

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204384Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 204384
Supplement #	
Applicant Name	Janssen Therapeutics
Date of Submission	June 28, 2012
Date of Receipt	June 29, 2012
PDUFA Goal Date	December 29, 2012
Proprietary Name / Established (USAN) Name	Sirturo bedaquiline
Dosage Forms / Strength	100 mg tablet
Proposed Indication(s)	(b) (4)
Indication	<p>SIRTURO is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR TB). Reserve SIRTURO for use when an effective treatment regimen cannot otherwise be provided. SIRTURO should be administered by directly observed therapy (DOT).</p> <p>This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR TB.</p> <p>Limitations of Use: The safety and efficacy of SIRTURO for the treatment of latent infection due to <i>Mycobacterium tuberculosis</i> has not been established. The safety and efficacy of SIRTURO for the treatment of drug-sensitive TB has not been established. In addition, there are no data on the treatment with SIRTURO of extra-pulmonary TB (e.g., central nervous system). Therefore, use of SIRTURO in these settings is not recommended.</p>
Action:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Ariel Porcalla
Statistical Review	Xianbin Li, Karen Higgins
Pharmacology Toxicology Reviews	Owen McMaster, Wendy Schmidt
CMC Review/OBP Reviews/	Celia Cruz, Lin Qi, Minerva Hughes, Angelica Dorantes, Terrance Ocheltree
Product Quality Microbiology	Jessica Cole, Bryan Riley
Clinical Microbiology	Lynette Berkley
IRT Consult	Janice Brodsky, Qianyu Dang, Justin Earp, Kevin Krudys, Monica Fiszman, Norman Stockbridge
Hepatic Consult	Leonard Seef, John Senior
Clinical Pharmacology Review	Dakshina Chilukuri, Zhixia (Grace) Yan, Seong Jang, Fang Li, Justin Earp, Kevin Krudys, Kimberly Bergman, Phil Colangelo, and Yanin Wang
OSI	Kassa Ayalew, Susan Liebenhaut, Susan Thompson
OSE/DMEPA	Aleksander Winiarski, Todd Bridges, Carol Holquist
OSE/DRISK	Julia Ju, Cynthia LaCivita, and Claudia Manzo
OMP/DMPP	Sharon W. Williams, Melissa I Hulett, Lashawn M Griffiths
CDTL Review	Eileen Navarro
Deputy Division Director's Review	Katie Laessig

OND=Office of New Drugs

OSI=Office of Scientific Investigations

CDTL=Cross-Discipline Team Leader

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

Bedaquiline is diarylquinoline antimycobacterial drug studied for the treatment of patients with multi-drug resistant tuberculosis. Bedaquiline acts through inhibition of mycobacterial ATP (adenosine 5'-triphosphate) synthetase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.

Bedaquiline received Fast Track designation on 4/22/2011 for treatment of multi-drug resistant (MDR) pulmonary tuberculosis (TB), orphan designation for treatment of active tuberculosis on 1/10/2005 and the NDA for bedaquiline received priority review as an option for treating patients with MDR pulmonary TB.

The application for bedaquiline for the treatment of adults patients with MDR pulmonary TB is submitted under 21 CFR 314.500, (Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses).

Tuberculosis is a major cause of global morbidity and mortality; tuberculosis ranks second as a global cause of death from an infectious disease, second to HIV/AIDS.¹ The U.S. Centers for Disease Control and Prevention (CDC) reports that there were 10,528 cases of tuberculosis reported in the United States in 2011.² Development of resistance to the drugs that are used to treat TB is an issue that impacts upon our ability treat patients with tuberculosis. Multi-drug resistant TB (MDR TB) has been defined by CDC as TB that is resistant to effective first-line therapeutic drugs, isoniazid and rifampin.³ CDC defines extensively drug-resistant TB (XDR TB) as MDR TB that also is resistant to second-line therapeutic drugs used commonly to treat MDR TB: fluoroquinolones and at least one of three injectable second-line drugs used to treat TB (amikacin, kanamycin, or capreomycin).⁴ New antimycobacterial agents to treat patients with MDR TB represent an important public health need.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of Sirturo (bedaquiline). For a detailed discussion of NDA 204384, the reader is referred to the individual discipline specific reviews. In addition Dr. Navarro's Cross-Discipline Team Leader Review and Dr. Laessig's Deputy Division Director Review summarize key issues in the NDA submission. This memorandum will focus on select issues from the NDA review.

CMC/Product Quality

The Office of New Drug Quality Assessment recommends approval of Sirturo (bedaquiline) tablets. Bedaquiline tablets are uncoated immediate release tablets containing 120.89 mg of bedaquiline fumarate equivalent to 100 mg of bedaquiline free base. The ONDQA reviewers find that the information in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support a 24-month shelf-life for the drug product in the current 160 mL HDPE bottle for all climatic zones and the product label statement of "store at (b) (4) 25°C ((b) (4) 77°F); excursions permitted to 15-30°C (59-86 °F)." As of December 17, 2012, the manufacturing facilities have been found to be acceptable. The application is also recommended for approval from the standpoint of Product Quality Microbiology.

