CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204384Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	(electronic stamp)
From	Katherine Laessig, MD
Subject	Deputy Division Director Summary Review
NDA #	204-384
Applicant Name	Janssen Pharmaceuticals
Date of Submission	June 29, 2012
PDUFA Goal Date	December 29, 2012
Established (USAN) Name	Bedaquiline, tradename Sirturo™
Dosage Forms / Strength	100 mg tablets
Proposed Indication(s)	Treatment of multi-drug resistant pulmonary tuberculosis in adults
Recommended Action:	Approval with indication as follows: Bedaquiline is indicated for treatment of pulmonary multi-drug resistant tuberculosis as part of combination therapy only when an effective treatment regimen cannot otherwise be provided.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ariel Porcalla
Statistical Review	Xianbin Li
Pharmacology Toxicology Review	Owen McMaster
Product Quality Reviews	Celia Cruz, Lin Qi, Minerva Hughes
Microbiology Review	Lynette Berkeley
Clinical Pharmacology Reviews	Dakshina Chilukuri, Fang Li, Zhixia (Grace) Yan, Seong Jang, Justin Earp, Kevin Krudys, Kimberly Bergman, Philip Colangelo, and Yaning Wang
CDTL Review	Eileen Navarro
Labeling Reviews	Aleksander Winiarski
QT-IRT	Monica Fiszman, Kevin Krudys
OSE	John Senior, Leonard Seeff

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
QT-IRT=QT Interdisciplinary Review Team
OSE=Office of Surveillance and Epidemiology

1.0 Background

Janssen has submitted NDA [redacted] (b) (4) in support of the requested indication of treatment of multi-drug resistant pulmonary tuberculosis (MDRTB) in adults under 21 CFR 314.500 (Subpart H), i.e. the accelerated approval regulations. The endpoint for the pivotal trials is sputum culture conversion, which was previously recommended as a surrogate marker reasonably likely to predict clinical benefit by the Anti-infective Drugs Advisory Committee convened in June 2009.

The World Health Organization estimated the incidence of global MDRTB at 310,000 in 2011; however, only 19% of MDRTB is reported to WHO.[1] In the United States, there were only ~100 cases of MDRTB reported to the CDC in 2010.[2] MDRTB is defined as resistant to isoniazid (INH) and rifampin (RIF), two of the first line drugs to treat MDRTB. The treatment of MDRTB is complicated and costly, and involves the use of drugs that are not indicated for tuberculosis and have significant associated toxicities. The treatment of MDRTB may last for 2 years, and compliance is problematic. The two most important classes of second-line anti-TB drugs are the injectable drugs (capreomycin [CAP], amikacin [AMK], and kanamycin [KAN]) and the fluoroquinolones (FQs). Other options include cycloserine, para-aminosalicylic acid, and ethionaminde. Mortality ranges from 8 to 21% for MDRTB, even on standard-of-care treatment regimens.[3]

This memo will summarize important findings and conclusions by review discipline. For further details, please refer to discipline specific reviews and the CDTL memo.

2.0 Product Quality

The application has been reviewed by three product quality reviewers: Dr. Celia Cruz (Drug Product), Dr. Lin Qi (Drug Substance), and Dr. Minerva Hughes (Biopharmaceutics). They have concluded that the information provided by the applicant is sufficient to assure the identity, strength, purity, and quality of the drug, and that the proposed dissolution method and acceptance criterion are acceptable. The Office of Compliance has made a final recommendation of acceptable for the manufacturing establishments filed in this NDA.

The drug product, Sirturo Tablets, 100 mg, are uncoated, immediate release tablets for oral administration, containing 120.89 mg of bedaquiline fumarate drug substance, equivalent to 100 mg bedaquiline free base. The tablet is white, round, biconvex, with a

[1] Accessed at: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf

[2] Accessed at http://www.cdc.gov/tb/statistics/reports/2010/pdf/report2010.pdf

[3] Wells CD. Tuberculosis among HIV-infected and other immunocompromised hosts: epidemiology, diagnosis, and strategies for management. Curr Infect Dis Rep. 2010; 12: 192-7

diameter of 11 mm. It is debossed with "T" over "207" on one side and "100" on the other side. The maximum daily dose is 400 mg per day.

The tablet formulation contains (b) (4)% loading of bedaquiline fumarate drug substance and the following compendial excipients: lactose monohydrate, corn starch, hypromellose 2910 15 mPA.s, polysorbate 20, purified water, microcrystalline cellulose, croscarmellose sodium, colloidal silicone dioxide, and magnesium stearate.

Bedaquiline tablets are manufactured (b) (4) All methods to assure drug product quality have been adequately validated and specification limits justified appropriately.

The stability results support a 24 month shelf life for the drug product in the current 160 mL HDPE bottle for all climatic zones and the proposed product label statement of "Store at (b) (4) 25ºC ((b) (4) 77ºF); excursions permitted to 15-30ºC (59-86ºF)." The data also support an alternative label of "Do not store above 30ºC" per WHO guidelines for Zone IV countries. The long term storage conditions for stability commitment batches is 30 ºC/75% RH.

The drug substance (DS), bedaquiline fumarate, is a white to almost white powder, (b) (4) . It is practically insoluble in aqueous media over a wide pH range. (b) (4) It is a single enantiomer containing two asymmetric carbon atoms with R- and S- configurations, respectively, for the (b) (4)

Bedaquiline fumarate is made from (b) (4) starting materials through (b) (4) . Critical Process Parameters (CPPs) and Proven Acceptable Ranges (PARs) establish an overall process control, in combination with normal GMP controls and release testing. Two genotoxic impurities, (b) (4) are controlled by (b) (4) specification and by demonstration of adequate purging during subsequent processing.

3.0 Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Owen McMaster, recommends approval. He notes that the nonclinical toxicology program was comprehensive and included in vitro and in vivo studies in mice, rats, dogs, rabbits, and guinea pigs. The applicant evaluated the effects of bedaquiline administration for up to three months in mice, six months in rats, and nine months in dogs via daily and intermittent dosing (two to three times weekly). There were also evaluations of genotoxic potential, embryofetal toxicity, effects

on pre- and postnatal development, local tolerance, immunotoxicity, and mechanistic studies.

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

Bedaquiline and M2 were shown to inhibit IKr in in hERG transfected kidney cells with IC_{50} values of 0.2 mcg/mL for both compounds. This is not considered a strong hERG blocker since the positive control, astemizole, which is known to prolong the QT interval, inhibited IKr with an IC_{50} in the nanomolar range. Bedaquiline did not increase the QT interval in dogs dosed with a single oral or IV dose or in telemetered dogs dosed with 100 mg/kg for six days. In one six month dog study, dogs showed slight increases in the QTc (+12 to +16%) interval after two months of dosing at 40 mg/kg/d. Cardiac troponin was increased at several time points, and cardiac lesions in these dogs consisted of minimal multifocal lymphohistiocytic infiltrates with degeneration of cardiomyocytes and/or minimal to slight endocardial fibrosis. These changes were also associated with elevated levels of total CK. However, no similar EKG changes or cardiac lesions were detected in a nine month dog study using a lower dose (18 mg/kg/d), despite increases in cardiac troponins.

Other findings of note in the animal toxicology studies included phospholipidosis, mainly in cells of the monocytic phagocytic system (MPS). All species showed accumulation of pigment-laden and/or foamy macrophages, mostly in the lymph nodes, spleen, lungs, liver, stomach, skeletal muscle, pancreas, and/or uterus. These findings were slowly reversible upon treatment cessation. Degenerative changes in skeletal muscles were seen in mice, rats, and dogs treated with high doses of bedaquiline. Myopathy was also observed in rats after six months of bedaquiline at 20 mg/kg/d, but this finding disappeared by the end of a 12 week, drug-free, reversibility period. In several studies, bedaquiline was associated with damage to the stomach lining. The degeneration and necrosis of the fundic mucosa of the stomach observed in one dog study of bedaquiline at 40 mg/kg/d after 13 weeks (exposure about four times the clinical exposure) was no longer seen when the dose was reduced to 20 mg/kg/d. In several studies, focal to multifocal chronic pancreatitis with acinar cell atrophy was observed in mice and dogs.

