Drug Use Research & Management Program
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New Drug Evaluation: Bedaquiline

Month/Year of Review: January 2014
Generic Name: Bedaquiline
PDL Class: None

End date of literature search: September 1, 2013
Brand Name (Manufacturer): Sirturo ™
Dossier Received: Yes

FDA Approved Indication:

Bedaquiline is indicated as part of combination therapy for the treatment of patients who are ≥ 18 years of age and have pulmonary multi-drug resistant tuberculosis (MDR-TB) when an effective treatment regimen cannot otherwise be provided. Bedaquiline is not indicated for latent, extra-pulmonary, or drug-sensitive TB.[1]

Research Questions:

- Is bedaquiline plus combination therapy for MDR-TB superior to combination therapy plus placebo (PLA) for preventing treatment failure, relapse, or death?
- Is there evidence bedaquiline is safer than other currently available agents for the treatment of MDR-TB?
- Are there subpopulations in which bedaquiline is either more effective or safer than other currently available agents?

Conclusions:

- At this time, the evidence supporting bedaquiline efficacy is low, due to the absence of phase 3 studies. Among the shortcomings of the phase 2 studies used as the basis for accelerated approval of bedaquiline are (1) small patient numbers, (2) short length of study, and (3) surrogate endpoints with limited specificity and sensitivity for predicting failure and relapse. Therefore, at this time, bedaquiline's ability to prevent treatment failure, relapse, or death remains largely uninvestigated. Accordingly, MDR-TB is intended for patients for whom other effective options for treating MDR-TB have been exhausted.

- Bedaquiline use comes with serious safety concerns, considerable monitoring, and several drug-drug interactions likely to be encountered in practice. Bedaquiline carries a black box warning for increased risk of death (NNH 11) and has been associated with QT prolongation and hepatic-related ADRs (NNH 20).

Unanswered safety questions include: What is the cause of or factors associated with increased risk of death in bedaquiline-treated patients? What is the safety profile of bedaquiline in pediatric, geriatric, and HIV patients as well as patients with severe renal or hepatic impairment and extrapulmonary TB? What is bedaquiline's safety profile when used beyond the limited number of patients within a phase 2 trial?

- Options for treating MDR-TB are limited; therefore, bedaquiline represents an important need, not only to affect a cure among infected individuals who may need another option to treat resistant strains but also to suppress the spread of the disease to others. Because increased risk of death among patients taking bedaquiline has been observed, the drug should only be used when an effective treatment regimen cannot otherwise be provided.

Recommendations:

- Currently no PDL class for antimycobacterial agents exists. However, for safety issues, prior authorize bedaquiline to limit its use to patients infected with active pulmonary MDR *M. tuberculosis* when
  - an effective antimycobacterial regimen cannot otherwise be provided and
  - the drug is used in association with an MDR-TB regimen that includes at least 3 drugs to which the patient's MDR-TB isolate is susceptible to *in vitro* or, if *in vitro* testing is unavailable, 4 other drugs to which the patient's isolate is likely susceptible.
- Documentation of the following should be provided:
  - diagnosis of active pulmonary MDR-TB (i.e., not latent or drug-sensitive TB)
  - resistance of the patient's isolate to at least isoniazid and rifampin
  - susceptibility of the patient's isolate to bedaquiline
  - prescriptions for 3 or 4 concomitant medications used to treat MDR-TB
  - the use of expert medical consultation
- Make bedaquiline non-preferred and consider reviewing the entire class in the future to identify preferred options.

Reason for Review:

Bedaquline, a recently approved agent for the treatment of MDR-TB, currently has no PDL class to manage either it or any other antimycobacterial agent. Prudence dictates bedaquiline should be used appropriately to ensure patient safety and prevention of further *M. tuberculosis* resistance to bedaquiline. Accordingly, this review will evaluate the evidence for bedaquiline's efficacy and focus on safety and appropriate use.

