CENTER FOR DRUG EVALUATION AND RESEARCH

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	18 December. 2012
From	Eileen Navarro, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 204384 (N 000) Original; IND 69,600
Applicant	Jannsen Research and Development, LLC
Date of Submission	28 June 2012
PDUFA Goal Date	28 December 2012
GRMP Goal Date	21 December 2012
Proprietary / USAN modified names	Sirturo™/ Bedaquiline/ bedaquiline fumarate
Dosage forms / Strength	100 mg tablets
Proposed Indication(s)	in adults (≥ 18 years) as part of combination therapy of pulmonary tuberculosis due to multi-drug resistant *Mycobacterium tuberculosis*.
Recommended:	Approval

Summary:
Sirturo is the first member of a new class of diarylquinoline agents to be developed for drug resistant TB. The drug acts intracellularly by inhibiting mitochondrial ATP synthase. This activity is predicted to be selective for *M tuberculosis* over the mammalian host, by 20,000 fold. In vitro tests show clear activity, achieving synergy with other TB drugs in relevant animal models. The drug binds to protein and membranes avidly. It has a prolonged half life of 5 months, achieved as drug is redistributed into the central compartment from tissue stores. Preclinical studies indicate QT prolongation, phospholipidosis, and hepatic effects, in addition to amylase elevation and muscle toxicity.

In patients with newly diagnosed MDR-TB, the addition of bedaquiline to a 5-drug MDR-TB treatment regimen for 24 weeks (C208 Stage 2) resulted in shorter time to conversion and a higher proportion of culture conversion compared to placebo. At Week 24, the median time to culture conversion was 83 [95% CI 56, 97] days in the bedaquiline group and 125 [95% CI 98, 168] days in the placebo group (log rank test p value 0.0005), and culture conversion rates were 77.6% in the bedaquiline group and 58% in the placebo group (20% difference [4.5, 35.6] p=0.014, missing evaluated as failure). The FDA sensitivity analyses reveals a relative risk for earlier culture conversion from 1.98 to 2.44, p value <0.0001 – 0.0015. In this small study, treatment effect was more modest at week 72, RR1.65-1.86, p0.0290- 0.0036. Relapses occurred early with bedaquiline compared to placebo. As well, an excess of deaths (9/79, 11.4% for bedaquiline vs 2/82, 2.5% for placebo) in the bedaquiline treated group remains unexplained and needs additional study. Nonetheless, a similar finding of earlier sputum clearance with bedaquiline was confirmed in the FDA review of a second placebo controlled study of 8 week bedaquiline exposure compared to placebo (C208 Stage 1) and provides strong support of early sputum conversion with bedaquiline. The culture conversion rate (80%) and median time to sputum conversion (57 days) in a larger open label study that enrolled previously treated patients (Study 209) provide further estimates of bedaquiline's early efficacy.

Although culture conversion is known to correlate with durable cures in drug sensitive TB, the current submission cannot be considered for standard approval as the estimates of efficacy are limited by the small trial size, the interim analyses provided for review, reliance on newer liquid culture media and the new population studied (patients with drug-resistant tuberculosis).

The durability of this early endpoint surrogate will be confirmed with the submission of the data and complete study reports from Studies 208 and 209 and the confirmatory study (Study 210). An early assessment of durable cure in the current placebo controlled study up to 72 weeks, was provided by the sponsor , with death, relapses and missing data considered failures. FDA similarly performed a more conservative 72 week analysis of durable cure. In this analysis, only patients that culture converted at week 24 for relapses were assessed for relapse, defined as a single positive sputum post conversion and overruled conversion that occurred beyond week 24. The results indicate that benefit is sustained up to 72 weeks, or 48 weeks from end of bedaquiline treatment.

FDA analysis of Sustained Sputum Conversion at Week 72 (Study C208 Stage 2, MITT)

Categories of response at Week 72	Bedaquiline Treatment Group N=66	Placebo Treatment Group N=66
Sustained conversion: Culture conversion at Week 24 and no positive culture up to week 72	37	18
Failure: [failure to convert, relapse based on at least 1 positive sputum culture, discontinuation, death, missing data]	29	48
Culture conversion at Week 24 but relapsed at Week 72*	10	16
Failure to convert at Week 24 up to Week 72	14	28
Discontinued with all negative culture results	5 (1 death)	2
No data available	0	2

Sirturo is indicated in the treatment in adults (≥ 18 years) as part of combination therapy of pulmonary tuberculosis due to multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB). Sirturo is to be used only when effective therapy cannot otherwise be provided, as per current treatment guidelines for MDR-TB. The product insert is to carry a black box warning regarding the findings of an excess of deaths noted at the 120 week timepoint (9/79, 11.4% for bedaquiline vs 2/82, 2.5%% for placebo). A black box warning regarding the occurrence of QT prolongation is unrelated to the excess in mortality. Use of Sirturo with other QT prolonging drugs is likely to occur in patietns with limited treatment options, and measures to mitigate this risk are described in the label, including serial EKG monitoring and repletion of serum electrolytes. A potential for hepatic toxicity was also added to the warnings section, with a caution regarding its use in hepatically impaired patients. Although aminotransferase elevations were modest, and no case of DILI was observed in this small safety database, one patient had concurrent bilirubin elevation in the bedaquiline treated group, compared to none in the placebo group. Concern for serious hepatic injury remains based on the drug's mechanism of action and the need for prolonged treatment with concurrent other TB drugs with similar toxicities. Both Qt prolongation and hepatic monitoring are recommended in the label. The label serves as the sole regulatory mechanism for managing the known and potential risks of bedaquiline; coupled by a Medication Guide and adequate communication to prescribers. The incident cases of MDRTB in the US are expected to be less than a hundred, all expected to be cared for in consultation with, and through the support of the public health system.

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Cross Discipline Team Leader Review Template

1. Introduction

Bedaquiline is a diarylquinoline and acts through the inhibition of mycobacterial adenosine 5'-triphosphate (ATP) synthase. The diarylquinoline class is the first new drug class developed for the treatment of tuberculosis (TB) in 40 years. Although much progress has been made in the control of tuberculosis, the development of highly resistant tuberculosis threatens those gains. The need for new therapies is particularly dire where the resources to contain the disease are least available. Although tuberculosis infects a third of the world's population, bedaquiline is proposed for the treatment of a much smaller segment of the TB-infected; the indication sought is for the treatment of adults with pulmonary multidrug resistant tuberculosis (MDRTB) where first line agents have been shown to be ineffective. Although many drugs are used to treat MDRTB, the efficacy of the individual agents in the treatment of MDRTB, and their combined toxicities not been assessed through the regulatory process. The assessment of attributable effect is challenging when a new drug is used in a regimen whose individual components contribute to the measured efficacy and toxicity. In dug resistant tuberculosis this complication is magnified due to a heterogenous patient population, that includes patients with newly acquired infections to patients with chronic cavitary disease that is refractory to first line therapy. Treatment is prolonged, and long term follow-up is required to assess durable benefit. The pathogen is similarly complex - multiple subpopulations of organisms exist that vary in their metabolic activity drug susceptibility, site of localization, ability to incite immune reaction and thus differential disease manifestation.

The foundation of bacterial pathogenesis was established through Koch's postulate, and thus, the finding of bacteria in sputum smear, and their elimination with successful therapy has guided discovery and development of new drugs. The utility of sputum culture conversion from positive to negative cultures in solid agar served as basis for approval of first line agents when followed by assessment of durable cure after 24 month followup. Recent TB drugs have been approved on the basis of 6 month cure off treatment as a surrogate for durable cure (non relapse) at 24 months [1,2], The utility of sputum culture conversion at 2 months as a surrogate for cure has been previously discussed in FDA-sponsored public meetings[2, 3]. Early sputum conversion is shown to predict durable cure in drug sensitive TB, but there is less experience regarding this correlation in MDRTB. Data from multiple meta-analyses since conducted[4,5] and the confirming study for this NDA can inform the endpoint's utility in this subpopulation. For this NDA, the time to sputum conversion, rather than the proportion of patients that achieve early conversion, is the proposed surrogate endpoint. The accelerated approval was based on an interim analysis of study 208 (conducted when all subjects reached at least 72 weeks post randomization or discontinued prior) and an interim analysis of study 209 (conducted when all subjects reached at least 24 weeks post randomized or discontinued prior). The completed study results from both Study 208 and Study 209 and the confirmatory study will be helpful in understanding the utility of the surrogate endpoint. Complete efficacy data for the final 120 week endpoint were presented by the applicant at the open public Advisory Committee meeting and submitted to the IND, but have not been submitted to the

[1] 1998 approval of Rifapentine
[2] June 3, 2009 Meeting of the Anti-Infective Drugs Advisory Committee on Development of Drugs for MDRTB, information available at http://www fda.gov/ForConsumers/ConsumerUpdates/ucm126290 htm
[3] 21 CFR 314.500 Subpart H: Accelerated Approval
[4] Falson D et al Resistance to fluoroquinolone and second line injectable drugs: impact on MDRTB outcomes ERJnExpress October 25, 2012 1347-2012
[5] Brust B et al PLOS 2011.

NDA at the time of this CDTL review. The confirmatory study, assessed under special protocol assessment (SPA) provisions, is a Phase 3, randomized, placebo-controlled clinical trial to assess durable culture conversion for bedaquiline compared to background regimen alone, inclusive of failure to sputum convert, relapse, death and discontinuation at least 6 months after all MDR-TB treatment is completed.

This CDTL review presents the clinical evidence of safety and effectiveness, informed by relevant findings from the preclinical toxicology, pharmacokinetics and mechanism of action of bedaquiline as described in the individual discipline reviews, complemented by advice of consulting cardiorenal, hepatic and risk analysis experts at CDER. Based upon the integration of this data, and pending a successful response to the manufacturing issues pending before the Office of Compliance, I recommend labeling bedaquiline as part of combination therapy that includes at least three other active drugs for MDRTB, in informed patients with limited treatment options treated through TB programs adequate to the task of responsible stewardship and risk management.

2. Background

Bedaquiline interferes with energy production in cells, by inhibiting the proton pump of mycobacterial ATP-synthase. There is no prior experience that could inform the observed clinical activity of bedaquiline; in the limited trail experience in the NDA and a greater emphasis on the preclinical aspects of the program guided the final thinking. The drug acts by binding to the enzyme subunit responsible for proton (H^+ or Na^{++}) flow from the intercristae region in mitochondria into the bacterial cytoplasm, respectively. this activity is felt to be more specific for *M tuberculosis* than human cells because in vitro tests show a selectivity for mycobacterial ATP synthase relative to eukaryotic mitochondria. Whether effectiveness in bacterial killing continues to exceed toxicity to the mammalian host, and in which patients, will be borne out in expanded human experience.

This NDA is submitted under 21 CFR 314.500 (Subpart H). based on early evidence that bedaquiline affords an advantage over existing therapy on the surrogate endpoint of time to sputum culture conversion up to week 24. The finding of early sputum clearance with bedaquiline was predicted from a study that looked at sputum colony counts following a very short 7 day exposure to bedaquiline alone (EBA Study 202). Although reduction in sputum counts was delayed with bedaquiline compared to INH and rifampin, bedaquiline is intended for infections caused by INH and rifampin resistant strains. Whether the delay in bedaquiline effect in this study is due its pharmacokinetic limitations (the study did not use a loading dose) or because its mechanism of action results in delayed bacterial kill is unclear at this time.

Two separate parallel stages of a phase 2 placebo controlled study (Study 208) provide clear evidence of Sirturo^{TM}'s early benefit in MDRTB. A larger noncomparative open label study provides similar findings, in treatment-experienced patients with more resistant organisms and less treatment options (Study 209), simulating the population where the risk-benefit may be more favorable for bedaquiline use. Although Study 209 was less intensively monitored, it was conducted in experienced centers in continental Europe and South America. This study showed similar early sputum conversion but a greater than four fold increase was seen in follow-on isolates from patients that failed therapy. Bedaquiline should be used when 3 other drugs are shown active, if its benefits are to be realized. In vitro, and in animal models bedaquiline is synergistic with moxifloxacin and pyrazinamide. Whether more resistant isolates can continue to be treated and with which drugs needs further study. The finding of successful conversion in 20 of 36 patients with TB isolates resistant to INH, rifampin, qluoroquinolones and aminoglycosides was helpful, however, as this study has not completed, durability of that effect is still uncertain.

Nonetheless, in the placebo controlled studies, an early time to culture conversion data was consistently observed. The follow up data extends beyond the primary endpoint up to 48 weeks (72 weeks) and provides limited evidence of the sustained benefit of early sputum conversion seen at week 24. Paradoxically, an unexplained mortality excess was seen in this study. Ascertaining cause of death and the methods employed in that analysis, in the absence of limited autopsy data and incomplete laboratory testing was challenging. Given the incomplete information, the observed numerical difference served as the dominating factor in planning risk management, monitoring requirements, and the final product label. FDA is unable to conclude that this was a finding due to chance alone and more experience will be needed to determine whether such a risk continues to be seen with bedaquiline and alters the risk benefit associated with its use.
Bedaquiline affects bonding to a range of receptors (hERG channel, histamine2 receptors, sodium channels and dopamine transporters and its action on these targets affects its safety profile. The preclinical signals of concern include QT prolongation, stomach findings, liver effects, pancreatitis, phospholipidosis and muscular toxicity. Current estimates of these events will likely change with greater experience with the product. The potential for energy depletion in mitochondria and the preclinical target organs (liver muscle, pancreas) led to investigation of the clinical database for evidence that the product could act as a mitochondrial toxin but no clear evidence of such was found in the small database. The remaining uncertainties will need systematic assessment in future studies. Based on the preclinical signal for cardiac toxicity, electrophysiologic studies, the QT prolongation observed in clinical trials, and upon labeling advice from the CardioRenal Thorough QT team and Dr. Norman Stockbridge, provisions for ECG monitoring are included in the label. Labeling advice from the clinicians in CardioRenal was to exclude QT prolongation in the box label and to exclude any cardiac contraindications for use. Given the limitations of the size of the database, the final product label retains QT prolongation in the box warning. There was no observed relationship between cardiac toxicity and the excess mortality observed in the pivotal trial. Risk assessment for relapse and death in patients on concurrent antibiotics for TB, antiretroviral therapies and in patients with other co-morbidities was not fully assessed in the NDA given the limited number of exposures.

3. CMC/Device

Summary
The reader is referred to Dr. Li Qin's review of the drug substance and methods validation, Dr. Celia Cruz's review of the drug product, method validation, master batch and labeling reviews for details. The CMC reviews conclude that the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. A 384 was issued following inspection of the commercial manufacturer (b) (4). The OC had not completed its review of the response to the 384 issues at the time of this review.

General CMC
Sirturo™ (bedaquiline) tablet, 100 mg, is an uncoated immediate release tablet for oral administration. The tablet contains 120.89 mg of the fumarate salt, equivalent to 100 mg of bedaquiline free base. The drug substance is an almost white (b) (4) powder that is insoluble in water. It is photosensitive, although the finished product is not. The tablets are available in polyethylene bottles containing 188 tablets sufficient for the 24 week dosing regimen. The product is labeled for directly observed therapy with instructions to protect from light by storing in the original container. Stability tests for the finished tablet product support a 24 months shelf life for all climactic zones under the approved storage conditions of (b) (4) 25ºC ((b) (4) 77ºF); with excursions permitted to 15-30 ºC (59-86 ºF). The stability data also

supports an alternative label of not to store above 30 ºC, as per WHO guidelines for products used in Zone IV countries with supporting data. The long term (12 month) storage condition for stability is 30 ºC/ 75% relative humidity. A BE-waiver was granted based on in vitro dissolution testing.

Formulation Development
During the course of development several drug product formulations were investigated in phase 1:

- aqueous oral solutions of different strengths (F3 and F4) were studied in the initial clinical studies
- immediate release oral solid dosage forms (capsule F6 and tablet F1) were developed and compared to solution F4 in a relative bioavailability study (c108 in Table below); leading to the selection of tablet F1 for further clinical investigation.
- a film-coated tablet of the same strength (G1) found to have lower bioavailability than F001 (study C111) , resulting in the decisions to commercialize formulation F001.

F001 also contains the inactive ingredients lactose monohydrate, maize starch, hypromellose, polysorbate, purified water, cellulose, croscarmellose sodium, colloidal anhydrous silica, and magnesium stearate.

Table 1 Phase 1 exposures to Developmental Formulations of SIRTURO

Phase 1 Study	N	Formulation, dose level
CDE-101(Great Britain) Single dose PK	54	F3-10, 30, 100, 300, 450, 700 mg F4-300 mg
CDE-C102 (Great Britain) Multi dose PK	27	F3 and F4 50, 150, and 400 mg
CDE 103 (Great Britain) Rifampin interaction	16	F4 300 mg F4 600 mg
C104 (Great Britain) INH/PZA interaction	24	F4 400 mg
C108 (Netherlands) Comparison of capsule/tablet to oral solution	12	F4 100 mg F6 100 mg /F1 100 mg
C109 (Belgium) Ketoconazole interaction	16	F4 400 mg
C112 (Germany) Hepatic Impairment	16	F1 400 mg
C111 (USA) Comparison of film coated vs Ph II tablet	28	F1 100 mg G1 100 mg (b) (4)
C110 (USA) LPV/rtv Interaction	16	F1 400 mg
C117 (South Africa) LPV/rtv Interaction	16	F1 400 mg
TBC1003 Thorough QT Study	44	F1 800 mg

Modified from: Bedaquiline NDA

Manufacturing
The finished product is manufactured by Kemwell Pvt. Ltd., Bangalore, India. (b) (4) manufactured the phase II product. The (b) (4) site is the intermediate step up phase III and commercial manufacturing site. Following manufacturing site inspection at (b) (4), a 384 was issued. At the time of this CDTL review, the Office of Compliance was reviewing the applicant's response to the 384. The CMC defers to the Office of Compliance for inspection issues and overall site recommendations and do not recommend approval until that determination is made. They do not recommend any postmarketing studies nor any risk management steps.

Other notable issues (resolved or outstanding)
The applicant intends to add an alternate commercial manufacturer in a future supplement.

4. Nonclinical Pharmacology/Toxicology

Summary

The reader is referred to Dr. Owen Mc Master's Clinical pharmacology review. Dr. Mc Master finds the nonclinical toxicology program comprehensive, inclusive of in vitro and in vivo short and long term studies using mice, rats, dogs, rabbits and guinea pig. He finds preclinical signals of QT prolongation, and phospholipidosis, the latter in the target tissues of the monocyte macrophage system, liver, pancreas, heart, and muscle, but not brain. Carcinogenicity studies were conducted but not completed for this NDA; mutagenic and clastogenic signals were negative. Bedaquiline was not genotoxic, had no adverse effects on mating, or fertility and was not teratogenic. Assessment of the implications of positive nonclinical study findings for clinical use were based on a comparison of the preclinical exposures to the clinical exposures achieved with the proposed human dose (highest exposures after 8 weeks of treatment with mean AUC(0-24h) 22 µg*h/mL for bedaquiline and 6 µg*h/mL for the M2 metabolite M2, whereas mean Cmax levels were at a high of 3.3 µg/mL during Week 2 and steady state plasma levels were about 0.9 µg/mL at Week 8). The findings selected for presentation below are deemed to be most relevant for clinical safety.

General Pharmacology:
Bedaquiline interferes with energy production in cells, by inhibiting the proton pump of mycobacterial ATP-synthase. It does so by binding to the enzyme subunit responsible for proton (H^+ or Na^{++}) flow from the periplasmic space in bacteria to the mitochondrial matrix and the bacterial cytoplasm (Figure1, modified from[6]). In vitro tests show a selectivity of drug for mycobacterial ATP synthase relative to eukaryotic mitochondria of about > 20,000-fold; . Bedaquiline inhibits binding to histamine2 receptors (by 87%), sodium channels (by 71%) and dopamine transporters (by 54%) at a concentration of 10 µM (5.6 µg/mL); evidence of off-target effects mediated by these receptors were sought in the clinical safety review.

Figure 1 Site of action of drugs that impair mitochondrial function, in comparison to bedaquiline.

[6] Drug-induced liver injury through mitochondrial dysfunction: mechanisms and detection during preclinical safety studies by Labbea,G et al Drug Safety Evaluation, Fundamental & Clinical Pharmacology 22 (2008) 335-53

Source: Modified from Labbea et al, Fundamentals of Pharmacology

In test species, bedaquiline bioavailability was between 36 and 79%, and achieved maximum plasma concentrations between 0.5 and 8 hours post dose. Bedaquiline is metabolized by (cytochrome P450 (CYP 3A4) to its major metabolite, M2, via *N*-demethylation. Tissues with the highest accumulation of drug were the adrenal gland, lung, spleen, liver, lymph nodes and thymus. Tissue concentrations of the metabolite M2 were higher than those of the parent compound; in contrast, M2 levels in humans are several fold lower than see in preclinical species. In bedaquiline-treated dams which had recently given birth, levels of bedaquiline and its metabolite M2 in milk were 4- to 12 times higher than plasma levels.

As a cationic, amphiphilic drugs, bedaquiline induced phospholipidosis in cells of the monocytic phagocytic system (MPS) in the lymph nodes, spleen, lungs, liver, stomach, skeletal muscle, pancreas and/or uterus. The intracytoplasmic lamellar inclusions in the affected tissues reflect phospholipid and drug accumulation in cells seen even at the lowest doses.