These changes appeared to be dose and duration related. Hepatocellular centrilobular hypertrophy was seen in all species and was often accompanied by increased liver weight and increases in liver enzymes. Although some changes, such as liver hypertrophy, were not detected at the end of a reversibility period in the recovery studies, in some instances, signs of phospholipidosis persisted, although diminished.

Bedaquiline showed no evidence of genotoxicity, no adverse effects on mating or fertility, and was not teratogenic. A two-year oral carcinogenicity study is ongoing.

4.0 Clinical Pharmacology

The clinical pharmacology review team finds that this information provided by the applicant in support of the accelerated approval is acceptable and supports the proposed dose regimen for bedaquiline for the treatment of MDRTB. The important findings from the clinical pharmacology review are discussed below.

The pharmacokinetics of bedaquiline are dose-proportional over the range of doses from 10-700 mg. The Tmax is ~5 h and a high fat meal increased Cmax and AUC by two-fold; therefore, bedaquiline should be administered with food. Protein binding is >99%. Bedaquiline is metabolized primarily by *N*-demethylation to M2 and M3 by CYP3A4 and fecal excretion is the major route of elimination. The terminal half-life is 4-5 months, likely as a result of the cationic amphiphilic characteristics and its propensity for accumulation in tissues. However, the effective half-life is approximately 24 hours, based on the approximately two-fold accumulation after two weeks of daily dosing. Bedaquiline is orally bioavailable, with the Cmax achieved around 5 hours after administration. In healthy subjects and DS-TB infected subjects, the exposure to bedaquiline increases in an approximately dose-proportional manner, indicating linear pharmacokinetics after repeated dosing to 400 mg.

Based on urine concentrations of bedaquiline in two Phase 1 trials, it appears that there is negligible renal excretion of unchanged bedaquiline. Creatinine clearance was not associated with bedaquiline exposure in the population pharmacokinetic analysis. The applicant has proposed no dose modification for patients with mild or moderate renal impairment, and use with caution in patients with severe renal impairment or ESRD. However, the clinical pharmacology team is recommending that a cohort of 6-8 subjects with severe renal impairment should be included in the confirmatory Phase 3 trial and PK evaluations conducted in those patients. No dose adjustment is needed in patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the PK of bedaquiline has not been studied. Given that bedaquiline is metabolized by hepatic enzymes, it is important to evaluate the PK in patients with severe hepatic impairment. Therefore, the confirmatory Phase 3 trial should also include a cohort of 6-8 subjects with severe hepatic impairment and PK collected from those subjects.

There is no clinically relevant effect of age, sex, body weight, HIV coinfection, or extent of *M. tuberculosis* resistance on the pharmacokinetics of bedaquiline. Population pharmacokinetic modeling indicated that bedaquiline exposure is 34% lower in black patients compared to other races. As no clear relationship between exposure and efficacy was seen in the Phase 2 trials, the lower exposures are not considered to be clinically relevant.

Bedaquiline has either no or only weak potential to induce or inhibit CYP isoenzyme activity. Thus, bedaquiline is unlikely to affect the exposure of coadministered drugs. Coadministration of bedaquiline with CYP3A4 inducers may decrease bedaquiline exposure, as observed in a drug-drug interaction trial with rifampin. Therefore, coadministration of bedaquiline with CYP3A4 inducers is not recommended.

Coadministration of bedaquiline with CYP3A4 inhibitors may increase bedaquiline exposure, as observed in a drug-drug interaction study with ketoconazole and lopinavir combined with low dose ritonavir. Therefore, coadministration of bedaquiline with moderate or strong CYP3A4 inhibitors for more than two weeks is not recommended. There was no significant effect of bedaquiline on the exposure to background TB regimen for ethambutol, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone.

There is no clear relationship between exposure to bedaquiline and efficacy in MDRTB infected subjects within the range of exposures with the proposed therapeutic regimen. The exposure-safety relationship indicates no strong relationship between exposure and incidence of most frequently reported AEs such as nausea, headache, chest pain, and arthralgia.

The single dose thorough QT study with 800 mg of bedaquiline showed no significant QT prolongation effect of bedaquiline. The largest upper bound of the two-sided 90% CI for the mean difference between bedaquiline and placebo was below 10 msec, the threshold for regulatory concern. However, the single dose QT trial was insufficient to characterize the potential of bedaquiline/M2 to prolong the QTc interval because since it was a single dose trial, M2 exposure never achieved clinically relevant concentrations. In addition, the finding of a positive concentration-QTc relationship suggests that M2 concentrations are responsible for the QTc prolongation observed in Trial C208. Therefore, the assessment of QT prolonging effects of bedaquiline is based primarily findings from Study C208 Stage 2 where patients received up to 24 weeks of bedaquiline treatment, as discussed in the Summary of Clinical Safety below. In the product labeling, the QT Interdisciplinary Review Team recommends that ECGs should be monitored for QT prolongation and coadministration with other QT prolonging medications should be avoided.

5.0 Clinical Microbiology

The clinical microbiology reviewer concluded that the microbiologic aspects of this application appeared scientific, thorough, methodological, and accurate. From her perspective, the application is recommended for approval. Notable findings from her review include:

- Bedaquiline, a diarylquinoline, represents a new class of antimycobacterial drugs. Its mechanism of action is via inhibition of ATP (adenosine 5'-triphosphate)-synthase 3 and inhibits production of energy in mycobacteria, and as a result, the bacteria die. In vitro, bedaquiline inhibits both actively replicating and non-replicating drug-sensitive (DS) and drug-resistant *Mycobacterium tuberculosis*. Drug-sensitive tuberculosis does not have decreased susceptibility to any available therapies used to treat TB, while drug-resistant TB is defined as resistance to at least isoniazid and rifampin. One study showed that bedaquiline killed dormant cells found in latent tuberculosis even though there are low cellular ATP levels during latency.
- Bedaquiline has > 20,000 fold lower affinity for human mitochondrial ATP synthase than it has for mycobacterial ATP synthase.
- The main resistance mechanism, based on in vitro studies, is due to mutations in the *atpE* gene. Recent in vitro studies have shown that major resistance is caused by substitutions in at least six different amino acids. The most common mutation conferring an increase in MIC of 133 fold was a substitution of Ala63 to Pro. This resulted in a dose dependent decrease in ATP. Notably, the MDRTB isolates from the clinical trials of bedaquiline that developed increased MICs to bedaquiline during the course of the studies were not found to have resistance mutations in the *atpE* gene. Therefore, at least one other mechanism of resistance to bedaquiline seems likely.
- Cross resistance was tested against other TB drugs (isoniazid, rifampin, streptomycin, ethambutol, pyrazinamide, PA-824, amikacin, moxifloxacin) and no cross-resistance with those drugs was identified.
- Mouse peritoneal macrophages and J774A.1 cells were used to investigate the intra- and extracellular activity of bedaquiline. The bactericidal effect of bedaquiline was slow extracellularly and rapid intracellularly.
- Bedaquiline was tested in vitro with other antimycobacterial drugs to evaluate for any interactions. There was no antagonistic effect with any of the drugs tested (pyrazinamide, moxifloxacin, isoniazid, and rifampin).
- Results of both agar and Reasurin Microtiter Assay (REMA) susceptibility testing indicated that there was no correlation between the MIC values, proposed breakpoints, and clinical outcomes. Although the microbiology reviewer proposed breakpoints for the package insert in her review, during internal discussion it was agreed that the data were insufficient to permit

recommendations for susceptibility criteria in the package insert, pending additional data from the confirmatory Phase 3 trial.