Background:

New drugs to treat MDR-TB are urgently needed, as treatment options are limited and an estimated one-third of the world's population is infected with *M. tuberculosis*. The overall mortality for MDR-TB is greater than 10% (range 8 to 21%) for patients in a good treatment program, and the case fatality rate of patients with MDR-TB and HIV is about 26%.[2]

In 2012, 61 verified cases of TB (1.6 cases per 100,000) occurred in Oregon, 74% of which were among foreign-born residents. About 8% of the isolates tested were resistant to isoniazid (INH), and one case of TB exhibited multidrug resistance (MDR). This compares to a TB rate of 3.2 cases per 100,000 nationally, with 98 cases of TB (1.3%) having MDR in 2011. About 83% of MDR-TB cases were foreign-born.[6]

Bedaquiline was developed to treat MDR-TB, which is defined as a strain resistant to at least isoniazid (INH) and rifampin (RMP). Extremely drug resistant (XDR) TB is a still rare type of TB that is resistant INH and RMP plus any fluoroquinolone (FQ) and at least one of three injectable second-line

drugs (i.e., amikacin, kanamycin, or capreomycin). Pre-XDR-TB is MDR-TB that has become resistant to at least one second-line injectable drug or to any fluoroquinolone [2,7]

The goals of TB therapy are to (1) cure patients and restore quality of life and productivity; (2) prevent death from active or the latent effects TB; (3) prevent TB relapse; (4) reduce the transmission of TB to others; and (5) prevent the development of and transmission of resistant organisms.[8]

Treatment for MDR-TB is complex and has a cure rate of 41-70%.[2] The general principles for designing MDR-TB treatment regimens are to use at least four drugs more certain to be effective. Effective drugs include those with known rare resistance, drug susceptibility tests (DST) showing susceptibility for drugs with good DST reliability (injectable agents and FQs, INH, and RMP), common use in the area, and no failure history in the patient or close contacts of the patient for whom the drugs are used. Drugs unsafe for the patient and drugs for which there is the possibility of cross-resistance should not be used.[8]

In the U.S., treatment of MDR-TB should be performed by or in consultation with an expert in its management. Treatment regimens employed are based on the pattern of drug resistance and typically include five drugs administered for durations up to 24 months. Patients should receive hospital-based or home-based DOT. Suggested regimens to treat MDR-TB include ethambutol and/or pyrazinamide; a fluoroquinolone (levofloxacin, ofloxacin, ciprofloxacin); an injectable (streptomycin, amikacin, kanamycin, capreomycin), and one or two alternative agents (cycloserine, ethionamide, p-aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid).[7] However, the optimal use and contribution of individual drugs to MDR-TB regimens is unknown, and many second-line drugs are associated with toxicities. Few randomized–controlled trials have assessed the risk-benefit profile of MDR-TB regimens. [2,7]

In evaluating TB regimens in clinical trials, the phase 3 primary endpoint is a composite outcome of failure at the end of treatment or relapse after stopping the treatment. Failure to culture TB organisms does not necessarily indicate a cure. An effective regimen is one that not only converts patients to culture-negative by treatment's end but also prevents relapse. Therefore, clinical trials to evaluate new regimens commonly include follow-up beyond the end of 18 to 24 month's treatment. A systematic review of sputum monitoring for predicting outcome to TB treatment found the two-month culture had limited sensitivity and specificity for predicting failure and relapse.[9]

October 2013, the Centers for Disease Control and Prevention (CDC) published provisional guidelines for the use and safety of bedaquiline.[10] These guidelines state bedaquiline may be used:

- *for 24 weeks of treatment in adults with laboratory-confirmed pulmonary MDR TB (TB with an isolate showing genotypic or phenotypic resistance to both INH and RIF) when an effective treatment regimen cannot otherwise be provided. (Quality of evidence: low)*
- *on a case-by-case basis in children, HIV-infected persons, pregnant women, persons with extrapulmonary MDR TB, and patients with comorbid conditions on concomitant medications when an effective treatment regimen cannot otherwise be provided. (Quality of evidence: insufficient)*
- *on a case-by-case basis for durations longer than 24 weeks when an effective treatment regimen cannot be provided otherwise. (Quality of evidence: insufficient)*

With regard to the second and third recommendations, the CDC further states the effectiveness and safety of bedaquiline have not been studied adequately in these populations or beyond 24-weeks' duration; therefore, general guidance cannot be provide for or against its use. However, because MDR TB has a high mortality rate and limited treatment options, providers might consider bedaquiline in treating certain patients in the groups listed above or for longer durations in some patients.