Cardiac Findings
Electrophysiology, Histology:
Bedaquiline and its M2 metabolite inhibit IKr in hERG transfected kidney cells at IC^{50} values of 0.2 µg/mL for both compounds. In a six-month dog study, increases of +12 to +16 % in the

QTc interval developed after two months of dosing at 40 mg/kg/day, corresponding to exposures of (AUC (0-24h) ~150 mcg*h/mL). Prolongation was not observed after dose reduction to 20 mg/kg/day (AUC (0-24h) ~130 mcg*h/mL) or with intermittent dosing of 140 mg/kg, biweekly for 6 mo. At 40 mg/kg/day, dogs were in poor condition with pronounced decreases in body weight, vomiting, decreased activity, salivation, as this dose was above the maximum tolerated dose for this specie. Troponin was increased in the 6 mo dog study at all doses tested above (20/40 mg/kg/day and 140 mg/kg twice weekly) except at the lowest dose of 10 mg/kg/day. Histopathologic evaluation revealed cardiomyocyte degeneration at 20/40mg /kg/day. No ECG changes & cardiac lesions developed w/ lower doses of 10 mg/kg/day (AUC(0-24h) 71 mcg*h/mL, corresponding to 3x the clinical exposure, and in a 9 mo dog at 18 mg/kg/day (AUC(0-24h) 154 mcg*h/mL).

Use with Moxifloxacin
In a mechanistic study (#1408-008), dogs dosed with 100 mg/kg bedaquiline for six days showed no increases in QT interval. When 100 mg/kg moxifloxacin was started on Day 7, the QT change was +17 % compared to control and moxifloxacin +bedaquiline together resulted in a modest increment of +20 % compared to control. Exposures (AUC (0-24h)) at 100 mg/kg in this experiment were much higher than expected clinical exposures.

Hepatic Findings
Centrilobular hypertrophy was seen in mice, rats, dogs, accompanied by aminotransferease elevation (AST,ALT) with no cholestasis (N bili), increased liver weight, and prominence of the endoplasmic reticulum. Hepatic micro or macrovesicular steatosis was not described. Single cell necrosis was seen in mice. Rodents experienced increased AST levels in a 13 week study at doses one-half the human bedaquiline exposure, attributed increased M2 levels, which accumulate in this specie to levels that exceed those in man. The NOAEL in rats was 5mg/kg/day 6 mo achieving exposure similar to 8 week human exposure (TMC AUC 22/M2 AUC 6)]. The NOAEL in dogs was 18 mg/kg 9 months (8 x higher than human exposures at 8 week), the safety margin higher for 24 wks human exposures.

Phospholipidosis
Lamellar inclusions occurred in all species and at all doses tested, including single doses. Phospholipidosis was reversible upon cessation of dosing and was most prominent in cells of the monocytic phagocytic system (MPS), in lymph nodes, spleen, lungs, liver, stomach, skeletal muscle, pancreas, and uterus, but not in the brain. The metabolites M2 and M3 induced phospholipidosis to a greater degree than the parent compound. In addition to the hepatic findings described above, the target organs demonstrated the following changes:
Pancreas: Focal to multifocal pancreatitis with acinar cell atrophy was described in mice and dogs dosed at40 mg/kg/day, for 13 wks.
Skeletal muscle: Degenerative and necrotic lesions in muscles developed in mice, dogs, and rats dosed at24 mg/kg, 13 wks. Reversible in rats.
Stomach: Necrosis of the fundic mucosa was seen in dogs at 40 and 160 mg/kg/day at 13 wks, (AUC(0to24h)) 94 μg*h/mL, about 4 times clinical exposure, with recovery at 20/40 weeks).

Carcinogenicity
Results of a two-year oral carcinogenicity study will be available after the due date for this NDA,

5. Clinical Pharmacology/Biopharmaceutics

Summary

The Clinical Pharmacology Review team consisted of Drs. Dakshina M. Chilukuri, Zhixia (Grace) Yan, Seong Jang, Fang Li, Justin Earp, Kevin Krudys, Kimberly Bergman, Philip Colangelo and Yaning Wang and the reviewer is referred to their reviews for additional detail. Information derived directly form the submission is identified in the text. The clinical pharmacology team reviewed 16 trials that evaluated the PK, drug interactions, and PK/PD of bedaquiline and find that the clinical pharmacology information provided by the applicant in support of the accelerated application is acceptable and supports the use of the proposed dose regimen for bedaquiline for the treatment of MDR-TB. Bedaquiline has a long half life of 4-5 months; this is attributed to the slow release of the intracellularly accumulated drug from its tissue sites. The drug is metabolized through Cyp 3A4 to M2 and M3 metabolites, of which M2 has activity. No relationship was found between serum concentrations and efficacy nor safety, save for a positive slope for the metabolite M2 and the degree of QT prolongation. Bedaquiline levels are reduced by strong CYP3A4 inducers; the drug is unlikely to inhibit or induce CYP isoenzymes. Clearance is increased in black patients, with no decrement in successful treatment. Its interaction profile supports caution in coadministration with strong CYP3A4 inhibitors for longer than 14 days. Use with strong CYP3A4 inducers is to be avoided. Its use is compatible with anti-TB mediations ethambutol, kanamycin, PZA, ofloxacin and cycloserine and the antiretrovirals Kaletra and nevirapine.

Pharmacokinetic properties of bedaquiline:

The team found that bedaquiline exhibited dose-proportional PK in the dose range of 10 to 700 mg., and that food increases the systemic exposure of bedaquiline 2-fold.

Table 2 Pharmacokinetic properties of bedaquiline

PK Property	PK Parameter
Dose proportionality	PK dose-proportional for doses 10 – 700 mg
Tmax (median)	~5 hr
Food Effect	High fat meal increased Cmax and AUC by 2-fold.
Distribution	~164 L
Protein Binding,	> 99%
Metabolism Pathways	Metabolized to M2 and M3 by CYP3A4.
Excretion	Fecal excretion is the major route of elimination
T1/2 term ~	4-5 months

Source: FDA ClinPharm review

Metabolism

Bedaquiline is oxidatively metabolized to M2 which is 4- to 6-fold less active against *M. tuberculosis* than the parent compound. Exposure to the parent compound is higher (2.03 fold higher bioavailability) in healthy subjects relative to patients. Bedaquiline is highly protein bound to human plasma and distributes extensively into the tissues.

Excretion is primarily through the feces, there is negligible renal excretion of unchanged drug. Renal /Hepatic Impairment: No dose modification is required in patients with mild or moderate renal impairment. The sponsor likewise recommends use with caution in severe renal impairment and in renal failure. The clinical pharmacology team is recommending that the confirmatory trial (C210) evaluate the pharmacokinetics of bedaquiline in a cohort of 6-8 patients with severe renal impairment. No dose adjustment is needed in patients with mild or moderate hepatic impairment.

Intrinsic factors:
No clinically relevant difference in exposure between men and women wasobserved. Enhanced clearance resulted in 34% lower systemic exposure in black patients than in patients from other race categories. No clear relationship between exposure to bedaquiline and response has been observed in clinical trials of MDR-TB and response as black patients with MDR-TB were successfully treated relative to other race categories in the clinical trials.

Drug-drug interactions
Bedaquiline had no significant effect on the exposure of the following background regimen drugs for TB: ethambutol, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone. However, the exposure of bedaquiline is reduced during coadministration with strong CYP3A4 inducers such as rifampin and concurrent use is not recommended. Bedaquiline is unlikely to induce or inhibit CYP isoenzymes. Coadministration with CYP3A4 inhibitors may increase exposure, as observed in drug-drug interaction trials with ketoconazole and lopinavir combined with low-dose ritonavir (LPV/rtv). Coadministration with moderate or strong CYP3A4 inhibitors for more than 2 weeks is not recommended.
These Drug-Drug Interactions are described in the label as reviewed by the Clinical Pharmacology team and reproduced below:

Ketoconazole
Co-administration of multiple-dose bedaquiline (400 mg once daily for 14 days) and multiple-dose ketoconazole (once daily 400 mg) for 4 days in healthy subjects increased the AUC_{24h}, C_{max} and C_{min} of bedaquiline by 22% [90%CI (12; 32)], 9% [90%CI (-2, 21)] and 33% [90% CI (24, 43)] respectively. Co-administration of bedaquiline and ketoconazole or other moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided unless the benefit outweighs the risk.

Rifampin
In a drug interaction study of single-dose 300 mg bedaquiline and multiple-dose rifampin (once daily 600 mg for 21 days) in healthy subjects, the exposure (AUC) to bedaquiline was reduced by 52% [90% CI (-57; -46)]. The combination of bedaquiline and rifamycins (rifampin, rifapentine and rifabutin) or other strong CYP3A4 inducers used systemically should be avoided.

Antimicrobial agents
The combination of multiple-dose 400 mg bedaquiline with multiple-dose isoniazid/pyrazinamide (300/2000 mg once daily) in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during combination with Sirturo™.
In a placebo-controlled study in patients with MDR-TB, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

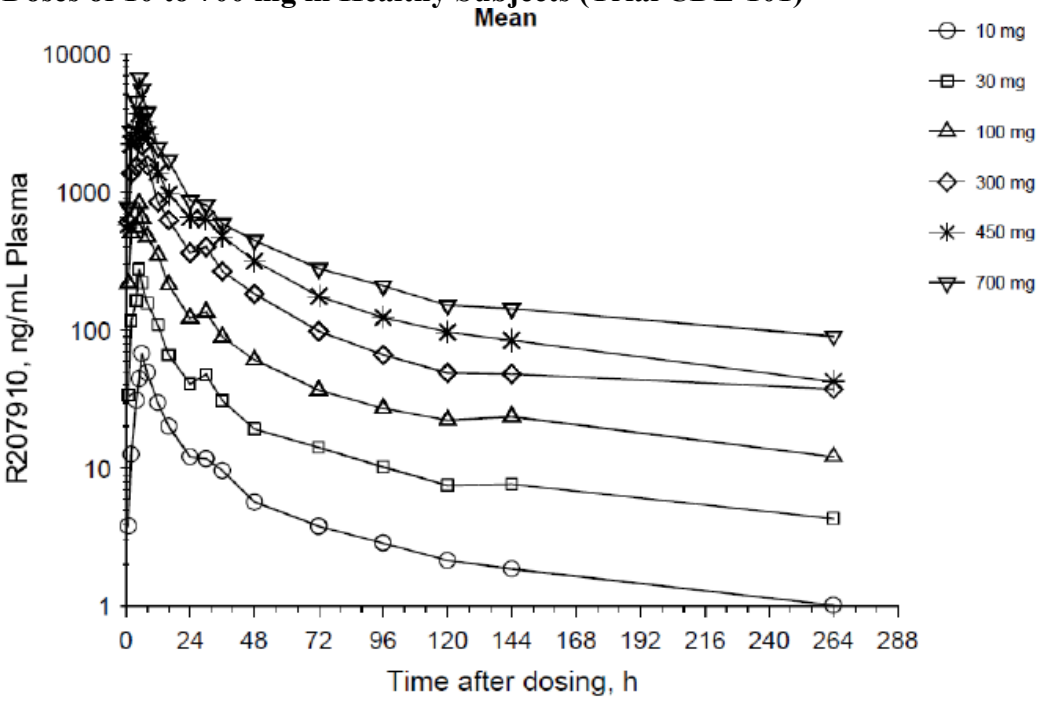
Kaletra lopinavir/ritonavir (400/100 mg
In a drug interaction study in healthy volunteers of single-dose bedaquiline (400 mg) and multiple-dose Kaletra (400/100 mg twice daily for 24 days), exposure to bedaquiline was increased by 22% [90% CI (11; 34)] while the mean C_{max} remained comparable.

Co-administration of multiple-dose nevirapine in HIV infected patients for 4 weeks (200 mg bid) with single-dose bedaquiline (400 mg)_did not result in clinically relevant changes in the exposure to bedaquiline.

Dose Selection

Target concentration for optimal dosing in humans was based on approximating the optimal ratio of M2 to bedaquiline. Nonclinical studies in mice showed minimal toxicity at the equivalent of bedaquiline plasma concentrations of approximately 600 ng/mL (i.e., 2 x 300 ng/mL, or an AUC24h of 14.4 µg.h/mL), assuming no significant contribution to activity by M2 concentrations, which are low in humans (i.e., the average M2 concentration in humans is approximately 20% of the average bedaquiline concentration after 2 weeks of q.d. dosing.) Following single doses of bedaquiline, tmax was achieved at 5-6H, but rapidly fell to below the target concentration.

Figure 3 Mean Plasma Concentration-Time Profiles of Bedaquiline After Administration as Single Doses of 10 to 700 mg in Healthy Subjects (Trial CDE-101)



N = 6 in each treatment group, R207901 = TMC207

Source: Bedaquiline NDA

The multiple dose pharmacokinetics of 50, 150 and 400 mg of bedaquiline is shown in the Table below. At 14 days, neither the 50 or 150 mg daily dose achieved a mean C24 that was at the initially proposed target of 600 ng/ml, compared to 400 mg qd. This data suggests that a loading dose is necessary if bedaquiline is to achieve early activity against tuberculosis.

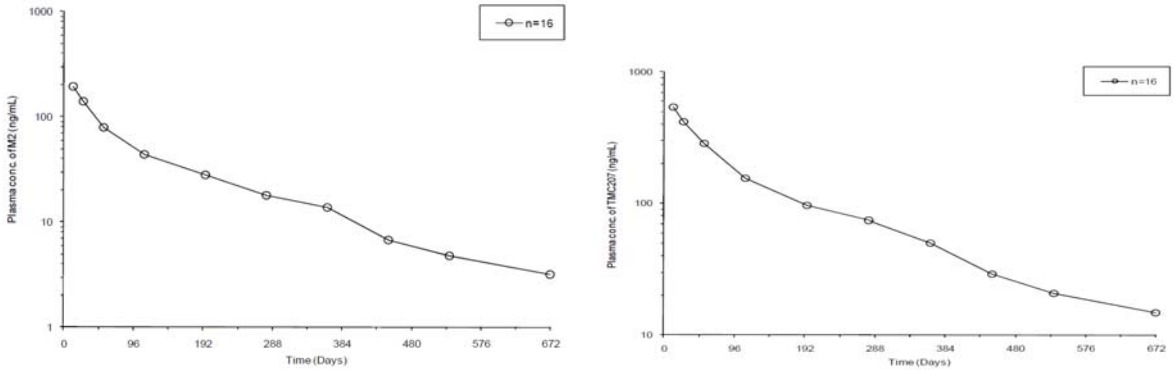
Table 3 Pharmacokinetics of Bedaquiline in Plasma After Administration as Multiple Doses of 50 to 400 mg q.d. in Healthy Subjects (Trial CDE-102)

Parameter	Mean ± SD; t_{max}: Median (Range)		
	TMC207 50 mg q.d.	TMC207 150 mg q.d.	TMC207 400 mg q.d.
Day 1			
N	6	6	6
t_{max}, h	5.0 (5.0 - 6.0)	5.0 (5.0 - 5.0)	4.0 (2.0 - 5.0)
C_{max}, ng/mL	428 ± 112	1132 ± 401	3005 ± 493
C_{24h}, ng/mL	63.4 ± 10.0	180 ± 53.0	512 ± 114
AUC_{24h}, ng.h/mL	3989 ± 830	9922 ± 3199	27206 ± 5361
Day 14			
N	6	5	6
t_{max}, h	5.0 (5.0 - 6.0)	5.0 (5.0 - 5.1)	5.0 (3.0 - 6.0)
C_{max}, ng/mL	590 ± 116	1972 ± 559	4298 ± 1315
C_{24h}, ng/mL	187 ± 44.0	604 ± 147	1280 ± 309
AUC_{24h}, ng.h/mL	7914 ± 2009	24265 ± 5670	51525 ± 10123
CL/F, L/h	6.66 ± 1.66	6.45 ± 1.45	8.03 ± 1.68
$t_{1/2}$, h [a]	169 ± 77	167 ± 48	173 ± 35

N = maximum number of subjects with data.
[a] Elimination $t_{1/2}$ as estimated over the sampling period, which does not represent the true elimination $t_{1/2,term}$.
Source: Bedaquiline NDA

Bedaquiline has a short tissue distribution phase followed by a very long terminal elimination phase (T1/2 = 4-5 months) representing the release of the drug from the tissue compartments, as the drug slowly equilibrates from tissue back into the plasma central compartment.

Figure 5 Half-life of the parent drug bedaquiline (Left) and its major metabolite M2 (Right) over time (in days)



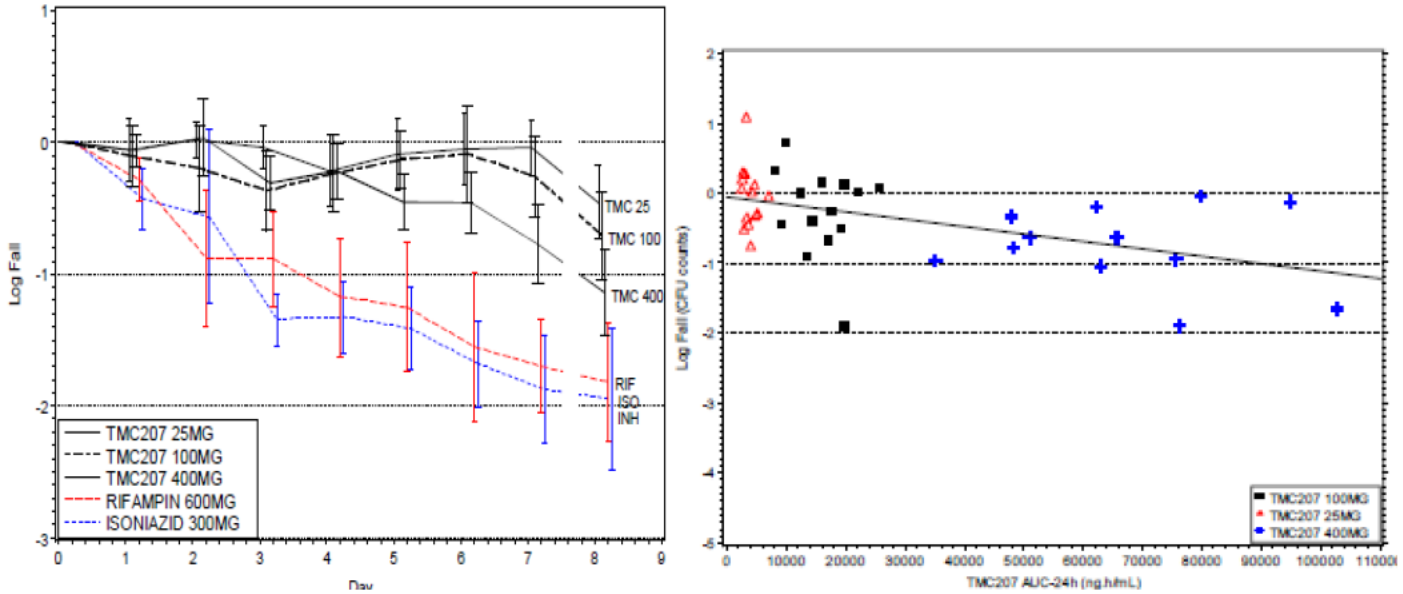
These figures were presented at the Advisory committee meeting , but not in the clinical Pharamcology review.
Source: Bedaquiline NDA

The clinical pharmacology review summarizes the dosing targets that guided the proposed dose of 400 mg daily for two weeks followed by 200 mg three times a week. The following considerations guided this selection:

1) Nonclinical data suggested that bedaquiline dosing should be in the range of linear pharmacokinetics to avoid over-proportional tissue distribution and potential toxicity.
2) Lower tissue distribution of bedaquiline and M2 during intermittent dosing versus daily dosing may account for the increased tolerability of intermittent dosing
3) The loading dose was selected based on the results of the EBA study 202 , a 7 day dose ranging study looking at early bactericidal activity of monotherapy with bedaquiline in drug sensitive TB. In this study, bactericidal response in the highest dose strata bedaquiline 400 mg group was apparent from Day 4 onwards. This

difference was a statistically significant from baseline on Days 3, 5, 6 and 7; whereas lower doses of bedaquiline were no different from baseline as shown below:

Figure 6 Change in log10 Sputum CFU counts Over time (95% CI) and poor correlation w/plasma AUC



Source: Bedaquiline NDA

Population pk modeling was performed to keep total exposure below the safety threshold (bedaquiline and M2 AUC 24 <100ug-hr/mL, based on nonclinical toxicology) below which there was no relevant target organ toxicity in nonclinical studies yet maintaining doses sufficient to achieve antimycobacterial activity. As well, the total simulated mean exposure during the intermittent dosing phase was not predicted to exceed the no observed adverse effect level (NOAEL) exposure after 6 months of daily dosing in the dog (AUC24h of 37.0 and 39.6. µg.h/mL in males and females, respectively.

These considerations led to the dosing recommendations of a flat dose of 400 mg daily for 14 days followed by 200 mg thrice weekly for a total of 24 weeks. At this dose, the safety margin for the exposures achieved from the phase 2 efficacy studies is summarized in the submission.