6.0 Summary of Clinical Efficacy

The statistical reviewer concludes that the efficacy of bedaquiline is supported by the trials contained in the application and the application is recommended for approval. However, he expressed concern regarding an imbalance in deaths seen in Study 208 Stage 2 and recommended that the imbalance in deaths should be conveyed in the product labeling. The imbalance in deaths will be discussed further in the Summary of Clinical Safety below.

In this NDA, data from two Phase 2 clinical trials were reviewed for efficacy. Study C208 is a Phase 2, multicenter, stratified, double-blind, randomized, placebo-controlled trial with two consecutive but separate stages. The first stage is exploratory and the second stage is a pivotal trial. C209 is a single-arm, open label study to provide additional efficacy and safety data. As this NDA is submitted under the accelerated approval regulations (21 CFR 314.500 Subpart H), a confirmatory Phase 3 trial is planned that will confirm the efficacy findings from trials C208 and C209 and provide additional safety data on another 300 subjects exposed to bedaquiline (total study N=600).

Study C208 Stage 1 was a Phase 2, double-blind, randomized, placebo-controlled study of 47 subjects with multi-drug resistant pulmonary tuberculosis (MDRTB), who were sputum smear positive, and randomized 1:1 to background regimen (BR) with either placebo or bedaquiline. Forty-four subjects were enrolled. Treatment with placebo or bedaquiline in addition to the background regimen was for 8 weeks, then the placebo or bedaquiline was discontinued and the background regimen was continued for a total of 72 to 96 weeks. Bedaquiline was dosed as 400 mg daily for the first two weeks, followed by 200 mg three times weekly for the following six weeks. All treatment was administered via directly observed therapy (DOT). Subjects were stratified by trial site and by the extent of lung cavitation (i.e. either no cavity or <2 cm, cavitation in one lung, or cavitation in both lungs, with cavitation defined as the presence of at least one cavity $\geq$ 2 cm), as determined by chest x-ray at screening. The primary endpoint was time to sputum culture conversion (SCC) during treatment with bedaquiline or placebo, which was based on the qualitative assessment of culture growth in the BACTEC™ MGIT™ (mycobacteria growth indicator tube) system. The culture conversion rate at 24 weeks was assessed as an important secondary endpoint.

Sputum culture conversion was defined as two consecutive negative cultures from sputa collected at least 25 days apart. All intermediate cultures had to be negative as well. Sputum culture conversion was negated when followed by a confirmed positive MGIT result (defined as two consecutive visits with positive sputum results, not taking into

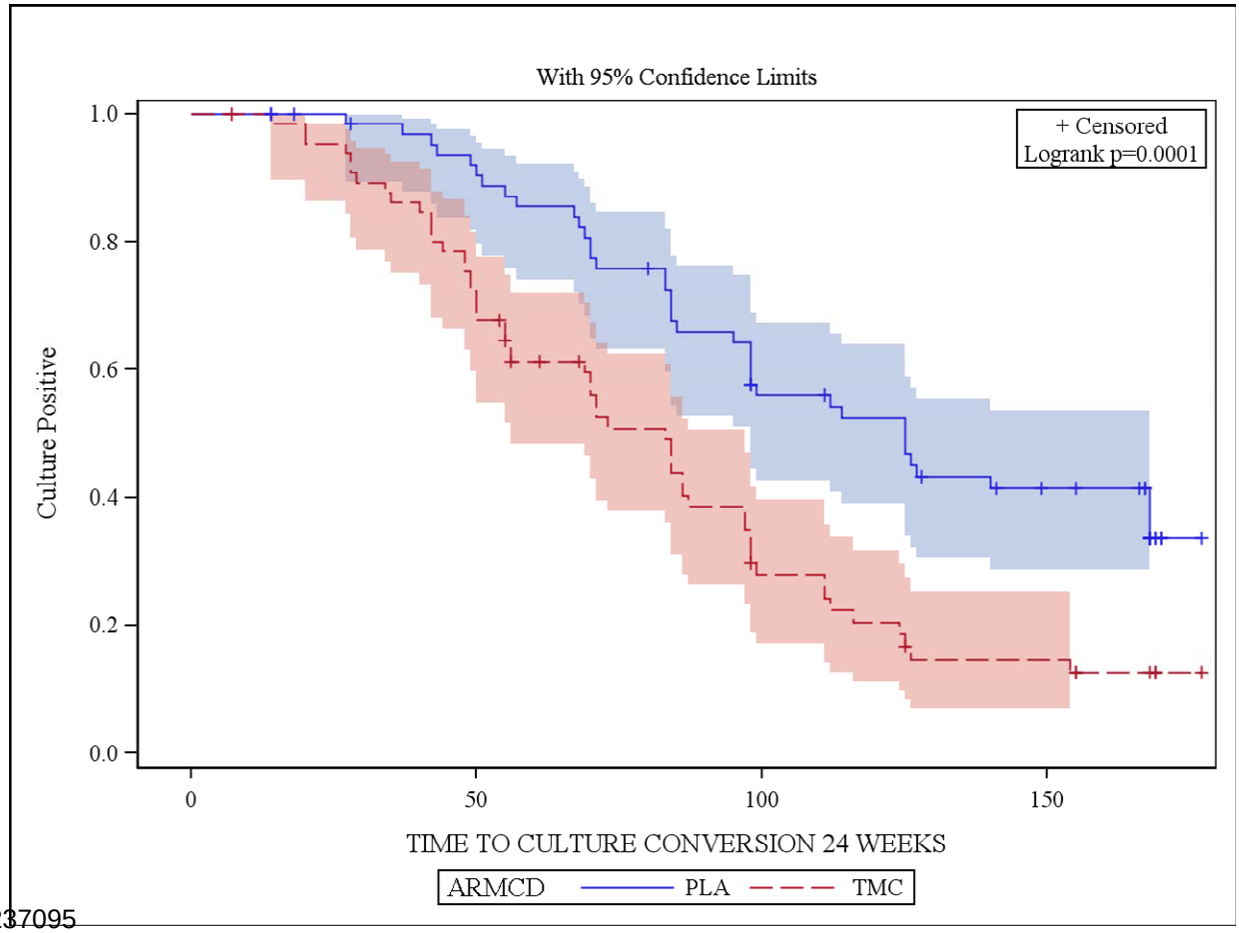
account intermittent, missing, or contaminated results, or a single positive sputum result after which the subject discontinued or completed study). Time to sputum culture conversion was calculated as the interval in days between the date of treatment initiation for MDRTB and the date of the first of two consecutive negative sputum cultures.

Stage 2 of Study C208 was similarly designed to Stage 1; however, 161 subjects were enrolled and treated with bedaquiline or placebo plus BR for 24 weeks, followed by continuation of BR for 72-96 weeks.

Study C209 is an ongoing, Phase 2, single-arm, open-label study to evaluate the efficacy, safety, and tolerability of bedaquiline plus BR in the treatment of adults with pulmonary MDRTB. The bedaquiline dose, treatment duration, and follow-up duration are the same as in Study C208 Stage 2. The primary efficacy endpoint and main secondary endpoints are the same as well. The NDA contains the results of a planned interim analysis that was performed when all subjects had completed 24 weeks of treatment with bedaquiline or had discontinued. Two hundred thirty-three subjects were enrolled in Study C209.

