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RESEARCH**

APPLICATION NUMBER:

204384Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # NDA 204 384
Product Name: SIRTURO (Bedaquiline)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	06/2013
	Study/Trial Completion:	08/2021
	Final Report Submission:	03/2022

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

NDA 204 384 was approved under Subpart H regulations (Accelerated Approval) because of the urgent need for new antimycobacterials to treat MDR-TB. The primary analysis in the pivotal trial evaluated a surrogate endpoint of time to sputum culture conversion at 24 weeks which was an acceptable primary endpoint under the Accelerated Approval Pathway. Under the Subpart H regulations, a confirmatory trial using traditional endpoints is required. The planned Phase 3 confirmatory trial will evaluate traditional endpoints of long-term failure, relapse, and mortality at a longer follow-up timepoint.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the confirmatory trial is to obtain confirmatory evidence of efficacy and safety data for bedaquiline using traditional endpoints for tuberculosis of late clinical response, relapse, and mortality at long term follow up.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☒ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☒ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA/BLA # NDA 204 384
Product Name: SIRTURO (bedaquiline)

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

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/2013</u>
	Interim Report Submission:	<u>06/2014</u>
		<u>06/2015</u>
		<u>06/2016</u>
		<u>06/2017</u>
		<u>06/2018</u>
		<u>12/2018</u>
	Study Completion	
	Final Report Submission:	<u>08/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☐ Long-term data needed
☒ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected

- ☐ Theoretical concern
☐ Other

From the limited safety and efficacy data from the current NDA submission, the use of bedaquiline is potentially associated with increased risk of death, prolongation of the QT interval elevation of serum transaminases. The prolonged treatment duration with bedaquiline, with a long terminal half life of 4-5 months, in combination with other anti-tuberculosis drugs with specific toxicities further complicate the use of bedaquiline. Taking these identified risks in context with the documented efficacy of bedaquiline in shortening the time to sputum culture conversion, a restricted use of bedaquiline in patients with very limited therapeutic options is warranted.

The objective of the patient registry is to closely monitor drug utilization parameters for bedaquiline (indications for drug, drug distribution mechanism, and use of expert medical consultation), patient outcomes, safety data and assessments, use of bedaquiline with concomitant medications, and minimum inhibitory concentration (MIC) data to monitor for resistance development.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Bedaquiline use is associated with potential risks such as increased deaths, QT prolongation, and hepatic-related adverse drug reactions. This PMR is needed to ensure and monitor safe use and distribution, clinical outcomes, and safety parameters to validate or refute the safety and efficacy data obtained from the Phase 2 clinical trials.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ **Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ **Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The Sponsor will maintain a patient registry capturing the information required above.

Required

- ☐ Observational pharmacoepidemiologic study
☒ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 204384, SIRTURO (bedaquiline) 100mg tablets.
Product Name:

PMR/PMC Description: **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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	03/31/2013
	Study/Trial Completion:	09/30/2014
	Final Report Submission:	12/31/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
Long-term data needed
☒ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

Long-term microbiologic surveillance data are needed to study development of bacterial resistance against bedaquiline. This study will confirm susceptibility parameters.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This Quality Control test is needed to better define the Quality Control ranges for *M.tuberculosis*. This will help in monitoring development of resistance in MDR-TB isolates over time.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☒ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in-vitro study to define quality control ranges of bedaquiline using standard proportion methods for multi-drug resistant TB isolates. This information is needed to conduct a prospective study over a five-year period on the susceptibility of MDR-TB isolates to bedaquiline.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- ☒ Are the objectives clear from the description of the PMR/PMC? Yes
- ☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
-

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 204384, SIRTURO (bedaquiline) 100mg tablets.
Product Name: _____

PMR/PMC Description: **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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/31/2013</u>
	Study/Trial Completion:	<u>09/30/2014</u>
	Final Report Submission:	<u>12/31/2014</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
Long-term data needed
☒ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

Long-term microbiologic surveillance data are needed to study development of bacterial resistance against bedaquiline. This study will confirm susceptibility parameters.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This Quality Control test is needed to better define the Quality Control ranges for *M.tuberculosis*. This will help in monitoring development of resistance in MDR-TB isolates over time.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in-vitro study to define quality control ranges of bedaquiline using methodologies that define the MIC ranges for multi-drug resistant TB isolates. This information is needed to conduct a prospective study over a five-year period on the susceptibility of MDR-TB to bedaquiline.

Required

- ☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- ☒ Are the objectives clear from the description of the PMR/PMC? Yes
- ☒ Has the applicant adequately justified the choice of schedule milestone dates? Yes
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
-

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 204384, SIRTURO (bedaquiline) 100mg tablets.
Product Name:

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

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/30/2015</u>
	Interim Report Submission:	<u>12/31/2016</u>
		<u>12/31/2017</u>
		<u>12/31/2018</u>
	Study/Trial Completion:	<u>09/30/2019</u>
	Final Report Submission:	<u>12/31/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
☐ Life-threatening condition
☒ Long-term data needed
☒ Only feasible to conduct post-approval
☐ Prior clinical experience indicates safety
☐ Small subpopulation affected
☐ Theoretical concern
☐ Other

Long-term microbiologic surveillance data are needed to study development of bedaquiline resistance in MDR-TB post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

To assess if resistance to bedaquiline occurs in MDR-TB isolates over time.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

X Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective study over a five-year period assessing the susceptibility of MDR-TB isolates to bedaquiline.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

X Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs? Yes
- X Are the objectives clear from the description of the PMR/PMC? Yes
- X Has the applicant adequately justified the choice of schedule milestone dates? Yes
- X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? Yes

PMR/PMC Development Coordinator:

X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # 204384
Product Name: SIRTURO (bedaquiline)

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	04/2013
	Study/Trial Completion:	10/2013
	Final Report Submission:	12/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

The potential for bedaquiline to inhibit or induce the activity of the two drug transporters, OATP1B1 and OATP1B3 is unknown and is a theoretical concern.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a need to gain an understanding of the potential for bedaquiline to inhibit or induce the activity of the two drug transporters, OATP1B1 and OATP1B3. The study would help evaluate this interaction.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☒ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An in vitro study to assess the potential for bedaquiline to inhibit or induce the activity of the two drug transporters, OATP1B1 and OATP1B3.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☒ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 204384

Product Name:

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/30/2013</u>
	Study/Trial Completion:	<u>N/A</u>
	Final Report Submission:	<u>09/30/2013</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☒ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

This is a drug-drug interaction study between bedaquiline and efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI) used to treat HIV infection. This study will be conducted in a subpopulation of patients with tuberculosis – patients co-infected with HIV.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Tuberculosis can develop in patients with HIV infection. As two medications that will typically be found in HIV and tuberculosis regimens to treat such co-infection, this drug-drug-interaction study would assess interactions between the two medications when given together to determine appropriate dosing regimens for the two drugs when given together.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Drug-drug interaction study between bedaquiline and efavirenz in patients with HIV and tuberculosis co-infection.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☒ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
-
- ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA/BLA # NDA 204 384
Product Name: SIRTURO (Bedaquiline)