Table 4 Comparison of Plasma Exposure (AUC) to bedaquiline and M2 in Nonclinical Studies and MDRTB infected Patients Following 8 or 24 Weeks of Treatment at the Recommended Dose

Clinical Trial/ Nonclinical Study	Dose	BEDAQUILINE AUC_{24h},	M2 AUC_{24h}, µg h/mL [a]	Safety Margin BEDAQUI	Safety Margin M2 [b]

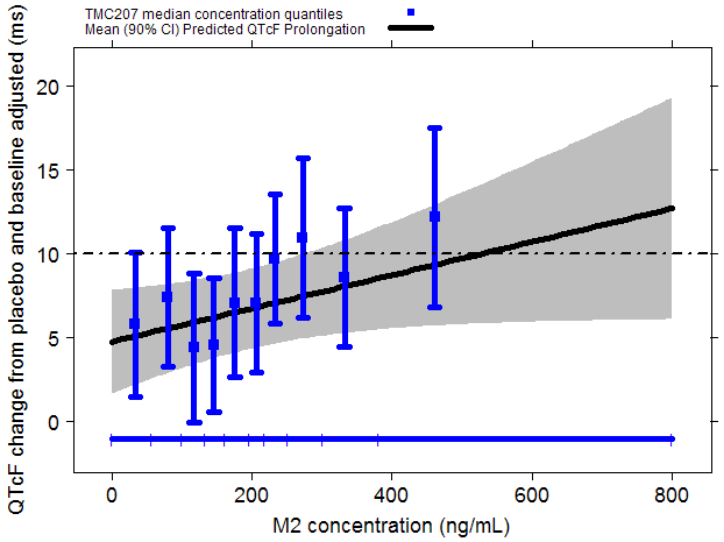
Humans (C208, Stage 1 and 2)	400 mg q.d. (2 weeks) followed by 200 mg t.i.w. (6 or 22 weeks) [c]	22 [d] - 14 [e]	6 [d] - 3.6 [e]	-	-
9-month dog	2 mg/kg/day	25	12	1 - 2	2 - 3
6-month rat	5 mg/kg/day [f]	12	7	0.5 - 1	1 - 2
6-month rat	20 mg/kg twice weekly	31	11	1 - 2	2 - 3

[a] Value derived from AUC_{48h} in trial C208; mean of male and female data in dog and rat.
[b] Ratio of animal/human.
[c] 6 weeks in Stage 1, 22 weeks in Stage 2.
[d] Value derived from AUC_{48h} at end of BEDAQUILINE treatment in C208 Stage 1 (subjects treated for 8 weeks). [e] Value derived from AUC_{48h} at end of BEDAQUILINE treatment in C208 Stage 2 (subjects treated for 24 weeks). [f] Not strictly a NOAEL, but associated with only minimal changes of questionable relevance.
Source: Bedaquiline NDA

Plasma levels of bedaquiline did not correlate with efficacy in MDR-TB infected subjects. The intracellular activity of bedaquiline may account for the lack of a clear relationship between plasma concentrations and sputum conversion.

Thorough QT study or other QT assessment.
While assay sensitivity is claimed due to the positive finding of QT prolongation with moxifloxacin, the single-dose TQT trial was insufficient to characterize the potential of bedaquiline/M2 to prolong the QTc interval. No significant QTc prolongation was seen for the test drug bedaquiline as the maximum mean difference between bedaquiline and placebo was below 10 ms. However, the study was conducted with a single multiple of the target dose (single dose of 800 mg bedaquiline) and does not reflect concentrations when the drug is at steady state.. In the efficacy study Trial C208, a positive concentration-QTc relationship suggests that M2 concentrations are responsible for the clear QTc prolongation observed this study.

Figure 7. Correlation of plasma levels of the metabolite M2 with QT prolongation



Source: Dr. Kevin Krudys QT-IRT review

6. Clinical Microbiology

Summary:
Please see Dr. Lynette Berkey's review for additional detail. Bedaquiline belongs to the diarylquinolines class and causes cell death by inhibiting mycobacterial ATP synthase. Its activity is time, rather than concentration dependent and is synergistic with PZA. Activity against active and dormant bacilli is demonstrated in vitro and invivo in relevant models of TB infection. Although resistance is mediated by a mutation of the atpE operon, enhanced sfflux appears to cause the majority of the four fold shift in MIC observed in the clinical trials. Distribution of wild type and clinical isolates show an MIC 90 of 0.06; the lack of a correlation to clinical outcomes in the small database precludes definition of a susceptibility breakpoint. Susceptibility methods are not fully validated and QC data is provisional. In the course of labeling, additional perspective was provided by additional members of the Microbiology Review team.

Mechanism of Action
Bedaquiline is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *M. tuberculosis*.

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

Activity in vivo
Indifference in mycobacterial activity was demonstrated in vitro when bedaquiline was combined with rifampin, whereas synergy was demonstrated with pyrazinamide (see AC backgrounder and NDA submission). In the murine model, the bactericidal activity obtained after 2 months of therapy with rifampin ®+isoniazid (H)+ pyrazinamide (Z) was similar to 1 month of bedaquiline containing regimens (bedaquiline + H Z and bedaquiline + RZ). As well, 3-4 months of treatment with bedaquiline-containing regimens was as effective as 6 months standard regimen. When added to second line TB drugs Amikacin (A), pyrazinamide, moxifloxacin and ethionamide, bedaquiline accelerated and augmented the bactericidal activity of the regimen. Furthermore, in the murine model of chronic infection, bedaquiline appeared to augment the sterilizing activity of second line drug regimens based on reduced relapse rates 3 months after the end of 6 months of treatment with the following drug combinations:

Table 5 Sterilizing Activity of Bedaquiline in Combination With Second-line Drugs in the Established Infection Murine TB Model

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

Compared to the demonstrated relapse rates of the standard regimen of 2HRZ4HR, Dr. Berkeley concurs that bedaquiline MZ and bedaquiline AEMZ show potential in shortening treatment duration for resistant tuberculosis.

The data presented in the NDA regarding the activity of bedaquiline against dormant bacilli is presented below:

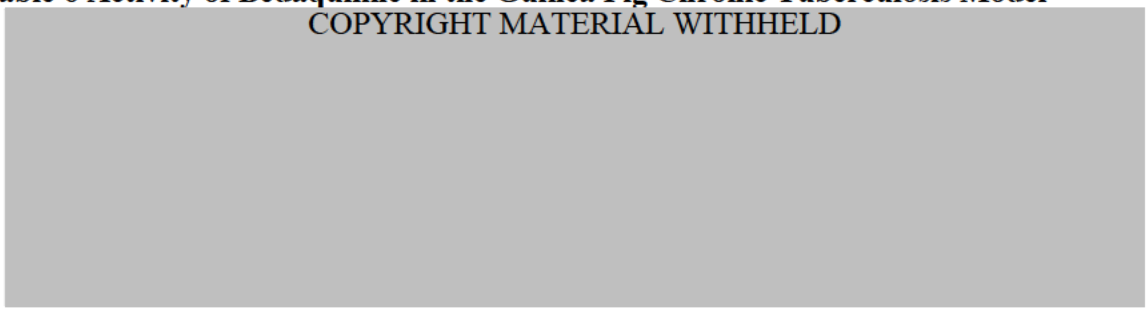
Invitro: A study was also conducted in wild type and laboratory strains of mtuberculosis driven to dormancy using oxygen deprivation to demonstrate that the drug is active against latent bacteria that are poorly metabolizing and had low ATP levels.

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

In vivo: Murine and guinea pig models for the study of dormant mycobacteria have been developed and show promise as predictors of drug activity in chronic human disease but need addition study to a confirm drug activity in persisters. The guinea pig model differs from other models in that it replicates certain histologic features of human infection not otherwise demonstrated in mice, such as necrosis, calcification and hypoxia. The lung lesions are established by aerosolization and differ from secondary lesions established by hematogenous dissemination (such as in the spleen).

The activity of bedaquiline was studied in this model of established tuberculosis infection, where 5-day treatment was initiated 30 days after infection and animals sacrificed 6 days after treatment completion. The table Dr. Berkeley reproduced from the original publication by Lenaertes[7] and others shows a dose related reduction in the lung mycobacterial burden compared to saline control. Reduction was also shown in the spleen but the results were less clearly dose related.

Table 6 Activity of Bedaquiline in the Guinea Pig Chronic Tuberculosis Model



Source Table: Lenaertes et al. 2007

Histopathologic assessment revealed that in animals treated with INH, Rifampin and pyrazinamide, as well as with bedaquiline, AFB were demonstrated only in the acellular necrotic rim of the pulmonary caseum (region between the central caseous lesion and the compressed foamy macrophage layer delineating the capsule), but not in the caseous lesion and raise the hypothesis that the acellular rim of a caseum may be the source of persisting bacilli that withstand drug treatment. No organisms were visible intracellularly within the

[7] Location of Persisting Mycobacteria in a Guinea Pig Model of Tuberculosis Revealed by R207910
Anne J. Lenaerts, Donald Hoff, Sahar Aly, Stefan Ehlers, Koen Andries, Luis Cantarero, Ian M. Orme, Randall J. Basaraba Antimicrob Agents Chemother. 2007 September; 51(9): 3338–3345. Published online 2007 May 21. doi: 10.1128/AAC.00276-07

capsule, and none were present within the normal perilesional parenchyma In the untreated guinea pigs, extracellular AFB were found within the central necrosis and intracellularly state throughout secondary lesions. However, activity against dormant bacilli was not specified in the label until clarity regarding the durable cure of bedaquiline is established in clinical trials. While relapse is shown to numerically favor bedaquiline in Trial 208 Stage 2, the finding of an excess of deaths and the observed early relapses require additional study.

Mechanisms of resistance

Mycobacterial resistance mechanisms that affect bedaquiline include modification of the atpE target gene. The following table (also listed as sponsor's Table 9), shows that baseline clinical isolates that contain the operon developed a fourfold shift in MIC postbaseline, further supporting the likelihood of overexpression of the efflux pump as a second putative mechanism of resistance. No cross resistance was found between bedaquiline and INH, RIF,

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

Subject CRF ID	Outcome (No Overruling[a] – All Available Data)[b]	MIC (REMA) µg/mL			MIC (Agar) µg/mL			Extent of Resistance at BL	*atp* Operon Variance in Coding Regions Between Strains (BL vs Post-BL)
		BL	Post-BL	F	BL	Post-BL	F		
C208 (Stage 1)									
208-3004	relapse	0.0313	0.0156 (W8)	0.5x	0.06	0.24 (W8)	4x	$MDR_{H\&R}$	no coding variation
C208 (Stage 2)									
208-4465	failure to convert	0.0156	0.25 (W24)	16x	0.06	0.24 (W24)	4x	Pre-XDR	no coding variation
C209									
209-0269	failure to convert	0.0625	0.25 (W24)	4x	0.06	0.48 (W24)	8x	Pre-XDR	no coding variation
209-0038	failure to convert	0.0625	0.25 (W24)	4x	0.06	> 0.48 (W24)	> 8x	Pre-XDR	no coding variation
209-0050	failure to convert	0.0313	0.50 (W24)	16x	0.06	0.48 (W24)	8x	Pre-XDR	no coding variation
209-0182	failure to convert	0.0625	0.25 (W24)	4x	0.06	> 0.48 (W24)	> 8x	XDR	no coding variation
209-0263	relapse	0.0313	0.25 (W24)	8x	0.06	0.48 (W24)	8x	XDR	no coding variation
209-0128	failure to convert	0.0625	0.50 (W24)	8x	0.06	> 0.48 (W24)	> 8x	XDR	no coding variation
209-0157	responder	0.0313	0.50 (W24)	16x	0.06	0.48 (W24)	8x	XDR	no coding variation
209-0267	failure to convert	0.0625	1 (W24)	16x	0.06	> 0.48 (W24)	> 8x	XDR	no coding variation

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

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

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

STREP, EMB, PZA, amikacin, or moxifloxacin.

Table 6 MIC shifts in PostBaseline Clinical Isolates Without the atpE Mutation

Spectrum of Activity

Bedaquiline has a narrow spectrum of activity and appears to be specific for Mycobacterium species. The inhibitory concentration for the parent drug bedaquiline for 50% and 90% of preclinical isolates (MIC50 and MIC90) of *M. tuberculosis* were 0.03 and 0.06 µg/mL, respectively, for both drug susceptible (DS-TB) and MDR-TB isolates. The activity of bedaquiline against laboratory isolates of *M. tuberculosis* is shown in the sponsor's Table below. The MIC distribution of clinical isolates is shown subsequently. Limited data was presented to assess in vitro activity against other relevant human mycobacterial pathogens.

Table 7 Bedaquiline MICs by *M. tuberculosis* Resistance Subtype

MTB Resistance Subtype	N	Bedaquiline MIC (µg/mL)			
		MIC Range	MIC_{50}	MIC_{90}	MIC_{95}
All	109	≤ 0.008 - 0.12	0.03	0.06	0.06
DS-TB	65	≤ 0.008 - 0.12	0.03	0.06	0.06
MDR-TB	44	≤ 0.008 - 0.12	0.03	0.06	0.06

Source: Bedaquiline NDA

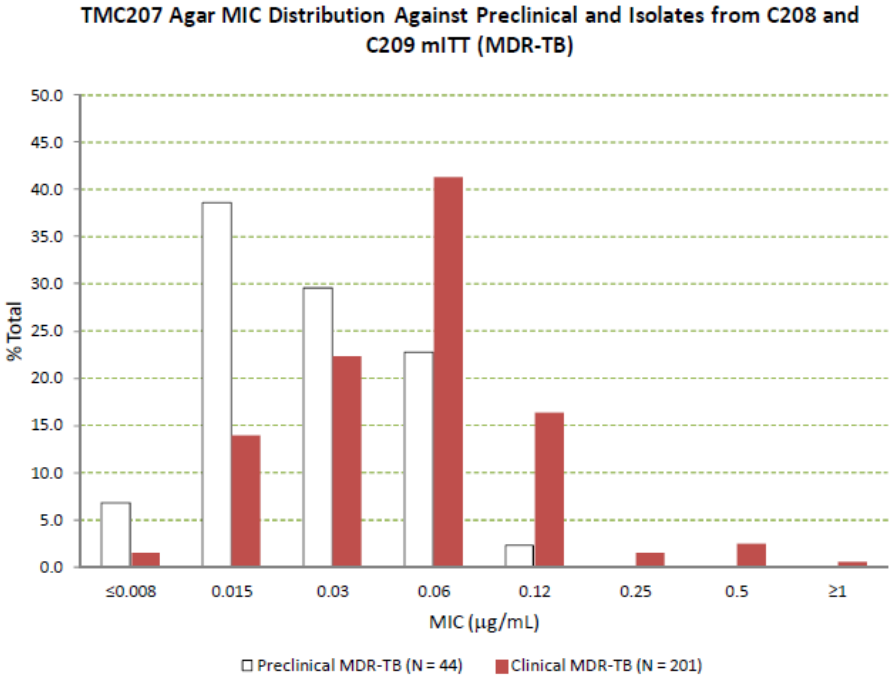
Susceptibility Testing and Interpretive Criteria

In the absence of defined critical concentrations for bedaquiline, the Applicant performed an agar dilution test, that proposes the tested concentrations where >=99% of isolates were visibly inhibited, as an "MIC". In addition to this hybrid test method, the resazurin microtiter assay (REMA) method was also performed. Neither have been submitted to the FDA CDRH, for review, although the CLSI M24 document refers to agar MIC methodology. Dr. Xianbin Li reports that the Pearson correlation coefficient between the baseline values from the Agar and REMA methods was 0.54 with a p-value < 0.0001, indicting a statistically significant but moderate correlation between these two methods.

The applicant's proposed provisional breakpoints for bedaquiline were based on the evaluation of distributions of populations of mycobacteria , assessing the frequency distribution of select laboratory stains combined with those from the clinical trials. The bar graph obtained from the NDA seems to indicate a bimodal distribution of MICs between the preclinical and clinical isolates for the MDR-TB isolates.

c

Figure 8 Bedaquiline Agar MIC Distribution Against Laboratory and Clinical Isolates



Source: Bedaquiline NDA

The microbiology reviewers in DAIP suggest that the bimodal MIC distribution may be suggestive of a wild type cutoff (0.12 - 0.25 mcg/mL).

Clinical Outcomes by MIC**:**
The following table 8, (also sponsor's Table 18) shows the correlation of MIC to clinical outcome, based on the 24 Week Primary Outcome Response. Out of the 223 bedaquiline treated subjects from the pooled C208 Stage 2 and C209 trials with an MDRTB, 177 (79.4%) had culture converted at Week 24. At the MIC level of 0.48 proposed by the applicant as a susceptible breakpoint, there were too few patients (4/5,or 80%) on which to conclude a stable estimate of efficacy, whereas lower outcomes were observed in the more numerous patients with an MIC of 0.06 (80/105 or 76.2).

Table 8 Culture conversion rates (Week 24 Selection, No overruling for Discontinuation) at Week 24 versus Baseline Bedaquiline Agar MIC

Table 18: Culture Conversion Rates (Week 24 Data Selection, No Overruling for Discontinuation) at Week 24 Versus Baseline Bedaquiline MIC for mITT Subjects (Agar Method)

Baseline MIC, µg/mL		Bedaquiline/BR 24-Week Responder[a,b]			
Original	Standardized	C208 Stage 1 n/N (%)	C208 Stage 2 n/N (%)	C209 n/N (%)	C208 Stage 2 & C209 n/N (%)
0.0075	≤ 0.008	1/1 (100)	1/1 (100)	1/1 (100)	2/2 (100)
0.015	0.015	1/2 (50.0)	5/5 (100)	10/13 (76.9)	15/18 (83.3)
0.03	0.03	5/5 (100)	16/17 (94.1)	24/32 (75.0)	40/49 (81.6)
0.06	0.06	7/7 (100)	13/24 (54.2)	67/81 (82.7)	80/105 (76.2)
0.12	0.12	2/2 (100)	7/7 (100)	28/34 (82.4)	35/41 (85.4)
0.24	0.25	0	1/2 (50.0)	0	1/2 (50.0)
0.48	0.5	0/1 (0)	1/1 (100)	3/4 (75.0)	4/5 (80.0)
> 0.48	≥ 1	1/1 (100)	0	0/1 (0)	0/1 (0)

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

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

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

Source: Module 5.3.5.4/TMC207-C208-Microbiology Report-Stage 1/Section 4.4.1.3, Module 5.3.5.4/TMC207-C208-Microbiology Report-Stage 2/Section 4.4.3.1, and Module 5.3.5.4/TMC207-C209-Microbiology Report/Section 4.3.1.3

The statistical review assessed outcomes by various strata and concludes that based on the present information, an MIC cutoff of 0.06 may better discriminate clinical outcome. As well, there was a concern that isolates with the atp mutation had MIC shifts to 0.48 (see FDA Table 6, sponsor's Table 9), which has putatively been described as a possible indicator of resistance, thus the proposed susceptibility breakpoint of 0.5 would abut this threshold. As most of the MIC shifts occurred in XDRTb isolates, where the influence of bedaquiline is more likely isolated from the influence of concurrent therapy, the MIC shift more convincingly reflects bedaquiline activity. Study 209 enrolled previously treated patients with cavitary disease and pre-XDR and XDR patients in Study 209. Patients with highly resistant TB should be treated with at least 3 drugs active against the TB isolate, postbaseline isolates should be tested for the development of resistance in all failures and treatment relapses.

It is the paucity of information regarding the clinical implication of a breakpoint rather than conclusions regarding the validity of the microbial methodology (that have not been formally assessed for regulatory purposes by the FDA) that precluded the inclusion of interpretive bedaquiline breakpoints in the label; Dr.Berkeley's assessment of the proposed methods are detailed in her review and will be important to revisit when adequate clinical data is available for reconsideration of an endpoint. As well the QC cutoffs are considered provisional until definitive Tier II multicenter studies are conducted and submitted to FDA.

7. Clinical Efficacy

Summary

The review team is in concordance with the statistical reviewer Dr. Xianbin Li's efficacy conclusions:

•For the primary endpoint, Study C208 Stage 2 (proof of efficacy study) demonstrated statistically significant treatment effects of bedaquiline in time to sputum conversion compared to placebo (relative risk 2.15, [95% CI 1.39, 3.31], p-value: 0.0005). Analysis of the time to convert at week 72, showed more modest but sustained treatment effects (relative risk 1.65, [95% CI:1.05, 2.59], p-value: 0.029).

Secondary endpoint analyses: Culture conversion at week 24 was also significantly different from placebo (52/67 or 78% in bedaquiline versus 38/66 or 58% in placebo, 20% difference (95% CI: 4.5%, 35.6%, p-value: 0.014), with discontinuations and deaths analyzed as failure to convert.