Pharmacology/Toxicology

The recommendation from the pharmacology/toxicology reviewer is for approval. In animal studies, Sirturo induced phospholipidosis at almost all dose levels and even after only short exposures. Phospholipidosis was noted mainly in cells of the monocytic phagocytic system. Drug-related increases in foamy macrophages were noted in the lymph nodes, spleen, lungs,

¹ *Global tuberculosis report 2012*. World Health Organization. p.3 available at http://www.who.int/tb/publications/global_report/en/

² CDC. *Reported Tuberculosis in the United States, 2011*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, October 2012. available at: <http://www.cdc.gov/tb/statistics/reports/2011/default.htm>

³ Plan to Combat Extensively Drug-Resistant Tuberculosis Recommendations of the Federal Tuberculosis Task Force. *MMWR Recommendations and Reports*. February 13, 2009 / 58(RR03);1-43.

⁴ CDC. *Reported Tuberculosis in the United States, 2011*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, October 2012. available at: <http://www.cdc.gov/tb/statistics/reports/2011/default.htm>

⁴ Plan to Combat Extensively Drug-Resistant Tuberculosis Recommendations of the Federal Tuberculosis Task Force. *MMWR Recommendations and Reports*. February 13, 2009 / 58(RR03);1-43.

liver, stomach, skeletal muscle, pancreas and/or uterus. The findings were reversible after treatment ended. Of note is that phospholipidosis in toxicology studies has been noted in a number of other approved drugs and has not been associated with specific adverse events.

Other findings noted in toxicology studies include muscle degeneration in several species at the highest doses tested. In rats muscle degeneration as observed in the following body sites, esophagus, diaphragm, quadriceps, and/or tongue were affected after 26 weeks of daily treatment at doses similar to human exposures based upon AUC comparisons. After a 12-week treatment free recovery period, these effects were not present. These effects were also not observed in rats given the same dose biweekly. Other findings noted in high dose animals included hepatocellular hypertrophy, degeneration of the fundic mucosa of the stomach, and pancreatitis.

Sirturo is labeled as Pregnancy Category B reflecting that there have not been studies in pregnant women and no significant embryo/fetal toxicity was observed in animal studies.

Clinical Microbiology

The Clinical Microbiology Review recommends approval for bedaquiline. The mechanism of action for bedaquiline is inhibition of mycobacterial ATP (adenosine 5'-triphosphate) synthetase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis* (MTB). The affinity of bedaquiline for the mycobacterial ATP synthetase is >20,000 fold greater compared to its affinity for eukaryotic ATP synthetase. Mechanisms of resistance to bedaquiline include modification of the *atpE* target gene. Of note is that some isolates from the clinical trials with elevated minimal inhibitory concentrations (MICs) do not have mutations in the *atp* operon suggesting the presence of another mechanism of resistance.

In vitro studies suggest the potential for the development to resistance for bedaquiline, particularly at lower bedaquiline concentrations. At a bedaquiline concentration of 0.3 mcg/mL (10x the MIC), the mutation rates ranged from 4.7×10^{-7} to 8.9×10^{-9} mutations per cell division. At a concentration of 1.0 mcg/mL (30x the MIC), the mutation rates ranged from 3.9×10^{-8} to 2.4×10^{-9} mutations per cell division. No resistant mutants were isolated at bedaquiline concentrations of 3 mcg/ml (100xMIC). Studies have shown that resistance can be caused by substitutions in at least six different amino acids in the mycobacterial (adenosine 5'-triphosphate) synthetase. The substitution of Ala63 to Pro mutation was associated with the greatest effects on resistance with a resulting increase in the MIC value by 133-fold. In addition, a second putative mechanism is postulated to be resistance conferred by an efflux pump. Testing for cross-resistance to isoniazid, rifampin, streptomycin, ethambutol, pyrazinamide, (b)(4) amikacin, and moxifloxacin using resistant mutant BK12 did not find evidence of cross-resistance to bedaquiline.

Examination of the limited information available on susceptibility of MTB isolates to bedaquiline did not allow for the establishment of susceptibility test interpretive criteria for bedaquiline. The product labeling for bedaquiline includes information on the distribution of bedaquiline MICs for baseline *Mycobacterium tuberculosis* (MTB) isolates, the results for sputum culture conversion by baseline bedaquiline MIC, and information on the range of

MICs for MTB isolates with at least a four-fold increase from baseline in patients with failure to convert or relapse.

In bedaquiline-treated patients from Study C208 stage 1 and stage 2 and Study C209 with at least a 4-fold increase in bedaquiline MIC from baseline and with *atp* operon sequencing results, no coding variations in the *atp* operon were seen, suggesting a mechanism of resistance other than mutations in the *atpE* gene. Of these subjects, for the agar method, patients who experienced failure to convert their sputum or relapsed (n=9) had post-baseline isolates with 4-fold to greater than 8-fold increases in MIC (corresponding to post-baseline MICs of 0.24 to greater than 0.48 microgram/mL). For the REMA method, patients who experienced failure or relapsed had post-baseline isolates with 4-fold to greater than 16-fold increases in MIC (corresponding to post-baseline MICs of 0.015 to 1.0 microgram/mL). All 9 subjects with increased MICs and failure or relapse were infected with MDR-TB isolates that were resistant to additional antimycobacterial drugs in their treatment regimen. One interpretation of these results is that for at least some of these isolates, the bedaquiline MICs that were attained have allowed the MTB isolates to escape the antimycobacterial effects of bedaquiline. The product labeling section on clinical microbiology and susceptibility testing recommends consultation with a specialist in treating patients with drug-resistant TB to evaluate therapeutic options. Additional data from the required confirmatory trial should provide additional information upon which to further evaluate possible bedaquiline susceptibility test interpretive criteria.