PMR/PMC Description: PMC: Submit final study report and electronic data for Study C208 Stage II

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	11/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☒ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

Trial C208 Stage 2 is the pivotal Phase 2 trial from which the efficacy and safety data for the initial NDA submission was partly based. The trial was completed during the initial NDA review. This PMC would ensure that the Sponsor would submit the complete study report and the complete datasets for review in a timely manner.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Bedaquiline use was assessed to have potential risk of increased death, QT interval prolongation, and increased serum transaminases, the complete study report would help in obtaining and reviewing the long term efficacy and safety data.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Bedaquiline use was assessed to have potential risk of increased death, QT interval prolongation, and increased serum transaminases, the complete study report would help in obtaining and reviewing the long term efficacy and safety data.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

This trial, still ongoing during the initial NDA review, was recently completed. This PMC was instituted to ensure the timely submission of the complete study report and the complete datasets for review.

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # NDA 204 384
Product Name: SIRTURO (Bedaquiline)

PMR/PMC Description: PMC: Submit final study report and electronic data for Study C209

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	01/2013
	Final Report Submission:	11/2013

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Trial C209 is a supportive trial from which the efficacy and safety data for the initial NDA submission was partly based. The trial was still ongoing during the initial NDA review. This PMC would ensure that, upon completion of the trial, the Sponsor would submit the complete study report and the complete datasets for review in a timely manner.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Bedaquiline use was assessed to have potential risk of increased death, QT interval prolongation, and increased serum transaminases, the complete study report would help in obtaining and reviewing the long term efficacy and safety data.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Bedaquiline use was assessed to have potential risk of increased death, QT interval prolongation, and increased serum transaminases, the complete study report would help in obtaining and reviewing the long term efficacy and safety data.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - ☐ Pharmacokinetic studies or clinical trials
 - ☐ Drug interaction or bioavailability studies or clinical trials
 - ☐ Dosing trials
 - ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
This trial is still ongoing during the initial NDA review. This PMC was instituted to ensure the timely submission of the complete study report and the complete datasets for review.
 - ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
 - ☐ Pharmacoeconomic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - ☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - ☐ Dose-response study or clinical trial performed for effectiveness
 - ☐ Nonclinical study, not safety-related (specify)
 - ☐ Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
 - ☒ Are the objectives clear from the description of the PMR/PMC?
 - ☒ Has the applicant adequately justified the choice of schedule milestone dates?
 - ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- ☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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

/s/

FARIBA IZADI

12/26/2012

SUMATHI NAMBIAR

12/26/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 21, 2012

TO: Fariba Izadi, Project Manager
Eileen Navarro Almario, M.D., Medical Team leader
Ariel Porcalla, Medical Officer
Division of Anti- Infective Products

FROM: Kassa Ayalew, M.D., Medical Officer
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigators

SUBJECT: Evaluation of Clinical Inspections

BLA: NDA#: 204384

APPLICANT: Janssen Research & Development, LLC (on behalf of Janssen
Therapeutics)

DRUG: SIRTURO™ (bedaquiline) 100 mg tablets

NME: Yes

THERAPEUTIC CLASSIFICATIONS: Original

INDICATION:	Treatment of Multi –Drug Resistant Tuberculosis
CONSULTATION REQUEST DATE:	July 16, 2012
INSPECTION SUMMARY GOAL DATE:	December 29, 2012
ACTION GOAL DATE:	December 29, 2012
PDUFA DATE:	December 29, 2012

I. BACKGROUND:

The Applicant, Janssen Products, LP, Janssen Research and Development, L.L.C., on behalf of Janssen Therapeutics submitted an original New Drug Application (NDA) for SIRTUO™ (bedaquiline) for the treatment of patients with multi-drug resistant tuberculosis (MDR-TB). SIRTUO™ (bedaquiline) is a diarylquinoline investigational compound that has a mechanism of anti-TB action by specifically inhibiting mycobacterial adenosine triphosphate (ATP) synthase.

The Office of Scientific Investigation received a consult from the Division of Anti-Infective Products to conduct clinical inspections of two studies, Study C208 and Study C209, that were provided as evidence to support the indication of SIRTUO™ (bedaquiline) for the treatment of patients with multi-drug resistant tuberculosis (MDR-TB). The two protocols that have been inspected are:

- Protocol C208 entitled “A Phase II, Placebo-controlled, Double-blind, Randomized Trial to Evaluate the Antibacterial Activity, Safety, and Tolerability of TMC207 in Subjects with Sputum Smear-positive Pulmonary Infection with Multi-drug Resistant *Mycobacterium Tuberculosis* (MDR-TB)”
- Protocol C209 entitled “A Phase II, Open-label Trial with TMC207 as Part of a Multi-drug resistant Tuberculosis (MDR-TB) Treatment Regimen in Subjects with Sputum Smear-positive Pulmonary Infection with MDR-TB”

Protocol C208 was a phase 2, placebo controlled, double blind, randomized multinational trial that was conducted to evaluate the antibacterial activity, safety, and tolerability of TMC207 when added to an individualized background regimen (BR) of MDR-TB therapy, compared to placebo plus BR, in subjects with newly diagnosed sputum smear-positive pulmonary MDR-TB infection. The primary outcome measure for study C208 was the time to sputum culture conversion during treatment with TMC207 or placebo. A total of 197 subjects were to be randomized to receive either TMC207 or placebo for 24 weeks in addition to a BR. This trial is conducted in 2 consecutive stages, an exploratory stage (Stage 1) and an ongoing proof-of-efficacy stage (Stage 2).

Study C209 is an ongoing phase 2, multicenter, open-label, single-arm trial to evaluate the safety, tolerability, and efficacy of TMC207 as part of an individualized MDR-TB treatment regimen in subjects with sputum smear positive (within 6 months prior to screening)

pulmonary MDR TB. Two hundred thirty three (233) adult subjects with sputum smear positive pulmonary infection with MDR-TB, pre-XDR-TB (pre-extensively drug resistant tuberculosis) or XDR-TB (extensively drug resistant tuberculosis) were enrolled in this study. The primary outcome parameter for study C209 was the time to sputum culture conversion during treatment with TMC207 or placebo.

