as commercially available capsules of 300 mg	5.3.3.4
TMC207-C108 (C)	<p><u>Design</u> Open-label, randomized, 3-way crossover, bioavailability trial</p> <p><u>Objectives</u></p> <ul style="list-style-type: none"> - To determine the relative bioavailability of TMC207 after single oral dosing with the capsule or the tablet formulation, as compared to the reference oral solution, under fed conditions. - To determine the effect of food on the relative bioavailability of TMC207 after single oral dosing with the capsule or the tablet formulation. - To determine the short-term safety and tolerability of TMC207 after single oral dosing, formulated as the capsule, the tablet and the reference oral solution. 	24	<p>Panel 1 (n = 12):</p> <ul style="list-style-type: none"> - single oral dose of 100 mg TMC207 (oral solution, fed) - single oral dose of 100 mg TMC207 (capsule, fed) - single oral dose of 100 mg TMC207 (capsule, fasted) <p>Panel 2 (n = 12):</p> <ul style="list-style-type: none"> - single oral dose of 100 mg TMC207 (oral solution, fed) - single oral dose of 100 mg TMC207 (tablet, fed) - single oral dose of 100 mg TMC207 (tablet, fasted) 	<p>TMC207 as F004^b TMC207 as F006^c TMC207 as F006^c</p> <p>TMC207 as F004^b TMC207 as F001^d TMC207 as F001^d</p>	5.3.1.1

C = completed trial

^a actual number of subjects per trial

^b F004: oral solution containing

(b) (4)

^c F006:

(b) (4)

^d F001: tablet containing eq. 100 mg TMC207 as the fumarate salt and the inactive ingredients lactose monohydrate, (b) (4), starch, hypromellose 2910 15mPa.s, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate

Clinical Review
Ariel R. Porcalla, MD, MPH
NDA 204 384
BEDAQUILINE (bedaquiline)

Trial Number (Status)	Trial Design and Trial Objectives	N ^a	Treatment	Formulation	Refer to Module
<i>Phase I Single-Dose Trials in Healthy Subjects, Cont'd</i>					
TMC207-C110 (C)	<u>Design</u> Open-label, randomized, 2-way crossover, interaction trial (TMC207/lopinavir/ritonavir) <u>Objective</u> The primary objective was to evaluate the effect of steady-state LPV/riv 400/100 mg b.i.d. on the pharmacokinetics of TMC207 and its <i>N</i> -monodesmethyl metabolite (M2) after single-dose administration of TMC207 400 mg in healthy subjects.	16	Treatment A (n = 16): - oral dose of 400 mg TMC207 q.d. on Day 1 Treatment B (n = 16): - oral doses of 400/100 mg b.i.d. lopinavir/ritonavir on Days 1-24 - oral dose of 400 mg TMC207 q.d. on Day 11	TMC207 as F001 ^b Lopinavir/ritonavir as commercially available tablets containing 200 mg lopinavir and 50 mg ritonavir	5.3.1.1
TMC207-C111 (C)	<u>Design</u> Open-label, 2-panel, randomized, 3-way crossover, bioavailability trial <u>Objective</u> The primary objective of the trial was to determine the relative bioavailability of TMC207 after single-dose oral administration of the Phase II clinical trial tablet formulation and after single dose oral administration of a newly developed tablet formulation, in fed and fasted conditions, in healthy subjects.	28	Panel A (n = 13): - single oral dose of 100 mg TMC207 (Phase II tablet, fed) - single oral dose of 100 mg TMC207 (fine API grade tablet, fed) - single oral dose of 100 mg TMC207 (coarse API grade tablet, fed) Panel B (n = 15): - single oral dose of 100 mg TMC207 (Phase II tablet, fasted) - single oral dose of 100 mg TMC207 (fine API grade tablet, fasted) - single oral dose of 100 mg TMC207 (coarse API grade tablet, fasted)	TMC207 as F001 ^b TMC207 as G001 ^c TMC207 as G001 ^c TMC207 as F001 ^b TMC207 as G001 ^c TMC207 as G001 ^c	5.3.3.4

C = completed trial

^a actual number of subjects per trial

^b F001: tablet containing eq. 100 mg TMC207 as the fumarate salt and the inactive ingredients lactose monohydrate, (b) (4) starch, hypromellose 2910 15mPa.s, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate

^c G001: (b) (4)