C208 Stage 2 is considered the pivotal trial for this application, with C208 Stage 1 and C209 providing supportive evidence. Analysis of the primary efficacy endpoint, time to SCC, for C208 Stage 2, demonstrated a median time of 83 days for the bedaquiline treatment group (95% CI: 56, 97) compared to 125 days for the placebo group (95% CI: 98, 168). Figure 1 below depicts the Kaplan Meier curve for time for this analysis.

Figure 1. C208 Stage 2: Primary efficacy analysis: Time to SCC



Source: FDA Statistical Review pg. 31

The results for culture conversion rates at week 24 in the microbiological intent-to-treat (mITT) population are shown in Table 1 below.

Table 1: Culture conversion rates at Week 24 in the mITT population, Study C208 Stage 2

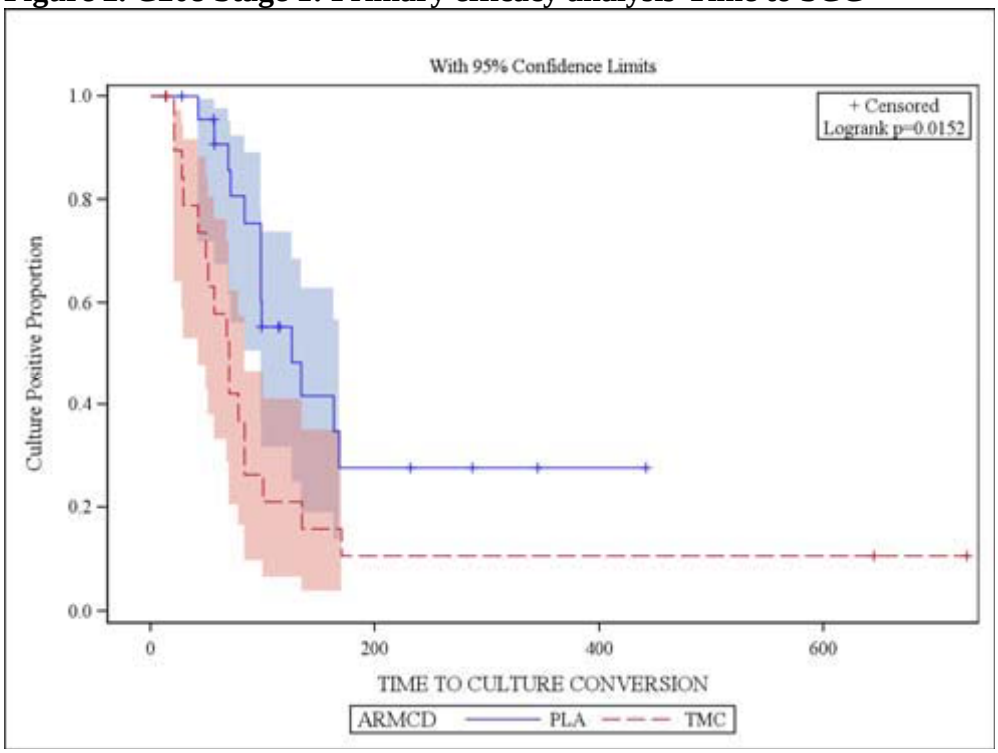
Microbiologic Status at Week 24	Bedaquiline	Placebo	Diff [95% CI] p-value
Treatment success	52 (79%)	38 (58%)	21% [5.7%, 36.7%] 0.008
Treatment failure	14 (21%)	28 (42%)	
Failure due to lack of conversion	5 (7.6%)	16 (24.2%)	
Failure due to discontinuation	9 (13.6%)	12 (18.1%)	

Source: FDA Statistical Review pg. 32. The reported 95% CI was calculated by the reviewer.

The difference between the rates for the bedaquiline treated subjects compared to the placebo treated subjects was 21%, and statistically significant.

Figure 2 below demonstrates the Kaplan Meier curves for the time to sputum culture conversion by week 8 for Study C208 Stage 1. The time to SCC was statistically significantly faster in the bedaquiline group compared to the placebo group.

Figure 2. C208 Stage 1: Primary efficacy analysis-Time to SCC



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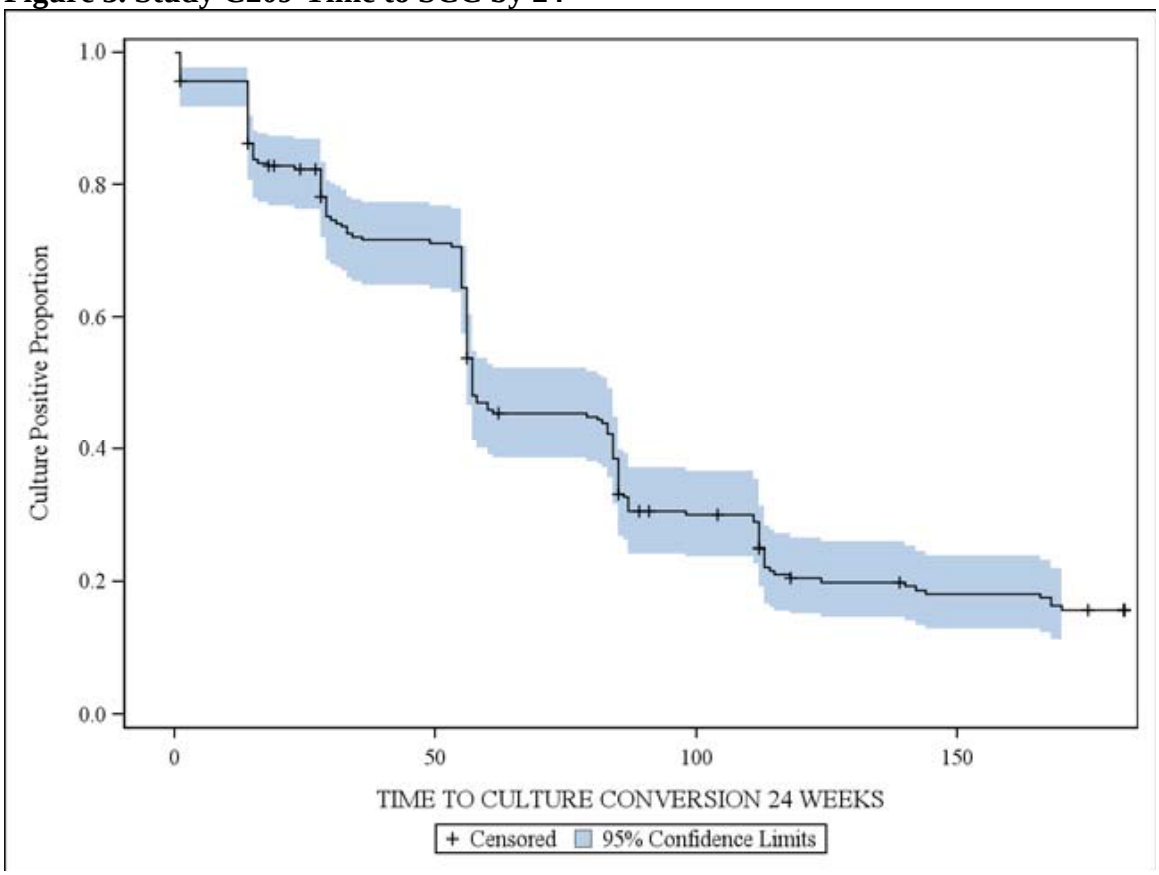
Source: FDA Statistical Review

Although Study C209 is a single arm study, the Kaplan Meier results for time to SCC by week 24 are shown in Figure 3 below. The median time to sputum culture conversion for the mITT population was 57 days, which is fairly consistent with the median time of 83 days in Stage 2 of C208.