II. RESULTS (by Site):

Name of CI or Sponsor and Location	Protocol # / # of Subjects randomized:	Inspection Date	Classification
Andreas Diacon, M.D. Brooklyn Chest Hospital Stanberry Road Ysterplaat, Cape Town 7405 South Africa	C208 Stage 1 N=18 Stage 2 N=35 C 209 N=38	October 15 to 19, 2012	NAI
Alexander Pym, M.D. King George V Hospital Stanley Copely Drive Durban 4001, South Africa	C208 Stage 1 N= 16 Stage 2 N= 28	October 22 to 26, 2012	NAI
Francesca Conradie, M.D. Sizwe Hospital Modderfontein Road Sandringham, Johannesburg 2131, South Africa	C208 Stage 1 N= 3 Stage 2 N= 24	October 29 to November 2, 2012	NAI
Qiu Lihua, M.D. Shandong Provincial Chest Hospital Tb Dept Lishan Rd N 46 Jinan 250013, China	C209 N=10	October 22 to 26, 2012	Pending (Preliminary Classification VAI)
Shenjie Tang, M.D. Shanghai Pulmonary Hospital Zhengmin Rd No 507 Shanghai 200433, China	C209 N=17	October 29 to November 2, 2012	Pending (Preliminary Classification VAI)
Sponsor: Janssen Pharmaceuticals, Inc. 1125 Trenton Harbourton Rd Titusville, NJ 08560-1503	Protocol C208 Protocol C 209	October 25 to November 16, 2012	Pending (Preliminary Classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete

review of EIR is pending.

1. Andreas Diacon, M.D.

Brooklyn Chest Hospital
Stanberry Road
Ysterplaat, Cape Town 7405
South Africa

A. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between October 15 to 19, 2012. This inspection was performed as a data audit for Protocol C208 and C209. There is one IND associated with the inspected entity in CDER's database, and the CI had no prior inspection.

For Study C208, at this site, 98 subjects (40 subjects for Stage 1 and 58 subjects for Stage 2) were screened. Forty five (45) subjects did not meet study protocol inclusion and exclusion criteria and were considered screen failures. Fifty three (53) subjects were enrolled and randomized into the study (18 subjects in Stage 1 and 35 subjects in Stage 2). A total of 25 subjects completed the study (five subjects in Stage 1 and 20 subjects in Stage 2). Twenty eight (28) subjects discontinued the study (13 in Stage 1 and 15 in Stage 2).

For study C209, 47 subjects were screened. Six subjects did not meet study protocol inclusion and exclusion criteria and were considered screen failures. Forty one (41) subjects were enrolled and 38 of them were randomized into the study (three subjects who were randomized withdrew consent prior to dosing). A total of 10 active subjects completed the study. There are currently 10 active subjects in the study. Twenty one (21) subjects discontinued the study. Most of the subjects in C208 and C209 discontinued the study due to noncompliance and withdrawal of consent.

There were no limitations to the inspection. Due to time constraints and the volume of information at the site because of the length of two studies, only three subjects' records for each study were reviewed. Records reviewed included, but were not limited to, source documents, protocol specified blinding/randomization procedures, inclusion/exclusion criteria, adverse events, primary efficacy endpoints, protocol deviations, concomitant therapies, and test article accountability. In addition, IRB correspondence, monitoring logs and correspondence, and financial disclosure documentation were reviewed.

B. General observations/commentary:

The study appears to have been executed appropriately at this site. No regulatory violations were noted, and a Form FDA 483 was not issued.

C. Assessment of data integrity:

The data generated by this site appear acceptable in support of the respective indication.

2. Alexander Pym, M.D.

King George V Hospital
Stanley Copely Drive
Durban 4001
South Africa

A. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between October 22 to 26, 2012. This inspection was performed a data audit for Protocol C208. There are no INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection.

At this site, 105 subjects were screened (48 subjects in Stage 1 and 57 subjects in Stage 2), 44 subjects were randomized (16 subjects in Stage 1 and 28 subjects in Stage 2), and 27 subjects completed the study (11 subjects in Stage 1 and 16 subjects in Stage 2). There were 61 subjects who did not meet the study protocol inclusion criteria.

An audit of six subjects' records was conducted. There were no limitations to the inspection. An in depth audit of the study records for all 6 subjects was conducted. The inspection included reviews of the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequacy of adverse experience reporting. In addition, drug accountability records, Informed Consents Documents, IRB approval and dates, and sponsor monitoring records were reviewed. All primary efficacy endpoint data were compared with the sponsor supplied line listings. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable.

B. General observations/commentary:

The study appears to have been executed appropriately at this site. No regulatory violations were noted and a Form FDA 483 was not issued.

C. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Francesca Conradie, M.D.

Sizwe Hospital
Modderfontein Road
Sandringham, Johannesburg 2131
South Africa

A. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811, between April 24 and 29, 2011. There are no INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection.

This inspection was performed as a data audit for Protocol C208. At this site, seven subjects were screened for Stage 1, and forty subjects were screened for Stage 2, for a total of 47 subjects screened. Three subjects were enrolled and randomized for Stage 1, and 24 subjects were enrolled and randomized for Stage 2, for a total of 27 subjects enrolled and randomized. A total of 16 subjects completed the study; two subjects completed Stage 1, and 14 subjects completed Stage 2. There were 11 subjects who discontinued the study, one from Stage 1 and 10 from Stage 2. Most of the subjects discontinued the study due to noncompliance and withdrawal of consent. The protocol required that subjects be followed for 120 weeks, a total of 29 visits.

An in depth audit of the study records for all 5 subjects was conducted. The inspection included reviews of the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequacy of adverse experience reporting. In addition, drug accountability records, Informed Consent Documents, IRB approval and dates, and sponsor monitoring records were reviewed. All primary efficacy endpoint data were compared with the sponsor supplied line listings. There were no limitations to the inspection.

B. General observations/commentary:

The investigator's source documents were organized, complete, and legible. There was no evidence of under-reporting of adverse events and the primary endpoint data were verifiable. No significant regulatory violations were noted and no Form FDA 483 was issued. The study appears to have been executed appropriately at this site. No regulatory violations were noted and a Form FDA 483 was not issued.

C. Assessment of data integrity:

The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Qiu Lihua, M.D.

Shandong Provincial
Chest Hospital Tb Dept
Lishan Rd N 46
Jinan 250013
China

Note: Final classification for Dr. Qiu Lihua's site is pending and will be determined when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the establishment inspection report (EIR), an inspection summary addendum will be generated.

A. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811 between October 22 to 26, 2012. There were 19 INDs associated with the inspected entity in CDER's database, and the CI had no prior inspection. This inspection was performed as a data audit for Protocol C209. At this site, 11 subjects were screened and 10 subjects were randomized. Of the 10 subjects, 8 have completed the study. Two subjects are still in follow up.

The inspection included reviews of the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequacy of adverse experience reporting. In addition, drug accountability records, Informed Consent Documents, IRB approval and dates, and sponsor monitoring records were reviewed. All primary efficacy endpoint data were compared with the sponsor supplied line listings. There were no limitations to the inspection.