Clinical Pharmacology and QT Interdisciplinary Review Team

The Clinical Pharmacology reviewer finds the data in the application for bedaquiline acceptable for its proposed use for the treatment of MDR pulmonary TB. Bedaquiline exposure is increased approximately 2-fold when taken with food; the product labeling recommends taking bedaquiline with food. The dosing regimen is 400mg daily for two weeks followed by 200 mg three times per week for 22 weeks. Bedaquiline is highly protein bound in human plasma (>99%), but the estimates of the apparent volume of distribution of approximately 164 L indicates that despite the high level of protein binding, the drug distributes extensively into tissues. The pharmacokinetics characteristics of bedaquiline also include a short distribution phase and a long terminal half-life of approximately 5 months.

Bedaquiline is a CYP3A4 substrate. CYP3A4 is the major CYP isoenzyme involved in bedaquiline metabolism. Bedaquiline is metabolized via CYP3A4 to the N-monodesmethyl metabolite, M2. M2 is 4 to 6-fold less active against *M. tuberculosis* compared to the parent compound. In addition, exposures to M2 are 23-31% lower than exposures to the parent compound. Systemic exposure to bedaquiline was decreased by 52% in the presence of strong CYP3A4 inducers such as rifampin and increased by 22% in the presence of strong CYP3A4 inhibitors such as ketoconazole. Based on in vitro studies and drug interaction studies, bedaquiline does not inhibit or induce cytochrome P450 enzymes. Over the exposure ranges studied, there was no discernable relationship of systemic exposure and sputum conversion; possible explanations include that the exposures studied are on a flat portion of the exposure-response curve and/or it is also possible that measurement of other levels other than plasma levels may provide better information to evaluate a relationship between exposure and response (e.g., intracellular concentrations of bedaquiline). In pharmacometric analyses, no

strong relationship was noted between bedaquiline exposures and frequently reported adverse drug reactions over the concentration range studied. A pharmacometric analysis of QT prolongation and concentrations of M2 found that M2 concentrations correlated with the degree of QT prolongation (see below).

The potential for bedaquiline to prolong the QT interval was assessed in the bedaquiline development program and evaluated by CDER's Interdisciplinary Review Team for evaluating QT effects. A Thorough QT study was performed using a single 800 mg dose of bedaquiline; this approach (a single dose of bedaquiline) does not allow for exposures to M2 (the metabolite that with a positive correlation between plasma concentration and degree of QT prolongation) that achieve clinically relevant concentrations. A multiple dose study that evaluated QT effects after 7 days of administration of bedaquiline found an effect on the QT interval. Similarly, ECGs obtained from patients in the clinical trials showed increases in the QT interval for the bedaquiline treatment group that were greater than the placebo treatment group (both groups received other drugs for the treatment of their MDR pulmonary TB). In one of the trials, the largest mean increase in QTc during the 24 weeks of bedaquiline treatment was 15.7 msec in the bedaquiline group and 6.2 msec in the placebo group. In a non-comparative trial, an increase in QTcF over baseline of 23.7 ms was noted in patients not receiving other QT prolonging drugs who were treated with bedaquiline. In patients receiving at least 2 other QT prolonging drugs, the increase in QTcF over baseline was 30.7 msec. The label provides information on QT prolongation in the Boxed Warning, the Warnings and Precautions section, other sections of the product labeling, and the Medication Guide.

In pharmacometric analyses, creatinine clearance was not found to influence the pharmacokinetic parameters of bedaquiline. Renal excretion of unchanged bedaquiline is minimal (<0.001%). Given these findings, no dosage adjustment is recommended for patients with mild to moderate renal impairment. Bedaquiline has been mainly studied in patients with normal renal function. Bedaquiline has not been studied in patients with severe renal dysfunction and should only be used with caution and increased monitoring for adverse effects.

No dose adjustment of Sirturo is required in the setting of mild or moderate hepatic impairment. Sirturo has not been studied in persons with severe hepatic impairment and should be used with caution only when the benefits outweigh the risks and with increased monitoring for adverse effects.

The labeling provides information on drug interactions with Sirturo including rifampin (a strong CYP3A4 inducer), ketoconazole (a strong CYP3A4 inhibitor), Kaletra (400 mg lopinavir/ 100 mg ritonavir) (lopinavir is metabolized by CYP3A4 and ritonavir is a CYP3A4 inhibitor that can also induce CYP3A4 metabolism), and nevirapine. In addition, the potential for additive effects on QT prolongation if used with other drugs that prolong the QT interval is noted in the Boxed Warning, Warnings and Precautions, and the Drug Interactions section of the product labeling.