Figure 3. Study C209-Time to SCC by 24



Source: FDA Statistical Review

One notable finding from Dr. Li's review is for Black subjects in Study C208 Stage 2, bedaquiline treated subjects had a similar culture conversion rate at week 24 compared to those receiving placebo. This appeared to be related to the high placebo rates of culture conversion among Black subjects of 72%, compared to the range of 35.3-83.3% for other racial groups. The culture conversion rate for the bedaquiline treated black subjects fell within the range for other racial groups (66.7-100%). The sample size for Black subjects was small at 49. Further investigations by demographic factors, HIV status, TB types, and lung cavitation did not provide an explanation for the high placebo response rate.

Dr Li's final conclusions are as follows, and I concur with them:

- C208 demonstrated statistically significant treatment effects of bedaquiline for the primary endpoint of time to SCC and for culture conversion rate at week 8 (Stage 1) and week 24 (Stage 2).
- Treatment effects in Study C208 appear to diminish over time.
- C209 efficacy results from week 24 are supportive with a median time to SCC of 57 days and a culture conversion rate of 80%.

8.0 Summary of Clinical Safety

The medical officer and CDTL conclude that adequate evidence of safety has been provided to support the use of bedaquiline to treat adults with pulmonary MDRTB who need bedaquiline to construct an effective antimycobacterial regimen. I concur with their assessment. The data supporting the safety of bedaquiline comes from 11 Phase 1 studies and 3 Phase 2 trials. Of the 11 Phase 1 studies, eight studies were in healthy subjects (five single-dose and three multiple-dose studies) and enrolled 265 who were exposed to bedaquiline. Another 45 subjects with drug sensitive subjects received various doses of bedaquiline for 7 days in a Phase 2a trial of early bacterial activity. From the Phase 2 trials (C208 and C209), 335 subjects were exposed to the to-be-marketed dose of bedaquiline; however, of those 335, 23 received only eight weeks of study drug in Stage 1 of Study 208 as opposed to the to-be-marketed duration of 24 weeks.

In Study C208, Stage 2, the bedaquiline and placebo treatment groups were comparable in terms of demographics. The ITT population was 63% men, had a median age of 35 years, and mean BMI of 20 kg/m^2. Sixty percent of subjects were from South Africa, 37% were Black, and 86% were HIV-negative. Demographics of the study population in C209 were relatively similar to C208 Stage 2.

The most notable finding from the safety review was the greater number of deaths reported among subjects receiving treatment with bedaquiline compared to subjects receiving placebo. A total of 36 deaths was reported during the entire clinical development program. The number of deaths from each trial by treatment group is shown in Table 2.

Table 2. Summary of Deaths in the Bedaquiline Development Program

	Type of Study	Bedaquiline	Placebo
Phase 1		0	0
Phase 2			
Study C202 Deaths	Randomized, open-label, dose-ranging EBA study	N=45 2 (4.4%)	N=30 (INH, RMP) 0

Trial C208 Stage 1 Deaths	Randomized, placebo-controlled, 8-week exposure	N=23 2 (8.7%)	N=24 2 (8.3%)
Trial C208 Stage 2 Deaths	Randomized, placebo-controlled, 24 week exposure	N=79 10 (12.6%)	N=81 2 (2.5%)
Trial C209 Deaths	Open-label, uncontrolled, 24-week exposure	N=233 16 (6.9%)	

Source: FDA Medical Officer's Review

The first death from Study C202 was in a 25 y.o. black woman who received bedaquiline for seven days, in addition to a Kombipak II. She was lost to follow-up for one month because she moved. Subsequently, she was admitted to the hospital with HIV and pulmonary TB, complaining of hemoptysis. She was noted to be wasted and dyspneic with a CD4 count of 80. She was begun on four drug anti-TB therapy with isoniazid, rifampin, ethambutol and pyrazinamide, however did not improve and died. Based on this narrative, it seems likely her death was from TB and immunocompromise, rather than related to bedaquiline therapy. The second death from C202 occurred in a 41 y.o. man who received only three days of bedaquiline. He was discontinued prematurely due to a positive urine drug test for cannabinoids. On chest x-ray, he had bilateral cavitary pulmonary disease and was immediately started on a four drug anti-TB regimen. Despite this therapy, he developed Grade 3 hemoptysis requiring embolization, which was not successful as he died from massive hemoptysis. Again, it is fairly clear this patient died from severe pulmonary TB and consequent hemoptysis rather than anything related to direct bedaquiline toxicity.

Review of the deaths from both stages of C208 revealed that all four of the deaths from the placebo group appeared to be related to progression of TB, while five of the deaths from the bedaquiline group also appeared to be related to TB. One of the deaths in the bedaquiline group was from a motor vehicle accident that occurred approximately 130 weeks after the last intake of bedaquiline. The rationale for attributing this death to bedaquiline when it occurred temporally so removed from the actual exposure is problematic at best. It has been removed from the analysis of deaths by the FDA statistical and clinical reviewers and I agree this is appropriate. The remaining six deaths from the bedaquiline treated group were reported to occur from a variety of causes including: MI with complete occlusion of the LAD about 4 months after bedaquiline treatment; unwitnessed death in a patient with a history of alcohol abuse found dead by the side of the road with a blood alcohol level of 3.73% two days after his last bedaquiline exposure; a CVA 556 days after bedaquiline exposure; septic shock likely due to peritonitis from a perforated viscus 513 days after the last bedaquiline exposure; and Grade 3 hepatitis and Grade 4 hepatic cirrhosis in a patient with a known history of alcohol abuse 86 days post-exposure to bedaquiline. Finally, no clear relationship

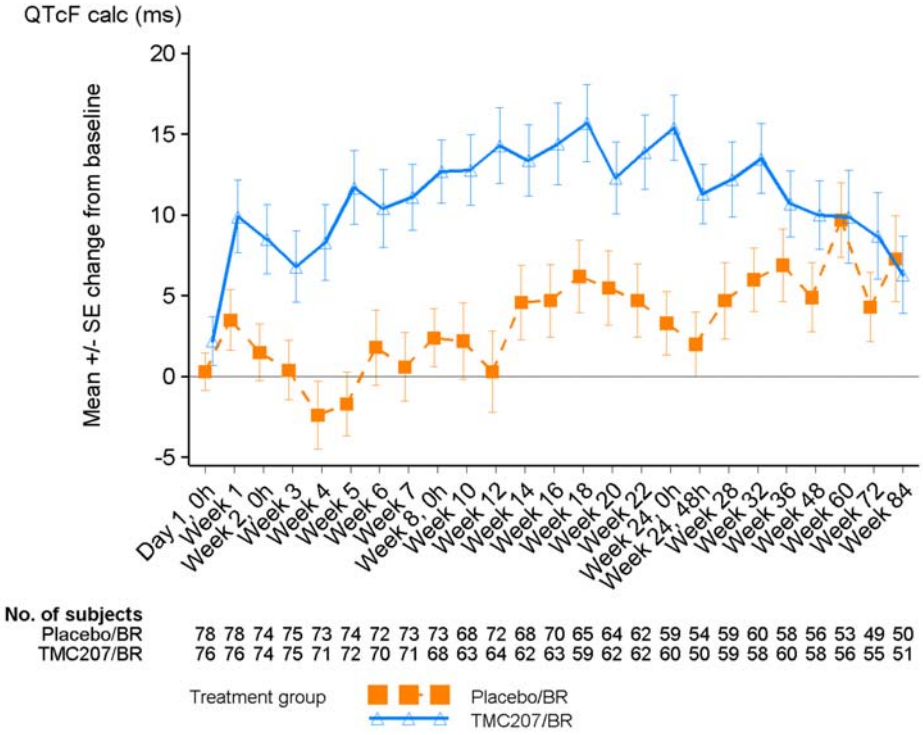
between death and SCC, relapse, sensitivity to BR, HIV status, or severity of disease (i.e. cavitation, multilobular disease) could be identified by either the medical review team, the applicant, the two expert panels convened by the applicant to review the deaths, or by members of the Anti-infective Drugs Advisory Committee. From an efficacy standpoint, it could be argued that the fact that approximately the same number of subjects died from TB in both arms casts some doubt on the treatment effect of bedaquiline. However, at least these some of the subjects had a week or less of bedaquiline treatment, which is hardly likely to be a sufficient exposure for the drug to have much, if any, treatment effect, while others had deaths that occurred well after bedaquiline treatment.

