

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204384Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration Center for  
Drug Evaluation and Research Office of  
Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Risk Management Options Review**

**Date:** December 19, 2012

**Reviewer(s):** Julia Ju, Pharm.D., Ph.D.  
Social Science Reviewer  
Division of Risk Management (DRISK)

**Through:** Cynthia LaCivita, Pharm.D., DRISK

**Division Director:** Claudia Manzo, Pharm. D., DRISK

**Drug Name(s):** Bedaquiline (TMC207)

**Therapeutic Class:** Mycobacterial ATP synthase inhibitor

**Dosage and Route:** 400 mg p.o, qd for 2 weeks followed by  
200 mg three times per week for 22  
weeks

**Application Type/Number:** NDA 204384

**Submission Number:** 001

**Applicant/sponsor:** Janssen Therapeutics

**OSE RCM #:** 2012-2203

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

## 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for the new molecular entity (NME) bedaquiline (TMC207). On July 11, 2012 the Division of Anti-Infective Products (DAIP) received a new drug application (NDA) 204384, from Janssen Therapeutics for bedaquiline. The proposed indication is in adults ( $\geq 18$  years) as part of combination therapy of pulmonary tuberculosis (TB) due to multi-drug resistant (MDR) *Mycobacterium tuberculosis*.

Bedaquiline has not been approved or marketed in the United States or any other country. The applicant did not submit a proposed REMS or risk management plan.

## 2 BACKGROUND

Bedaquiline is a diarylquinoline with a novel mode of inhibition of mycobacterial adenosine 5'-triphosphate (ATP) synthase. Thus, bedaquiline introduces a new class of anti-TB drugs. The distinct target of bedaquiline minimizes the potential for cross-resistance with existing anti-TB drugs. The recommended dosage of bedaquiline for MDRTB is:

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

The total duration of treatment with bedaquiline is 24 weeks. After reaching  $C_{max}$ , bedaquiline concentrations decline tri-exponentially with a long terminal half-life ( $t_{1/2, term}$ ) of approximately 4-5 months; however, the effective half-life of bedaquiline is approximately 24-30 hours, based on the approximately 2-fold accumulation after 2 weeks of daily dosing.

TB is a leading cause of death from infectious disease worldwide. 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<sup>1</sup>.

In 2011, a total of 10,521 new tuberculosis (TB) cases were reported in the United States, an incidence of 3.4 cases per 100,000 population. There were a total of 109 cases of multidrug-resistant TB (MDR TB) reported in the United States in 2010, the most recent year for which complete drug-susceptibility data were available. The percentage of MDR TB cases among persons without a previous history of TB has remained stable at approximately 1.0% since 1997. For persons with a previous history of TB, the percentage with MDR TB in 2010 was approximately four times greater than among persons not previously treated for TB. In 2010, foreign-born persons accounted for 90 (82.6%) of the 109 MDR TB cases in the US. Four cases of extensively drug-resistant TB (all occurring in foreign-born persons) have been reported for 2011. Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have MDR-TB. Geographically, the burden of TB is highest in Asia and Africa.

If approved in the US, the company stated that bedaquiline will be administered by local and state health authorities.

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<sup>1</sup> Global tuberculosis report 2012. [http://www.who.int/tb/publications/global\\_report/gtbr12\\_executivesummary.pdf](http://www.who.int/tb/publications/global_report/gtbr12_executivesummary.pdf)

### **3 MATERIALS REVIEWED**

We reviewed the following materials from the May 29, 2012 NDA submission:

- Summary of Clinical Efficacy
- Summary of Clinical Safety

We reviewed the following additional materials, generated during the Agency review of the NDA:

- Clinical safety analysis presented at the midcycle meeting
- Efficacy analysis presented at the midcycle meeting
- Interdisciplinary Review Team for QT Studies Consultation
- FDA edited product labeling
- The Agency's Briefing Package for the November 28, 2012 Division of Anti-infective Drugs Advisory Committee Meeting