B. General observations/commentary:

In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued to this investigator for:

1. Failure to prepare or maintain adequate and accurate case histories with respect to drug disposition records [21 CFR 312.62 (b)]. Specifically, the outpatient notes for each study subject were generated using Microsoft Word as a typewriting tool to generate paper records. The document generated on a computer using MS word was printed and the file was deleted. There is no way to verify the printed document with the original information or to determine if changes have been made from the original.

OSI Reviewer Comments: Based on OSI's review of Dr. Qiu Lihua's response to this observation in a letter dated November 9, 2012, the CI typed the information in MS word, printed the document immediately, verified it as being accurate and completed, and then signed and dated it to authenticate the paper record. All subsequent decisions and trial related activities were based on the signed paper record. Changes and correction and /or

additions are made on the originally signed and dated paper record. The CI used the computer to collect data.

Since all changes and corrections and /or additions are made on the originally signed and dated paper records the observation does not impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study. OSI does not consider this to be a regulatory violation.

C. Assessment of data integrity:

Data derived from Dr. Qiu Lihua's site are considered reliable.

5. Shenjie Tang, M.D.

Shanghai Pulmonary
Hospital
Zhengmin Rd No 507
Shanghai 200433
China

Note: Final classification for Dr . Shenjie Tang's site is pending and will be determined when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the EIR, an inspection summary addendum will be generated.

A. What was inspected?

This inspection was conducted in accordance with Compliance Program 7348.811 between October 29 to November 2, 2012. There was no IND associated with the inspected entity in CDER's database, and the CI had no prior inspection.

This inspection was performed as a data audit for Protocol C209. At this site, a total of 17 subjects were screened and randomized. One subject discontinued the study. Eleven (11) subjects completed the study, and 5 subjects are currently in follow up.

The inspection included reviews of the following items: 1) entry criteria, 2) diagnosis of target disease, 3) efficacy variables, and 4) adequacy of adverse experience reporting. In addition, drug accountability records, Informed Consent Documents, IRB approval and dates, and sponsor monitoring records were reviewed. All primary efficacy endpoint data were compared with the sponsor supplied line listings. There were no limitations to the inspection.

B. General observations/commentary: In general, the study was conducted appropriately. However, a Form FDA 483, Inspectional Observations, was issued to this investigator for:

1. Failure to prepare or maintain adequate and accurate case histories with respect to drug disposition records [21 CFR 312.62 (b)]. Specifically, the outpatient notes for

each study subject were generated using Microsoft Word as a typewriting tool to generate paper records. The document generated on a computer using MS word was printed and the file was deleted. There is now way to verify the printed document with the original information or to determine if changes have been made from the original.

OSI Reviewer Comments: Based on OSI's review of Dr. Shenjie Tang's response to this observation in a letter dated November 22, 2012, the CI typed the information in MS word, printed the document immediately, verified it as being accurate and completed, signed, and dated it to authenticate the paper record and identify the information. All subsequent decisions and trial related activities were based on the signed paper record. Changes and correction and /or additions are made on the originally signed and dated paper record. The CI used the computer to collect data.

Since all changes and corrections and /or additions are made on the originally signed and dated paper records the observation does not impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study. The CI used the computer to collect and ensure data legality. OSI does not consider this to be a regulatory violation.

2. Failure to conduct the study in accordance with the signed statement of investigator and investigational plan [21 CFR 312.60]. Specifically,
 - a. One subject (Subject # 2090263) received gatifloxacin from 3/17/10-4/4/2012. Concomitant administration of gatifloxacin was not allowed during the administration of TMC 207.

OSI Reviewer Comments: the clinical investigator administered gatifloxacin to one subject although gatifloxacin was not allowed during the administration of TMC 207. Dr. Shenjie Tang's response (dated November 22, 2012) to the Form FDA 483 issued acknowledges the above observation that was also reported to the Medical Monitor and sponsor as a protocol violation. Additionally Dr. Shenjie Tag's response states that corrective actions to prevent similar occurrences in future have been implemented. Although the clinical investigator administered a disallowed medication to one subject for few days, which is a regulatory violation, the finding was isolated in nature, clinically insignificant and unlikely to impact overall reliability of efficacy and safety data from the site.

- b. Chest xrays were not performed per the protocol in five subjects (Subject #2090269 at Weeks 72, 84, and 96; Subject # 2090271 at Weeks 24, 36, 48 and 84; Subject # 2090272 at Week 24; Subject # 2090275 at Weeks 24 and 48; and Subject # 2090277 at Weeks 12 and 24)

OSI Reviewer Comments: Although the clinical investigator failed to appropriately perform chest xrays per protocol in five subjects at some time point/s during the study according to the investigational plan, which is a regulatory violation, this finding is unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study.

Dr. Shenjie Tang's response (dated November 22, 2012) to the Form FDA 483 issued acknowledges the above observation which was reported to the Medical Monitor and sponsor as a protocol violation. Dr. Shenjie Tang's response states that corrective actions to prevent similar occurrences in future have been implemented.

3. Failure to prepare or maintain adequate and accurate drug disposition records with respect to dates. [21 CFR 312.62 (b)]. Specifically, the dates documented for Day 1 dispensing of the study drug on the drug accountability form are one day before in the following subjects: 2090269, 2090273, 2090275, 2090276, and 2090277.

OSI Reviewer Comments: The clinical investigator failed to appropriately document drug disposition with respect to dates by one day. Dr. Shenjie Tang's response (dated November 22, 2012) to the Form FDA 483 acknowledges the above observation which was reported to the Medical Monitor and sponsor as a protocol violation. Dr. Shenjie Tag's response states that corrective actions to prevent similar occurrences in future have been implemented., This finding is unlikely to impact data reliability because alternate source documents are available to document study drug administration.

C. Assessment of data integrity: Although regulatory violations were observed at this site, it is unlikely based on the nature of the violations that they significantly affect the overall reliability of safety and efficacy data from the site. Data derived from Dr . Shenjie Tang's site are considered reliable.

6. Janssen Pharmaceuticals, Inc.

1125 Trenton Harborton Rd
Titusville, NJ 08560-1503

Note: Final classification for Sponsor/Applicant, Janssen Pharmaceuticals Inc. is pending and will be determined when the final EIR and associated exhibits are received/reviewed and/or finalized. Should the conclusions change upon receipt and review of the EIR, an inspection summary addendum will be generated.

A. What was inspected?

This sponsor inspection was conducted in accordance with Compliance Program 7348.811, between October 25 - November 16, 2012.

This was a directed inspection; the FDA investigator specifically evaluated sponsor/monitor obligations as related to the conduct of Protocol C208 and Protocol C209, studies submitted in support the indication sought in the NDA.