Trial Number (Status)	Trial Design and Trial Objectives	N ^a	Treatment	Formulation	Refer to Module
<i>Phase I Single-Dose Trials in Healthy Subjects, Cont'd</i>					
TMC207-C112 (C)	<u>Design</u> Open-label, single-dose trial in healthy subjects and subjects with moderate hepatic impairment. <u>Objectives</u> - To assess the pharmacokinetics of TMC207 and M2 in subjects with moderate hepatic impairment and in matched healthy controls after single-dose administration of TMC207 400 mg. - To assess the safety and tolerability of single-dose TMC207 400 mg in subjects with moderate hepatic impairment and in matched healthy controls.	16	All subjects: 400 mg TMC207 on Day 1 (8 healthy subjects / 8 subjects with moderate hepatic impairment)	TMC207 as F001 ^b	5.3.3.3
TMC207TBC1003 (C)	<u>Design</u> Double-blind, randomized, placebo- and positive-controlled, parallel-group trial. <u>Objective</u> - To evaluate the effect of single-dose administration of TMC207 at 800 mg versus placebo on the QT and QTc interval in healthy subjects.	88	Treatment A (n = 44): - a single oral dose of TMC207 800 mg on Day 1 + a single oral dose of moxifloxacin placebo on Day 2; fed conditions Treatment B (n = 44): - a single oral dose of TMC207 placebo on Day 1 + a single oral dose of moxifloxacin 400 mg on Day 2; fed conditions	TMC207 as F001 ^b	5.3.5.4

C = completed trial

^a actual number of subjects per trial

^b F001: tablet containing eq. 100 mg TMC207 as the fumarate salt and the inactive ingredients lactose monohydrate, (b) (4) starch, hypromellose 2910 15mPa.s, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate

Clinical Review
Ariel R. Porcalla, MD, MPH
NDA 204 384
BEDAQUILINE (bedaquiline)

Trial Number (Status)	Trial Design and Trial Objectives	N*	Treatment	Formulation	Refer to Module
Phase I Multiple-Dose Trials in Healthy Subjects					
R207910-CDE-102 (C)	<u>Design</u> Double-blind, randomized, placebo-controlled, multiple ascending dose trial <u>Objective</u> To assess the safety, tolerability, and pharmacokinetics of multiple oral doses of TMC207 in healthy male subjects.	27	Panel 1: oral doses of 50 mg TMC207 q.d. on Days 1-14 Panel 2: oral doses of 150 mg TMC207 q.d. on Days 1-14 Panel 3: oral doses of 400 mg TMC207 q.d. on Days 1-14 (per dose level: n = 6 TMC207, n = 3 placebo)	TMC207 as F003 ^b TMC207 as F004 ^c	5.3.3.1
TMC207-C104 (C)	<u>Design</u> Open-label, 1-way crossover, interaction trial (TMC207/isoniazid/pyrazinamide) <u>Objectives</u> - To evaluate the effect of repeated doses of TMC207 on the pharmacokinetics of H/Z; - To evaluate the effect of repeated doses of H/Z on the pharmacokinetics of TMC207 and the N-monodesmethyl metabolite; - To evaluate the short-term safety and tolerability of coadministration of TMC207 and H/Z.	24	Treatment A (n = 24): - oral doses of 300 mg isoniazid q.d. on Days 1-5 - oral doses of 2000 mg pyrazinamide q.d. on Days 1-5 Treatment B (n = 23): - oral doses of 400 mg TMC207 q.d. on Days 1-15 - oral doses of 300 mg isoniazid q.d. on Days 11-15 - oral doses of 2000 mg pyrazinamide q.d. on Days 11-15	TMC207 as F004 ^c Isoniazid as commercially available tablets of 300 mg Pyrazinamide as commercially available tablets of 500 mg	5.3.3.4

C = completed trial

* actual number of subjects per trial

^b F003: oral solution containing (b) (4)