• Dr. Li finds that efficacy results from C208 Stage 1 supportive. In C208 Stage 1, time to culture conversion from bedaquiline (n=21) was significantly different from placebo (n=23) (relative risk 11.77 [95% CI: 2.26 – 61.23], p-value: 0.0034). The differences in culture conversion similarly favored bedaquiline at the week 8 (38.9% [95% CI 12.3%, 63.1%] p-value: 0.004), week 24 (14.8% [95% CI:-11.9%, 41.9%] p-value: 0.29], and the final week 104 followup. (4.6% [95% CI: -25.5%, 34.1%], p-value: 0.76]. There were 2 deaths in each group in this completed trial.
Dr. Li finds C209 efficacy results supportive. The median culture conversion time was 57 days and the conversion rate was 80%, comparable with the culture conversion rates observed in Study C208 Stage 2. In the mITT population, 80% (163/205) of subjects achieved culture conversion at the end of Week 24 (95% CI: 73%, 85%]). Five deaths have been reported from this ongoing trial

- Includes discussion of notable efficacy issues both resolved and outstanding

Clinical Efficacy Database
Study 208 Stage 2 provides the basis for the efficacy estimate in this NDA. In total, 4 phase 2 studies conducted in patients with tuberculosis comprise the effectiveness database for TMC:
Phase 2 a Proof of concept: Study C202 is a dose ranging early bactericidal study conducted in South Africa that compared the counts of drug sensitive *M. tuberculosis* in sputum following 7 day treatment with 25, 100 and 400 mg of bedaquiline compared to isoniazid and rifampin. The results are described in the clinical pharmacology section; this study identified 400 mg as the dose that resulted in a significant decrement in sputum colony counts of *M. tuberculosis* and served as basis for a bedaquiline regimen to carry forward in the phase IIb studies. As well, Study 202 is the only study that assesses sputum conversion attributable to bedaquiline alone. **Table 9**

Trial Number (Status)	Trial Design and Trial Objectives	N[a]	Treatment	Formulation
Phase IIa Multiple-Dose Trials in Infected, Treatment-Naïve Subjects				
TMC207-C202 (C)	Design Open-label, randomized trial Objective 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 *M. tuberculosis* in sputum in treatment-naïve subjects with pulmonary *M. tuberculosis* infection, compared to the effects of treatment with standard doses of rifampin or isoniazid, also administered over a 7-day period as monotherapy.	75	Treatment A: 25 mg TMC207 q.d. on Days 1-7 Treatment B: 100 mg TMC207 q.d. on Days 1-7 Treatment C: 400 mg TMC207 q.d. on Days 1-7 Treatment D: 600 mg rifampin q.d. on Days 1-7 Treatment E: 300 mg isoniazid q.d. on Days 1-7	TMC207 as F003[b] TMC207 as F004[c] TMC207 as F004[c] Rifampin as commercially available capsules of 300 mg Isoniazid as commercially available tablets of 300 mg

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

The phase IIb program consisted of 2 studies that assessed the efficacy of bedaquiline and background regimen in patients with MDRTB – Study 208 was a placebo controlled study in 2 stages conducted independently, where bedaquiline and placebo were used in concert with a five drug stable background and a non controlled study 209.
Exploratory: C208 Stage 1 was a double-blind, phase 2 study in the indication of interest, intended to show superiority of bedaquiline plus background therapy over a 5 drug standard background therapy for the surrogate endpoint of time to sputum conversion up to 8 weeks of treatment in treatment naïve MDRTB patients. The strength of this study is its placebo controlled design. Follow up after bedaquiline treatment was equivalent to 4 half lives of bedaquiline , to week 104 or 96 weeks from end of 8 week treatment.
Proof of Efficacy: C208 Stage 2 was a double blind phase 2 study in the indication of interest, similarly intended to show superiority of bedaquiline plus background therapy over a standard 5 drug background therapy alone for the surrogate endpoint of time to sputum conversion up to 24 weeks of treatment in treatment naïve MDRTB patients. The strength of this study is its placebo controlled design, and the intensive on treatment monitoring (26 visit while on treatment) for safety and efficacy. Follow up after bedaquiline treatment was equivalent to 4 half lives of bedaquiline, to week 120 or 96 weeks from end of 24 week treatment. (**Table 10**)

Trial Number (Status)	Trial Design and Trial Objectives	N[a]	Treatment	Formulation
Phase IIb Multiple-Dose Trials in Infected, Treatment-Naïve Subjects				
TMC207-C208 (O)	Design Placebo-controlled, double-blind, randomized trial Objective Stage 1 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. Objective Stage 2 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.	47 160	Stage 1: Investigational Treatment Period (8 weeks): 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 Background Treatment Period (96 weeks): MDR-TB treatment for 18-24 months, at least 12 months after the first documented negative culture Stage 2: 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 Background Treatment Period (96 weeks): MDR-TB treatment for 18-24 months, at least 12 months after the first documented negative culture	TMC207 as F001[b]

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 15m polysorbate 20, microcrystalline cellulose, croscarmellose sodium, (b) (4) and magnesium stearate

Supportive: C209 was a phase 2 open label study that assessed the efficacy of bedaquiline as part of a individualized background therapy for 24 weeks. This uncontrolled study enrolled patients with limited treatment options; 36/233 or 16% had infections caused by XDR-TB, and

85.4% had previous treatment with 2nd line drugs (for up to a maximum of 2369 days). The open label design limits the ability to rely on the estimate of a treatment effect, and on-treatment safety monitoring was less intensive (15 on treatment visits) (**Table 11**).

Trial Number (Status)	Trial Design and Trial Objectives	N[a]	Treatment	Formulation
Phase IIb Multiple-Dose Trials in Infected, Treatment-Experienced Subjects				
TMC207-C209 (O)	Design Open-label trial Objectives – 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 15 polysorbate 20, microcrystalline cellulose, croscarmellose sodium, (b) (4) and magnesium stearate

Study 208 Stage 2 provides a reliable estimate of efficacy of the intended treatment duration. Study 202 presented limited data showing activity of 7 day monotherapy in drug sensitive TB, Study 208 enrolled newly diagnosed MDRTB and Study 209 consisted of previously treated MDRTB. The trials provide a range of exposures from short term 7 day monotherapy in drug sensitive TB in Study C202, to 8 or 24 weeks week intensive (new drug plus WHO standard 5 drug background) and continued maintenance with background in Study 208, to 24 weeks exposure with highly variable background regimens in Study 209. Study 202 provides experience that most reflects attributable drug effect and Study C209 reflects use in the broadest population.

The designs of these trials are consistent with the draft guidance to industry: development of therapy for the treatment of pulmonary infections due to MDRTB. FDA provided study design advice during product development and Dr. Li confirms that the sponsor has generally adhered to such guidance. For this NDA, the time to sputum conversion, rather than the proportion of patients that achieve early conversion, is the proposed surrogate endpoint. The accelerated approval was based on an interim analysis of study 208 (conducted when all subjects reached at least 72 weeks post randomization or discontinued prior) and an interim analysis of study 209 (conducted when all subjects reached at least 24 weeks post randomized or discontinued prior). The completed study results from both Study 208 and Study 209 and the confirmatory study will be helpful in understanding the utility of the surrogate endpoint. Complete efficacy data for the final 120 week endpoint were presented by the applicant at the open public Advisory Committee meeting and submitted to the IND, but have not been submitted to the NDA at the time of this CDTL review. The confirmatory study, assessed under special protocol assessment (SPA) provisions, is a Phase 3, randomized, placebo-controlled clinical trial to assess durable culture conversion for bedaquiline compared to background regimen alone, inclusive of failure to sputum convert, relapse, death and discontinuation at least 6 months after all MDR-TB treatment is completed. Dr. Li analysed durable response in Study 208 Stage 2 (converted with no relapse, death and discontinuation) using a stricter definition of relapse based on the data available in the NDA at 72 weeks. treatment. Secondary endpoints assessed in the program include clinical symptoms (evaluated in 209 only and added upon discussions with the FDA SEALD team), chest x-rays (208 and 209, and reviewed by Dr. Li), change in weight (208 Stage 2 and 209).

The primary analytic population in these studies was the Modified ITT, the majority of patients were black, although Study 208 Stage 2 had more Hispanic patients and 209 had more Caucasian and Asian patients. Most patients had cavitary disease. Study 208 Stage 2 had the most patients with drug sensitive TB, Study 209 had most XDRTB.

For Study C208 Stage 2 two issues described in Dr. Li's review were the only significant analyses issues raised during review:

- *The treatment effect in Black subjects in South Africa 2 was not shown at Week 24 culture conversion rate and the reviewer is unable to conclude that race influenced outcome estimate, due to the confounding influence of study region and HIV status. Dr. Li recommends that the influence of race on long-term treatment effect be examined in detail in a review of the final study report. Given the small study size ,*
- *Another issue is the lack of complete study data up to the end of study treatment. As previously agreed to, study C208 would not have complete data to week 120, but all patients would have data to week 72. thus Study C208 was not "completed" at the time of the NDA submission. A study report with completed data was submitted to the IND. A full review of the final study will help to better understand the durable treatment effect, and effects in subgroups.*

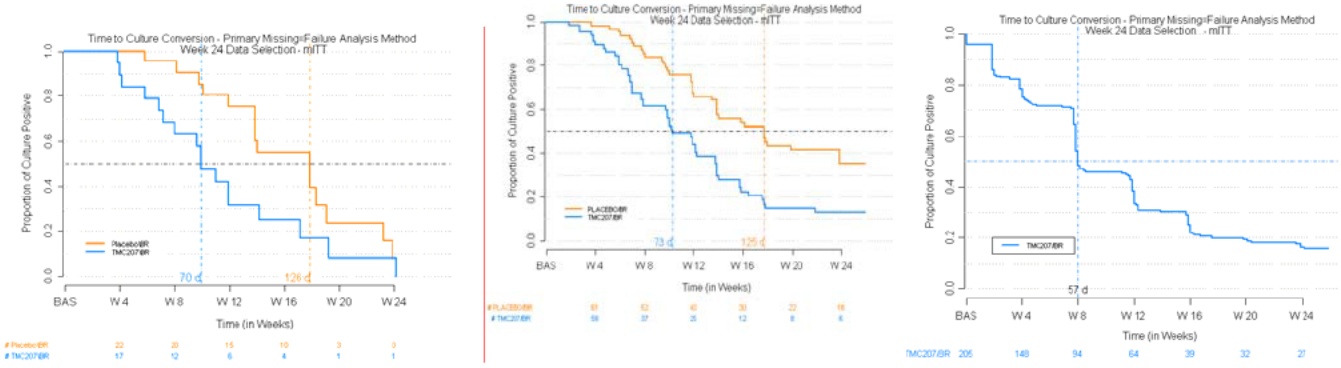
Two other issues regarding the inclusion of 1 subject with positive culture result at baseline excluded from the mITT population and the change in definitions of primary endpoints made prior to data lock do not raise concern regarding the study conduct and the ability to rely on the study findings.

Efficacy Findings

Sponsor's Efficacy: Primary Endpoint

For the primary efficacy variable 'time to culture conversion' according to the primary missing = failure analysis method, subjects who prematurely discontinued were considered as not converted and their time to culture conversion was assigned to the last available MGIT culture result (see conversion curves for Study 208 Stage 1 and 2 and Study 209 - placebo in orange, bedaquiline in blue). (**Figure 9**)

Study 208 Stage 1 Stage 2 Study 209



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FDA's Primary Analyses in Pivotal Study C208 Stage 2

Study 208 Stage 2 served as the PIVOTAL efficacy study, where subjects received investigational treatment (bedaquiline or placebo in combination with a preferred BR of MDR-TB treatment) for 24 weeks followed by background regimen for 48 to 72 weeks (thus a total of 72 to 96 weeks of BR treatment in total).

Primary endpoint

At Week 24, median time to culture conversion was 83 days in the bedaquiline group and 125 days in the placebo group of C208 Stage 2. There was a difference in median time to conversion of 42 days. A Cox proportional hazards model with covariates treatment, lung cavitation, and pooled center (region) showed a statistically significant treatment effect [relative risk 2.15, [95% CI 1.39, 3.31], p-value: 0.0005). Additional FDA sensitivity analyses showed robust effect in a risk to early sputum conversion for bedaquiline.

Table 12: The Relative Risk to Culture Conversion Estimated from Cox Proportional Hazards Models on Wk24 and 72 Time to Culture Conversion, mITT

Week 24 Endpoint	Relative Risk	95% CI	p-value	Week 72 Endpoint	Relative Risk	95% CI	p-value
Stage 2 Primary Endpoint	2.44	1.57, 3.80	<0.0001	Interim Primary Endpoint	1.65	1.05, 2.59	0.0290
Interim Primary Endpoint	2.41	1.55, 3.75	<0.0001	Interim End Censored	1.56	1.00, 2.43	0.0487
Interim End-censored	2.22	1.43, 3.43	0.0003	Interim Sensitivity 2	1.86	1.22, 2.82	0.0036
Interim Sensitivity 2	1.98	1. 30, 3. 02	0.0015				

Modified from Dr. Li's review

Compared with subjects with no cavity present or with cavity less than 2 cm, subjects with cavity ≥ 2cm in both lungs or in one lung only were statistically significantly less likely to have culture conversion.

Secondary endpoints

Time to Culture Conversion at Week 24 and Culture conversion rates at Week 24 and 72

The median time to culture conversion was 73 days in the bedaquiline group and 125 days in the placebo group of C208 Stage 2. The shift in time to convert from the primary and secondary analyses is due to samples with time to growth of 42 days or higher that were negative at the interim analysis – secondary, but turned positive after week 24. The treatment effect of Bedaquiline from the Cox proportional hazards models on Week 72 data remains robust with three methods for handling missing data although the treatment effect was slightly reduced compared to week 24.

Table 13 FDA Culture Conversion Rates (C208 Stage 2, Interim Analysis / All Available Data Selection) − mITT

Time Point	Bedaquiline/BR	Placebo/BR	Rate difference	Pvalue
Week 24	52 (78)	38 (58)	20%	0.0135* (5.3, 36.2)
Week 72	47 (71)	37 (56)	15%	0.07 (-1.1, 31.4) 0.159

*FDA analysis diffred slightly from sponsor's by 1 patient Modified from Dr. Li's review

Relapse

In the mITT population, 5 subjects (7.6%) in the Bedaquiline group and 8 subjects (12.1%) in the placebo group experienced relapse. The time from onset of treatment to culture conversion (broken line) and time from culture conversion to relapse (solid line) with disposition type (ongoing, discontinued, or completed) in the mITT population is shown in the following **Figure 10**.

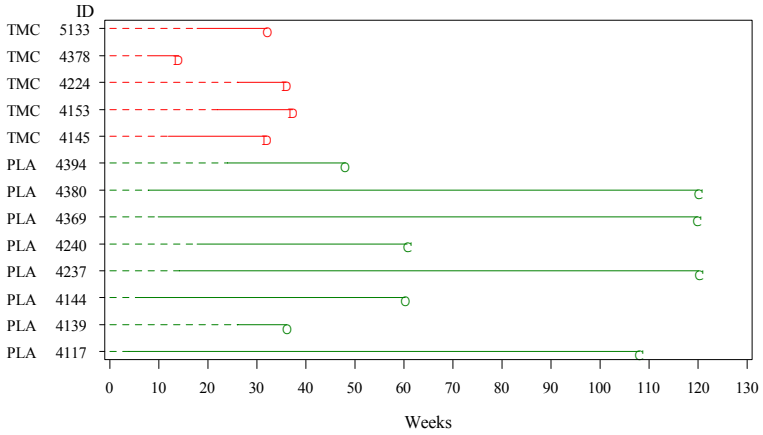


Figure 10 Time to culture conversion (broken line) and relapse (solid line) In Study 208 Stage 2
Source: Dr. Li's review

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

The durability of the surrogate early endpoint will be only confirmed with the submission of a confirming study (Study 210) that evaluates durable cure. However, as all patients in the current placebo controlled study had followup to 72 weeks, the sponsor provided estimates of durable cure with death, relapses and missing data considered failures.

FDA performed an additional 72 week analysis of durable cure that assessed only patients that culture converted at week 24 for relapses and where any positive sputum is a relapse and overrules conversion that occurred beyond week 24. These findings are shown below:

Table 14 FDA analysis of Sustained Sputum Conversion at Week 72 (Study C208 Stage 2, MITT)

Categories of response at Week 72	**Bedaquiline N=66**	**Placebo N=66**
Sustained conversion: Culture conversion at Week 24 and no positive culture up to week 72	37	18
Failure: [failure to convert, relapse based on at least 1 positive sputum culture, discontinuation, death, missing data]	29	48
Culture conversion at Week 24 but relapsed at Week 72*	10	16
Failure to convert at Week 24 up to Week 72	14	28
Discontinued with all negative culture results	5 (1 death)	2
No data available	0	2

Modified from Dr. Li's review

A caveat regarding these conclusions is that the analyses are based on liquid culture media and not on solid media. Whether these rates differ with cultures on solid media and whether the culture conversion is less "durable" based on liquid cultures will need future confirmation.

Conversion by resistance level
FDA Analysis by MDR/XDR status

For MDR-TB and Pre-XDR subjects, the Bedaquiline group had higher conversion rates. For DS-TB or XDR-TB, the numbers of subjects were too smaller to make meaningful comparisons. The data from Study C209 shows that 20/36 patients with XDRTB converted from positive to negative, supporting bedaquiline benefit in patients with limited options.

Table 15 Culture conversion rate at Week 24 by baseline TB type, ITT

TB type	Bedaquiline	Placebo	Difference in %
DS	1/4 (25.0%)	1/4 (25.0%)	0
MDR	32/40 (80.1%)	29/46 (63.0%)	17.1
Pre-XDR	12/16 (75.0%)	4/12 (33.3%)	41.7
XDR	2/3 (66.6%).	3/4 (25.0%)	41.6
Missing values	12/16 (75.0%)	9/15 (60.0%)	15.0
Total	59/79 (74.7%)	46/81 (56.8%)	17.9

FDA analysis of 208 Stage 1 (exploratory Study)
Primary- Time to Culture Conversion at Week 8
Significant difference in time to sputum conversion between the treatment groups (p = 0.0034) in favor of the bedaquiline group (hazard ratio [95% CI]: 11.77 [2.26; 61.23]). As treatment in this stage was limited to 8 weeks there was no requirement that the consecutive negative sample be separated by at least 25 days in this analysis.

Secondary endpoints
1. Time to Culture Conversion at Week 24
Median time to culture conversion was 70 days in the bedaquiline group and 126 days in the placebo group (difference of 56 days). A significant difference in time to sputum conversion between the treatment groups (p = 0.0022) favored bedaquiline (hazard ratio [95% CI]: 3.14 [1.51; 6.53]).

Efficacy in Subpopulations:
There was no apparent imbalance in outcomes by gender and age. The culture conversion rates at Week 24 by race are shown below: although it appears that black patients had lower outcomes when treated with bedaquiline compared to Hispanic or Asian patients, the estimate of efficacy is unstable in these much smaller subgroups. As well, notable is that black patients that received placebo had far better outcomes than other placebo treated groups.

Table 16 Culture conversion rates at Wk 24 by race in the mITT population, Study C208 Stage 2

	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*

When analysed by region, the outcome in back patients appeared driven by one study site in Africa (Site 2), although this site passed DSI inspection..

Table 17 Successful Sputum Conversion by Region in Study 208 Stage 2

Region	Bedaquiline	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

In all races bedaquiline demonstrated a consistently higher culture conversion rate than the placebo, except in patients from this one site, although the treatment effects varied among difference races. Further investigations by Dr. Li by demographic factors, HIV status, TB types, and lung cavitation did not explain the observed outcomes. The high conversion rate in this placebo group contributed to a smaller overall treatment effect between the two treatment groups. Black patients have an apparent clearance of bedaquiline that is 52% higher than subjects of other races. In a population pharmacokinetic analysis of TB patients treated with bedaquiline, systemic exposure (AUC) to bedaquiline was projected to be 34% lower in black patients than in patients from other race categories. This lower systemic exposure was not considered to be clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed in clinical trials. The outcome in black patients needs to further study.

8. Safety

Summary

This CDTL was completed based on Dr. Porcalla's safety presentation to the Advisory committee , Dr. Xianbin's safety review, analyses conducted by the QT-IRT team, Dr. Joy Li's MAED analyses, and consultation with CardioRenal and Hepatic Safety teams in OSE.

Table 18 Investigation of preclinical findings in the clinical Program for Bedaquiline

Nonclinical findings:	Safety laboratory assessments[a]:	SMQ used to probe database for AEs of interest:
Pancreas Mice, Dogs histopathological changes in pancreas; increased enzymes.	pancreatic amylase, lipase trypsin-like immunoreactivity	Acute pancreatitis SMQ
Musculoskeletal System In mice, rats and dogs, myopathies , raised CK	CPK LDH	Rhabdomyolysis/myopathy SMQ
Cardiac Muscle Minimal myocyte degeneration, QT prolongation in dogs , increased troponin I and creatine kinase.	troponin I CPK-MB ECG	Torsade de Pointes/QT prolongation SMQ
Liver mice (single cell necrosis), rats (centrilobular hypertrophy vacuolation), dogs (decreased glycogen-like content)	AST ALT ALP GGT bilirubin (total, direct, indirect)	Selected sub-SMQs from drug-related hepatic disorders SMQ
Stomach Degenerative lesions stomach of mice and dogs not associated w/ gastrin	Gastrin pepsinogen 1 and 2	None

This CDTL describes the Adverse Events in Study 208 and other safety areas of concern, as identified from phase 1 and preclinical studies (see above table which describes the laboratory and adverse event investigations carried out).