Additional drug interaction studies will be required (as postmarketing requirements) to evaluate (1) the potential for drug interactions of bedaquiline and efavirenz to determine an

appropriate dose for both drugs in TB and HIV co-infected patients, and (2) the potential of bedaquiline or its major metabolite to act as a substrate, inhibitor, or inducer of OATP1B1 and OATP1B3 drug transporters.

Clinical Efficacy, Safety, and Statistical Evaluation

The applicant submitted results from studies C208 stage 1, C208 stage 2, and study C209 to provide information on the safety and efficacy of bedaquiline for the treatment of MDR pulmonary TB in adult patients. C208 was a multi-center, double-blind, placebo-controlled comparative trial in which patients were randomized to receive bedaquiline or placebo, both in combination with other drugs used to treat MDR TB. Study C208 included two consecutive, but completely separate stages, Stage 1 and Stage 2. Study C209 was an open-label single arm study in patients with MDR TB; patients received bedaquiline in combination with other drugs used to treat MDR TB. These studies were conducted in areas of the world where the frequency of occurrence of MDR TB allows for the conduct of clinical trials (including areas within Eastern Europe, South Africa, Asia, and South America). The data from these trials provides information relevant to US patients with MDR pulmonary TB.

In study C208 stage 2, the primary analysis was time to sputum culture conversion to negative for the 24-week study drug treatment period. Patients were randomized to receive either bedaquiline or placebo for 24-weeks, both in combination with other drugs used to treat MDR TB. Note that treatment with other drugs used to treat MDR TB continued beyond the 24-week study drug treatment period. In the FDA analysis, 67 and 66 patients were included in the mITT analysis population from the 160 patients total that were randomized. The mITT analysis population included patients with MDR TB based upon positive culture results and susceptibility testing and did not include patients with drug-sensitive TB or XDR TB, or those with a negative culture for TB prior to or during the first 8-weeks of the study. Using a Cox proportional hazards model there was a statistically significant treatment effect (earlier time to sputum culture conversion to negative) with a relative risk of 2.15; 95%CI (1.39, 3.31); p-value=0.0005 in favor of bedaquiline. The secondary endpoint of proportion of patients with sputum culture conversion to negative similarly demonstrated a statistically significant treatment effect for bedaquiline with 78% (52/67) of bedaquiline treatment group patients converting to negative by week 24, and 58% (38/66) of the placebo treatment group patients converting to negative by week 24 for a treatment difference of 20%; 95%CI (4.5%, 35.6%); p-value=0.014. Additional analyses when all patients had completed 72 weeks of treatment showed a statistically significant, but smaller treatment effect for bedaquiline with a relative risk of 1.65; 95% CI (1.05, 2.59); p-value=0.029.

Study C208 stage 1 was similar in design to C208 stage 2, except that treatment with study drug (bedaquiline or placebo) was only for 8-weeks. Both arms also received treatment with other drugs used to treat MDR TB during and continuing after the study drug treatment period. In stage 1 of C208 in an analysis of time to sputum culture conversion to negative in the mITT population (n=21 for the bedaquiline arm and n=23 for the placebo arm) there was a statistically significant treatment effect with a relative risk of 11.17; 95%CI (2.26-61.23, p-value=0.0034 in favor of bedaquiline. The proportion of patients with sputum culture conversion to negative by treatment arm was also evaluated. The results for the differences in

the proportion of patients with a negative sputum culture (bedaquiline treatment arm - placebo treatment arm) were as follows: 8 weeks 38.9%, 95% CI (12.3%, 63.1%), p-value 0.004; 24-weeks, 14.8%, 95% CI (-11.9%, 41.9%), p-value=0.029; final analysis 4.6% 95% CI (-25.5%, 34.1%), p-value=0.76. The results show a greater proportion of patients with sputum culture conversion at 8-weeks in the bedaquiline arm, (8-weeks is the time period during which patients received study drug (bedaquiline or placebo)), with a subsequent decreasing degree of difference in the proportion of patients achieving sputum culture conversion to negative at later time points.

Study C209 was a non-comparative study in which patients with pulmonary MDR TB received bedaquiline in combination with other drugs used to treat MDR TB. In the mITT population, 80% (163/205), 95% CI (73%, 85%) of patients achieved sputum culture conversion to negative at the end of week 24.

The safety database for bedaquiline includes 189 subjects who were exposed to bedaquiline in phase 1 trials and 335 patients from phase 2 studies exposed to bedaquiline. In the phase 2 studies, 305 of the patients with MDR TB received bedaquiline 400mg daily for 2 weeks followed by 200mg three times a week for 22 weeks.