Clinical Efficacy:

The FDA based accelerated approval of bedaquiline on two phase 2 clinical trials: a two-stage study called C208 and study C209. Study C208 stage 2 was considered the pivotal trial, while C208 stage 1 was considered exploratory and provided supportive evidence along with study C209. These studies assessed the ability of a bedaquiline MDR-TB regimen to reduce the time to sputum culture conversion after 8 or 24 weeks and increase the proportion of patients with negative sputum cultures vs an MDR-TB regimen plus placebo. A phase 3 trial is planned to further assess bedaquiline efficacy and safety.[2]

C208 was a multicenter, stratified, double-blind, randomized, placebo-controlled trial. The study's two stages were separate and consecutive. C208 stage 2 randomized subjects with sputum-positive pulmonary MDR-TB to receive a recommended 5-drug background regimen (BR) with either placebo (PLA) or bedaquiline for 24 weeks. After the bedaquiline and PLA treatment period, BR was continued to 72-96 weeks. Patients in the bedaquiline arm (n=21) received 400 mg daily weeks 1 and 2 and, then, bedaquiline 200 mg thrice weekly for weeks 3 through 24. The BR consisted of kanamycin, ofloxacin, ethionamide, pyrazinamide, and cycloserine or terizidone, with modifications allowed based on susceptibility test results during the course of the study, adverse events, or drug supply interruption. All treatment was administered via directly observed therapy (DOT). Stratification was by trial site and by the extent of lung cavitation: <2 cm, cavitation (≥2 cm) unilaterally, or ≥2 cm bilaterally. The primary endpoint was TSCC during treatment, which was defined as the time interval from initiation of bedaquiline or placebo treatment to the first of two consecutive negative cultures from sputa collected 25 days apart. [2]

The analysis population was predominantly male (64%), black (37%), and HIV negative (86%) with a median age of 33 years. At least 89% of patients had previous use of TB drug treatment and 83% had cavitary pulmonary disease. Differences in baseline characteristics between treatment groups included more HIV infected patients in the PLA group (21%) vs the bedaquiline group (8%), more $MDR_{H\&R}$-TB patients enrolled in the placebo group (68%) compared to the bedaquiline group (59%), and more pre-XDR TB isolates (a protocol violation) in the bedaquiline group (23%) vs the PLA group (18%). Analyses used a modified intent to treat (mITT) population that excluded patients with (1) DS-TB, XDR-TB, or unconfirmed MDR-TB or (2) no evidence of culture positivity prior to baseline or no results during the first 8 weeks after baseline. Analysis of the primary efficacy endpoint revealed a median TSCC at 24 weeks of 83 days for the bedaquiline group (CI: 56 to 97) and 125 days for the PLA group (CI: 98 to 168). Culture conversion rates at 24 weeks, the secondary endpoint, were 78% for the bedaquiline group and 58% for the placebo group for a NNT of 5. However, the difference in conversion rates were not significant at 72 weeks.[2]

C208 stage 1 was similarly designed to stage 2 but differed in that 44 subjects, randomized 1:1, comprised the mITT population and subjects were treated with bedaquiline or PLA plus BR for 8 weeks. The primary endpoint was TSCC during treatment, which was defined as the time interval from initiation of bedaquiline or placebo treatment to the first of two consecutive negative weekly cultures. In this study, the bedaquiline group again more quickly converted positive sputum cultures to negative: HR 11.8 (CI: 2.3 to 61.3, p=0.003). The actual mean TSCCs for each group were not provided. The rates of conversion were 48% (10/21) for the bedaquiline group and 9% (2/23) for the PLA group (difference 38.9%; CI: 12.3% to 63.1%; p=0.004) for a NNH of 3. However, no significant difference in conversion rates was evident at 24 and 104 weeks. [2–4]

Study C209 was a 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 MDR-TB, including pre-XDR-TB and XDR-TB. The bedaquiline dose, treatment duration, primary efficacy endpoint, and main secondary endpoint were the same as C208 stage 2. The mean TSCC was 57 days (CI: 56 to 83). The culture conversion rate at 24 weeks was 79.5%.[2,5]

Among the shortcomings of the phase 2 studies used as the basis for accelerated approval of bedaquiline are small patient numbers, short length of study, and surrogate endpoints. At this time, bedaquiline's ability to prevent treatment failure, relapse, or death remains largely uninvestigated. Importantly, these studies leave open the following efficacy questions:
What is the efficacy of bedaquiline in phase 3 trials with treatment failure, relapse, and mortality as endpoints?
How will bedaquiline perform in the United States? These studies took place predominantly in South Africa, which has different demographics, resistance patterns, and drug availability from the United States and has endemic TB.
How will bedaquiline perform in HIV patients? Too few HIV patients were used in the trials to make this determination.