Nonetheless, until additional data from the confirmatory phase 3 trial and post-marketing information are available to evaluate the potential for bedaquiline treatment failure and bedaquiline-associated toxicities, the mortality finding has implications for the appropriate use of this drug, which should be limited to MDRTB patients for whom a viable antimycobacterial regimen cannot be constructed without it. The indication will be limited accordingly and this imbalance will be described in the product labeling in a Boxed Warning, in WARNINGS AND PRECAUTIONS, and in ADVERSE REACTIONS.

Since Study 209 is uncontrolled and ongoing, it is difficult to assess the relationship between death and bedaquiline exposure.

Another adverse event of interest based on nonclinical findings of inhibition of the hERG assay and QT prolongation in one of the dog studies was effects on the QT interval in clinical trials. Mean absolute values in QTcF increased compared to placebo and compared to baseline were greater in the bedaquiline treated group in Study 208 Stage 2. The largest mean increase for the bedaquiline group occurred was 15.7 msec at Week 18, compared to 6.2 msec for the placebo group. Figure 4 illustrates these changes out to Week 84.

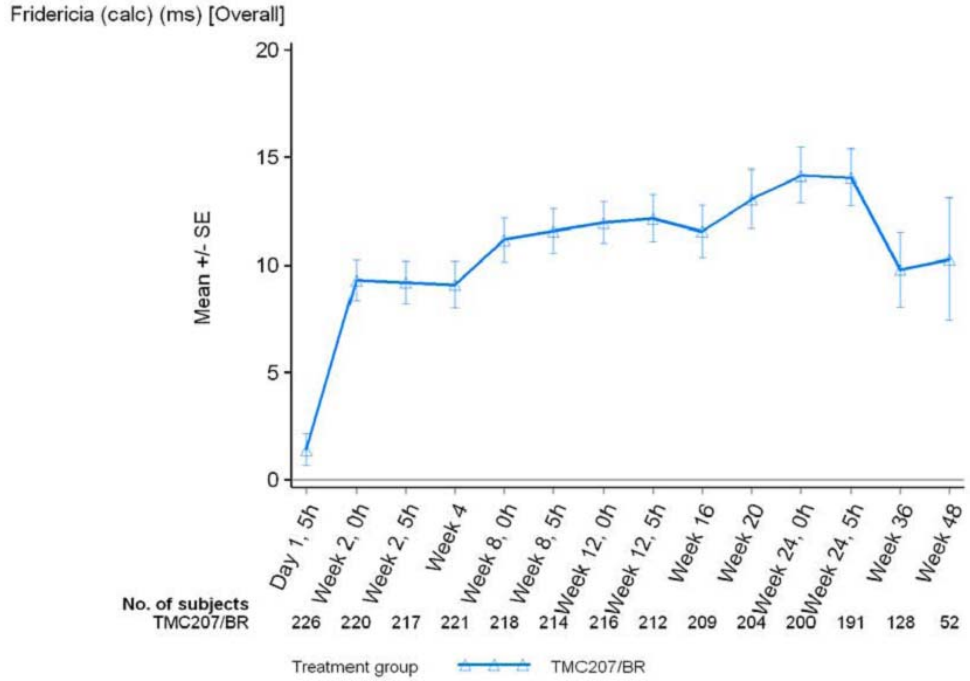
Figure 4. Mean Change from Reference in QTcF



Source: NDA 204-384 Summary of Clinical Safety

Similar changes in QTcF were noted in Study 209, as shown in Figure 5.

Figure 5. Mean Change from Baseline in QTcF



Source: NDA 204-384 Clinical Study Report C209 Interim Analysis

Another important analysis was that done to demonstrate the additive effect that concomitant QT prolonging medication in Study C209 had on the QT interval, as shown in Table 3. The greater the number of QT prolonging drugs taken in addition to bedaquiline, the more marked the increase of the QT interval.

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

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

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

Source: NDA 204382 SN0018

The applicant conducted another post hoc analysis to evaluate the effect of concomitant clofazimine administration with bedaquiline. Not previously known to be a QT prolonging drug, use of clofazimine with bedaquiline had a significant additive effect on QT prolongation, as shown in Table 4.

Table 4. Changes from Reference for QTcB and QTcF in Patients with Concomitant Use of Clofazimine at Week 24.

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

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

Despite these QT changes, there were no adverse drug reactions (ADRs) of torsades des pointes or sudden death reported during any of the trials. The QT Interdisciplinary Review Team has provided consultation on bedaquiline, with suggestions for the product

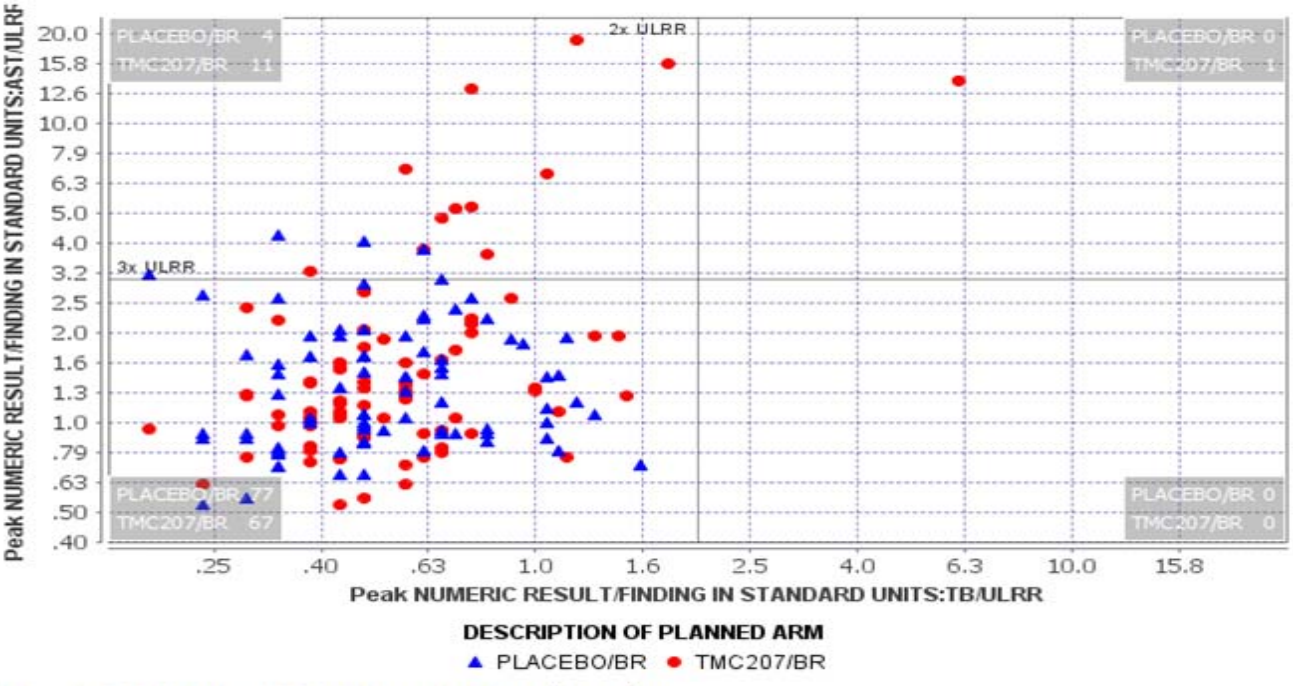
labeling regarding monitoring and management to reduce the potential for QT prolongation and possible sequelae. These have been reviewed and integrated in the package insert, as appropriate.