In Study C208 stage 2, there were more deaths in the bedaquiline treatment group compared to the placebo treatment group in the 120-week visit window. In the bedaquiline treatment group the mortality rate was 9/79 (11.4%) compared to 2/81 (2.5%) in the placebo arm for the 120-week visit window. Five of the 9 deaths in the bedaquiline arm were TB-related and both of the 2 deaths in the placebo arm were categorized as TB-related. For the deaths in the bedaquiline treatment group categorized as TB-related, the numbers of days after completion of the bedaquiline treatment when the deaths occurred were, 252 days, 262 days, 314 days, 344 days, and 787 days after bedaquiline treatment. For the placebo arm, the two TB-related deaths occurred 105 and 709 days after placebo therapy was completed (as noted previously patients received other drugs to treat their MDR TB). One of the 9 deaths (not a death classified as TB-related) in the bedaquiline treated patients occurred during the 24-week treatment period; this patient died at Study Day 111. The narrative notes that the patient was found dead at the roadside and was found to have a blood alcohol level of 3.73%. His death was attributed to alcohol poisoning. There were three other deaths in the bedaquiline treatment group categorized as not TB-related; these three deaths occurred after the 24-week study drug treatment period up to the 120-week visit window. The adverse events that were reported for these patients and the study day of death after last bedaquiline treatment were as follows: (1) hepatitis, hepatic cirrhosis, alcoholic cirrhosis, ascites, volume depletion, malnutrition 86 days after bedaquiline; (2) infectious peritonitis and septic shock 513 days after bedaquiline; and (3) cerebrovascular accident (probably from hypertension) 556 days after bedaquiline.

The number of deaths from the studies in the bedaquiline development program are summarized in the Table below.

Table. Number of Deaths by Study in the Bedaquiline Development Program

	Type of Study	Bedaquiline Treatment Group	Placebo* Treatment Group
Phase 1		0	0
Phase 2			
Study C202	Randomized, open-label, dose-ranging Early Bactericidal Activity study	N=45	N=30 (INH, RMP)
Deaths		2 (4.4%)	0 (0 %)
Trial C208 Stage 1	Randomized, placebo-controlled, 8-week exposure	N=23	N=24
Deaths		2 (8.7%)	2 (8.3%)
Trial C208 Stage 2 (120-week visit window)	Randomized, placebo-controlled, 24 week exposure	N=79	N=81
Deaths		9 (11.4%)	2 (2.5%)
Trial C209	Open-label, uncontrolled, 24-week exposure	N=233	
Deaths		16 (6.9%)	

*Note: patients received study drug (either bedaquiline or placebo) in combination with other drugs for the treatment of their TB except in C202, the EBA study where patient received short courses of different doses of bedaquiline or other drugs to treat TB.

Source: FDA Medical Officer's Review

The deaths from the bedaquiline development program were reviewed extensively to further understand these deaths and possible contributing factors (please see the Medical Officer, CDTL, and Deputy Division Director Reviews for additional details). Examination for a possible relationship between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, HIV status and severity of disease (i.e., cavitation and multilobar disease) was evaluated; a relationship between these factors and death could not be identified. In addition, data mining techniques were explored in search of common factors among the patients who died that were different from those who survived; the exploration did not identify factors more common in persons who died.

The results from the analysis of mortality from the other studies provide only limited additional information on mortality with bedaquiline. C209 is an uncontrolled study and patients in C208 stage 1 in the bedaquiline treatment group only received bedaquiline for 8 weeks.

The mortality difference was also an issue that was discussed and evaluated at the November 28, 2012 Anti-Infective Drugs Advisory Committee meeting (see the discussion in the section on the Anti-Infective Drugs Advisory Committee meeting). As noted the Committee recommended that the information regarding the imbalance in mortality in C208 stage 2 be provided so that healthcare providers and patients could consider this information. The product labeling includes a Boxed Warning, a statement in Warnings and Precautions, and a summary description of the deaths in the Adverse Reactions section of the product labeling. The accompanying Medication Guide also provides information for patients on the observed

mortality difference. It will be important for healthcare providers and patients to consider this information when evaluating bedaquiline as a possible component of a patient's treatment regimen for MDR TB.

As noted in the section of this memo discussing clinical pharmacology and the QT IRT evaluation, bedaquiline can prolong the QT interval. The effect on the QT interval appears to be additive in the setting where other QT prolonging drugs are administered in combination with bedaquiline. During the clinical trials, there were no reported adverse events of Torsades des Pointes or sudden death. The product labeling provides information on QT prolongation in the Boxed Warning, the Warnings and Precautions section, other sections of the product labeling and the Medication Guide. The information provided describes risks for QT prolongation, including the risks of combining bedaquiline with other QT prolonging drugs, steps that can be taken to monitor for QT prolongation, and some steps that can be taken intended to mitigate the risk of QT prolongation.

Hepatic-related adverse drug reactions developed in more patients treated with bedaquiline and other drugs used for the treatment of MDR TB than in patients that received placebo and other drugs for the treatment of their MDR TB. In studies C208 stage 1 and stage 2, reversible transaminase elevations of at least 3x the upper limit of normal were observed in 10.8% (11/102) patients in the bedaquiline treatment arm compared to 5.7% (6/105) in the placebo treatment arms. Similarly, more adverse drug reactions were reported in Study C208 stage 2 for the bedaquiline treatment group 8.9% (7/79) compared to 1.2% (1/81) in the placebo treatment group. A consult to evaluate for the hepatic adverse effects of bedaquiline did not find, within the limitations of the available data, evidence of direct hepatotoxic effects of bedaquiline. Given the effects on laboratory findings, reported adverse drug reactions, and the limitations of the available data, the labeling will include information in the Warnings and Precautions section on hepatic-related adverse drug reactions (ADRs) and additional information in the Adverse Reactions section of the product labeling on hepatic-related ADRs.