### **4 REVIEW OF RISK MANAGEMENT OPTIONS**

#### **4.1 OVERVIEW OF CLINICAL PROGRAM**

The clinical evaluation of bedaquiline for the treatment of pulmonary TB due to multidrug resistant (MDR) *M. tuberculosis* as part of combination therapy in adults is based on data from:

- 1 proof-of-principle Phase IIa trial in drug-susceptible (DS)-TB subjects (C202),
- 2 independent sequential stages in a randomized placebo-controlled Phase IIb trial in MDR-TB subjects who were treatment-naïve for second-line anti-TB medication (C208 Stage 1 and C208 Stage 2), and
- 1 uncontrolled Phase IIb trial in newly diagnosed or treatment-experienced MDR-TB subjects (C209).

Results from the Phase IIa trial C202 demonstrated a statistically significant decrease from baseline in log<sub>10</sub> sputum colony forming units (CFU) counts following 7 days of monotherapy with bedaquiline at 400 mg once daily in subjects with DS-TB.

In the C208 Stage 1 study, newly diagnosed MDR-TB subjects received bedaquiline or placebo for 8 weeks in combination with a preferred 5-drug background regimen (BR) of MDR-TB therapy that was continued afterwards. The bedaquiline regimen started with 400 mg q.d. for 2 weeks followed by 200 mg dosed intermittently at 3 times weekly (t.i.w.) during the remainder of the investigational treatment period. Results after 8 weeks of treatment showed a significantly shorter time to mycobacteria growth indicator tube (MGIT) culture conversion and a higher proportion of subjects in the bedaquiline group (47.6%) compared to the placebo group (8.7%) with culture conversion.

The pivotal proof-of-efficacy Phase IIb trial C208 Stage 2 was designed to demonstrate superiority in the antibacterial activity of bedaquiline compared to placebo when added to a preferred 5-drug BR of MDR-TB treatment for 24 weeks. After 24 weeks of MDR-TB treatment, time to sputum culture conversion (i.e., the primary efficacy endpoint) was significantly shorter with addition of bedaquiline compared to placebo: median time to culture conversion was 73 days in the bedaquiline versus 125 days in the placebo group. Similar results were obtained using this analysis method for the intent to treat (ITT) population as well as according to two sensitivity analysis methods ('end-censored missing = failure' and 'no overruling for discontinuation' method). In the interim analysis as well as in the primary efficacy analysis of C208 Stage 2, a Cox proportional hazards model adjusting for lung cavitation and pooled center showed a statistically significant difference in time to culture conversion between the treatment groups ( $p < 0.0001$ ) in favor of bedaquiline .

The superior treatment effect of bedaquiline was supported by results from C208 Stage 1 with a statistically significantly shorter time to culture conversion when using 24-week data ( $p = 0.0022$ ) and higher conversion rates at Week 24 compared to placebo. Efficacy results from the single-arm C209 trial (ongoing trial in which all subjects had completed the Week 24 visit or discontinued earlier at the data cut-off date of the interim analysis) were also generally consistent with those of C208 Stage 2.

**Table 1: Median Time to MGIT Culture Conversion in Phase IIb Trials C208 Stage 1, C208 Stage 2, and C209 (24-Week Data Selection) - mITT Population**

Analysis Method	C208 Stage 1		C208 Stage 2 <sup>a</sup>		C209 <sup>b</sup>
	Bedaquiline /BR	Placebo/BR N = 23	Bedaquiline /BR	Placebo/BR N = 66	Bedaquiline /BR
Primary missing = failure analysis	70 days	126 days	73 days	125 days	57 days
End-censored missing = failure	78 days	129 days	84 days	127 days	57 days
No overruling for discontinuation	NA	NA	72 days	99 days	57 days

N = number of subjects; NA = not analyzed

<sup>a</sup> Result from the interim analysis with efficacy cut-off date 10 May 2011 using the 24-week data selection.

<sup>b</sup> Result from the interim analysis with cut-off date 29 March 2011 using the 24-week data selection.

## 4.2 KEY SAFETY FINDINGS

The safety and tolerability of bedaquiline for the treatment of pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients as part of combination therapy is supported by the safety data from 14 trials: 11 completed Phase I trials in non-TB-infected subjects and 3 Phase II trials in TB-infected subjects, which included 380 patients who received bedaquiline in the drug development program and 265 normal volunteers.