An in-depth audit of the study records for five sites for the two protocols was conducted. For the given sites, evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO was evaluated, as well as safety and efficacy endpoints, test article accountability, adverse events (AEs) evaluation and reporting, delegation of responsibilities, contractual agreements, and general site monitoring practices.

B. General observations/commentary:

The inspection of the Sponsor/Applicant, Janssen Pharmaceuticals Inc., did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

C. Assessment of data integrity:

Based on the FDA field investigator's preliminary report of the inspection, Janssen Pharmaceuticals Inc., Inc adequately fulfilled sponsor/monitor obligations in the conduct of Protocol C208 and Protocol C209. The data generated by these two studies can be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The final classifications of the Clinical Investigator inspections of Drs. Pym's, Conradie's and Diacon's sites are No Official Action Indicated (NAI). The preliminary classification of inspection of the sponsor, Janssen Pharmaceuticals Inc., is NAI. The preliminary classifications of the Clinical Investigator inspections of Drs. Tang's and Lihuas' sites are Voluntary Action Indicated (VAI). The data generated by these two studies and submitted by the sponsor can be used in support of the respective indication.

Note: Final headquarters classifications for Drs. Tang and Lihuas' sites and for the sponsor are pending at this time. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

{See appended electronic signature page}

Kassa Ayalew, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

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Susan Thompson, M.D.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KASSA AYALEW
12/21/2012

SUSAN LEIBENHAUT
12/21/2012

SUSAN D THOMPSON
12/21/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 204384 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Sirturo Established/Proper Name: Bedaquiline (TMC-207) Dosage Form: Oral Tablet Strengths: 100 mg		
Applicant: Janssen Therapeutics Agent for Applicant (if applicable):		
Date of Application: 06-29-12 Date of Receipt: 06-29-12 Date clock started after UN: 06-29-12		
PDUFA Goal Date: 12-29-12	Action Goal Date (if different): 12-29-12	
Filing Date: 08-28-12	Date of Filing Meeting: 07-25-12	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME-Type 1		
Proposed indication(s)/Proposed change(s): Multi Drug Resistant Pulmonary Tuberculosis.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 5px;"><input checked="" type="checkbox"/> 505(b)(1)</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> 505(b)(2)</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> 505(b)(1)</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> 505(b)(2)</div> </div>	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 10px;"><input type="checkbox"/> Standard</div> <div style="margin-bottom: 10px;"><input checked="" type="checkbox"/> Priority</div> <div style="margin-bottom: 10px;"><input type="checkbox"/> Tropical Disease Priority Review Voucher submitted</div> </div>
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<div style="display: flex; flex-direction: column;"> <div style="margin-bottom: 5px;"><input type="checkbox"/> Convenience kit/Co-package</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.)</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.)</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Device coated/impregnated/combined with drug</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Device coated/impregnated/combined with biologic</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Separate products requiring cross-labeling</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Drug/Biologic</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Possible combination based on cross-labeling of separate products</div> <div style="margin-bottom: 5px;"><input type="checkbox"/> Other (drug/device/biological product)</div> </div>	

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input checked="" type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 69600				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	x			
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names correct in tracking system?	x			
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>				Orphan
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		x		
If yes, explain in comment column.			x	
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			x	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				x	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				x	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				x	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm				x	
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm			x		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			x	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>				
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		x		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			x	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>	NA			
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	x			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	x			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	x			

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			x	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			x	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			x	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			x	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			x	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			3542 a
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	x			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	x			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	x			
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			x	
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>		X		
Does the application trigger PREA?				
<i>If yes, notify PeRC RPM (PeRC meeting is required)²</i>				
<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?			X	
<i>If no, request in 74-day letter</i>				
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?			X	
<i>If no, request in 74-day letter</i>				
<u>BPCA</u> (NDAs/NDA efficacy supplements only):		X		
Is this submission a complete response to a pediatric Written Request?				
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?		X		
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input checked="" type="checkbox"/> Other (specify) patient counseling			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	x			
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	x			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			x	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	x			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			x	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	x			
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	x			
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	x			QT consult
<i>If yes, specify consult(s) and date(s) sent: July 10, 2012</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 02/09/2011 (clinical) 11/05/2009 (CMC)				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): October 07, 2011				
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):				
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 07-25-12

BLA/NDA/Supp #: NDA 204384

PROPRIETARY NAME: Sirturo (Primary) Bacrida (alternative)

ESTABLISHED/PROPER NAME: Bedaquiline

DOSAGE FORM/STRENGTH: 100 MG Tablets

APPLICANT: Janssen Research & Development

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of Multi-Drug Resistant Tuberculosis.

BACKGROUND: This NDA is requesting a PRIORITY 6 month review clock. It was granted Orphan Drug Designation (Jan 10, 2005) and Fast-track designation on (April 22, 2011).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Fariba Izadi	Y
	CPMS/TL:	Frances LeSane, Maureen Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	Eileen Navarro Almario		Y
Clinical	Reviewer:	Ariel Porcalla	Y
	TL:	Eileen Navarro Almario	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Lynette Berkeley	Y
	TL:	Frederic Marsik	

Clinical Pharmacology	Reviewer:	Dakshina Chilukuri Grace Yan, Seong Jang	Y
	TL:	Kimberly Bergman	Y
Biostatistics	Reviewer:		
	TL:		
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Owen McMaster	Y
	TL:	Wendelyn Schmidt	Y
Statistics (carcinogenicity)	Reviewer:	Xianbin Li	Y
	TL:	Karen Higgins	Y
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Celia Cruz-Drug Product Lin Qi-Drug Substance	Y
	TL:	Dorota Matecka	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	N
	TL:		
CMC Labeling Review	Reviewer:	Celia Cruz Lin Qi	Y
	TL:	Dorota Matecka	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Alek Winiarski	Y
	TL:	Jamie Wilkin Parker	N
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Kassa Ayalew	Phone
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Minerva Hughes-Biopharmaceutics Angelica Dorantes –Team Leader Fang Li- pharmacometric, Pharmacovigilance-Chris Jones		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain: clin-micro Article in French</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>Comments:</p> <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the</i></p>	<input checked="" type="checkbox"/> YES Date if known: 11-28-12 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<p>reason. For example:</p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ed Cox Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): Sept 24, 2012 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter No labeling issues.
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://erom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

FARIBA IZADI
12/18/2012

MEMORANDUM

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

DATE: 12-18-12

TO:

THROUGH:

FROM:

SUBJECT: Labeling, Post Marketing Commitments (PMC), Post Marketing Requirements (PMR), Risk Management

APPLICATION/DRUG: NDA 204384

The Division of Anti-Infective Products (DAIP), Janssen, and the Centers for Disease Prevention and Control (CDC) held a teleconference on December 18, 2012. The subjects addressed during the telecon included labeling, PMCs, PMRs and a risk management program. The telecon began between DAIP and Janssen only and included the following points:

- The Division does not believe a Risk Evaluation and Mitigation Strategy (REMS) is needed because the current public health infrastructure is sufficient. Safety monitoring is in place and the CDC has strategies for ensuring appropriate distribution and use of the drug.
- The drug will be distributed using a centralized drug distribution system.
- The label and Medication Guide will provide the necessary information to ensure safe use of the drug.
- A Boxed Warning at the beginning of the label will emphasize the increased risk of death that is independent of QT prolongation.
- Janssen will provide additional clinical microbiology information for the label.