The required confirmatory trial that accompanies this accelerated approval will provide an opportunity to obtain additional data on the clinical efficacy and safety of bedaquiline in the treatment of patients with MDR-TB, gather additional data in patients co-infected with TB and HIV, and additional data in patients of different races/ethnicities. To further evaluate the mortality imbalance observed in C208 stage 2, a controlled trial will be needed. The proposed required confirmatory trial, C210, will provide additional information to further address these findings and issues.

Anti-Infective Drugs Advisory Committee Meeting

The application for Sirturo (bedaquiline) was presented to the Anti-Infective Drugs Advisory Committee (AIDAC) on November 28, 2012. The committee voted 18 Yes; 0 No, on the question on whether the efficacy of bedaquiline had been shown based upon the surrogate endpoint of time to sputum culture conversion at 24 weeks. The committee discussed that the data were adequate for accelerated approval but not for a full approval. Some committee members also noted that safety issues were impacting their advice that the data were adequate for accelerated approval, but not for full approval. On the question of whether the safety of

bedaquiline had been shown, the Committee voted 11 Yes; and 7 No. Many Committee members cited the mortality imbalance against bedaquiline in Study C208 stage 2. They also noted no clear common apparent pattern to explain the observed difference in mortality making assessment of causality difficult to assess. Most deaths occurred well after the 24-week treatment period (within the 120 week follow-up period). The Committee also mentioned that the drug has a 5-month terminal half-life. Many of the "No" votes regarding safety stated that they still thought it was OK to move forward with an accelerated approval based on the available safety data. The Committee also went on to discuss that information on the mortality imbalance, the effect on QT and caution regarding use with other QT prolonging medications and adverse hepatic effects should be included in the product labeling. The Committee also discussed that additional data from the required confirmatory trial would provide additional information to help further characterize the safety and efficacy of bedaquiline.

Office of Scientific Investigations Assessment

The assessment by CDER's Office of Scientific Investigations finds that the data from studies C208 and C209 can be used in support of the respective indication.

Discussion

I agree with the review team, the Cross Discipline Team Leader, and the Deputy Division Director that the overall benefits and risks support the accelerated approval of NDA 204384 for Sirturo (bedaquiline) for the treatment of adults with pulmonary tuberculosis due to multi-drug resistant *Mycobacterium tuberculosis* (MDR TB) when bedaquiline is needed in order to construct an effective regimen of a combination of drugs to treat a patient's pulmonary MDR TB.

This approval is under the Agency's accelerated approval regulations (21CFR 314.500-560) that apply to drugs for the treatment of a serious or life-threatening illness that provide meaningful therapeutic benefit for the treatment of patients over existing therapies. The accelerated approval regulations provide for approval based upon a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Sputum culture conversion to negative for MTB is the surrogate endpoint being relied upon for this accelerated approval. The results of Study C208 stage 2 demonstrate a statistically significant earlier time of sputum culture conversion to negative with 24 weeks of study drug treatment in patients in the bedaquiline treatment group compared to the placebo treatment group (in both groups patients received other drugs to treat TB). The results from Study C208 stage 1, where patients were randomized to received bedaquiline or placebo for 8 weeks, both in combination with other drugs for the treatment of MDR-TB, showed a statistically significant earlier time to sputum culture conversion to negative in the bedaquiline treatment group. The results from Study C208 stage 1 provide supportive information for the results from Study C208 stage 2. Study C209, an open-label non-

comparative study in which patients received bedaquiline for the treatment of MDR pulmonary TB also provides some supportive information on the safety and efficacy of bedaquiline.

Conversion of a sputum culture to negative for MTB is reasonably likely to predict successful treatment of tuberculosis and has been an assessment relied upon for years in the treatment of patients with pulmonary TB. The use of sputum culture conversion to negative as a surrogate endpoint for approval was supported by the Anti-Infective Drugs Advisory Committee vote on the first question asking whether the efficacy of bedaquiline had been demonstrated for bedaquiline; the Committee voted 18 Yes; 0 No on this question.