A total of 600 subjects received bedaquiline in the drug development program. This included 265 non TB patients in phase I who received single or multiple doses of bedaquiline including 16 hepatically impaired individuals. Various developmental formulations of bedaquiline were employed in this program, including oral solutions in beta hydroxycyclodextrin. The safety data from the phase 1 program is summarized in Dr. Porcalla's review.

In Phase II, 335 TB patients received the to-be-marketed formulation of bedaquiline at the proposed dose, 45 patients received the drug for 7 days (Study 202), 23 for 8 weeks (Study 208 Stage 1) and 312 for 24 weeks (208 Stage 2 and 209). Therefore, in total, the 312 patient exposures at the proposed dose and duration allows one to exclude a serious event occurring at 1%. The majority were male in their early 30s, with a broad representation of races (see Table 19). In these 2 studies combined, the biggest racial group was black, 12.5% were white or caucasian, 9.4% were asian, and 25.6% were of another race. A total of 8 of 79 (10.1%) patients in the bedaquiline group and 16 of 81 (19.7%) patients in the placebo group were HIV-infected. Seven (8.9%) bedaquiline-treated patients and six (7.4%) placebo-treated patients discontinued Study C208 Stage 2 because of an adverse event.

Study 208 Stage 2 (79 bedaquiline exposed vs 81 placebo) provides safety from newly diagnosed patients on a 5 drug regimen proposed as the standard by the World Health organization (kanamycin, ofloxacin, ethambutol, pyrazinamide, ofloxacin, and cycloserine /terizidone). QT prolonging drugs used in the treatment of MDRTB (such as the fluoroquinolone moxifloxacin, a macrolides azithromycin, and an oxazolidinone linezolid) were excluded from concurrent use in this study.

Study 209 provides the largest safety database amongst the studies conducted. As well, the population studied included a broader patient population than Stage 1 and 2 of Study 208. 209 enrolled more Caucasians and American or Alaskan natives, whereas 208 enrolled Hispanics and other racial subtypes. Study 208 enrolled newly diagnosed patients on a standard 5 drug regimen, Study 209 enrolled both newly diagnosed and highly treatment experienced patients with cavitary disease, on individualized background regimens and thus exposure to a broad range of second line drugs. Therefore this study provides experience in the concurrent use of bedaquiline with QT prolonging medications. As in Study 208, this study allowed treatment of pre XDR TB, but in addition enrolled 36 patients with XDR isolates. HIV infected patients enrolled

Table 19 Demographic Characteristics of Patients Enrolled in the Phase IIb Program for Bedaquiline.

Parameter	Value	C208 Stage 1			C208 Stage 2		
		bedaquiline/BR N = 23	**Placebo/BR N = 24**	**All Subjects N = 47**	**bedaquiline/BR**	**Placebo/BR N = 81**	**All Subje N = 16**
Gender, n (%)	Female	5 (21.7)	7 (29.2)	12 (25.5)	27 (34.2)	32 (39.5)	59 (36.9
	Male	18 (78.3)	17 (70.8)	35 (74.5)	52 (65.8)	49 (60.5)	101 (63.
Median Age at	**y** (range)	33.0 (18-57)	33.0 (19-57)	33.0 (18-57)	31.0 (18-63)	35.0 (18-61)	34.0 (18-
Ethnic origin, n (%)	American-Indian or Alaska	0	0	0	0	0	0
	Asian	0	0	0	9 (11.4)	6 (7.4)	15 (9.4
	Black	13 (56.5)	13 (54.2)	26 (55.3)	29 (36.7)	27 (33.3)	56 (35.0
	Caucasian/White	0	1 (4.2)	1 (2.1)	8 (10.1)	12 (14.8)	20 (12.5
	Hispanic	0	0	0	13 (16.5)	15 (18.5)	28 (17.5
	Other	10 (43.5)	10 (41.7)	20 (42.6)	20 (25.3)	21 (25.9)	41 (25.6
Cavitation[d] (stratified for C208: n (%)	Cavitation in both lungs	6 (26.1)	7 (29.2)	13 (27.7)	13 (16.5)	16 (19.8)	29 (18.1
	Cavitation in one lung	14 (60.9)	13 (54.2)	27 (57.4)	50 (63.3)	49 (60.5)	99 (61.9
	No cavitation	3 (13.0)	4 (16.7)	7 (14.9)	16 (20.3)	16 (19.8)	32 (20.0
Extent of resistance n (%)	DS-TB	0	0	0	4 (5.1)	4 (5.2)	8 (5.1)
	MDR-TB[e]	23 (100)	24 (100)	47 (100)	75 (94.9)	73 (94.8)	148 (94.9
	$MDR_{H\&R}$-TB	*15 (65.2)*	*16 (66.7)*	*31 (66.0)*	*40 (50.6)*	*46 (59.7)*	*86 (55*
	pre-XDR-TB	*2 (8.7)*	*4 (16.7)*	*6 (12.8)*	*16 (20.3)*	*12 (15.6)*	*28 (17*
	XDR-TB	*1 (4.3)*	*1 (4.2)*	*2 (4.3)*	*3 (3.8)*	*4 (5.2)*	*7 (4.5*
HIV status at screeningf, n (%)	**Negative**	20 (87.0)	21 (87.5)	41 (87.2)	**71 (89.9)**	**65 (80.2)**	**136 (85**
	Positive	3 (13.0)	3 (12.5)	6 (12.8)	**8 (10.1)**	**16 (19.8)**	**24 (15.0**
	Amoxicillin+clavulanic	1 (4.3)	1 (4.2)	2 (4.3)	3 (3.8)	5 (6.2)	8 (5.0)
	Capreomycin	0	0	0	0	0	0
	Clofazimine	8 (34.8)	8 (33.3)	16 (34.0)	18 (22.8)	20 (24.7)	38 (23.8
	Cycloserine	15 (65.2)	15 (62.5)	30 (63.8)	53 (67.1)	51 (63.0)	104 (65.
	Ethambutol	23 (100)	24 (100)	47 (100)	70 (88.6)	65 (80.2)	135 (84.
	Ethionamide	0	0	0	0	0	0
	Imipenem Isoniazid	0	0	0	0	0	0
	Linezolid	0	0	0	0	0	0
	Pas-C Protionamide	0	1 (4.2)	1 (2.1)	4 (5.1)	8 (9.9)	12 (7.5
	Pyrazinamide	0	0	0	8 (10.1)	13 (16.0)	21 (13.1
	Rifampicin[b]	23 (100)	24 (100)	47 (100)	75 (94.9)	74 (91.4)	149 (93.
	Terizidone	0	0	0	0	0	0
	Thiacetazone	4 (17.4)	4 (16.7)	8 (17.0)	13 (16.5)	16 (19.8)	29 (18.1
		0	0	0	0	0	0

Safety in Phase 1

A total of 60.3% of subjects enrolled in Phase 1developed adverse events (AEs), 6.9% of whom developed an event of at least a Grade 3 severity AE (hyperuricemia n=9, lipase increased n=3, fever n=1,) of which 3 (1.6%) led to drug discontinuation (urinary tract infection, pharyngolaryngeal pain and pyrexia, increased lipase). System organ class reports were related to the nervous system (24.3%) and gastrointestinal tract (16.9%). Bedaquiline does not enter the blood brain barrier and prominence of nervous system events is unexpected, the most frequent event was headache (34/189 subjects, 18.0%), and dizziness (10/189 subjects, 5.3%). Dry mouth, diarrhea, fatigue, hyperuricemia, and erythema occurred in more than 5%. No severe cutaneous reactions were observed in the program, although erythema was noted in the phase 1 program.

Safety in Phase 2a Trial C202

Phase 2a Trial (Trial C202) 7 day monotherapy

This study was conducted in South Africa in centers experienced with EBA testing and with patients with fully drug-sensitive TB. Seventy-five subjects were randomized to 5 groups administered a 7-day study drug treatment regimen. Bedaquiline (n=75) was given once daily in different doses for each group (25 mg, 100 mg, 400 mg); comparative groups were given INH (300 mg) or rifampin (600 mg) once daily as monotherapy. A dose related trend in the bedaquiline AE rate was seen with bedaquiline. 2 patients (13%) in 25 mg of bedaquiline, 6 patients (38%) in 100 mg of bedaquiline, and 9 (64%) in 400 mg of bedaquiline compared to 7 (47%) rifampin and 3 (20%) INH patietns reported AEs. The only serious AEs were reported with INH (hemoptysis). Disease-related events such as hemoptysis were reported as non serious AES, in bedaquiline. Otherwise, the AE rates were similar to those reported in phase 1. Two deaths, both on the bedaquiline arm, died during the follow-up period after completion of 7 days of bedaquiline and while on treatment regimen for DS-TB (RMP, INH, PZA, and EMB) Neither death appears to be related to drug therapy.

Table 20 Profile of 2 deaths in the Bedaquiline Treated Group in the 7- day EBA Study 202

Patient 1	
- a 25 year-old black female with HIV and low CD4 count (80)	
7/15 to 7/21/2005	bedaquiline 400 mg daily for 7 days
7/22/2005	treatment RMP, INH, PZA, EMB started
	lost to follow-up for 1 month
(b) (6)	hospitalized for hemoptysis, general body pains and night sweats. was wasted, dyspneic afebrile, with increased JVP, widespread chest crackles, and with tender hepatomegaly. Sputum was positive for *M. tuberculosis* sputum culture, and positive serology for HIV with CD4 count of 80.
(b) (6)	dried from HIV and TB
Patient 1	
- a 41 year-old male extensive bilateral TB and positive sputum	
9/13-9/15/2005	bedaquiline 400 mg daily for 3 days
9/15/2005	withdrawn on D3 (+) UA test for cannabinoids
(b) (6)	treatment RMP, INH, PZA, EMB, hemoptysis despite arterial embolization
(b) (6)	massive hemoptysis and expired

Phase 2b Trials
A total of 335 MDRTB patients received bedaquiline in this phase of drug development.

Table 21 Summary of Bedaquiline Exposure in MDR-TB Patients in Phase 2b Trials

Exposure in TB infected, treatment-naïve subjects in Phase 2b trials	$N_{bedaquiline}$	Duration of exposure	Available followup in NDA
Number of subjects treated Phase 2b trial C208 Stage 1	23	8 weeks	104
Number of subjects treated Phase 2b trial C208 Stage 2	79	24 weeks	72
SUBTOTAL MDR-TB- bedaquiline treated subjects Phase 2 trials	***102***		
Exposure in TB infected, treatment-experienced subjects in Phase 2b trials			
Number of subjects treated with bedaquiline in the Phase 2b trial C209	233	24 weeks	24
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 follow up safety data was roughly equivalent to 4 half lives of bedaquiline in Study 208 Stage 1 and 3 half lives for Stage 2

Trial C208 Stage 1

Conducted in South Africa this small study of 23 bedaquiline patients and 24 placebo patients had comparable treatment duration and similar premature discontinuation rates in both arms. The severity and frequency of adverse events were similar in both groups except for gastrointestinal disorders which were more frequent in the bedaquiline group (30.4% versus 8.3%), such as nausea and diarrhea reported for respectively 5 (21.7%) and 3 (13.0%) subjects in the bedaquiline group compared to none of the placebo. Clinically relevant changes in laboratory values that were more common with bedaquiline include: increase in uric acid, creatinine, hemoglobin, AST and lymphocytes (%), and a decrease in neutrophil count, platelet count, ALP, ALT, GGT, and total cholesterol. Unique AES in this study not described the rest of the phase II program include 1 each of diabetic ketoacidosis (bedaquiline) and pneumothorax (placebo). The 2 deaths that occurred in each treatment arm of the study occurred beyond the 8 week treatment period. Three deaths were due to tuberculosis (2 inplacebo and one in bedaquiline) whereas one death on the bedaquiline arm was caused by an MI. The death due to a myocardial infarct was proven on autopsy to be due to an occluded LAD in a 33-year-old, HIV-positive, female with a BMI of14.10 kg/m². Baseline ECGs showed T wave inversions.. 115 days after the last intake of bedaquiline she died of an acute myocardial infarction. 100% obstruction of the lumen of the left anterior descending coronary artery, recent infarction of the left ventricle at the apex, anterior wall, and intra-ventricular septum confirms death was consistent with acute myocardial infarction.

Table 21 C208 Stage 1:Overview of Subjects with Survival Data who Died

Subject ID	Treatment Arm	Cause of Death	First Intake of Study	Last Intake of Study	Duration of Treatm	Date of Death	Days After Trial	Days After Last Intake
208-3010*	Placebo	TB	19 Jun	13 Aug	56	(b) (6)		
208-3049*	Placebo	Pulmonary TB	10 Oct	15 Oct	6			
208-3100*	BEDAQUILINE	Pulmonary TB	10 Oct	15 Oct	6			

Source: Post hoc analysis Source: NDA 204,384

The cardiovascular and hepatic safety of Study 208 is not notably different from the rest of the phase 2 program and is discussed subsequently.

Trials C208 Stage 2

In study 208, serious AEs (SAEs), and higher grade AEs were more often reported for bedaquiline compared to placebo in both phases of treatment; albeit more pronounced in the overall treatment phase. The reported terms for the bedaquiline SAEs were alcohol intoxication (fatal), suicidal thoughts, haemoptysis, right bronchiectasis and right (lung) empyema worsening, right ear severe conductive hearing loss and left ear mild conductive hearing loss.

Table 22 Summary of subjects with adverse events in the ITT population, Study C208 Stage 2

	BEDAQUILINE		Placebo	
AE Category	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)
Any AE at least grade 2	51 (64.6)	63 (79.7)	56 (69.1)	65 (80.2)
Any AE at least grade 3	22 (27.8)	34 (43.0)	19 (23.5)	29 (35.8)
Any AE grade 4	5 (6.3)	11 (13.9)	3 (3.7)	6 (7.4)
Any SAE	6 (7.6)	19 (24.1)	1 (1.2)	15 (18.5)
Any AE leading to discontinuation	4 (5.1)	4 (5.1)	5 (6.2)	5 (6.2)
Any AE of at least grade 3, leading to a permanent discontinuation, or SAE	22 (27.8)	34 (43.0)	21 (25.9)	31 (38.3)

Adverse events by body system or organ class in >5% subjects in the overall treatment phase revealed more frequent AEs in the blood/lymphatic disorders, nervous system/psychiatric and respiratory systems for bedaquiline and immune disorders, cardiac, eye, injury /poisoning and reproductive disorders favoring placebo. These differences were not consistent across the treatment phases. Dr. Porcalla's safety review details his assessments of potential safety signals predicted based on the preclinical signals, the mechanism of action of the drug and the invitro studies conducted by the sponsor. Due to the cationic ampiphilic properties of the drug and its phopholipidosis inducing properties, he assessed the potential for skeletal, cardiac, pancreatic, hepatic, gastric and metabolic events. An analysis looking at individual adverse event terms, both for preferred, low level group terms, high level group terms was performed, as well as Standard Medra Queries for cardiac and hepatic events, to validate the sponsor's review of the same. The narrow search for terms for rhabdomyolysis or myopathy showed that no events of rhabdomyolysis or myopathy in the two groups; whereas a serious adverse event of pancreatitis was reported in the bedaquiline grouping addition to 2 patients reported to develop increased amylase in the bedaquiline group. Proportion of events based on preferred terms related to the stomach (nausea, vomiting, upper abdominal pain, and gastritis) were similar between bedaquiline and placebo. Dr. Porcalla found no reported events of metabolic acidosis.

Table 23 Adverse Reactions by System Organ Class in Study 208 Stage 2

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)

Rhabdomyolysis/ Myopathy (SMQ)	0	0
Gastrointestinal Disorders	53 (67.1)	53 (65.4)
Pancreatitis Acute(SAE)	1 (1.3)	0
Increased amylase	2 (2.5)	1 (1.2)
Nausea	32 (40.5)	30 (37.0)
Vomiting	23 (29.1)	22 (27.2)
Abdominal pain upper	10 (12.7)	7 (8.6)
Gastritis	7 (8.9)	16 (19.8)

Source Dr. Porcalla's AC slides, based on Joy Li's analysis.

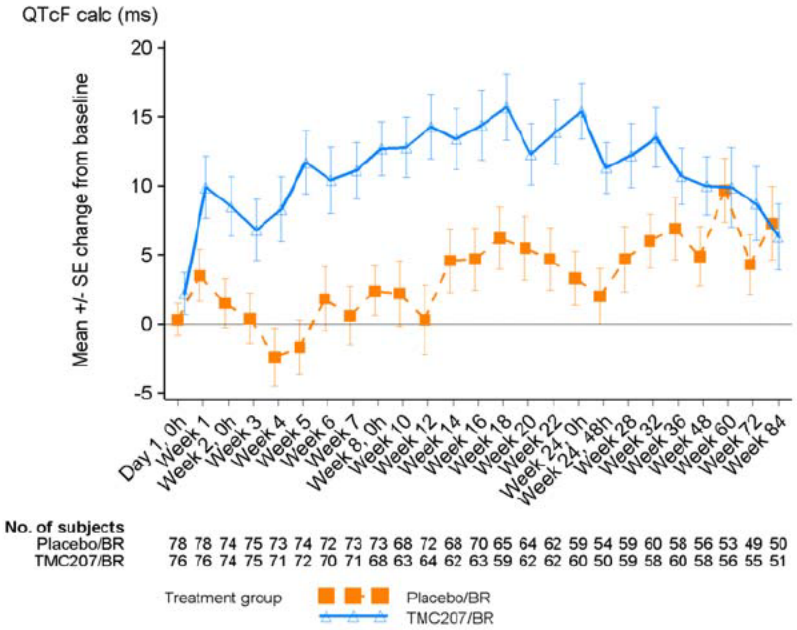
Cardiovascular safety: QT prolongation

Summary: Dr. Porcalla concludes that in the aggregate safety database of 600 (265 normal subjects and 335 patients) there were no reported cases of Torsade des Pointes and sudden death, despite the definite increase in QT noted with the use of bedaquiline over placebo. The risk and magnitude of the QT prolongation was additive. when bedaquiline was coadministered with QT prolonging medications. A similar proportion of patients in the bedaquiline group reported adverse reactions related to cardiac rhythm and conduction, compared to the placebo group. More patients in the bedaquiline group developed cardiac failure compared to the placebo group but the association between cardiac failure and bedaquiline is difficult to establish. Details of the individual patient studies are provided below:

Thorough QT trial (TBC1003) and EBA Study. No significant QTc prolongation effect was observed after a single 800-mgdose of bedaquiline in this study. A multiple dose phase 2a study (study C202) subsequently showed a QT effect of approximately 12 ms after 7 days of administration of a 400-mg dose of bedaquiline. The QT-IRT team from the Division of CardioRenal Products concludes that the single-dose TQT study failed to characterize the potential of bedaquiline to prolong the QTc interval because it was insufficient to achieve significant exposures of the major metabolite M2. Exposure-response data from C208 and the TQT study suggests that an exposure-QTcF relationship exists for the metabolite M2 after a 14-day dosing period. This correlation was not seen with the parent drug.

(C208 Stage 2) In the pivotal placebo controlled study,the largest bound of the 2-sided 90% CI for the mean difference between bedaquiline and placebo during the treatment period was 18 ms observed at 12 weeks. The time profile of the mean QTcF for bedaquiline and placebo over time shows that QT prolongation was observed within the first week of treatment, was maximal at week 18 (although the difference from placebo was largest at week 12) and persisted beyond the 24 week treatment. More patients in the bedaquiline group had QTcF values 450-480 ms (26.6% vs 8.6%) and developed a > 60 ms increase from reference values group (9.1% vs 2.5%)

Figure 11



Investigator-reported Events in C208 reveal 3 patients with QTcF prolongation events and 1 patient with syncope in bedaquiline arm, none reported in placebo arm. None developed Torsade des Pointes.

Trial C209 showed data consistent with those shown in Trial C208 Stage 2. Additionally, the additive effect of concurrent use with other QT prolonging drugs (including clofazimine) was clarified in this study, as QT prolonging drugs were allowed when their use could not be avoided due to the resistance pattern of the baseline isolate. The following drugs were listed as concomitant medications in Study 209: moxifloxacin, levofloxacin, clofazimine, azithromycin, linezolid, clarithromycin, erythromycin, amitryptyline, astemizole, aztreonam, loratadine, domperidone, fluconazole, fluoxetine, haloperidol, hydroxyzine.

Table 24 Maximum measured QT (top) and increase (bottom) by the number of QT prolonging drugs during the investigational Treatment Phase of Study C209

QT correction Number of QT Prolonging Drugs	TMC207/BR							
	n	Mean	SE	Min	1st Quartile	Median	3rd Quartile	Max
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	32	441.7	3.76	393	432.5	439.5	445.5	516
QT correction Number of QT Prolonging Drugs	**TMC207/BR**							
	n	**Mean**	**SE**	**Min**	**1st Quartile**	**Median**	**3rd Quartile**	**Max**
QTC FRIDERICIA (calculated) (ms)								
0	128	23.7	1.33	-14	13.5	24.0	33.0	68
1	65	25.8	2.01	-7	15.0	24.0	29.0	82
>=2	32	30.7	3.18	0	20.5	27.0	36.0	74

Source: NDA 204384, response to request for information

The mean QTC increase (third column) appears to increase proportional to the number of QT prolonging drugs in the regimen. This increase was particularly notable with concurrent treatment with clofazimine, dosed at 100 mg/day (following table). In an FDA review of the postmarketing safety of clofazimine, QT prolongation was noted with the doses of 300 mg or higher, but not at the 100 mg dose, further supporting additive QT prolongation with concurrent use of these antibacterials.