The Phase I pooled analysis (8 trials) included data from 217 healthy subjects, of whom 189 received at least one dose of bedaquiline up to 700 mg. The pooled Phase IIb analysis included safety data from 335 adult subjects with TB who received at least one dose of bedaquiline (102 from the controlled trial C208 and 233 from the open-label trial C209) and from 105 adult subjects with TB who received at least one dose of placebo (C208 trial). In this pooled Phase IIb analysis, subjects received 400 mg once daily (q.d.) for 2 weeks after which 200 mg was dosed 3 times per week (t.i.w.) during the remaining weeks of the Investigational Treatment phase (i.e., Weeks 3-8 in C208 Stage 1 and Weeks 3-24 in C208 Stage 2 and C209). Subjects included in both stages of the C208 trial were newly diagnosed with a pulmonary MDR-TB infection and were sputum smear-positive. These subjects had never been treated for MDR-TB before or had only received first-line anti-TB drugs. The population in C209 differed from that in C208 Stage 2 in the fact that most subjects (85.8%) were receiving second-line anti-TB drugs at screening and subjects infected with extensively drug resistant TB (XDR-TB) were also allowed to participate.

The most frequently reported adverse events (AE) in the bedaquiline group (> 20.0% of subjects) were nausea, arthralgia, headache, hyperuricemia, and vomiting. No additional safety signals were identified based on review of the pooled controlled and uncontrolled trials, and the Phase I/IIa trials.

### **Death**

Overall in the bedaquiline clinical development program, 30 subjects died (26 in the bedaquiline treatment groups and 4 in the placebo group).

**Table 2. Summary Mortality Data in Bedaquiline Clinical Development Programs**

<b>Phase/Study</b>	<b>Type of Study</b>	<b>Bedaquiline</b>	<b>Placebo</b>
Phase 1 Deaths	Dose-ranging, 2 week exposure	N=189 0	N=27 0
Phase 2			
Trial C202 Death	Randomized, open-label, dose-ranging, 1 week exposure	N=45 2 (4.4%)	N=30 0
Trial C208 Stage 1 Death	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 (12.7%)	N=81 2 (2.5)
Trial C209 Deaths	Open-label, uncontrolled, 24 week exposure	N=233 16 (6.9)	N=0

- Two deaths occurred in the follow up period of TMC 207 treatment group in the Phase IIa trial (C202) (causes of death were retroviral infection/pulmonary tuberculosis and hemoptysis).
- In the controlled Phase IIb trial (C208 Stage 2), there was an imbalance in the number of deaths with 10 observed in the bedaquiline group and 2 in the placebo group. The reason for imbalance in deaths is unknown.
  - Deaths in the placebo group were attributed to hemoptysis (1) and one was determined to be due to TB.
  - Deaths in the treatment group were one each related to alcohol poisoning, hepatitis/hepatic cirrhosis; septic shock/peritonitis, CVA/hypertension, and 6 were determined to be related to TB.
- In the uncontrolled trial (C209), 16 deaths were reported so far. The 4 month safety update report stated this trial was ongoing.

**Reviewer Comments:**

*The imbalance of deaths in the bedaquiline and placebo groups is concerning. The reason for this imbalance is unknown. The role of bedaquiline in deaths where hepatotoxicity and cardiac failure are contributory could not be ruled out.*

**QT prolongation**

No consistent QT increases were seen in the nonclinical studies. The events reported in the Drug-Drug Interaction study (bedaquiline and ketoconazole) demonstrate some of the QT prolongation issues associated with bedaquiline. First, QT prolongation was reported in a patient that received bedaquiline alone. As well, mean increases in the QTcF interval were greater with combined use of bedaquiline and ketoconazole than with either drug alone. As ketoconazole has the potential to cause

QT prolongation, the observation that greater increases in QTcF were observed with multiple doses of bedaquiline and ketoconazole in combination than when these drugs were given independently demonstrate the potential additive effect of drugs with QT prolonging effects when administered together. This may be attributable to a drug interaction, as ketoconazole can increase bedaquiline systemic exposure, or due to additive effects on QT prolongation independent of the drug interaction. Additional 4 bedaquiline-treated subjects were noted to have prolonged QTcF intervals in other Phase I studies.