Pulmonary tuberculosis is a serious and life-threatening illness. It remains a major cause of morbidity and mortality around the globe. The WHO's *Global Tuberculosis Report 2012*⁵ states that "the global burden of TB remains enormous. In 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430,000 among people who were HIV-positive. TB is one of the top killers of women, with 300,000 deaths among HIV-negative women and 200,000 deaths among HIV-positive women in 2011." Regarding multi-drug resistant TB, the WHO's *Global Tuberculosis Report 2012* notes that "Drug-resistant TB (DR-TB) threatens global TB control and is a major public health concern in several countries." The WHO Report also provides the following figures on burden of disease for MDR TB; "there were an estimated 310,000 (range, 220,000–400,000) MDR-TB cases among notified TB patients with pulmonary TB in 2011. Almost 60% of these cases were in India, China and the Russian Federation. Extensively drug-resistant TB, or XDR-TB, has been identified in 84 countries; the average proportion of MDR-TB cases with XDR-TB is 9.0% (6.7–11.2%)." The development of resistance to the antimycobacterial drugs that are relied upon to treat patients with TB limits the available treatment options. Use of an inadequate number of active drugs to treat TB (or poor compliance with treatment) can lead to treatment failures and the successive development of resistance. The WHO Report also reminds us of the outcomes of untreated tuberculosis: "Without treatment, mortality rates are high. In studies of the natural history of the disease among sputum smear-positive and HIV-negative cases of pulmonary TB, around 70% died within 10 years; among culture-positive (but smear-negative) cases, 20% died within 10 years." The WHO's *Global Tuberculosis Report 2012* helps to put into perspective the disease that tuberculosis causes, the global burden of disease, and the burden of drug-resistant tuberculosis.

For the United States, the Centers for Disease Control and Prevention publishes statistics on tuberculosis in the US. The CDC's Report *Tuberculosis in the United States, 2011*,⁶ states the following regarding tuberculosis in the U.S.: "10,528 TB cases were reported to CDC from the 50 states and the District of Columbia (DC) for 2011, representing a 5.8% decrease from 2010." The report also provides information on cases of multi-drug resistant TB; "From 1993, when the RVCT [Report of Verified Case of Tuberculosis] was expanded to include drug-susceptibility results, the proportion of patients with primary multidrug-resistant (MDR) TB,

⁵ Global tuberculosis report 2012. World Health Organization. p. available at http://www.who.int/tb/publications/global_report/en/

⁶ CDC. *Reported Tuberculosis in the United States, 2011*. Atlanta, GA: U.S. Department of Health and Human Services, CDC, October 2012.

which is defined as no previous history of TB disease and resistance to at least isoniazid and rifampin, decreased from 2.5% to 1.0% by 1998. However, there has been a slight increase in the percentage of primary MDR TB cases, from 0.9% of the total number of reported TB cases in 2008 (88 cases), to 1.1% percent in 2009 (86 cases), to 1.2% in 2010 (89 cases), to 1.3% in 2011 (98 cases). With regard to extensively drug-resistant (XDR) TB, “XDR TB is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs (i.e., amikacin, kanamycin, or capreomycin).^{7,8} Six cases were reported as XDR TB in 2011, compared with 1 case in 2010, 0 cases in 2009, and 5 in 2008.”

In summary, tuberculosis is a serious and life-threatening disease. The development of resistance leading to MDR or XDR TB causing disease in human limits the therapeutic options available to treat patients with TB. Lack of an adequate number of active drugs to treat a patient with MDR or XDR TB can lead to treatment failure and the successive development of resistance to available therapies.

Bedaquiline is a diarylquinoline antimycobacterial drug. Bedaquiline has a mechanism of action that is different than other drugs used to treat tuberculosis and hence should retain activity against MTB isolates with resistance mechanisms specific to other antimycobacterial drugs. Bedaquiline therefore can provide an option for the treatment of cases of tuberculosis that are resistant to multiple other antimycobacterial drugs (i.e., MDR TB). The availability of a safe and effective drug that operates by a mechanism of action different than existing therapies for tuberculosis (specifically for the treatment of MDR-TB, when an effective regimen cannot otherwise be provided to treat a patient) provides a meaningful therapeutic benefit to patients. Such an agent could be used in circumstances when an effective regimen cannot otherwise be constructed to treat a patient with an effective combination of drugs active against the patient’s MDR pulmonary TB (note XDR-TB is a subset of MDR-TB).

The risks of bedaquiline treatment were topics of considerable evaluation and deliberation during the review of this application. These risks include the observed higher mortality rate in the bedaquiline-treated group in Study C208, stage 2, the effect of bedaquiline on the QT interval and the use of bedaquiline with other drugs that can prolong the QT interval, hepatic adverse effects, and other adverse effects of bedaquiline. These findings and the limitations of the currently available data have led us to the current labeling to describe the appropriate use of bedaquiline. As stated in the product labeling, bedaquiline is indicated “as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR TB). Reserve SIRTURO (bedaquiline) for use when an effective treatment regimen cannot otherwise be provided.” The balance of risks and benefits supports a positive benefit risk assessment in the indicated patient population; patients in whom an effective treatment regimen for MDR-TB cannot otherwise be provided.

⁷ Centers for Disease Control and Prevention. Revised Definition of Extensively Drug-Resistant Tuberculosis. *MMWR Morb Mortal Wkly Rep* 2006;55:1176.

⁸ Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. *Wkly Epidemiol Rec* 2006;81:430-2.