The third safety assessment of interest based on the findings of phospholipidosis in animals and the mechanism of action of bedaquiline of mitochondrial ATP synthase inhibition, is the effect of bedaquiline on the liver. Drs. John Senior and Leonard Seeff from the Office of Surveillance and epidemiology were consulted to assist in understanding the liver-related laboratory changes and adverse events that were reported in the safety database. They have concluded that based on the limited data available at this time, bedaquiline does not appear to be directly hepatotoxic, however recommended including language in the label to monitor for hepatic-related adverse reactions and how to treat them should they occur. The Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Evaluation" was also consulted.

In Study C208 Stage 2, increased transaminases were reported for four bedaquiline treated subjects compared to none of the placebo-treated subjects. In addition, hepatic-related adverse events including liver-related signs and symptoms, hepatic disorders, possible drug-related hepatic disorders, hepatitis (non-infectious), hepatic failure, fibrosis, cirrhosis, and liver damage related conditions were reported more frequently in the bedaquiline treated group.

Figures 6 and 7 below demonstrate the distribution of peak AST and total bilirubin values for Stage 2 of Study C208 and C209, respectively. In Study C208, Stage 2, one subject developed peak AST values > 3x ULN and peak total bilirubin values > 2x ULN. Hy's Law criteria for drug-induced liver injury were not met as review of his case indicated it was likely related to his extensive alcohol use and alcoholic hepatitis rather than related to bedaquiline.

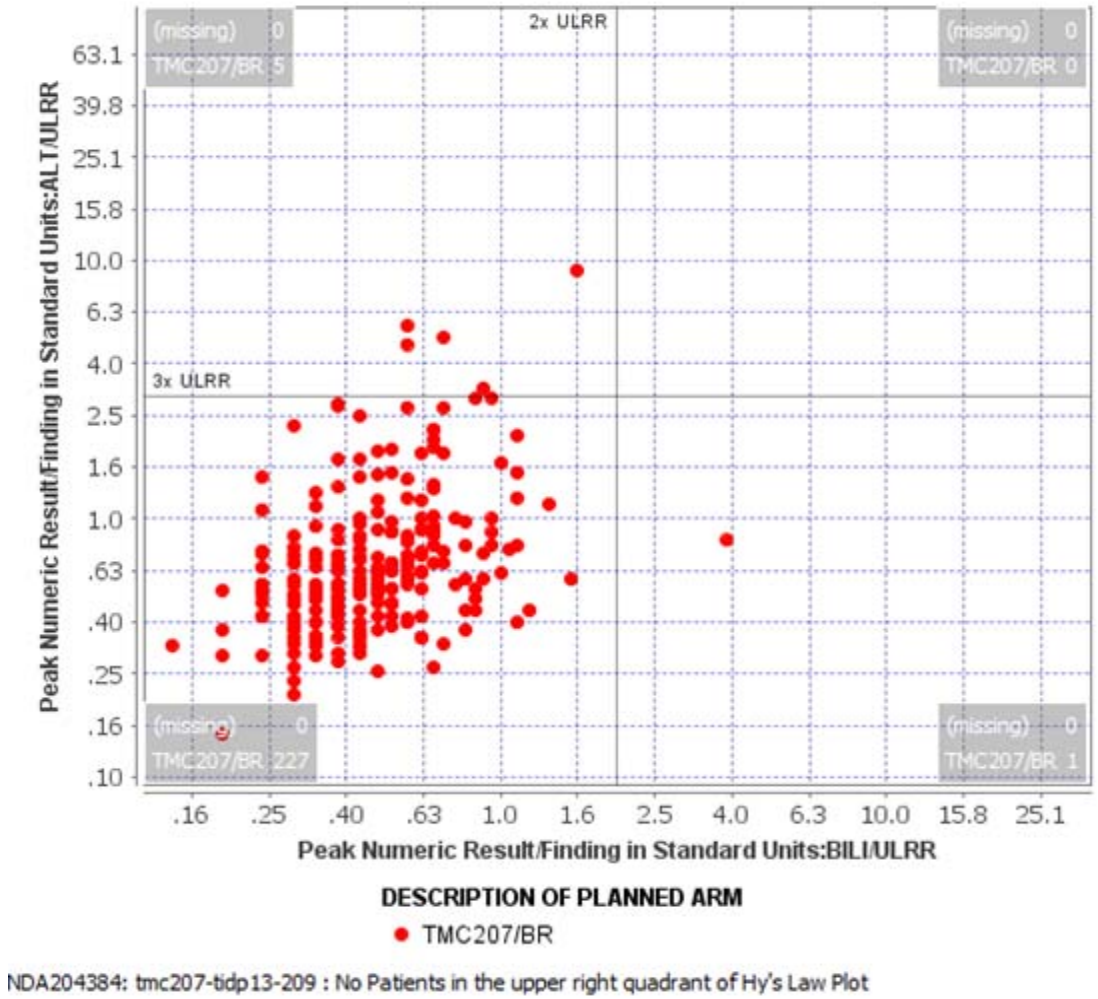
Figure 6. Peak AST and Total Bilirubin Values for Subjects in Trial C208 Stage 2



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

Source: FDA Clinical Review

Figure 7. Peak AST and Total Bilirubin Levels in Trial C209 Subjects



Source: FDA Clinical Review

Per the recommendations of the clinical review team and Drs. Seeff and Senior, with which I concur, hepatic-related adverse reactions will be described in the product labeling with recommendations for monitoring and treatment, as appropriate.

In Study C208 Stage 1, three bedaquiline-treated subjects and three-placebo treated subjects experienced SAEs. In the bedaquiline group, one subject died of an acute myocardial infaction, another had Grade 4 diabetic ketoacidosis, and third was involved

in a motor vehicle accident. In the placebo treatment group, one subject experienced Grade 3 cycloserine intoxication, another subject experienced Grade 4 relapse of MDR-TB with Grade 4 lobar pneumonia, Grade 4 symptomatic anemia, and Grade 4 right lower extremity DVT. The final bedaquiline subject who experienced an SAE had a Grade 4 pneumothorax.

In Study C208 Stage 2, 19 bedaquiline-treated subjects experienced an SAE (24%) compared to 15 placebo-treated subjects (18.5%) during the entire investigational treatment phase. Of those, six bedaquiline-treated subjects and one placebo-treated subjects experienced the SAE during the 24 week study drug treatment phase. The most common SAE occurred in the system organ class (SOC) term "infections and infestations" with 6 bedaquiline-treated subjects (7.6%) and 4 placebo-treated subjects (4.9%) having this event. Events captured under this SOC for the bedaquiline-treated subjects were: bronchiectasis, pneumonia, pulmonary TB, pyothorax, and TB. Note that each subject could have more than one SAE. For the placebo-treated subjects, the events were: pulmonary TB, and TB.

In ongoing Study C209, 27 (11.6%) of subjects developed one or more SAEs during the overall treatment phase. The most frequent SAEs were pneumothorax (3 patients), lung infection, pneumonia, tuberculosis, and dyspnea (2 patients each). These SAEs are consistent with those noted in C208 Stage 2.