Based on ECG measurements from the pooled Phase IIb studies, mean QTcF intervals increased 10 to 15 ms over the 24-week treatment period with bedaquiline and values decreased after the end of bedaquiline treatment. In the placebo group, mean QTcF changes from reference were generally < 10 ms. Overall, few subjects had a QTcF value above 500 ms during the Investigational Treatment phase. ECG abnormalities observed more frequently in the bedaquiline group than in the placebo group included QTcF increases from reference of > 60 ms (10.1% and 4.0% of subjects, respectively), increases of 30 to 60 ms (52.5% and 32.7% of subjects, respectively) and QTcF actual values between 450 and 480 ms (22.5% and 6.7%, respectively).

**Controlled Trials:** During the Investigational Treatment phase of the C208 trials, the percentage of subjects with Torsade de Pointes/QT prolongation Standardized MedDRA Query (SMQ) events was similar in the bedaquiline and placebo groups (3.9% and 3.8%, respectively). None of the Torsade de Pointes/QT prolongation SMQ events was considered serious or led to discontinuation of investigational medication. There were no reports of Torsade de Pointes, serious ventricular arrhythmias, or unexplained sudden death during the Investigational Treatment phase.

**Uncontrolled Trial:** During the Investigational Treatment phase in the uncontrolled trial (C209), 1 subject in the bedaquiline group experienced the SAE electrocardiogram (ECG) QT prolonged (QTcF = 461 ms; change from reference = 11 ms), treatment was discontinued. Mean increase in QTcF was larger in the subset of subjects with concomitant clofazimine use (N = 17, Week 24, 0 h: 31.94 ms) than in subjects without concomitant clofazimine use (N = 177, Week 24, 0 h: 12.28 ms).

**Reviewer Comments:** *Clofazimine has shown activity against MDR-TB, however experience with it appears to be limited.*

**Single-dose Trial:** The QT study (TBC1003), which utilized a single dose (800 mg) of bedaquiline, was negative. However, it is important to note that this was a single-dose trial which may not fully reflect the potential effect of multiple doses of bedaquiline on the QTc interval.

**Reviewer Comments:**

*The negative results from the QT Study (TBC1003) should be interpreted with caution since a single-dose trial may not fully reflect the potential effect of multiple doses of bedaquiline on the QTc interval. Based on the available data, the review team agreed that the increase in QTcF interval associated with bedaquiline is considered moderate and is amenable to routine clinical monitoring. However, the multiple dose exposure and long half life (4-5 months) of bedaquiline evidence the need for long-term safety investigations of bedaquiline's cardiac toxicity.*

**Hepatic toxicity**

The incidence of events retrieved by the drug-related hepatic disorders was higher in the bedaquiline group (8.8% of subjects) compared to the placebo group (1.9% of subjects) in the C208 stage 1 and stage 2 trials. This difference was primarily driven by the preferred terms transaminases increased and aspartate aminotransferase (AST) increased. There was no signal for cholestasis or

hyperbilirubinemia associated with bedaquiline in the Phase IIB trials. Only 1 subject (bedaquiline group) met the laboratory criteria for Hy's Law. Medical assessment suggests the hepatic toxicity in this subject was more likely caused by the background TB regimen and alcohol abuse than by bedaquiline.

**Reviewer Comments:**

*Bedaquiline's contribution to hepatotoxicity cannot be excluded. Long-term safety data are needed because of the long half-life of bedaquiline.*

**4.3 PRODUCT LABELING**

The FDA-edited proposed labeling includes the following adverse reactions in the Warnings and Precautions section of the labeling.

- Obtain an ECG prior to and after initiation of therapy with bedaquiline to monitor the QTc interval.
- Conduct monthly ECGs if initiating bedaquiline treatment in patients with QTcF interval > 450 ms.
- Discontinue bedaquiline treatment if patients develop clinically significant ventricular arrhythmia or a confirmed prolonged QTcF interval > 500 ms.
- Co-administration with drugs that prolong the QTc interval may cause an additive or synergistic effect on QTc prolongation.