Steps to mitigate the risks of bedaquiline include its indication for use only when an effective treatment regimen cannot otherwise be provided. In addition, the product labeling includes a Boxed Warning that describes the greater number of deaths in Study C208 stage 2. The Boxed Warning also reinforces that bedaquiline should only be used when an effective treatment regimen cannot otherwise be provided. The Boxed Warning also alerts healthcare providers to the potential for QT prolongation that may be additive if used with other drugs that prolong the QT. The prominent display of this information will allow healthcare providers to carefully consider under what circumstances use of bedaquiline is appropriate. Additional information regarding the observed increased mortality, QT prolongation, hepatic adverse effects, and other risks, are described in the Warnings and Precautions section of the product labeling and other sections of the labeling. In addition, a Medication Guide with patient information describing the benefits and risks of bedaquiline is part of the product labeling.

We also considered whether a Risk Evaluation and Mitigation Strategy (REMS) was needed for bedaquiline and discussed the issue with OSE's Division of Risk Management (DRISK). Given that TB is a reportable disease, pulmonary TB is serious disease, and that it is managed largely through the public health system within the US, our assessment was that these existing networks and mechanisms that are already in place will be adequate for the use of this drug for its indication of treatment of adult patients with MDR TB when it is needed to construct an effective regimen for the treatment of patients with MDR TB. This is consistent with the assessment of DRISK. We also had the opportunity to discuss this issue and get input from Drs. Jenkins, Temple, and Kweder regarding how the approach for bedaquiline relates to the broader perspective on the management of safety issues across therapeutic areas.

Although not requirements for the approval of bedaquiline for its indication of treatment of patients with MDR pulmonary TB when an effective regimen cannot otherwise be provided, Janssen plans to make bedaquiline available only through a single point of distribution. Janssen has consulted with the Centers for Disease Control and Prevention's Division of Tuberculosis Elimination regarding incorporating information on the risks and benefits, and appropriate use of bedaquiline into the CDC's existing TB Education and Training Network and the CDC's Regional Training and Medical Consultation Centers.

In summary, the overall benefits and risks support the accelerated approval of NDA 204384 for bedaquiline for the treatment of adults with pulmonary tuberculosis due to multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB) when bedaquiline is needed in order to construct an effective regimen of a combination of drugs to treat a patient's pulmonary MDR-TB. The product labeling adequately describes the safety and efficacy findings. As described below, postmarketing studies will provide additional information to verify and describe the clinical benefit of bedaquiline the treatment of MDR-TB as required under the accelerated approval regulations, provide additional information on adverse effects and use including through a registry for patients receiving bedaquiline, information on clinical microbiology and susceptibility testing for bedaquiline, and drug interactions.

Pediatric Research Equity Act

With regard to the Pediatric Research Equity Act (PREA), because bedaquiline has an orphan drug designation for treatment of active TB, it is exempt from the PREA requirements.

Tropical Disease Priority Review Voucher

The approval of bedaquiline is accompanied by the granting of a tropical disease priority review voucher to the applicant as provided under section 524 of the FDCA.⁹

Accelerated Approval Requirements, Postmarketing Requirements and Postmarketing Commitments

Selected portions of the descriptions of the Accelerated Approval Requirements, Postmarketing Requirements and Postmarketing Commitments are excerpted from the Approval Letter and provided below. For a complete description of these requirements and commitments the reader is referred to the Approval Letter.

Accelerated Approval Requirement

The required study to verify and describe clinical benefit of bedaquiline for the treatment of MDR pulmonary TB is as follows:

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

Final Protocol Submission:	06/2013
Trial Completion:	08/2021
Final Report Submission:	03/2022

Postmarketing Requirements Under 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of increased mortality, assess a signal of development of decreased bedaquiline susceptibility in MDR-TB isolates, and identify an unexpected serious risk of increased drug levels of SIRTURO (bedaquiline) in HIV patients co-infected with MDR-TB.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

⁹ For additional information, please see FDA's guidance, *Tropical Disease Priority Review Vouchers*, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf>.

Therefore, based on appropriate scientific data, FDA has determined that the applicant is required to conduct the following:

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 MDR-TB isolate (in patients who have relapsed/at end of treatment)
- c. drug utilization data
- d. information on the drug distribution mechanisms used
- e. information on how the drug was actually distributed to patients
- f. patient outcomes (clinical and microbiologic)
- g. safety assessments in bedaquiline-treated patients, including deaths
- h. concomitant medications

Final Protocol Submission:	06/2013
Interim Report Submission:	06/2014
	06/2015
	06/2016
	06/2017
	06/2018
Study Completion:	12/2018
Final Report Submission:	08/2019

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.

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

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.

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

1988-005: Conduct a prospective in vitro study over a five-year period after introduction of SIRTURO (bedaquiline) to the market to determine MICs of MDR-TB isolates 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.

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

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.

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

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased drug levels of SIRTURO (bedaquiline) in HIV patients co-infected with MDR-TB.

Therefore, based on appropriate scientific data, FDA has determined that the Applicant is required to conduct the following:

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.

Final Protocol Submission: 03/30/2013
Final Report Submission: 09/30/2013

Postmarketing Commitments

The Applicant's postmarketing commitments include the following:

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

Final Report Submission: 11/2013

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

Trial Completion: 01/2013
Final Report Submission: 11/2013

Please see the Approval letter for the complete listing and description of postmarketing requirements and postmarketing studies.

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

/s/

EDWARD M COX
12/28/2012