The CDC participated in the remainder of the telecon with DAIP and Janssen. The CDC wanted to discuss their concerns for an adequate risk management program. Based on an earlier conversation that took place between Janssen and the CDC, the major points of discussion included:

- a) Proper distribution to eligible patients
- b) Proper use of the medication
- c) Tracking of patients with exposure to the drug
- d) A methodology to systematically monitor and follow up on safety (i.e. drug-drug interaction)
- e) Possibility of creating a registry of those receiving the drug

Both Janssen and the CDC sought the Division's input on the above points of discussion. The Division emphasized that the labeling would be an important guide for proper use and distribution of the drug. With the public health structure that is in place, which includes educational activities by the CDC, additional materials besides the comprehensive label would be available to the healthcare practitioners. The CDC also mentioned the possibility of having a registry with local health departments. All of these measures, i.e., the label, the medication guide, education of the appropriate population eligible for use of the drug, a possible registry would be sufficient to ensure proper use of the drug. The Division believes a REMS program is not necessary with these safeguards in place.

The CDC mentioned their concern for the possible development of drug resistance and drug-drug interactions (DDI). They suggested healthcare practitioners include screening by a CDC medical officer when they are deciding to use the drug. The Division would not require such a precaution and stated such a precaution would be a policy issue between the CDC and Janssen.

The Division acknowledged that improper use of the drug is a medical risk. Prevention of improper use requires reliance on the public health system authorities. The CDC is confronted by the problem that a time lag exists from the time information can take up to a year to for them to receive. They do not routinely receive DDI or adverse event information. They currently have access to limited information about mortality and completion of therapy. They are willing to provide their input into creating a registry and ensuring that information is received in a timely manner.

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/s/

FARIBA IZADI
12/26/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: December 17, 2012

To: Fariba Izadi, Pharm.D. Regulatory Project Manager,
Division of Anti-infective Products (DAIP)

From: Adora Ndu, Regulatory Review Officer,
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 204384
DCDP comments for SIRTURO™ (bedaquiline) tablets
Medication Guide

On September 9, 2012, DCDP received a consult request from DAIP to review the proposed Medication Guide for SIRTURO™ (bedaquiline) tablets.

DCDP has reviewed the proposed labeling using the following versions of the proposed labels received from DAIP and DMPP on December 15, and December 17, 2012 respectively:

- bedaquiline (SIRTURO) 204384 DMPP MG Dec -2012 clean.doc
- revised Document 12-13-12I_bedaquiline_draftlabeling_text(Fledits) (2).docx

After review of the proposed labeling, DCDP offers the following comments.

If you have any questions regarding the patient labeling, please contact Adora Ndu at 301-796-5114 or adora.ndu@fda.hhs.gov.

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/s/

ADORA NDU
12/17/2012

From: Izadi, Fariba
Sent: Thursday, December 13, 2012 1:47 PM
To: 'Lewis, Gary [JRDUS]'
Subject: NDA 204384 (bedaquiline) -Container Label

Importance: High

Attachments: Picture (Enhanced Metafile)

Dear Mr. Lewis,

Below, please find our recommendation for the container label of the NDA 204384 (bedaquiline).

A. Container Label

1. Place the proprietary name “Sirturo” in title case, similar to the current place holder (Tradename) in font type, style, and size.

Remove the italic formatting from “*bedaquiline*” tablets”. The established name should have a prominence commensurate with the prominence of the proprietary name including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
2. The statement of quantity “188 Tablets” competes for prominence with the statement of strength 100 mg. To decrease the prominence of the net quantity statement, decrease the size of the statement “188 Tablets”, remove the bold formatting, and relocate it to the bottom portion of the label. Additionally, remove the bolded line that appears below the statement “188 Tablets”.
3. To decrease clutter and ensure that the proprietary name, established name and strength are prominently displayed on the principal display, relocate the statement “Each tablet contains bedaquiline fumarate equivalent to 100 mg of bedaquiline” to the side panel.
4. To ensure Sirturo is not stored outside of the original bottle for longer than the three month established stability, revise the storage statement to read as follows and relocate it to the principal display panel.

Attention Pharmacist: Dispense in original container. Tablets dispensed outside the original container should be stored in a tight light-resistant container with an expiration date not to exceed 3 months. Store at 25°C (77°F); Excursions permitted to 15°C-30°C (59°F - 86°F).[See USP Controlled Room Temperature].

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

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/s/

FARIBA IZADI
12/13/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: **December 12, 2012**

To: John Farley, M.D.
Acting Director
Division of Anti-Infective Products (DAIP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Melissa Hulett, RN, BSN, MSBA
Team Leader, Patient Labeling Team
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, RN, BSN, MSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): SIRTURO (bedaquiline)

Dosage Form and Route: Tablets

Application Type/Number: NDA 204384

Applicant: Janseen Research & Development, LLC

1 INTRODUCTION

On January 10, 2005, TMC207 (bedaquiline) was granted orphan-drug designation by the Office of Orphan Products Development, FDA, for the treatment of active tuberculosis. TMC207 (bedaquiline) was granted fast-track designation on April 22, 2011. Janseen Research & Development, LLC submitted for the agency's review an original New Drug Application, SIRTURO (bedaquiline) indicated for the treatment of multi-drug resistant tuberculosis (MDR-TB) on June 28, 2012.

This review is written in response to a request by the Division of Anti-Infective Products (DAIP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide for SIRTURO (bedaquiline) Tablets.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAIP under separate cover.

2 MATERIAL REVIEWED

- Draft SIRTURO (bedaquiline) MG received on December 4, 2012 and received by DMPP on December 7, 2012.
- Draft SIRTURO (bedaquiline) Prescribing Information (PI) received June 28, 2012 revised throughout the review cycle and received by DMPP on December 7, 2012.