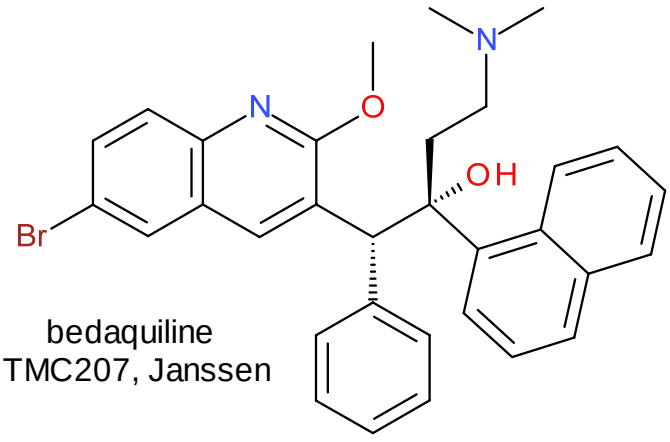
Table 25 Mean change in measured QT In Patients Receiving Bedaquiline With or Without Clofazimine

ECG Parameter	**Change in QT in patients receiving Sirturo and clofazimine**									
	WITHOUT Clofazimine					**WITH Clofazimine**				
Timepoint	N	Mean	SE	Median	Max	N	Mean	SE	Median	Max
Change in QTcF (calc) (ms)										
WEEK 24, 0 h	177	12.3	1.23	13.00	67.0	17	31.94	5.73	27.00	82.0
WEEK 24, 5 h	170	12.4	1.26	11.50	60.0	16	28.81	5.67	29.00	82.0

Other cardiovascular events in the pooled dataset identified two bedaquiline-treated patients who developed cardiac failure during the two trials, one in Trial C208 Stage 2 and one in Trial C209. There were no cases of Torsade de Pointes.

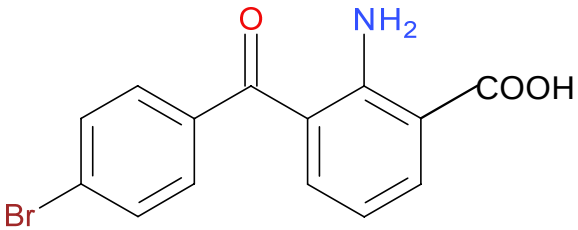
Laboratory Findings and Hepatic Safety

Summary:
There is no previous experience with the use of diarylquinolines to predict its hepatic toxicity. Given its mechanism of action, there is concern that it could act as a mitochondrial toxin in eukaryotic cells to the same extent as it does in mycobacteria. This is a realistic concern given the limitations of our understanding in terms of how variable human susceptibility is to drugs such as this class. In consult with the OSE Dr. John Senior alludes to the experience with FIAU, which on postmarket was associated with hepatic failure due to unrealized variation in human metabolism of the drug, as well as to bromfenac, associated with cases of liver failure. This concern is related to the drug's molecular structure has similarities to bedaquiline.



bedaquiline
TMC207, Janssen

bromfenac
DURACT, Wyeth-Ayerst
withdrawn 1998



Preclinical animal studies indicate hepatic findings of extensive phospholipidosis in multiple tissues, most prominently in liver, pancreas, muscle, thyroid, and adrenals at concentrations

several fold than expected in humans. High doses of the drug in animals have caused increased liver weight, hepatic centrilobular hypertrophy, and increases in aminotransferase levels. Clinical studies have shown aminotransferase increases by 3-fold comparable to those seen in patient treated with other TB drugs. Nonetheless, one bedaquline treated patient had raised bilirubin compared to none of those given background therapy and increased serum enzyme levels were more often reported in bedaquiline treated patients compared to none among those treated with placebo. Symptomatic drug-related hepatic disorders or " adverse events" were noted in 8.8% of those treated with bedaquiline vs in 1.9% treated with placebo. There were three deaths of initial concern regarding the possibility of drug induced liver injury for which we consulted with the Office of Safety Epidemiology, Dr. Leonard Seef and John Senior draw the following conclusions:

1) *"The data do not support consideration of bedaquiline as a potentially hepatotoxic drug, but neither do they disprove its possibility. The available clinical data are too few to reach any conclusion, and much more experience is needed.*
2) *If this promising new agent for treating mdrTB is approved, continued caution should be exercised, including both monitoring of treated patients and additional controlled trials in which vigilance is exercised toward detecting possible cases.*
3) *The sponsor, and through them to the investigator in Thailand, should be tasked to explain ….to clarify the mixed-up data….with the two patients reposted as serious problems"*

The hepatic safety of bedaquiline in this CDTL is discussed with the rest of the laboratory findings because the toxicity to the liver must be viewed with an eye to the potential mechanisms of hepatic injury.

- As a mitochondrial toxin – based on the drug's mechanism of action
- As a direct hepatotoxin – see analysis of Hy's law
- Through phospholipidosis -

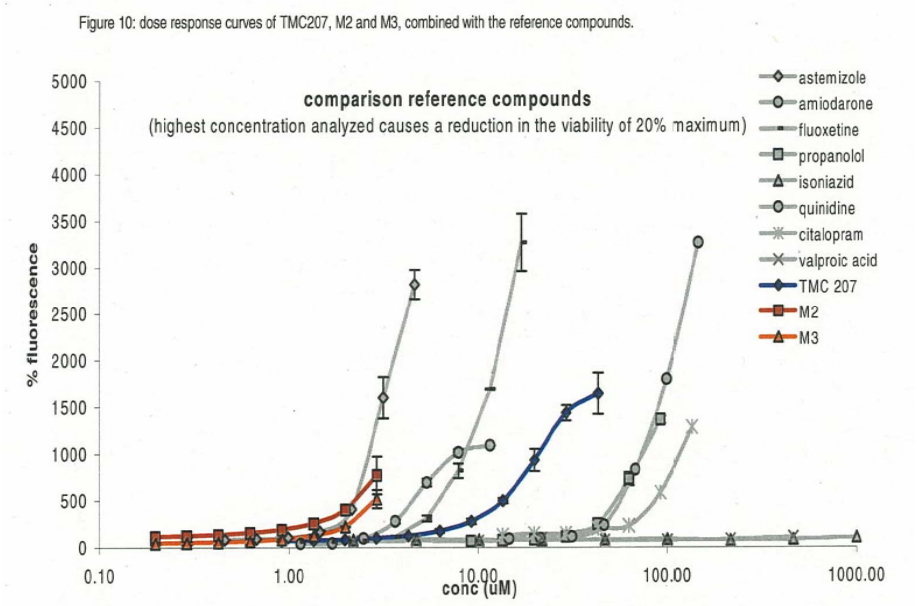
Histologic features of mitochondrial toxicity suggesting disordered fatty acid metabolism (micro or macrovesicular steatosis) and general clinical manifestations, such as hyperlactataemia, lactic acidosis, peripheral neuropathy or lipoatrophy were not described to have occurred in the preclinical program by Dr. Owen Mc Master. However, myopathy, stomach ulcers, pancreatitis, and hepatic changes were described, however, as phospholipidosis also affects these tissues, the etiology of these changes are hard to tease out. In the safety database of 600 exposed to any dose of bedaquiline and 300 exposed at the label dose and duration, Dr. Porcalla does not report the concurrent finding of lactatemia, acidosis, CPK elevation, and pancreatitis with hepatitis . There was one report of unrelated diabetic ketoacidos in the clinical trials.

Phospholipidosis : In vitro, bedaquiline was compared to strong phospholipid inducers chloroquine, astemizole, amiodaron and fluoxetine, medium inducers sucha s citaprolam, quinidine and propranolol and weak inducers procaine and non inducers such as isoniazid. The concentrations that induce phsopholipidosis are shows in the graph below, obtained by this reviewer in the NDA.

The sponsor concludes that the parent compound bedaquiline induces phospholipidosis (an accumulation in the cell of normally reprocessed phospholipids) at concentrations that exceed those of known strong phospholipid inducers. The metabolites are clearly stronger agents, and also induce more cytotoxicity, as shown in separate LDH release assays. The limitation of these invitro studies is that the concentrations tested may not reflect phospholipidosis activity due to the accumulation that occurs over time in clinical use. The clinical manifestations of

phospholipidosis depend on the target organs, in addition to the liver. As Dr. Mc Master points out, with bedaquiline, the liver, pancreas, stomach and muscle are the targets of action. Although not stated described in the preclinical studies the drug accumulates in monocytes and macrophages; these cells could also be a target for this action and hypothetically could explain some of the relapses of tuberculosis. The clinical signals related to the stomach (nausea, vomiting,) are too ubiquitous to assess in relation to hepatitis. As well, although drug accumulation and evidence of phospholipidosis were noted in the adrenals, Dr. Mc Master found no other histologic changes in the gland to suggest adrenal insufficiency. In the clinical studies, there were no obvious cases that suggest adrenal insufficiency. Conversely, while phospholipidosis was not seen in the brain, headache and dizziness were prominent adverse reactions in the clinical trials.

Figure 12



As expected from a drug that induces phospholipidosis, aminotransferase elevations are seen with bedaquiline relative to placebo, see following from the integrated summary of

"*For the controlled trials, the most frequently observed laboratory abnormalities (> 20.0% in Any bedaquiline group)*

- *hyperuricemia (90.1% and 88.5% in the Any bedaquiline and Any Placebo groups,*
- *AST increased (45.5% and 33.7%, respectively),*
- *WBC increased (23.8% and 17.3%, respectively).*

Differences were observed between the Any bedaquiline and Any Placebo groups in the percentage of subjects with graded laboratory abnormalities (difference > 5.0%) for

- *AST increased (45.5% and 33.7%, respectively),*
- *ALP increased (11.9% and 5.8%, respectively),*
- *ALT increased (19.8% and 5.8%, respectively),*
- *GGT increased (9.9% and 3.8%, respectively).*
- *hypernatremia (10.9% and 1.9%, respectively),*
- *WBC increased (23.8% and 17.3%, respectively)*

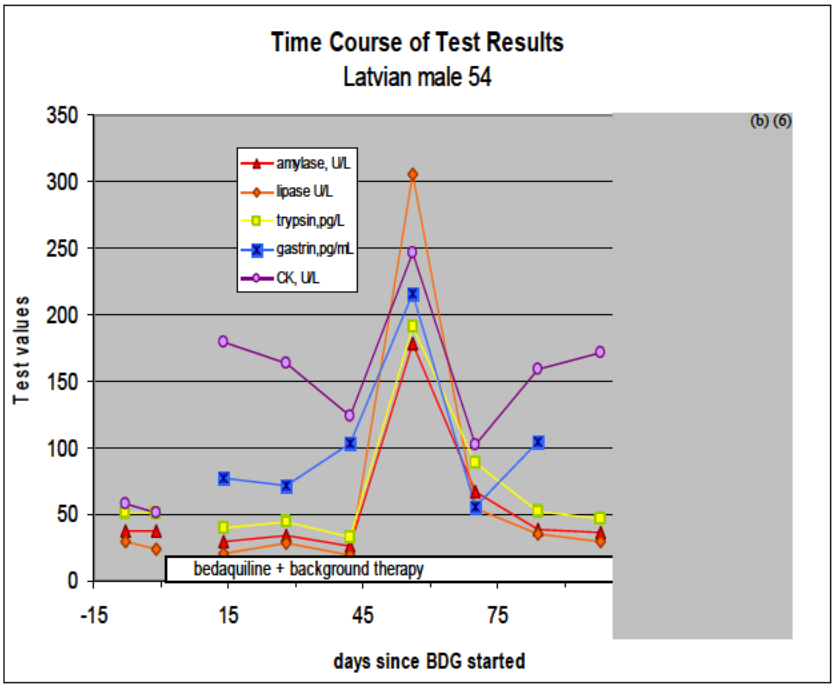
Grade 3 or 4 laboratory toxicities of were observed in ≥5.0% of subjects

- *WBC increased (in 9.9% and 4.8%,respectively),*
- *AST increased (6.9% and 0.0%, respectively),*
- *GGTincreased (5.0% and 1.9%, respectively), and*
- *ALT increased (5.0% and 1.0%, respectively).*

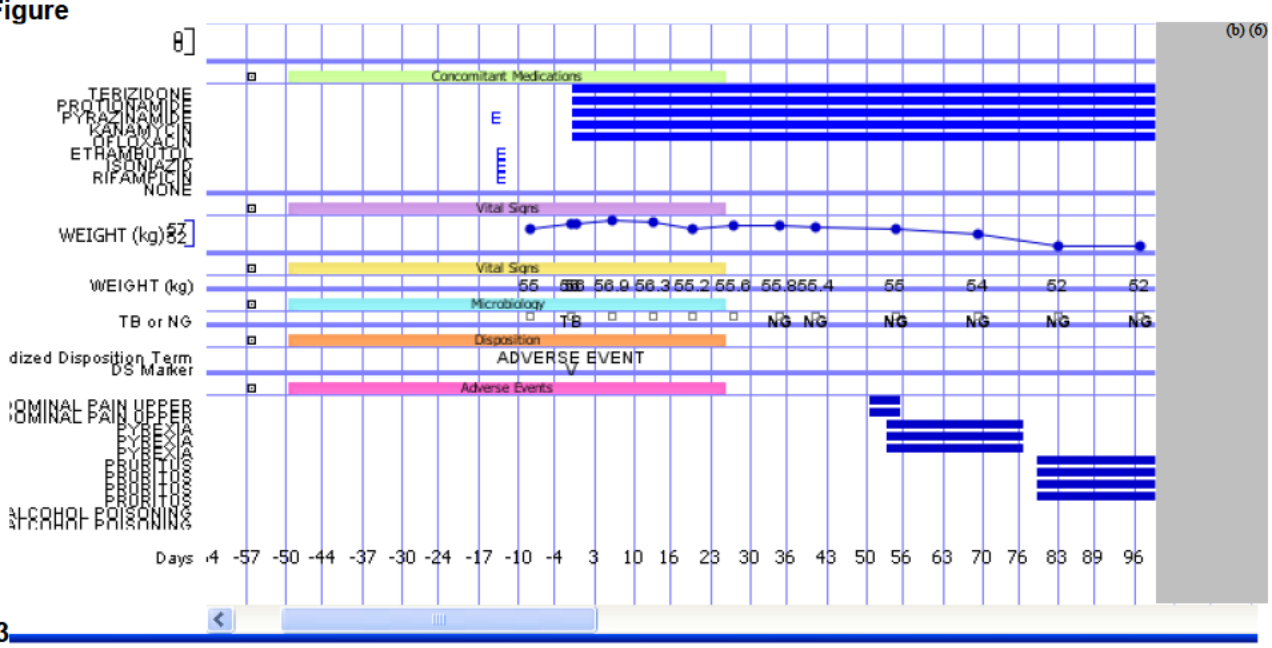
As for the concurrent finding of pancreatitis, cardiac and skeletal muscle with hepatitis, Dr. Porcalla found one patient (208-6000) with a past med history of alcoholism and chronic pancreatitis who also had elevated alk phos, GGT, amylase, and lipase at baseline/screening. He completed 24 weeks of bedaquiline but at week 40 was noted to have more pronounced GGT, and amylase. On Wk (b) (6), the patient experienced abdominal pain, was hospitalized, and a CT scan revealed reoccurrence of the pancreatitis. Grade 3 elevation of amylase was noted. This improved but recurred on D579 (Wk 80) following alcohol consumption. GGT (also increased at baseline) was raised between Wks 40-96 (Max at Wk 96 2202 N=10-61). Amylase which was elevated at baseline, was intermittently high but maximal at Wk 60 (129 N=1-46) AND Wk 96 (122). Lipase was also elevated at baseline but was normal during the bedaquiline treatment, and at Gr 3 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 (mild elevation of ALT) and GGT was confounded by alcohol use and prior history of chronic pancreatitis. Lactatemia and metabolic acidosis are not described as concurrent events.

One other patient (also described in the hepatic deaths) had concurrent elevations of analytes related to the stomach, muscle and pancreas on week 8. Patient 8 208-4041 was a 54 year old Caucasian male from (b) (6) with cavitary MDRTB who initiated therapy with bedaquiline on March 31, 2009 to July 17, 2009. He had no relevant past medical history, at screening his baseline symptoms included cough with sputum, fever, and night sweats. He did not have a history of drug allergy or hypersensitivity. Physical examination at screening revealed only abnormal cough with sputum. A serology screen for HIV was negative. The subject was randomized to bedaquiline treatment in combination with a BR consisting of KAN, OFL, protionamide, PZA, and TRD. He was confirmed to have converted to sputum negative at week 8, as well as on week 14. He developed abdominal pain on Week 8 (May 21 to 25), then fever a few days later (May 24-june 15), following defervescence, he developed pruritus (June 19 to July 14) and discontinued TMC. On week 8 the creatine kinase was 247 (N=18-198), pancreatitis (lipase of 306) (N=0-100), amylase of 178. Pancreatitis resolved at week 10 down to 67 (N=1-46) and fever and abdominal pain had resolved. Gastrin and trypsin were also mildly elevated at week 8 at 216 (N=25-111 pg/mL) and 190.8 (N=20.5-132.5 ng/mL), respectively. Pentoxyfylline, omeprazole, ranitidine, clemastine were administered and bedaquiline discontinued (17 July 2009 Day 109). He left the hospital on Day (b) (6)) and died on (b) (6)). Laboratory tests and patient profile are shown:

Time	Aphos	GRADE	ALT	Grade	AST	GRADE	BILI	Grade	EVENTS
ULN	131		43		36		7		
SCREENING	67		10		17		<2		
SCREENING	69		13		18		<2		
BASELINE	67	GRADE 0	10	GRADE 0	17	GRADE 0	<2	WITHIN	
WEEK 2	73	GRADE 0	11	GRADE 0	22	GRADE 0	<2	WITHIN	
WEEK 4	73	GRADE 0	6	GRADE 0	23	GRADE 0	<2	WITHIN	
WEEK 6	74	GRADE 0	8	GRADE 0	22	GRADE 0	2	WITHIN	
WEEK 8	74	GRADE 0	8	GRADE 0	35	GRADE 0	2	WITHIN	pnacreatitis
WEEK (b) (6)	GRADE 0	6	GRADE 0	14	GRADE 0	<2	WITHIN	fever pruritus	
WEEK	GRADE 0	24	GRADE 0	19	GRADE 0	<2	WITHIN	pruritus	
WEEK	GRADE 0	6	GRADE 0	21	GRADE 0	<2	WITHIN		



Figure



13

Figure 14 No other cases of concurrent hepatitis, pancreatitis,or muscle injury as seen.

Table 26 Laboratory Abnormalities in the Controlled and Uncontrolled (209) Bedaquiline Studies.