Clinical Safety:[1]

An increased risk of death was observed in the treatment group receiving bedaquiline plus BR versus the group receiving PLA plus BR: 11.4% (9/79) v. 2.5% (2/81); NNH 11. One death occurred during the 24-week bedaquiline treatment period, while the median time to death for the remaining decedents was 329 days after the last bedaquiline dose. The imbalance in deaths remains unexplained and, thus far, appears unrelated to sputum culture conversion, relapse, sensitivity to other TB drugs used, or disease severity. Bedaquiline also has been associated with QT prolongation. In a RCT, the largest mean increase in QTc was 15.7 ms for the bedaquiline group and 6.2 ms for the placebo group at week 18 of 24 weeks of treatment. These increases persisted after bedaquiline treatment ended.

More hepatic-related ADRs were observed in patients taking bedaquiline plus background therapy vs. those on other MDR-TB regimens. In two studies, 10.8% (11/102) of bedaquiline-treated patients versus 5.7% (6/105) of placebo-treated patients developed aminotransferase elevations at least 3 times the ULN (NNH 20). Limited data exist on the use of bedaquiline in patients with HIV (n=22), and these patients were not receiving antiretroviral therapy.

In a 24-week phase 2b study, adverse reactions occurring in ≥10% of subjects treated with bedaquiline (n=79) and at a frequency greater than placebo (n=81) were nausea (38% v 32.1%), arthralgia (32.9% v. 22.2%), headache (27.8% v. 12.3%), hemoptysis (17.7% v. 11.1%), and chest pain (11.4% v. 7.4%).

Unanswered safety questions include the following:
What is the cause of or factors associated with increased risk of death in bedaquiline-treated patients? What is the safety profile of bedaquiline in pediatric, geriatric, and HIV patients as well as patients with severe renal or hepatic impairment and extrapulmonary TB? What is bedaquiline's safety profile when used beyond the limited number of patients within a phase 2 trial?

COMPARATIVE CLINICAL EFFICACY[2–5]

Relevant Endpoints:

1) Failure at the end of treatment
2) Relapse after stopping treatment
3) Morbidity and mortality
4) Serious adverse effects

Primary Study Endpoint:

1) Time to sputum culture conversion (TSCC) from positive to negative, defined as the interval between the date of treatment initiation and the date of acquisition of the first of at least two consecutive negative weekly cultures.
2) Serious adverse effects

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (95% CI, p-values)	ARR NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. C208 Stage 2 Phase 2, DB, RCT, stratified, MC from FDA Medical Review	1. BED/BR: BED 400 mg QD + BR weeks 1-2 then BED 200 mg 3 times/wk + weeks 3-24 (then BR per guidelines) 2. PLA /BR weeks 1-24 (then BR alone per guidelines) Investigational duration: 24 weeks (final analysis at 120 weeks)	**Demographics (mITT):** Age (median): 34, 33 ・Male: 68%, 61% ・Race: Black: 36%, 38% White race: 9%, 12% Other race: 55%, 50% ・HIV + : 8%, 21% (CD4+ cell count [median]: 463, 433) ・Lung cavitation (%): ≥2 cm cavity bilaterally: 18%, 23% ≥2 cm cavity unilaterally: 64%, 62% no cavity ≥2 cm: 18%, 15% ・Resistance extent: MDR-TB: 100%, 100% $MDR_{H\&R}$-TB: 59%, 68% Pre-XDR-TB: 23%, 18% ・Any previous use of TB drug treatment: 91%, 88% **Inclusion Criteria:** ・age 18−65 ・newly diagnosed pulmonary TB resistant to INH and RMP ・treatment naïve or first-	**mITT** 1. 67 2. 66	**Median TSCC at 24 weeks:** 1. BED/BR: 83 days (CI: 56 to 97) 2. PLA/BR: 125 days (CI: 98 to 168) Relative risk: 2.15 [1.39 to 3.31, p=0.0005] **Secondary endpoints: Culture conversion rates:** **at 24 weeks:** 1. BED/BR: 78% 2. PLA/BR: 58% (Difference 20% [CI: 4.5% to 35.6%, p=0.014]) **at 72 weeks**	NA 20/5	**Any SAEs overall treatment phase:** BED/BR: 24.1% PLA/BR: 18.5% **Deaths up to 120 weeks:** BED/BR: 11.4% PLA/BR: 2.5% (CI: 1.1 to 18.2, p=0.031) **TEAEs leading to D/C of study drug:** BED/BR: 9.1% PLA/BR: 7.6%	5.6/18 8.9/11 1.5/66	**Quality rating:** Poor **Internal Validity:** ・This study possessed the shortcomings of a phase 2 study, including small, inadequate patient numbers, insufficient length of study, and the use of surrogate endpoints. ・More HIV+ patients enrolled in the PLA group than BED group. More $MDR_{H\&R}$-TB patients enrolled in PLA group than BED group. Pre-XDR patients were enrolled in the study (protocol violation) More pre-XDR TB isolates in the BED group than the PLA group. The background regimen was modified in 39% of patients. **External Validity:** ・Use of known CYP3A4 inducers and inhibitors and drugs with proarrhythmic potential were prohibited during the study. Many HIV antiviral regimens include CYP3A4 substrates, inducers, and inhibitors. ・Performance of bedaquiline in a population with demographics the same or similar to the U.S. is unknown as trial participants were predominantly from South Africa (54%). Also, the numbers of HIV-positive patients in the study were insufficient to determine the efficacy and safety of bedaquiline in that population. ・TB is endemic to the population used in this trial and most have previous experience with TB drugs. ・Culture conversion rates may not be durable.