**4.4 PROPOSED POSTMARKETING STUDIES/REQUIREMENTS**

- The sponsor will be required to conduct a confirmatory randomized double blind placebo controlled multicenter phase 3 trial (C210) in subjects with sputum smear-positive pulmonary 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.
- The sponsor will also be required to develop a patient registry for bedaquiline-treated patients to assess incidence rates of serious adverse events. The registry should capture the following information: indication for use, including utilization of expert medical consultation; Minimum Inhibitory Concentration (MIC) data for baseline and any subsequent isolate (in patients who have relapsed/at end of treatment) of MDR-TB; drug utilization data; patient outcomes (clinical and microbiologic); safety assessments in bedaquiline-treated patients, including deaths; and concomitant medications.
- In addition they should 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 to bedaquiline for the first 5 years from marketing.

**4.5 Advisory Committee**

The Anti-infective Drugs Advisory Committee (ADAC) convened on November 28, 2012 to consider this application for accelerated approval. The AC was asked to vote on the following questions: "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 as part of combination therapy in adults?" and "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 as part of combination therapy in adults?". All 18 voting members voted

“Yes” to the efficacy question. Eleven voted “Yes” and seven voted “No” to the safety question. The main concerns of the safety data were long-term safety data in liver, heart, death, and pediatric use.

## **5 DISCUSSION**

The clinical trial data showed that after 24 weeks of MDR-TB treatment, time to sputum culture conversion was significantly shorter with addition of bedaquiline compared to placebo: median time to culture conversion was 73 days in the bedaquiline versus 125 days in the placebo group. Sputum culture was a surrogate endpoint for efficacy.

The clinical team determined that the increase in QT interval associated with bedaquiline is considered moderate and is amenable to routine clinical monitoring. However, an additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other drugs that prolong the QT interval cannot be excluded. The potential risk of QT prolongation with bedaquiline when concomitantly prescribed with medications that have a potential for QT prolongation, the need to monitor with ECGs will be addressed in labeling.

There were two hepatic-related deaths; the underlying cause of hepatotoxicity are confounded by concomitant alcohol use/abuse and medication use. Unfortunately, hepatitis serology was not conducted on either patient. Based on the available data, the risk of hepatotoxicity cannot be excluded.

The cause of the imbalance in the number of deaths in patients treated with bedaquiline is not known. The majority of the deaths in the treatment arm were attributed to TB, the other 4 causes of death varied.

Because of the imbalance in deaths and the concerns raised during the ADAC meeting, DAIP and DRISK re-evaluated the possible need for a REMS. A REMS might mitigate a risk of death if there was a clear cause that could be attributed to the deaths and an intervention that could mitigate the risk for the individual. An example might be that patients would be required under a REMS to have a baseline ECG and laboratory values if it was determined that the QT prolonging effect. The phase III clinical trial and other post-marketing studies are needed to better characterize the risks of QT prolongation, hepatotoxicity and increased risk of death. Based on the available data, at this time, DRISK does not recommend a REMS. DRISK recommends maximizing labeling to communicate the potential risks QT prolongation, hepatotoxicity and potential risk of increased mortality. If new safety information becomes available this decision should be re-evaluated.

## **6 CONCLUSION**

DRISK does not recommend a REMS for bedaquiline. At this time the risks associated with bedaquiline can be managed through labeling. If new safety information becomes available this decision should be re-evaluated.

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12/19/2012

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12-13-12

**TO:**

**THROUGH:**

**FROM:**

**SUBJECT:** Risk Management

**APPLICATION/DRUG:** NDA 204384

A teleconference was held between the Division of Anti-Infective products and Janssen on December 13, 2012. The purpose of the teleconference was to discuss the Sponsor's Risk Management Program relative to outcomes of the Sponsor's prior meeting with the CDC (see attached memo from CDC/Janssen teleconference):

(b) (4)





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12/26/2012