3 REVIEW METHODS

Review of new NDA and BLA Patient Package Insert and Medication Guide submissions will reflect changes to previous patient labeling practice. These changes are designed to decrease the length of patient information while maintaining consistency with the Regulations as specified in 21 CFR 208.20.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the MG is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
12/12/2012

MELISSA I HULETT
12/12/2012

LASHAWN M GRIFFITHS
12/12/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

Memorandum

*****Pre-Decisional Agency Information*****

Date: December 9, 2012

To: Fariba Izadi, Pharm.D., Regulatory Project Manager
Division of Anti-Infective Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)

Subject: NDA #204384
SIRTURO (bedaquiline) tablets

As requested in your consult dated September 14, 2012, DPDP has reviewed the draft PI for SIRTURO (bedaquiline) tablets.

DPDP's PI comments are based on the substantially complete version of the labeling titled, "12-0Merged Document 12-07-12I_bedaquiline_draftlabeling_text(Fledits) (11)" which was received from the Division of Anti-Infective Products eRoom on December 7, 2012 (listed as Version 14 in the eRoom).

DPDP's comments are provided in the attached, clean version of the labeling.

If you have any questions about DPDP's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov

Thank you for the opportunity to provide comments on this PI.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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/s/

CHRISTINE G CORSER
12/09/2012



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: December 6, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Fariba Izadi, RPM
DAIP

Subject: QT-IRT Consult to NDA 204384

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated October 22nd regarding labeling review. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT consult review, October 16, 2012

QT-IRT'S PROPOSED LABELING

5.4 Warning and Precautions

(b) (4)

BACKGROUND

QT-IRT reviewed the TQT study report for bedaquiline (QT-IRT consult review, October 16, 2012). In study TMC207TBC1003 no significant QTc prolongation effect after a single 800-mg dose of bedaquiline was detected. On the contrary, sponsor conducted a multiple dose phase 2a study in healthy subjects (study C202) that showed a QT effect of approximately 12 ms after 7 days of administration of a 400-mg dose of bedaquiline.

We concluded that the single-dose TQT study failed to characterize the potential of TMC207 to prolong the QTc interval because it was insufficient to achieve exposures of the major metabolite that cover the high-exposure scenario in the clinical setting. The clinically relevant exposure of M2 occurs after 14 days of 400-mg q.d. dosing, because of the long terminal half-life of the metabolite (5.3 months).

Exposure-response data from both study C208 and the TQT study suggest that an exposure-QTcF relationship exists for the metabolite M2. No exposure-QTcF relationship was evident with TMC207 exposure.

QT-IRT Analysis of Study C208 Stage 2

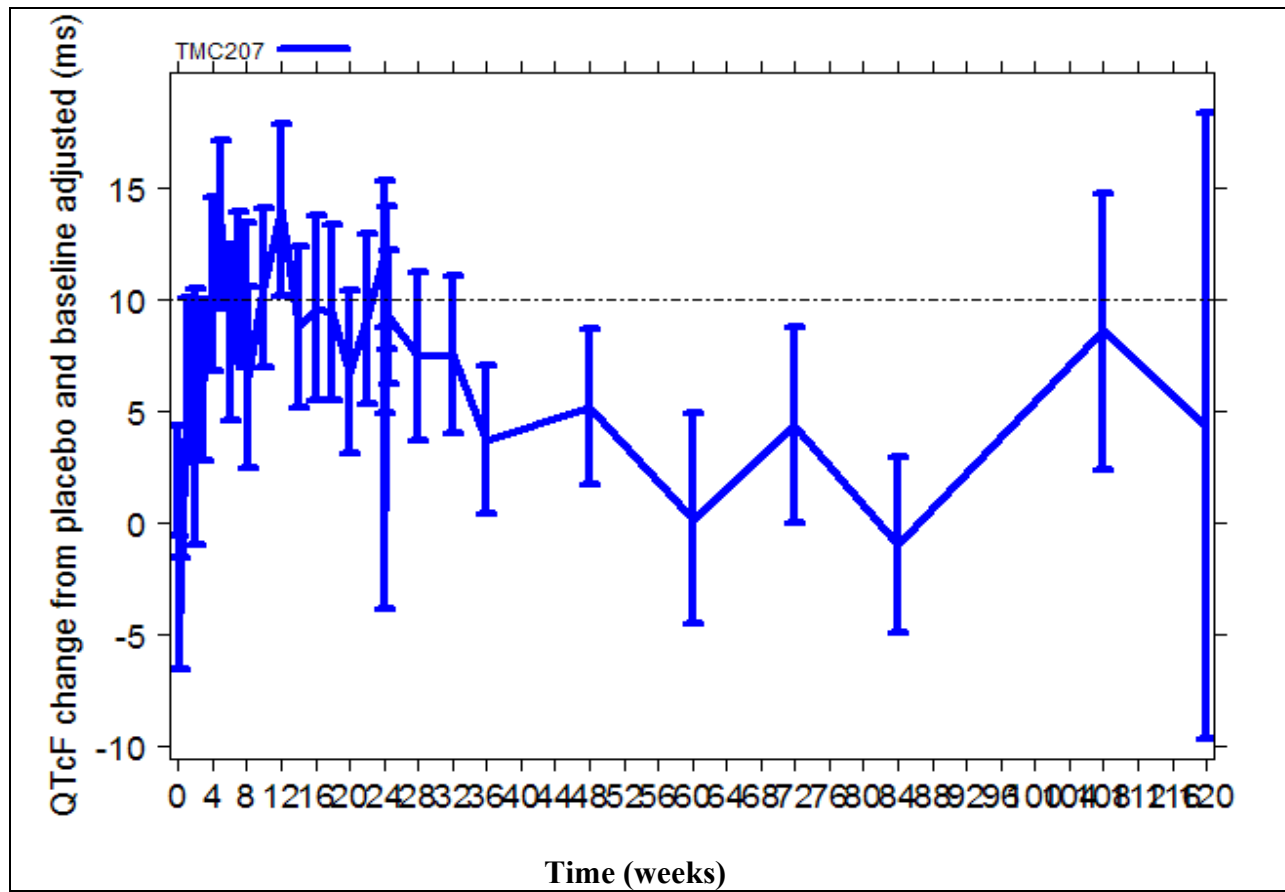
C208 Stage 2 was a phase 2 trial in 160 subjects with newly diagnosed MDR-TB of whom 79 received bedaquiline and 81 received placebo up to 24 weeks in combination with a standardized background regimen for MDR-TB. The 24-week investigational treatment period was followed by a 96-week follow-up period. Standard 12-lead ECGs (supine after at least 5 minutes rest) were collected at Days -1, 2, 7 and Weeks 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 24, 32, 36, 48, 60, 72, 84, 108 and 120. Triplicate ECGs were taken at screening, Days -1 and 1 and Weeks 2, 8 and 24. ECGs were obtained at pre-dose and 5 hours post-dose. Time-matched baseline QTcF values were used in the analysis. Pharmacokinetic samples were obtained on Day 7 and Weeks 2, 4, 8, 12, 16, 24, 28, 32, 36, 48, 60, 72, 84, 96 and 120. A pharmacokinetic sub-study was also conducted in patients at weeks 2 (n=26) and 24 (n=17) where samples were collected at 1, 3, 5, 6, 8, 12 and 24 hours post-dose. At weeks 8 and 24, pharmacokinetic samples were also collected at 36 and 48 hours post-dose.