		line drug experience (INH, RMP, EMB, PZA, or SM) · able to produce sputum ≥10 mL nightly · D/C all TB meds 7 d before baseline assessment **Exclusion Criteria:** · pregnancy or breastfeeding · isolates not susceptible to aminoglycosides other than SM and FQs · HIV (+) w/ CD4 count <300 cells/µL or antifungal or antiretroviral therapy in previous 90 d · significant cardiac arrhythmia · alcohol/drug use that would compromise compliance · concomitant severe illness or deteriorating health, including immunodeficienc or GI disorder interfering with BED absorption · medical condition that would interfere with trial participation · at risk for QT/QTc prolongation · significant lab abnormalities · TB strain not susceptible to at least 3 of 5 drug classes for treating MDR-TB · chorioretinitis, optic neuritis, uveitis		1. BED/BR: 71% 2. PLA/BR: 56% (Difference 15% [CI: -1.1% to 31.4%, p=0.070])	NS			**Analysis:** · The results of this exploratory study suggest bedaquiline could successfully treat MDR-TB, but the effect over the full treatment duration may be no better than current regimens. Furthermore, the drug comes with serious safety concerns that may include death. Therefore, it should be considered a last-line therapy. Phase 3 trials are needed to fully assess its efficacy and safety. · The cause of imbalance in deaths between the bedaquiline and placebo arms is unknown.
2.Study C208 Stage Phase 2, DB, RCT, stratified, South Africa	1. BED/BR: BED 400 mg QD + BR weeks 1-2 then BED 200 mg 3 times/wk + BR weeks 3-8 (then BR per guidelines) *	**Demographics (ITT)**: (BED/BR, PLA/BR): · Age (median): 33, 33 · Male: 78%, 71%	**mITT** 1. 21 2. 23	**TSCC at 8 weeks:** HR 11.8 (CI: 2.3 to 61.3,		**SAEs DB treatment phase:** 1. BED/BR:		**Quality Rating:** Poor **Internal Validity:** · This study possessed the shortcomings of a phase 2 study, including small, inadequate patient numbers,