Laboratory parameter, Abnormality, n (%)	Investigational Treatment Phase					
	Controlled Trials				Controlled + Uncontrolled Trials	
	BEDAQUILINE		Placebo		BEDAQUILINE	
	24 Weeks	Any	24 Weeks	Any	24 Weeks	Any
Hyperglycemia, N	**78**	**101**	**80**	**104**	**307**	**330**
Grade 3	2 (2.6)	2 (2.0)	3 (3.8)	3 (2.9)	6 (2.0)	6 (1.8)
Grade 4	0	0	1 (1.3)	1 (1.0)	2 (0.7)	2 (0.6)
Any Grade	20 (25.6)	25 (24.8)	21 (26.3)	27 (26.0)	48 (15.6)	53 (16.1)
Hypoglycemia, N	**78**	**101**	**80**	**104**	**307**	**330**
Any Grade	12 (15.4)	14 (13.9)	10 (12.5)	11 (10.6)	21 (6.8)	23 (7.0)
ALT increased, N	**78**	**101**	**80**	**104**	**307**	**330**
Grade 3	4 (5.1)	4 (4.0)	1 (1.3)	1 (1.0)	8 (2.6)	8 (2.4)
Grade 4	1 (1.3)	1 (1.0)	0	0	2 (0.7)	2 (0.6)
Any Grade	19 (24.4)	20 (19.8)	6 (7.5)	6 (5.8)	45 (14.7)	46 (13.9)
ALP increased, N	**78**	**101**	**80**	**104**	**307**	**330**
Grade 3	2 (2.6)	2 (2.0)	0	0	2 (0.7)	2 (0.6)
Any Grade	10 (12.8)	12 (11.9)	6 (7.5)	6 (5.8)	12 (3.9)	14 (4.2)
AST increased, N	**78**	**101**	**80**	**104**	**307**	**330**
Grade 3	3 (3.8)	3 (3.0)	0	0	9 (2.9)	9 (2.7)
Grade 4	4 (5.1)	4 (4.0)	0	0	6 (2.0)	6 (1.8)
Any Grade	39 (50.0)	46 (45.5)	31 (38.8)	35 (33.7)	99 (32.2)	106 (32.1)
GGT increased, N	**78**	**101**	**80**	**104**	**307**	**330**
Grade 3	3 (3.8)	3 (3.0)	2 (2.5)	2 (1.9)	4 (1.3)	4 (1.2)
Grade 4	2 (2.6)	2 (2.0)	0	0	4 (1.3)	4 (1.2)
Any Grade	7 (9.0)	10 (9.9)	4 (5.0)	4 (3.8)	37 (12.1)	40 (12.1)

N = number of ITT subjects with data; n = number of ITT subjects with this observation
The number of ITT subjects with 'any grade' represents the total number of ITT subjects with that laboratory abnormality. For each laboratory parameter, only the worst abnormality (grade 1, 2, 3, or 4) of an ITT subject during the Investigational Treatment phase was taken into account (i.e., worst-case analysis), after which the total number of ITT subjects with grade 1, 2, 3, or 4 abnormalities is presented. In addition to the 'any grade' row, abnormalities of grade 3 or 4 are also mentioned separately (if applicable).
Note: The cut-off was applied to the total number of subjects with a laboratory abnormality ('any grade'). For laboratory parameters above the cut-off, grade 3 and grade 4 abnormalities are presented without cut-off for clarity. [a] hypercalcemia adjusted for albumin
Source: Module 2.7.4/BEDAQUILINE-C0000002-Anal-SAF-LAB/Display SAF.79

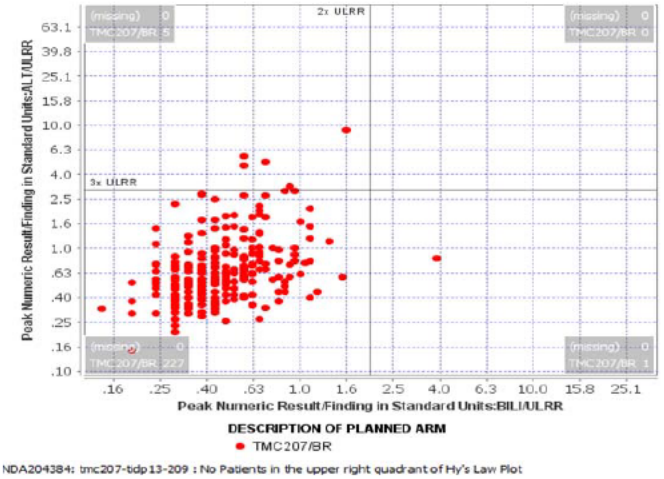
Laboratory parameters considered possibly reflective of musculoskeletal toxicity include CPK and LDH. were observed more frequently in the Any bedaquiline group (18.8%) than in the Any Placebo group (5.8%), LDH values were similar in both groups, and remained <2 X ULN , and were grade 1:

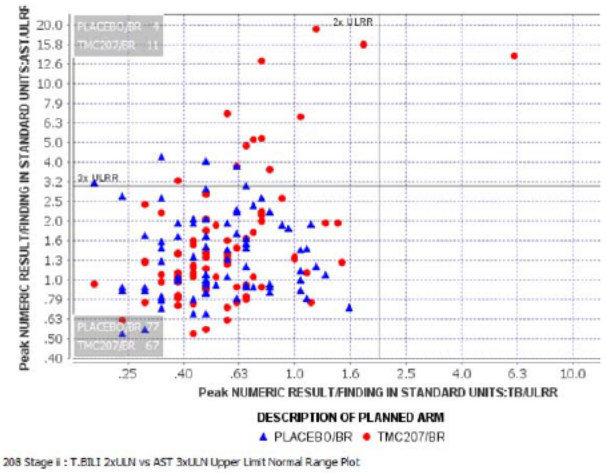
Assessment of Drug Induced Liver Injuries: Hy's law analysis

Laboratory testing for any of the viral hepatitides was not carried out, even in the endemic countries in Asia, we are unable to exclude DILI in this review. To determine if elevations of transaminases and total bilirubin met the criteria for Hy' s Law, FDA conducted an analysis of the peak transaminase (in this graph, the peak aspartate serum transaminase) and the peak total bilirubin values for each patient in Trial C208 Stage 2 and represented them in a scatter plot distribution graph. 12 bedaquiline-treated patients compared to 4 placebo-treated patients developed a peak AST of greater than 3x the upper limit of normal. Only one patient developed a peak total bilirubin lab value of greater than 2x the upper limit of normal in the noncomparative

study 209 (left) and the comparative study 208 (right). Note that elevations of aminotransferases beyond 3X ULN was infrequent in both studies.

Figure 15





•The proportion of patients who developed 3X aminotransferase elevation over ULN was greater with bedaquiline (11/79 or 16.7%) than placebo (4/81 or 6.06%) in 208 Stage 2. In Stage 1 the rate was 0 for bedaquiline and 224 for placebo in 208 stage 1 and 12/233 in Study 209, for an overall rate of 6 or 6% for placebo and 23 or 7% for bedaquiline in he entire phase 2 program One patient in Study 208 fulfilled the laboratory criteria of Hy's law. No other patients in the entire database fulfilled the criteria. The sole case is described in greater detail in the discussion of deaths below.

Deaths

The overall death rate in the development program for bedaquiline is lower than that reported in contemporaneous published studies in MDRTB [89]. The following table summarizes all deaths in the development program.

Table 27. Deaths in the Bedaquiline Clinical Program

Study	Design/ Exposure	Bedaquiline	Comparator	Difference
Study C202	Active controlled, open-label, dose-ranging, EBA study / 7 day	N=45	N = 30 (INH,RMP)	
	Deaths	2 (4.4%)	0	4.4%
C208 St. 1	Placebo controlled / 8 week	N=23	N=24	
	Deaths	2 (8.7%)	2 (8.3%)	0.4%
C208 St. 2	Placebo-controlled / 24 week	N=79	N=81	
	Deaths	9 (11.4%)	2 (2.9%)	7.5%
C209	Uncontrolled, open-label / 24 week	N=233		
	Deaths	16 (6.9%)		

The exposures in Study 202 were brief (3 and 7 days, respectively), deaths occurred off treatment and are unrelated to the drug. The rate difference in Stage1 is an artifact of the difference in denominators. There was an excess of mortality in the bedaquiline groups in one of two phase 2 placebo studies that assessed MDRTB. The statistical review team initially performed an analyses of the unexplained excess in mortality and a risk (death)-benefit (sputum conversion) analysis in the pivotal efficacy study (see Dr. Li's review). The estimate

[8] 3. Brust B et al PLOS 2011.
[9] 1. Kurbatova, E 2012 IJTLD,

of mortality changed at various time in the review process, depending on the available information. The statistical analysis of the difference in mortality and the statistical significance of the difference in rates at various times is shown below:

Table 8 Difference in Reported Death Rate for Bedaquiline and Placebo (all cause and TB related) based on FDA Statistical Reviewer's Analysis

Data source	Data Cutoff	All Deaths		TB Deaths	
		Bedaquiline	Placebo	Bedaquiline	Placebo
N0000	10 June 2011*	4/79 (5.1%)	1/81 (1.2%)	2/4**	1/1
		Difference 3.9%,, CI not stated			
4 month safety update	25 October 2012	10/79 (12%)	2/81 (2.5%)	5/10	2/2
		Difference 9.5%, CI not stated, p-value:0.017			
Response to RFI	6 December 2012	10/79 (12.7%)	4/81 (4.9%)	5/10	4/4
		Difference 7.7% [1.3%, 17.6%], p-value 0.099			
4 month safety update	25 October 2012 (120 week	9/79 (11.4%)	2/81 (2.9%)	5/10	2/2
		Difference 7.5%, [1.1%, 18.7%] p-value 0.03			

*Note that cutoff date for efficacy differed (10 May 2011) – per the protocol, patients were to be followed up by all available means up to 6 months after the last followup, thus if last seen at week 120, death reporting expected up to 6 month from end of study
**2 other early deaths were alcohol poisoning and hepatic cirrhosis

The initial estimates of death are in Dr. Li's review. Following the Advisory Committee with the sponsor's disclosure of two additional deaths based on "complete follow up data", a request for information was sent to the sponsor for clarification. The analysis for significance is provided by Dr. Li, although not in his review. The final data represented in the label comes form Dr. Li's analysis, following the statistical reviewers' decision that the cutoff of 120 weeks should be used to report all deaths to allay concerns about differential follow up of deaths between the 2 study arms following unblinding.

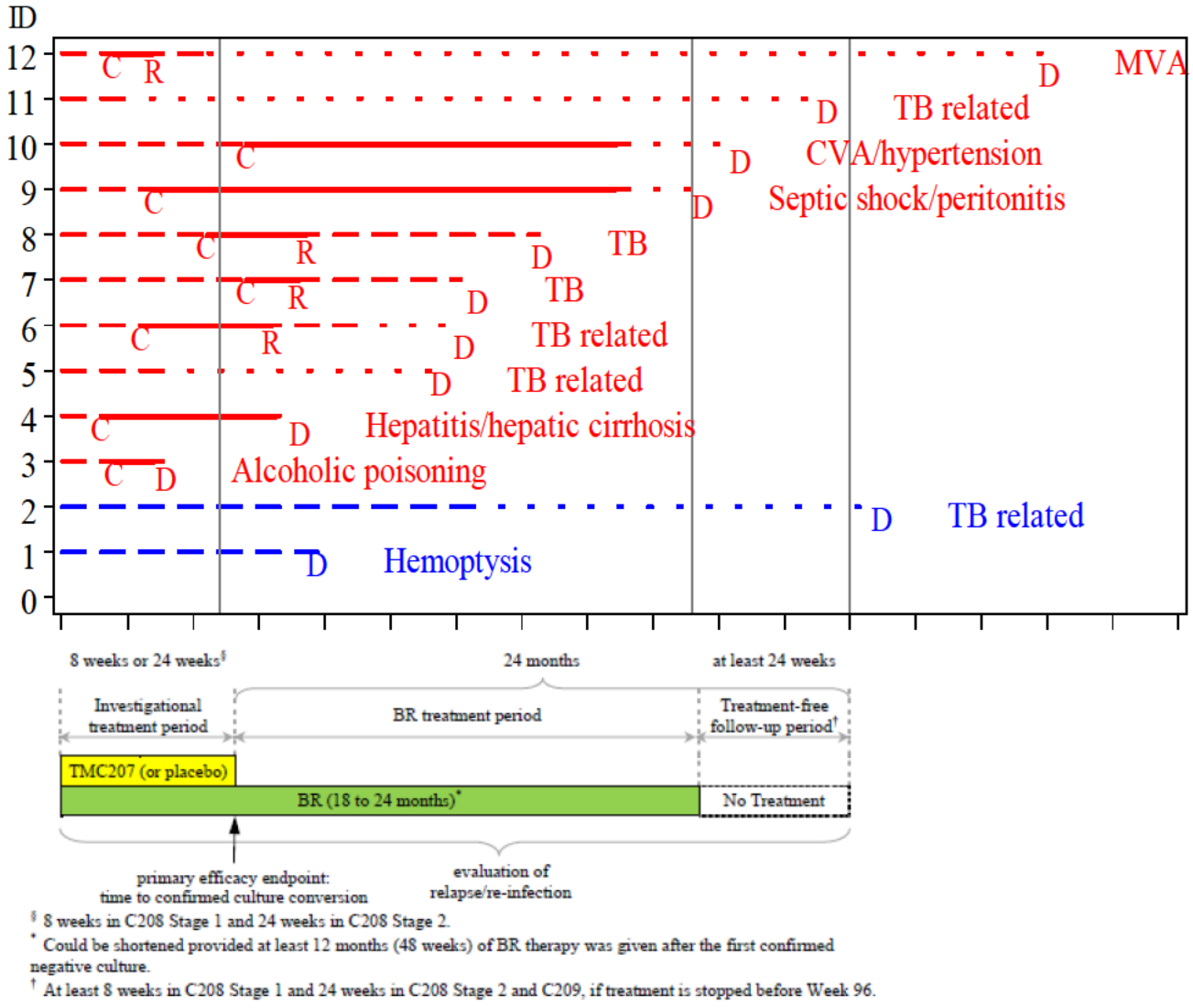
These analyses consistently showed an excess of deaths in the bedaquiline treated group, albeit the statistical significance varied depending on when the rate is assessed. Five of 10 bedaquiline deaths (1,2,3,4,and 11 in Dr. Li' figure below) and all 4 placebo deaths were caused by tuberculosis. This excess in deaths is labeled as a black box. Dr. Porcalla's clinical review of the clinical details and Dr. Li's risk factor analysis for deaths due to tuberculosis do not reveal a consistent pattern that explains the rate difference in relapse and treatment failure for TB.

Due to the potential contribution of bedaquiline to the five non tuberculous deaths and concern regarding a similar occurrence in the postmarket experience with bedaquiline, we consulted with various experts in CDER, the QT-IRT and Dr. Norman Stockbridge regarding the QT prolongation and cardiac risks with bedaquiline, and the Office of Safety Epidemiology Hepatic Team (Dr. Leonard Seef and Dr. John Senior).

Possible Cardiovascular deaths:
Due to the QT prolonging effect of bedaquiline, there was a concern that unwitnessed deaths could represent a fatal arrhythmia. Review of these deaths was not convincing of a fatal arrhythmia to the consultants, the CVA (#10)death was in a patient that had recently suffered a transient ischemic attack, the greater likelihood for the fatal event was completion of a cerebrovacular occlusion or development of a hemorrhagic stroke than an arrhythmia. The death due to a vehicular accident (#12) was concerning to some due to the long half life of

bedaquiline, but the patient was off all therapy at this point, and beyond 4 halflives of bedaquiline. Lastly the patient that had an unwitnessed death (#1) was confirmed by testing to be due to alcoholic poisoning although he also received treatment with an anti histamine not evaluated for its QT prolonging potential. (The deaths, outcomes of treatment and timing of death in relation to treatment and followup is shown below, juxtaposed with the study timeline for Study C208 Stage 2).

Figure 16



§ 8 weeks in C208 Stage 1 and 24 weeks in C208 Stage 2.
* Could be shortened provided at least 12 months (48 weeks) of BR therapy was given after the first confirmed negative culture.
† At least 8 weeks in C208 Stage 1 and 24 weeks in C208 Stage 2 and C209, if treatment is stopped before Week 96.

Hepatic contribution to death.
Relevant sections of the consult from Drs. Senior and Seeff is reproduced below in regards the assessment of potential deaths due to DILI: :

ID 208-4041 (summarized in the Hepatic Safety section (above)
"Comment LBS: Given that all liver chemistries obtained at 2 week intervals up to 2 weeks before death were normal, it seems highly unlikely that his death was a consequence of drug-induced liver injury. Since the last laboratory values reported were 2 weeks before death, it is possible that abnormal values would have been detected had blood tests been obtained closer to the time of his death. However, had hepatic failure from liver injury accounted for his death, it is very likely that he would have developed jaundice, but this was not reported when he left the

hospital 2 days before he died. ***I do not believe that his death was a result of liver injury from bedaquiline.*** *Whether or not it was indeed a consequence of alcohol intoxication is not entirely clear but the high blood alcohol level certainly points in that direction. It is important to request from the sponsor what the histologic findings were in the liver as established at autopsy since this would help determine whether he indeed had any evidence of liver disease.*
Comment JRS: Review of the report for the second part of Study 208 and inspection of the data listed for subject-patient #4041 shows that he was investigated and treated at (b) (6) *He did not give a history of alcohol abuse and denied drug allergy or hypersensitivity. …..*
Obviously there were several major deficiencies in management or reporting, and it appeared as though he had a bout of acute pancreatitis in May, not reported in the narrative. However, I concur with Dr. Seeff that this death was ***probably not*** *attributable to study drug. We can make no statement about possible liver problems due to lack of information. We recommend that the investigator be required to provide the missing information, even though it was more than three years ago, and answer the questions raised.*

ID 208-5069
A 63 year-old Asian male (not stated where he resides) with drug resistant TB, was randomized to receive treatment with study drug TMC201 on September 22, 2009. In addition, he was given kanamycin, ethionamide, ofloxacin, pyrazinamide, and ciprofloxacin (?). Baseline screening studies revealed that his liver-related chemistries were normal (ALT 12 U/L, AST 29 U/L, ALP 110 U/L, total bilirubin 5 micromols). On week 16 (January, 2010; week 16), the patient's AST value increased from the baseline of 29 U/L to 50 U/L, and remained abnormal at about the same level through week 24. Interestingly, the ALT values remained completely normal during this period as did the serum bilirubin level. No explanation was given for these abnormalities. On (b) (6), almost (b) (6) months after starting treatment, the patient developed anemia and was admitted to hospital. The study drug treatment duration had been reached and it was therefore discontinued on this date, as were the other anti-TB drugs, the latter because the investigator thought that they may have been responsible for the anemia. The patient was treated with multivitamins, folic acid, neurobion (naturally occurring multivitamins), fer-B-cal and packed red blood cells. The anemia improved and the patient was discharged from the hospital. A couple of months later (b) (6) now (b) (6) months from start of the study drug and approximately 2 months after its discontinuation, the patient was re-hospitalized because of fatigue and abdominal pain. At this time, he was diagnosed to have "hepatitis and hepatic cirrhosis." No further information is given about the hepatitis; astonishingly, there is no report on hepatitis serology so the etiology for the cirrhosis is unknown. He was found to have ascites At this time, his AST rose to 189 U/L and now for the first time, he had a raised ALT value, 89 U/L. Serum bilirubin was normal. These were the last values reported, obtained several months after the preceding series of tests. He was given a number of drugs for fluid overload and antibiotics for unstated reasons, possibly to treat spontaneous bacterial peritonitis. He died on (b) (6), stated to be the consequence of hepatitis and hepatic cirrhosis.

Comment LBS: This is not a case of dili for several reasons. The initial abnormality was only mild AST increases with consistently normal ALT and bilirubin values. The serious end-stage presentation occurred several months after stopping the study drug. The patient had all the features of chronic liver disease including cirrhosis, hardly likely to have developed so early after starting the drug, certainly in the absence of overt liver disease while on the drug. ***So this is clearly not bedaquiline dili.*** *…because only the AST is abnormal while the ALT remains normal, it is unlikely that this patient had chronic hepatitis B or C as the cause for the cirrhosis. … no*

information is given regarding alcoholism, and his weight is not indicated. In my opinion, it is important to query the sponsor about the viral hepatitis serology and what they think the cause is for the cirrhosis.

Comment JRS: Subject-patient #5069 was a very thin (BMI 16.89, 38 kg, 1.5 m) Thai male aged 63 investigated and treated by Dr. (b) (6) in Thailand from September 2009 to March 2010, and followed until his death on (b) (6). The investigator attributed death to "hepatitis and hepatic cirrhosis" but provided little or no evidence to support that opinion, and ***peritonitis was reported****.. He was treated only until 10 February 2010 (Day 170). He was then hospitalized (b) (6) for anemia, said to show ocular jaundice, and history of heavy alcohol use, and received his last dose of study medication that day (168). He was hospitalized again in (b) (6), and was followed until his death on (b) (6)). Concur:* ***not bedaquiline liver toxicity.***

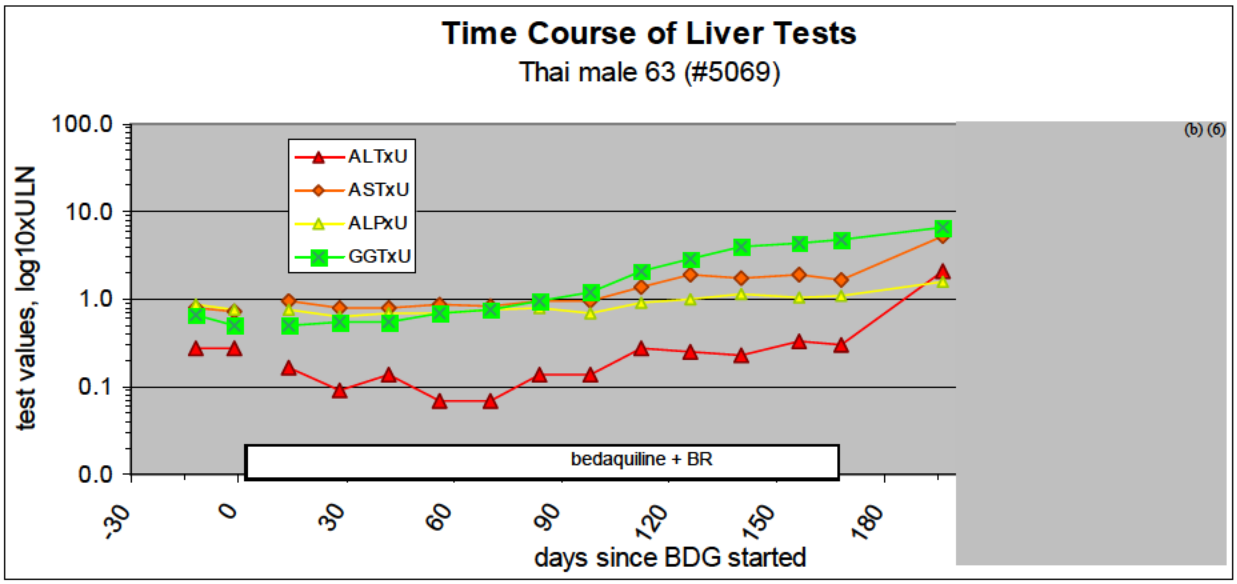


Figure 18 ID 208-5067

This was a 43 year-old man with TB and a questionable diagnosis of HIV infection who was begun on treatment with bedaquiline on a date not specified. He also received BR amikacin, cycloserine, ethionamide, ofloxacin, and pyrazinamide. His baseline liver-related chemistries were quite normal. Repeat tests were obtained at 2 week intervals until week 24 and at 4 to 12 week intervals thereafter until week 60. Slight AST abnormalities were noted on weeks 8 and 10 with normal values for the ALT. The bilirubin value was normal The AST value returned to normal until week 16 and then increased and remained fluctuatingly abnormal throughout the remainder of follow-up to week 60, the ALT value remaining normal throughout, with one exception. On week 24, the AST value increased considerably from 94 U/L to 501 U/L, with an increase in the ALT value on this occasion only to 118 U/L, a modest increase in the ALP level and an increase total serum bilirubin to a little more than twice the upper limit of normal; approximately half of this increase consisted of the indirect bilirubin value. This coincided with the completed treatment with the study drug which was discontinued at this timer. The ALT value returned to and remained normal throughout the remainder of follow-up while the AST value decreased but remained moderately abnormal throughout the remainder of follow-up. At week 84, with a normal ALT value and a moderately elevated AST value, the total serum bilirubin value suddenly increased again to a level higher than earlier, approximately three quarters representing direct-acting bilirubin. This is the last set of values shown. Beginning on week 79, the patient developed anorexia, fatigue, vomiting and on week 84, jaundice. On week

96, he developed fever, nausea and vomiting, and abdominal pain, and was diagnosed to have peritonitis. At each episode of hyperbilirubinemia, his ALP level increased modestly and then returned to normal. He was admitted to hospital to have a diagnostic work-up but died (b) (6) later with a diagnosis of peritonitis and sepsis.