^c F004: oral solution containing

Trial Number (Status)	Trial Design and Trial Objectives	N*	Treatment	Formulation	Refer to Module
Phase I Multiple-Dose Trials in Healthy Subjects, Cont'd					
TMC207-C109 (C)	<u>Design</u> Open-label, 1-way crossover, interaction trial (TMC207/ketoconazole) <u>Objectives</u> - To evaluate the effect of repeated doses of ketoconazole on the pharmacokinetics of TMC207 and its N-monodesmethyl metabolite; - To evaluate the effect of repeated doses of TMC207 on the pharmacokinetics of ketoconazole; - To evaluate the short term safety and tolerability of coadministration of TMC207 and ketoconazole.	16	Treatment A (n = 16): - oral doses of 400 mg ketoconazole q.d. on Days 1-3 Treatment B (n = 16): - oral doses of 400 mg TMC207 q.d. on Days 1-14 - oral doses of 400 mg ketoconazole q.d. on Days 12-14	TMC207 as F004 ^b Ketoconazole as commercially available tablets of 200 mg	5.3.3.4
Phase I Single-Dose Trial in HIV-1 Infected Subjects (without TB infection)					
TMC207-C117 (C)	<u>Design</u> Open-label, single-sequence, interaction trial (TMC207/nevirapine) <u>Objective</u> The primary objective was to evaluate the effect of steady-state NVP 200 mg b.i.d. on the pharmacokinetics of TMC207 and its M2 metabolite after single-dose administration of TMC207 400 mg in ARV-naïve HIV-1 infected subjects.	16	Treatment A (n = 16): - single oral dose of 400 mg TMC207 on Day 1 - start nevirapine (200 mg p.o. q.d. for 2 weeks followed by 200 mg p.o. b.i.d. for 4 weeks) + 2 N(t)RTIs Treatment B (n = 16): - single oral dose of 400 mg TMC207 on Day 1 - continue nevirapine (200 mg p.o. b.i.d.) + 2 N(t)RTIs	TMC207 as F001 ^c Nevirapine as commercially available tablets of 200 mg	5.3.3.4

C = completed trial

* actual number of subjects per trial

^b F004: oral solution containing (b) (4)

^c F001: tablet containing eq. 100 mg TMC207 as the fumarate salt and the inactive ingredients lactose monohydrate, (b) (4) starch, hypromellose 2910 15mPa.s, polysorbate 20, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate

¹ <<http://www.who.int/mediacentre/factsheets/fs310/en/index.html>>

² <http://www.who.int/tb/publications/2011/factsheet_tb_2011.pdf>

³ Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. WHO Progress Report 2011.

⁴ Multidrug and extensively drug resistant TB (M/XDR-TB) 2010 global report on surveillance and response

<http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf>

⁵ Wells CD. Tuberculosis among HIV-infected and other immunocompromised hosts: epidemiology, diagnosis, and strategies for management. *Curr Infect Dis Rep*. 2010; 12: 192-7.

⁶ Falzon D, Jaramillo E, Schunemann HJ, et. al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur respir J*. 2011 Sep; 38(3); 516-28. Epub 2011 Aug 4.

⁷ Huitric E, Verhasselt P, et. al. In vitro antimycobacterial spectrum of a diarylquinoline ATP synthase inhibitor. *Antimicrob Agents Chemother* 2007; 51: 4202-04.

⁸ Koul A, Vranckx L, et. al. Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed homeostasis. *J Biol Chem* 2008; 283: 25273-80.

⁹ Andries K, Verhasselt P, et. al. A diarylquinoline drug active on the ATP synthase of mycobacterium tuberculosis. *Science* 2005;307:223-7.

¹⁰ Rao SP, Alonso S, et. al. The protonmotive force is required for maintaining ATP homeostasis and viability of hypoxic, nonreplicating Mycobacterium tuberculosis. *PNAS* 2008;106:11945-11950.

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/s/

ARIEL R PORCALLA
12/28/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204,384

Applicant: Janssen Research and Development, LLC **Stamp Date: June 29, 2012**

**Drug Name: Bedaquiline
(TMC207)**

NDA/BLA Type: NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: TMC207-C202 Study Title: Open-Label, Randomized Study to Evaluate the Extended Early Bactericidal Activity of Multiple Oral Doses of TMC-207 Over a 7-Day Period on Sputum viable Counts, compared to Treatment with RMP or NIH over a 7-Day period Sample Size: 75 Arms: 5 Location in submission: Module 5.3.5.2	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Study C208 Stage 1 (Exploratory Stage) Indication: Patients with Sputum-Smear Positive MDR-TB Infection Pivotal Study #2: Study C208 Stage 2 (Proof-of-Efficacy Stage) Indication: Patients with Sputum-Smear Positive MDR-TB Infection	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			According to the Special Protocol Agreement, the efficacy studies in the submission appear to be acceptable.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		Orphan Drug Designation
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				No data yet.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The Medical Officer has not identified any potential review issues that need to be communicated to the Applicant in the 74-day letter.

The Consulting Reviewer from the Office of Scientific Investigations (OSI), Dr. Kassa Ayalew, requested site-specific individual subject data listings for a number of identified investigators. The requested information includes key information regarding study sites (listing for each subject/number screened, subject listing for randomization, subject listing of drop-outs and reason for dropping out, etc.).

Ariel R. Porcalla, MD, MPH	August 27, 2012
Reviewing Medical Officer	Date
Eileen Navarro Almario, MD	August 27, 2012
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARIEL R PORCALLA

09/05/2012

EILEEN E NAVARRO ALMARIO

09/09/2012