No subjects in Study C208 Stage 1 discontinued due to an AE. In Study C208 Stage 2, 4 bedaquiline-treated subjects discontinued due to an AE compared to five placebo-treated subjects. Transaminase increased was the reason for discontinuation for three of the bedaquiline-treated subjects, and pregnancy was the reason for two of the placebo-treated subjects. In ongoing Study C209, six bedaquiline treated subjects discontinued due to AEs. The reasons for discontinuation included vomiting, TB, drug exposure during pregnancy, ECG QT prolonged, inadequately controlled diabetes, and hallucination.

In Study C208 Stage 1, the most frequent AEs (rate >10% in the bedaquiline treatment group) were nausea, diarrhea, arthralgia, and dizziness. In C208 Stage 2, the most frequent AEs occurring at >10% in the bedaquiline-treated group were nausea, vomiting, upper abdominal pain, hemoptysis, and chest pain.

Review of changes in laboratory parameters while on study drug in Study C208 Stage 1 revealed that increased amylase and increased ALT, AST, GGT, and PT occurred more commonly in bedaquiline-treated subjects compared to placebo-treated subjects. The majority of these changes were Grade 1. For Study C208 Stage 2, mean AST values were higher in bedaquiline-treated subjects compared to placebo-treated subjects.

In summary, the most significant safety findings were the imbalance in mortality, the QT prolongation, and the possible signal for hepatic events. All of these will be addressed in product labeling, as described above.

9.0 Advisory Committee Meeting

The NDA for bedaquiline for the treatment of pulmonary MDRTB in adults was presented at a meeting of the Anti-infective Drugs Advisory Committee (AIDAC) on November 28, 2012. Two questions were posed to the committee:

1. Do the data provided by the applicant provide substantial evidence of the efficacy of bedaquiline for the proposed indication of treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* as part of combination therapy in adults (≥ 18 years)? VOTE
    a. If not, what additional data are required?
    b. If so, please discuss whether 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).
    c. If so, please discuss any recommendations for labeling and use of bedaquiline.

All eighteen members voted "yes" with no abstentions. The majority of the members felt that sputum culture conversion was adequate as a surrogate endpoint reasonably likely to predict clinical benefit but that it was not adequate to serve as an endpoint for traditional approval and that the confirmatory trial was still needed. Some members mentioned the clinical cure endpoint recommended by WHO. Others noted that more information was needed in Black subjects, those with HIV coinfection, and in pediatrics.

2. Do the data provided by the applicant provide substantial evidence of the safety of bedaquiline for the proposed indication of treatment of pulmonary tuberculosis due to MDR *M. tuberculosis* as part of combination therapy in adults (≥ 18 years)?
    a. If not, what additional data are required?
    b. If so, please discuss any recommendations for labeling and risk management.

Eleven of 18 members voted "yes" while seven voted "no". There were no abstentions. Irrespective of whether a member voted "yes" or "no", virtually all of them were very concerned about the imbalance in deaths. Further, the inadequate data in HIV coinfected subjects, as well as the perplexing findings in Blacks were also of concern. One of the cardiologists was not concerned by the QT findings while the other was. Lastly, the hepatotoxicity signal was also problematic, as was the potential for drug-drug interactions. Among those who voted "yes" as well as for a few who voted "no", the mortality, QT effects and hepatic signal all needed to be addressed in labeling. For risk

management, the members agreed that CDC could be an integral part to ensure use of the drug where the benefit-to-risk for a particular patient with MDRTB was favorable.

10.0 Pediatrics

Pulmonary tuberculosis caused by MDRTB has received orphan designation and therefore requirements under PREA are waived.

11.0 Other Regulatory Issues

Five international clinical trial sites were inspected by OSI, three in South Africa and two in China. These sites were selected because they enrolled the largest number of study subjects in Studies C208 and 209. All three of the South African sites were NAI and the two Chinese sites were VAI (preliminary). The preliminary classification for the applicant is NAI. The deviations at the Chinese sites were minor and, in the opinion of the OSI reviewer, do not impact the reliability of the data or the rights, safety, and welfare of subjects in the study.

The carton and container labeling have been reviewed by ONDQA and DMEPA and recommendations incorporated. The proprietary name Sirturo has been found acceptable by DMEPA. The Medication Guide has been reviewed by DMPP and their recommendations have been incorporated.

12.0 Benefit/Risk Assessment and Recommendation

I concur with the findings and the recommendations of the review team that sufficient evidence of safety and efficacy has been submitted to support the approval of bedaquiline under 21 CFR 314.500 (Subpart H), i.e. the accelerated approval regulations. The findings from Study C208, with support from Study C209, demonstrated a statistically significant treatment effect of bedaquiline on the surrogate endpoint of time to sputum culture conversion, which has previously been recommended by the AIDAC to be reasonably likely to predict clinical benefit among subjects with pulmonary TB. However, because of the safety findings of increased mortality, QT prolongation, and possibly more hepatic-related events, the requested indication of "treatment of adults with pulmonary MDRTB as part of combination therapy" is too broad. Until the results of the confirmatory trial C210 are available, the indication should be restricted such that bedaquiline use is reserved for use when an effective antimycobacterial regimen cannot otherwise be provided. These safety findings do not preclude approval because pulmonary MDRTB is a serious and life-threatening disease, and other available options are not approved, and also have significant toxicities.

In order to ensure that only appropriate patients receive bedaquiline, Janssen plans to [redacted] (b) (4) . CDC provides certification for public health officials involved in treatment of TB, and will incorporate information regarding bedaquiline into the training programs. Since the public health infrastructure to provide directly observed therapy to TB patients is already in existence, measures such as restricted distribution would provide little added value to limit access to bedaquiline. In addition, the package insert contains a Boxed Warning regarding the imbalance in deaths and the risk of QT prolongation, as well as a WARNING AND PRECAUTION regarding hepatic-related adverse drug reactions. A patient Medication Guide has been developed to provide information to patients regarding important safety aspects of bedaquiline use. Together, these measures are sufficient to make bedaquiline available to those who need it, and limit access to those who don't.

The applicant has agreed to the following PMRs:

1988-001: Conduct a confirmatory randomized double blind placebo controlled multicenter Phase 3 trial in subjects with sputum smear-positive pulmonary multidrug resistant tuberculosis (MDR-TB). This trial should assess long term outcomes of failure or relapse or death at least 6 months after all MDR-TB treatment is completed.

1988-002: Develop a patient registry for bedaquiline-treated patients to assess incidence rates of serious adverse events, including death. The registry should capture the information listed below:

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

1988-003: In order to inform PMR 1988-005, conduct a study to define the Quality Control ranges of bedaquiline for MDR-TB isolates using standard proportion methods.

1988-004: In order to inform PMR 1988-005, conduct a study to define the Quality Control ranges of bedaquiline for MDR-TB isolates using MIC methods.

1988-005: Conduct a prospective in vitro study over a five-year period after introduction of SIRTURO (bedaquiline) to the market to determine minimum inhibitory concentrations (MICs) of multi drug resistant tuberculosis (MDR-TB) to bedaquiline for the first 5 years from marketing. Report interpretation of these MICs once additional quality control testing methods are developed as noted in the required postmarketing studies PMR 1988-03 and PMR 1988-04. Provide a detailed protocol describing the study to the Agency for review and comment before commencing the study.

1988-006: 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.

1988-007: Conduct a drug interaction trial of bedaquiline and efavirenz to determine a safe and effective dose regimen of both drugs when they are co-administered in HIV co-infected MDR-TB patients. Alternatively, adequate data from a previously conducted drug interaction trial may be submitted.

The applicant has agreed to the following PMCs:

1988-008: Submit final study report and electronic data for Study C208 Stage II

1988-009: Submit final study report and electronic data for C209

Katherine A. Laessig, M.D.

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

/s/

KATHERINE A LAESSIG
12/27/2012