Comment LBS: This patient developed only a single abnormal ALT value whereas AST values that became abnormal at week 8 of therapy remained abnormal, although fluctuating, for the remainder of follow-up to week 84. ..... Regardless, I am not aware of dili associated with persistent elevations of the AST alone so in my opinion, ***this patient did not develop bedaquiline-related drug-induced liver disease.***

Comment JRS: ***The sponsor appears to have confused the two cases #5067 and 5069, both from Thailand (Investigator: Dr. Tawatchi Wiwatorapan***
In the report of Study 208, part 2 submitted with the NDA 204384 on 29 June 2012, and entered into DARRTS as 0000(0) ORIG-1, it is stated in the detailed reports under section 5.3.5.1.3 for the narratives from study 208 stage ii that Deaths were recorded for #4041 (Latvian man 54, pages 3-21 of 1234) and #5069 (the Thai man aged 63, pages 117-138 of 1234), the latter from "hepatitis and hepatic cirrhosis" on (b) (6).

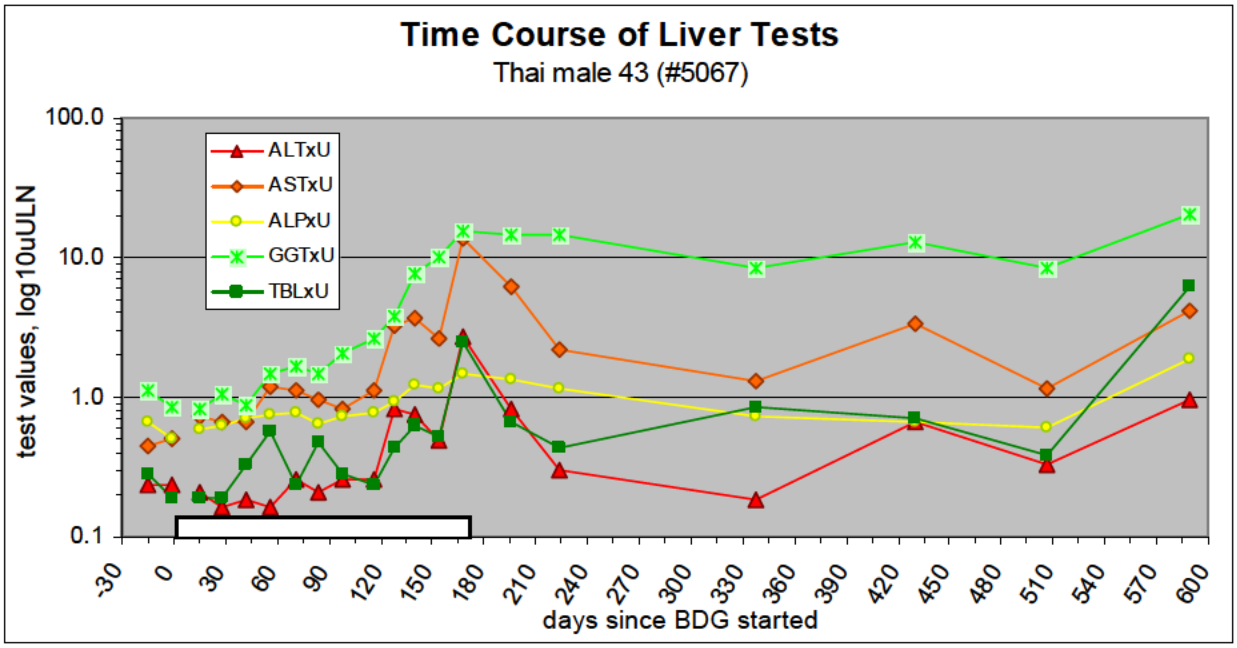


Figure 19
Case #5067, also from the same investigator in Thailand, was for the 43 year-old man who was not recorded to have died but was followed 14 months after stopping the 14-week course of study medications on 10 February 2010 when he was first found to have elevated serum total bilirubin to 52 mmol/L or 2.5xULN. That subject did not have a history of alcohol abuse recorded nor any liver test abnormalities at baseline but was followed until April 2011, about 14 months after the end of the study. The case was reported as a non-fatal Grade 3 or 4 SMQ Event (see pages 1181-1211 of the 1234 pages of those narratives).

Summary (LBS): The concern for potential hepatotoxicity from bedaqueline presumably derives from the evidence that it appears to be associated with the development of phospho-lipidosis, that there was an imbalance in serum enzyme elevations in the clinical trial, and that there are apparently three patients with liver dysfunction who died. It seems unlikely that

any of the cases presented here developed phospholipidosis to account for the biochemical abnormalities that occurred in the latter two cases since the abnormalities developed quite early, but this can only be confirmed by performing a liver biopsy. Undoubtedly, an imbalance was noted that needs confirmation. In regard to the three cases reviewed here, none appear to be a consequence of drug-induced liver injury. I cannot say with certainty that this drug is entirely cleared from an association with drug-induced liver injury in view of the limited number of persons who have received the drug. However, in my view, the current data do not support this association so that I cannot label this at present a drug of concern that needs to be labeled as requiring routine monitoring.

(JRS): I agree that these three cases do not provide evidence for a hepatotoxicity problem due to bedaquiline-induced liver injury, BUT **neither are they persuasive evidence against** possible occurrence of future cases. The clinical experience is far too limited to draw conclusions that this new drug has no likely hepatotoxicity, at least in *some* patients. Even isoniazid, well known to be a serious risk to some people because of hepatotoxicity, causes increased serum aminotransferase activities in perhaps 20% of people initially exposed, but most of them adapt even if the drug is continued, and become tolerant. Only 1 or 2 per 1000 fail to show this adaptive response and can progress to serious liver injury and to fatality if the drug is not stopped. To have a reasonable chance to detect serious liver injury in relatively rare patients, some thousands would need to be observed carefully. This new drug cannot be judged as liver-safe, based upon such a limited experience., and additional large scale evidence needs to be gathered before concluding it is at least safer than isoniazid. This is difficult to do after approval, where poor quality and scanty reports are submitted by busy practicing physicians attempting to help seriously ill patients with MDR TB.

9. Advisory Committee Meeting

An Advisory Committee discussion was held for this NDA on November 29, 2012.
The meeting materials are available at
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm293600.htm

The response and discussions to the following questions posed to the Committee are summarized in the official minutes reproduced in part below:

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

   YES: 18 ***NO: 0*** ***ABSTAIN: 0***

   Committee Discussion: *The committee unanimously agreed that the data provided by the applicant provide substantial evidence of the efficacy of bedaquiline for the proposed indication of treatment of pulmonary tuberculosis due to MDR M. tuberculosis as part of combination therapy in adults. The committee clarified that the data provided is sufficient for accelerated approval of the first drug with a new mechanism of action to treat tuberculosis in many years. Additionally, most of the committee members stated that the applicant has not provided substantial evidence of efficiacy to support traditional approval, noting that clinical cure endpoints would need to be defined and met.*

Several committee members noted the need for additional agents to combat MDR tuberculosis, particularly drugs employing a novel mechanism of action.

a. **DISCUSSION:** If not, what additional data are required?

Committee Discussion: *The committee suggested that additional data related to definitive clinical cure endpoints and consistent with World Health Organization guidelines would need to be developed and provided to support traditional approval. The committee recommended that better clinical study practices regarding patient profiles be utilized to improve data analysis and provide much more information regarding efficacy of the product in specific patient populations, including children, persons infected with HIV, and African Americans. Some committee members also stated that more data is needed on use of this product in non-pulmonary TB.*

b. **DISCUSSION:** If so, please discuss if the use of the endpoint of sputum culture conversion for the primary efficacy analysis is adequate to support traditional approval (as opposed to accelerated approval).

Committee Discussion: *The committee did not agree that the use of the endpoint of sputum culture conversion for the primary efficacy analysis is adequate to support traditional approval (as opposed to accelerated approval). The committee recommended that the applicant develop clinical efficacy data, using a definition of cure and clinical cure endpoints in order to support traditional approval. Some committee members noted that sputum conversion data is not a substitute for clinical efficacy data required for full approval.*

c. **DISCUSSION:** If so, please discuss any recommendations for labeling and use of bedaquiline.

Committee Discussion: *Regarding efficacy, some committee members recommended that there be information in the labeling about clearance differences in the African American population and the potential effects on bedaquiline efficacy.*

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

YES: 11 NO: 7 ABSTAIN: 0

Committee Discussion: *The majority of the committee voted "Yes", agreeing that the data provided by the applicant provide substantial evidence of the safety of bedaquiline for the proposed indication of treatment of pulmonary tuberculosis due to MDR M. tuberculosis as part of combination therapy of adults. Several of the committee members noted that evidence of more deaths in the bedaquiline-treated study arm was concerning yet inadequately addressed in the evidence presented. Others noted that there was not enough evidence to assess the safety of bedaquiline in HIV patients and Blacks Additionally, several committee members stated that QTcF changes and related risks were not adequately addressed, while others commended that dangerous drug-drug interactions have not been explored adequately. Some said their concerns were heightened by the long half-life of the drug and its hepatotoxic effects. Panel members voting 'yes' largely said their vote only applied if the drug were undergoing accelerated approval. Additional evidence would be needed for*

traditional approval. Those voting yes said they still had concerns about the safety evidence, including the unexplained mortality difference, but some noted they could not find a "theme" related to a bedaquiline cause and effect in the deaths. One panel member said the QTcF change evidence denotes a bit of risk, but given the seriousness of tuberculosis, would not be of such a major concern. Some voting yes noted that the drug is badly needed in the MDR tuberculosis treatment armamentarium.

a. **DISCUSSION:** If not, what additional data are required?

Committee Discussion: *The committee members who voted "No" were concerned about the higher mortality rates in the bedaquiline-treated study arm, as well as cardiotoxic and hepatotoxic effects of the drug. Several committee members commented that more patients need to be studied to provide additional evidence to explain the significance of these adverse effects.*

b. **DISCUSSION:** If so, please discuss any recommendations for labeling and risk management.

Committee Discussion: *The committee members who voted "Yes" were in agreement that mortality differences discovered in the clinical trials need to be included in the product labeling, noting that strong product labeling about QTcF prolongation and ways to mitigate cardiac risk through patient selection and monitoring must also be included. The committee suggested that information about clearance differentials in Black patients and use in HIV-TB patients would lead to safer use of the drug. Additionally, it was noted that there also needs to be information about drug-drug interactions in the labeling, including moxifloxacin and anti-retroviral drugs. For risk management, some committee members expressed concerns about the development of resistance to bedaquiline and suggested that measures be taken by FDA and CDC to promote judicious use of the product. One member specifically called on FDA and the applicant to outline plans for safe use of the product and minimizing development of resistance.*

10. Pediatrics

Tuberculosis is an orphan disease in the United States and in accordance with the requirements of PREA, the sponsor has not provided a pediatric assessment for Sirturo (bedaquiline) due to its orphan-drug designation. Discussions are ongoing about the need for a Written Request.

11. Other Relevant Regulatory Issues

- *Exclusivity or patent issues of concern,*

JANNSEN holds a general patent for the drug substance and drug product and the method of use for the treatment of MDR TB.

On 10 January 2005, bedaquiline was granted orphan-drug designation by the Office of Orphan Products Development, FDA, under request # 04-1993 for the treatment of active tuberculosis.

On 22 April 2011, bedaquiline was granted fast-track designation by FDA.
Bedaquiline) was granted priority review in accordance with Section 506(c) of the Federal Food, Drug, and Cosmetic Act and FDA's Guidance for Industry, "Fast Track Drug Development Programs-Designation, Development, and Application Review," January 2006.

Under the provision of 21 CFR §314.108(b)(2), bedaquiline will be granted marketing exclusivity in accordance with 21 CFR §314.50(j).

Upon marketing of the product a tropical disease voucher is to be issued.

As communicated in the Agency's 17 May 2012 correspondence, the sponsor is requesting a waiver of a bioequivalence study between tablets manufactured at the intended commercial site Kemwell and clinical Phase 2b tablets from Janssen R&D. The Office of Compliance is assessing the response to a 384 issued to the Kemwell manufacturing site in Bangalore, India.

- *DSI audits,*

All clinical sites passed DSI inspection.

- *other discipline consults*

A consult to QT-IRT guided the review of ECG data. A consult to Dr. Leonard Seef guided the assessment of hepatic adverse reactions. The CSC provided review support. The Office of Medical Policy and DPDP and DRISK reviewed the Medication Guide, communication plan and MedGuide.

12. Labeling

Proprietary name Sirturo ^{TM} is the approved proprietary name.
Label, Labeling and Packaging Review by Alksander Winiarski, DMEPA and Celia Cruz ONDQA concurred with the labeling information addressing repackaging. The instructions on the bottle are specifically for pharmacists, to enable repackaging in the event the tablets need to be repackaged or dispensed outside the original bottle.. This takes into consideration the possible distribution by health care provider (e.g. hospital pharmacy under supervised care), based on the expected use of this product through the national health care system. The label change was supported by additional data submitted by the Applicant, in response to ONDQA; IR on repackaging. .
The Medication Guide was reviewed by Sharon William from the OMP/DMPP/Patient Product Information Reviewer

- Risk Benefit Assessment

In both stages of the placebo controlled study C208, bedaquiline was demonstrated to confer benefit of early sputum conversion, and higher rates of conversion at end of treatment to background regimen alone. Further, at the proposed dose and duration of treatment assessed in Stage 2, some durability of sputum conversion is seen at week 72 in preliminary FDA analyses that used a stricter definition of relapse. An open label, noncomparative study also shows a similar time to sputum conversion in patient with more extensive cavitary disease and previous treatment with second line drugs. Moreover, this study enrolled patients with more limited treatment options, such as infection with XDRTB where bedaquiline was administered with QT prolonging drugs (moxifloxacin, azithromycin) and drugs associated with known mortality imbalance and lactic acidosis (linezolid). Nonetheless, the finding of mortality due to TB (3vs 1 at cutoff for the NDA, 5 vs 2 at 120 weeks and 5 vs 4 with "complete" followup), the finding early relapses, and the fourfold increase in MICs in patients whose isolates contain the atp mutation, temper the efficacy findings.

The main safety concern in the NDA was the finding of an excess mortality in the main comparative "pivotal" trials C208 Stage 2. The safety signals of QT prolongation,

aminotransferases elevations, pancreatitis, and myopathy do not distinguish bedaquiline from drugs used to treat tuberculosis. There has been no clear signal that the drug' induces mitochondrial toxicity – only wider experience can clarify this. As well, the drugs that we would prefer to use for tuberculosis, isoniazid and rifampin, have definite inherent risks, although for the intended population of MDRTB, drug resistance deprives any benefit to be gained from their use. The safety of current treatment approaches that necessitate various combinations of at least 3 active drugs , have not been systematically studied, although certainly improved outcomes have been seen as greater experience is gained in the treatment of the disease.

The finding of a favorable risk benefit is driven by a recognition that TB is a fatal disease treated with toxic therapies. Uncertainty regarding the durability of benefit and concerns about serious toxicity remain. The small database and incomplete study results from the pivotal studies preclude traditional approval for bedaquiline and mandates continued study. The submission and review of complete final outcome data from Studies 208 and 209, and data from the study 210, will need to confirm that the surrogate endpoint of time to sputum conversion does correlate with durable cure, or in the least is not associated with poorer outcomes. An excess of deaths from causes other than TB is unexplained as well; although none are related to QT prolongation and none are considered to be related to DILI. The small studies result in a very unstable event estimate and the incomplete information collected (such as viral hepatitis serologies) do not allow definitive causality assessments. The serious events of concern (QT prolongation, pancreatitis, potential for hepatic injury) are monitorable. Restricting use to patients with limited options (at least 3 other drugs that can be used to effectively treat drug resistant TB), a requirement to monitor for expected toxicity (ECGs, aminotransferases and bilirubin), advice to avoidance of concurrent hepatotoxins such as alcohol and to adhere to directly observed therapy, together with issuance of a medication guide are the mechanisms to preserve benefit and mitigate risk through in a non REMS risk management program. This approach is consistent with other drugs for serious disease that are also associated with serious risk, such as oncologic cancer agents. Tuberculosis is a reportable disease in the US and care of TB patients is inevitable a partnership with the public health care system. The US public health system provides training and management expertise, diagnostic infrastructure, and surveillance and reporting mechanisms to support TB treatment. Until greater experience is gained and the use studied more broadly, the use of bedaquiline outside this setting may not deliver anticipated benefit or be associated with increased risk.

There is limited experience in patients with HIV, the elderly (aged >65 years), pediatric patients (aged < 18 years), nursing mothers, and during pregnancy. Patients with severe hepatic insufficiency should be treated only if the benefit outweighs the risk.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The sponsor proposed the following components of a Risk Minimization Plan:

1. a Medication Guide
2. Distribution through the public health authorities
3. A communication plan
4. Patient registry

The approval letter provides details of the final elements of this plan developed with the FDA.

- Recommendation for other Postmarketing Requirements and Commitments

At the time of completion of this review, the following were the PMRs and PMCs being considered:

1. Conduct a confirmatory trial: Randomized double blind placebo controlled 2 arm multicenter phase III trial in subjects with sputum smear-positive pulmonary infection with MDR-TB. This study should assess long term outcome of failure or relapse or death at least 6 months after all MDR-TB treatment is completed.

- Final Protocol Submission:June 2013
- Trial Completion: July 2020
- Final Report Submission: March 2021

2. Develop a patient registry for bedaquiline-treated patients that captures the following:
   a. indication for use
   b. susceptibility data for baseline and repeated when there is clinically suspected relapse or failure or when no culture conversion is seen after 6 months of treatment
   c. drug utilization data
   e. patient outcomes (clinical and microbiologic)
   f. safety assessments in bedaquiline-treated patients, including deaths.
   g. Concomitant TB medications

- Feasibility assessment of implementing a registry by Mid March 2013
- Final Protocol Submission: June 2013
- Trial Completion: December 2018
- Final Report Submission: August 2019

3. Provide information on the planned drug distribution mechanism

- Submission: By March 30, 2013

4. Conduct a prospective study over a five-year period after introduction of SIRTURO (bedaquiline) to the market to determine susceptibility of MDR TB to bedaquiline for the first 5 years from marketing. Provide a detailed protocol describing the study to the Agency for review and comment before commencing the study.

- Final Protocol Submission: April 30, 2013
- First Interim Report: xxx, and then annually Dec 31, 2014
- Trial Completion: Sept 30, 2017
- Final Report Submission: Dec 31, 2017

5. Provide data on the interaction of bedaquiline and efavirenz to determine a safe and effective dose regimen of both drugs when they are coadministered in HIV co-infected MDR-TB patients.

- Submission of Existing report: March 30, 2013
- Submission of final report from subsequent analyses: September 30, 2013

Post Marketing Commitments:

1. 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: April 2013
- Trial Completion: October 2013
- Final Report Submission: December 2013

2. Conduct a study to define the Quality Control ranges of bedaquiline for *M. tuberculosis* isolates using Agar MIC method.

- Final Protocol Submission: March 31, 2013
- Trial Completion: September 30, 2014
- Final Report Submission: December 31, 2014
-

Conduct a study to define the Quality Control ranges of bedaquiline for *M. tuberculosis* isolates using liquid based MIC methods.

- Final Protocol Submission: March 31, 2013
- Trial Completion: September 30, 2014
- Final Report Submission: December 31, 2014

Submit the complete study report for Study C208 and C209.

- Recommended Comments to Applicant

Eileen Navarro, MD
Cross-Discipline Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EILEEN E NAVARRO ALMARIO
12/21/2012