from Diacon et al (2009 and 2012) and FDA Medical Review	2. PLA /BR (then BR per guidelines) Investigational duration: 8 weeks Final analysis at 104 weeks *Subsequent intermittent doing of bedaquiline 200 mg thrice weekly was selected to maintain plasma concentrations above target average Css of 600 ng/µL	・Race Black: 56%, 54%・・ White: 0%, 4% Other: 44%, 42% ・HIV positive: 13%, 12% ・Lung cavitation (%): ≥2 cm cavity bilaterally: 26%, 29% ≥2 cm cavity unilaterally: 61%, 54% no cavity ≥2 cm: 13%, 17% ・Resistance results: pyrazinamide: 59%, 70% ethambutol: 65%, 55% kanamycin: 6%, 10% ofloxacin: 6%, 10% ethionamide: 12%, 5% ・Background Regimen: KAN or AMK, ETA, + PZA: 100%, 100% OFX: 100%, 96% EMB: 61%, 62% TZD or cycloserine: 52%, 67% **Inclusion criteria:** ・age 18−65 ・newly diagnosed pulmonary TB resistant to INH and RMP **Exclusion criteria:** ・isolates not susceptible to aminoglycosides (other than SM) and FQs or if previously treated for MDR-TB ・severe extrapulmonary manifestations of TB ・HIV+ with a CD4+ <300 or had received antiretroviral or antifungal meds in the previous 90 days		p=0.003) TSCC at 24 weeks: HR 2.25 (CI: 1.08 to 4.71, p=0.031) **Secondary endpoint: Culture conversion rates:** **at 8 weeks:** 1. BED/BR: 47.6% 2. PLA/BR: 8.7% (difference 38.9% [CI: 12.3% to 63.1%, p=0.004]) **at 24 weeks:** 1. BED/BR: 81% 2. PLA/BR: 65.2% (difference 14.8% [CI: -11.9% to 41.9%, p=0.29]) **at 104 weeks:** 1. BED/BR: 52.4% 2. PLA/BR: 47.8% (difference 4.6% [CI: -25.5% to 34.1%, p=0.76])	NA 39/3 NS NS	4.8% (n=1) 2. PLA/BR: 4.3% (n=1) **Deaths:** 0 **TEAEs leading to D/C of study drug:** 1. BED/PR: 0% 4. PLA/BR: 0%	 NS NA NS	insufficient length of study, and the use of surrogate endpoints. ・The actual median TSCC was not reported. **External Validity:** ・Use of known CYP3A4 inducers and inhibitors and drugs with proarrhythmic potential were prohibited during the study. Many HIV antiviral regimens include CYP3A4 substrates, inducers, and inhibitors. ・Performance of bedaquiline in a population with demographics the same or similar to the U.S. is unknown as the trial location was South Africa and only one patient, in the PLA group, was Caucasian. Also, the numbers of HIV-positive patients in the study were insufficient to determine the efficacy and safety of bedaquiline in that population. ・TB is endemic to the population used in this trial and most have previous experience with TB drugs. ・Subsequent intermittent dosing of bedaquiline 200 mg thrice weekly was selected to maintain plasma concentrations above target average Css of 600 ng/µL. This protocol is not included in prescribing information for bedaquiline. ・Culture conversion rates may not be durable. **Analysis:** ・The results of this exploratory study suggest bedaquiline could successfully treat MDR-TB, but the effect over the full treatment duration may be no better than current regimens. Phase 3 trials are needed to fully assess its efficacy and safety. Therefore, it should be considered a last-line therapy.

		・Alcohol or drug abuse ・Concomitant illness ・Abnormal laboratory values ・Pregnancy or breastfeeding						
3. C209 Phase 2, open-label, single-arm, MC from Clinicaltrials.gov (10/6/2013) and FDA Medical Review	BED/BR: BED 400 mg QD weeks 1-2 + BR then BED 200 mg 3 times/wk weeks 3-24 then BR (then BR per guidelines) Duration: 24 weeks	**Demographics (mITT):** Age (median): 32 ・Male: 64% ・Race: Black: 33% White race: 23% Asian: 41% Native American: 3% ・HIV positive (%): 5% (CD4+ cell count [median]: 692, 656) ・Lung cavitation (%): bilaterally: 13% unilaterally: 53% no cavity: 34% ・Resistance extent: MDR-TB: 100% $MDR_{H\&R}$-TB: 45% Pre-XDR-TB: 22% XDR-TB: 18% ・Any previous use of TB drug treatment: 91%, 88% **Inclusion Criteria:** ・Females on contraception or abstaining ・Pulmonary MDR-TB, including XDR-TB **Exclusion Criteria:** ・Significant cardiac arrhythmias ・Complicated or severe extrapulmonary TB ・Certain QT/QTc characteristics ・Pregnant or breastfeeding	**mITT** 205	**Median TSCC:** 57 days (CI: 56 to 83) **Secondary endpoints:** **Culture conversion rates at 24 weeks:** 79.5**%**	NA NA	**Any SAEs overall treatment phase:** 11.6%	NA	**Quality rating:** Poor As an open-label, single-arm study, this study does not constitute an adequate, well-controlled study.

		women						

BED: bedaquiline, BR: background regimen (standard five-drug, second-line TB regimen: kanamycin or amikacin, ofloxacin or ciprofloxacin, ethionamide or prothionamide, cycloserine or terizidone or ethambutol, or other substitutions indicated by susceptibility testing), AMK: amikacin, EMB: ethambutol, ETA: ethionamide, FQ: fluoroquinolone, INH: isoniazid, KAN: kanamycin, OFX: ofloxacin, PZA: pyrazinamide, RMP: rifampin, SM: streptomycin, TZD: terizidone, AEs: adverse events , DB: double blind, D/C: discontinuation, DS-TB: drug-susceptible TB, mITT: modified intent to treat, a subset of the ITT population that excludes patients with DS-TB, XDR-TB, or unconfirmed MDR-TB and patients with no evidence of culture positivity before baseline or no results during the first 8 weeks after baseline, NA: not applicable, PF: placebo-free, MC: multicenter, PLA: placebo, RCT: randomized controlled trial, SAE: serious adverse event, TEAE: treatment emergent adverse event

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1,11]

Bedaquiline is a diarylquinoline, a new class of antimycobacterial drug. Bedaquiline inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase 3 in *M. tuberculosis*. Bedaquiline is active against most isolates of *M. tuberculosis*. Resistance mechanisms that affect bedaquiline include modification of the mycobacterial *atpE* gene. However, at least one other as yet unknown resistance mechanism exists. No cross-resistance with other TB drugs has been identified.

PHARMACOKINETICS[1,11]

Parameter	Result
Oral Bioavailability	36 to 79%
Protein Binding	>99.9%
Elimination	Fecal*
Half-Life	5.5 months
Metabolism	CYP3A4 (major)

*Fecal elimination of bedaquiline predominates and urinary excretion is < 0.001%, indicating that renal clearance of unchanged drug is insignificant.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
100 mg	oral	once daily weeks 1 and 2, then 3 times weekly weeks 3 to 24	400 mg daily week 1 and 2, then 200 mg 3 times weekly (at least 48 hours apart) weeks 3 to 24	None in patients with mild or moderate renal impairment. Not studied in patients with severe impairment or ESRD, so caution advised.	None in patients with mild or moderate hepatic impairment. Not studied in patients with severe impairment, so caution advised.	Safety and efficacy not established in patients <18 years old	Insufficient information on patients ≥65 years old	• Should be given in association with a MDR-TB regimen that includes at least 3 drugs to which the patient's MDR-TB isolate is susceptible to *in vitro* or, if *in vitro* testing is unavailable, 4 other drugs to which the patient's isolate is likely susceptible • Should be administered by directly observed therapy (DOT) • Take with food. • Swallow whole with water. • Avoid alcohol use while on therapy. • Re. a missed dose week 1 or 2: Continue the usual dosing schedule without making up the missed dose. • Re. a missed dose weeks 3 through 24: Take a missed 200-mg dose as soon as possible

								and resume the thrice weekly regimen.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

BBW: An increased risk of death was observed in the treatment group receiving bedaquiline plus background regimen versus the group receiving placebo plus background regimen: 11.4% (9/79) v. 2.5% (2/81), respectively (NNH 11). One death occurred during the 24-week bedaquiline treatment period, while the median time to death for the remaining decedents was 329 days after the last bedaquiline dose. Five of the 9 deaths from the bedaquiline group and 2 from the placebo group were TB-related. The imbalance in deaths remains unexplained and, thus far, appears unrelated to sputum culture conversion, relapse, sensitivity to other TB drugs used, or disease severity. Therefore, bedaquiline should only be used when other regimens would be or are ineffective. Bedaquiline also has been associated with QT prolongation. In a RCT, the largest mean increase in QTc was 15.7 ms with bedaquiline treatment and 6.2 ms without at week 18 of 24 weeks of treatment. These increases persisted after bedaquiline treatment ended.

Warnings and Precautions: More hepatic-related ADRs were observed in patients taking bedaquiline. In two studies, 10.8% (11/102) of bedaquiline-treated patients versus 5.7% (6/105) of placebo-treated patients developed aminotransferase elevations at least 3 times the ULN (NNH 20). Therefore, alcohol and hepatotoxic drugs should be avoided, and bedaquiline discontinued if aminotransferase elevations are accompanied by total bilirubin elevation >2 times the ULN, aminotransferase elevations are >8 times the ULN or elevations persist >2 weeks. Limited data exist on the use of bedaquiline in patients with HIV (n=22), and these patients were not receiving antiretroviral therapy. Bedaquiline should be administered by DOT in combination with at least 3 drugs active against the TB isolate. Bedaquiline minimum inhibitory concentration should be determined for isolates from patients who fail to convert or relapse.

Monitoring: Baseline electrocardiogram should be obtained before treatment initiation and again at 12, 24, and 24 weeks initiating therapy. Baseline serum potassium, calcium, and magnesium should be measured and corrected if abnormal. ECGs also should be monitored when (1) administering bedaquiline concomitantly with other QT prolonging drugs, including fluoroquinolones, macrolides, and clofazimine, (2) patients have a history of tosades de pointes, congenital long QT syndrome, hypothyroidism, bradyarrhythmias, and uncompensated heart failure, and (3) below normal calcium, magnesium, and potassium levels. Baseline, monthly, and as-needed liver function tests should be obtained and monitoring for symptoms of liver dysfunction performed. If serum aminotranferase levels increase 3 times the ULN, a repeat test should be performed as well as a viral hepatitis test, and hepatotoxic drugs should be discontinued.

Drug-Drug interactions: One should avoid concomitant use of bedaquiline with strong CYP3A4 inducers used systemically, including rifampin, rifapentine, and rifabutin. Concomitant use of bedaquiline with strong CYP3A4 inhibitors used systemically for >14 days should be avoided. No clinical data on the combined use of antiretroviral agents and bedaquiline in HIV patients co-infected with HIV exist thus far. Caution must be observed with concomitant use of Kaletra (400 mg lopiavir/100 mg ritonavir) and bedaquiline, as exposure (AUC) to bedaquiline may be increased. Co-administration of nevirapine, isoniazid, or pyrazinamide with bedaquiline requires no dose adjustment. No major pharmacokinetic changes have been observed when bedaquiline is co-administered with ethambutol, kanamycin, pyrazinamide, ofloxacin, or cycloserine.

Food-Drug Interactions: Not reported

Allergy/Cross Reactive Substances: Not reported

Pregnancy/lactation rating: Category B. No evidence of fetal harm has been observed in reproduction studies in rats and rabbits with a plasma exposure (AUC) corresponding to 2 times that of humans. However, the drug should be used during pregnancy only if clearly need, because no studies have been performed with pregnant women. Whether bedaquiline or its metabolites are excreted in human milk is unknown; however, rat studies show concentration of the drug in breast milk 6- to 12-fold higher than the maximum concentration in maternal plasma with doses 1 to 2 times the clinical dose. These breastfeeding pups showed reduced body weights. Therefore, one should decide whether to discontinue nursing or the drug in breastfeeding women.

HIV/MDR-TB co-infected patients: No clinical data or only limited clinical data exist on the use of bedaquiline in HIV patients taking antiretroviral therapy or not taking antiretroviral therapy (n=22), respectively.

Carcinogenesis/Mutagenesis: The drug was negative on tests for mutagenesis, clastogenesis, fertility, reproduction, and development.

Dose Index (efficacy/toxic): Bedaquiline induces reversible phospholipidosis, mainly in cells of the monocytic phagocytic system, at nearly every dose in animals, resulting in increases in pigment-laden or foamy macrophages, mostly in the lymph nodes, spleen, lungs, liver, stomach, skeletal muscle, pancreas, and uterus. Reversible muscle degeneration was observed in animals; for example, the diaphragm, esophagus, quadriceps, and tongue of rats were affected after 26 weeks of treatment at doses similar to clinical exposures. Degeneration of the stomach fundic mucosa, hepatocellular hypertrophy, and pancreatitis also were observed.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

NME Drug Name	Lexicomp	Clinical Judgment
LA/SA for bedaquiline	none	none
LA/SA for Sirturo	none	none

ADVERSE REACTIONS[1]

Table 1: Select Adverse Drug Reactions from Study 1 That Occurred More Frequently Than

	Adverse Drug Reactions SIRTURO Treatment Group N = 79 n (%)	Placebo During Treatment with SIRTURO Placebo Treatment Group N = 81 n (%)
Nausea	30 (38.0)	26 (32.1)
Arthralgia	26 (32.9)	18 (22.2)
Headache	22 (27.8)	10 (12.3)
Transaminases Increased*	7 (8.9)	1 (1.2)
Blood Amylase Increased	2 (2.5)	1 (1.2)
Hemoptysis†	14 (17.7)	9 (11.1)
Chest Pain†	9 (11.4)	6 (7.4)
Anorexia†	7 (8.9)	3 (3.7)
Rash†	6 (7.6)	3 (3.7)

** Terms represented by 'transaminases increased' included transaminases increased, AST increased, ALT increased, hepatic enzyme increased, and hepatic function abnormal.*

† Reported Adverse Events with a greater incidence in the SIRTURO treatment group but which were not identified as adverse drug reactions.