The reviewer used a mixed model to analyze QTcF change from placebo and baseline adjusted ($\Delta\Delta\text{QTcF}$). The results are listed in Table 1. The largest bound of the 2-sided 90% CI for the mean difference between bedaquiline and placebo during the treatment period was 18 ms observed at 12 weeks. Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for bedaquiline over time.

Table 1: Analysis Results of $\Delta\Delta\text{QTcF}$ for Bedaquiline

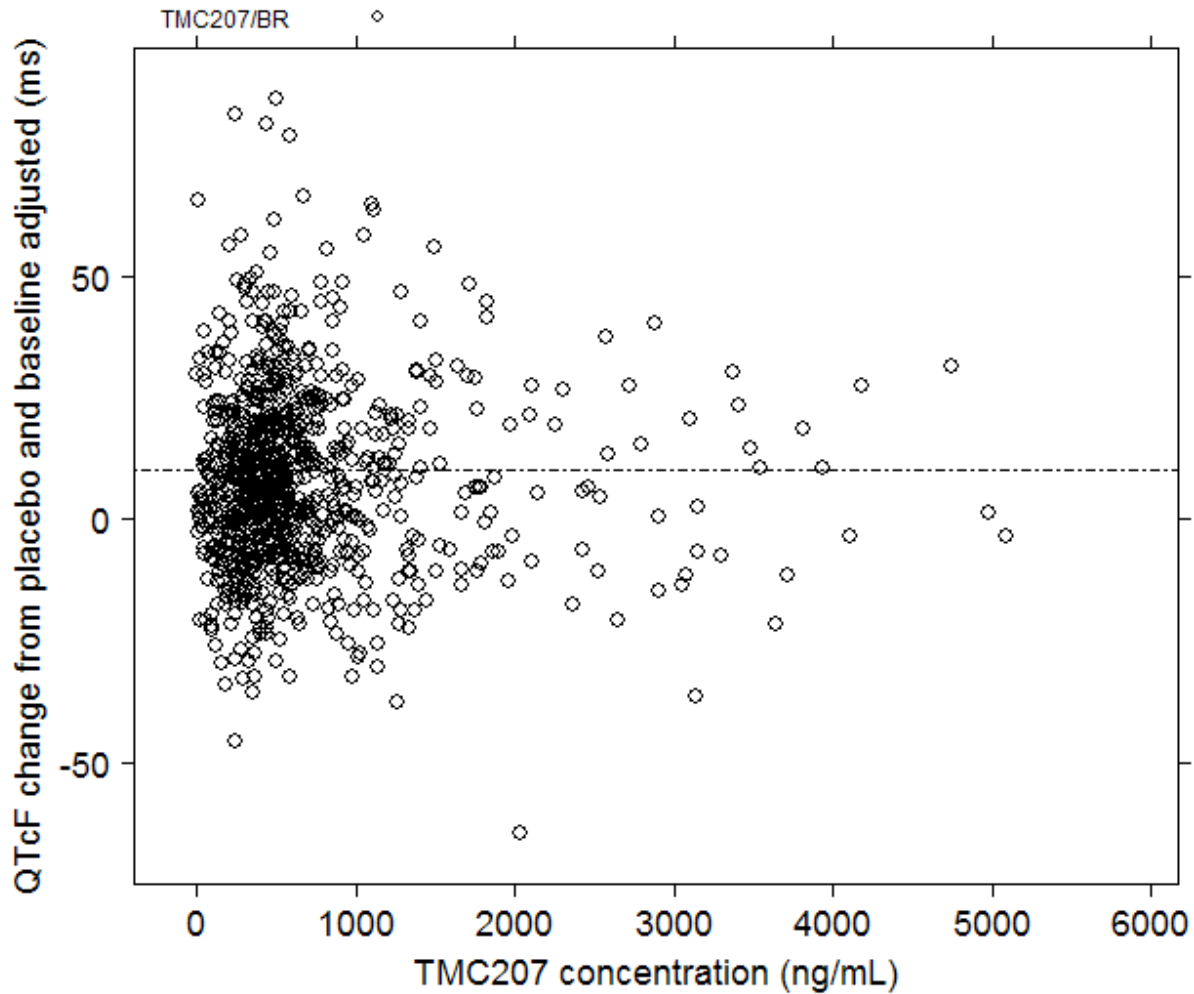
Time (weeks)	$\Delta\Delta\text{QTcF}$		
	Mean (ms)	Standard Error (ms)	90% CI
Day 1	-4.1	1.5	(-6.6, -1.5)
Day 7	6.4	2.3	(2.7, 10.2)
Week 2 (pre-dose)	7.0	2.1	(3.4, 10.5)
Week 2 (post-dose)	3.0	2.4	(-1.1, 7.0)
Week 3	6.4	2.2	(2.7, 10.1)
Week 4	10.7	2.4	(6.8, 14.7)
Week 5	13.4	2.3	(9.6, 17.2)
Week 6	8.6	2.4	(4.5, 12.6)
Week 7	10.6	2.1	(7.2, 14.0)
Week 8 (pre-dose)	10.2	2.0	(7.0, 13.5)
Week 8 (post-dose)	6.6	2.5	(2.4, 10.7)
Week 10	10.6	2.2	(6.9, 14.2)
Week 12	14.1	2.4	(10.1, 18.0)
Week 14	8.8	2.2	(5.1, 12.5)
Week 16	9.7	2.5	(5.4, 13.9)
Week 18	9.5	2.4	(5.5, 13.5)
Week 20	6.8	2.2	(3.1, 10.5)
Week 22	9.2	2.3	(5.3, 13.0)
Week 24 (pre-dose)	12.1	2.0	(8.7, 15.5)
Week 24 (post-dose)	0.6	2.7	(-3.9, 5.1)
Week 24 (post-dose)	11.0	2.0	(7.7, 14.3)
Week 24 (post-dose)	9.3	1.8	(6.2, 12.3)
Week 28	7.4	2.3	(3.6, 11.3)
Week 32	7.6	2.2	(3.9, 11.2)
Week 36	3.7	2.0	(0.3, 7.1)
Week 48	5.2	2.1	(1.6, 8.7)
Week 60	0.2	2.9	(-4.6, 5.0)
Week 72	4.4	2.7	(-0.1, 8.9)
Week 84	-1.0	2.4	(-5.0, 3.0)
Week 108	8.6	3.8	(2.0, 15.1)

Figure 1: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



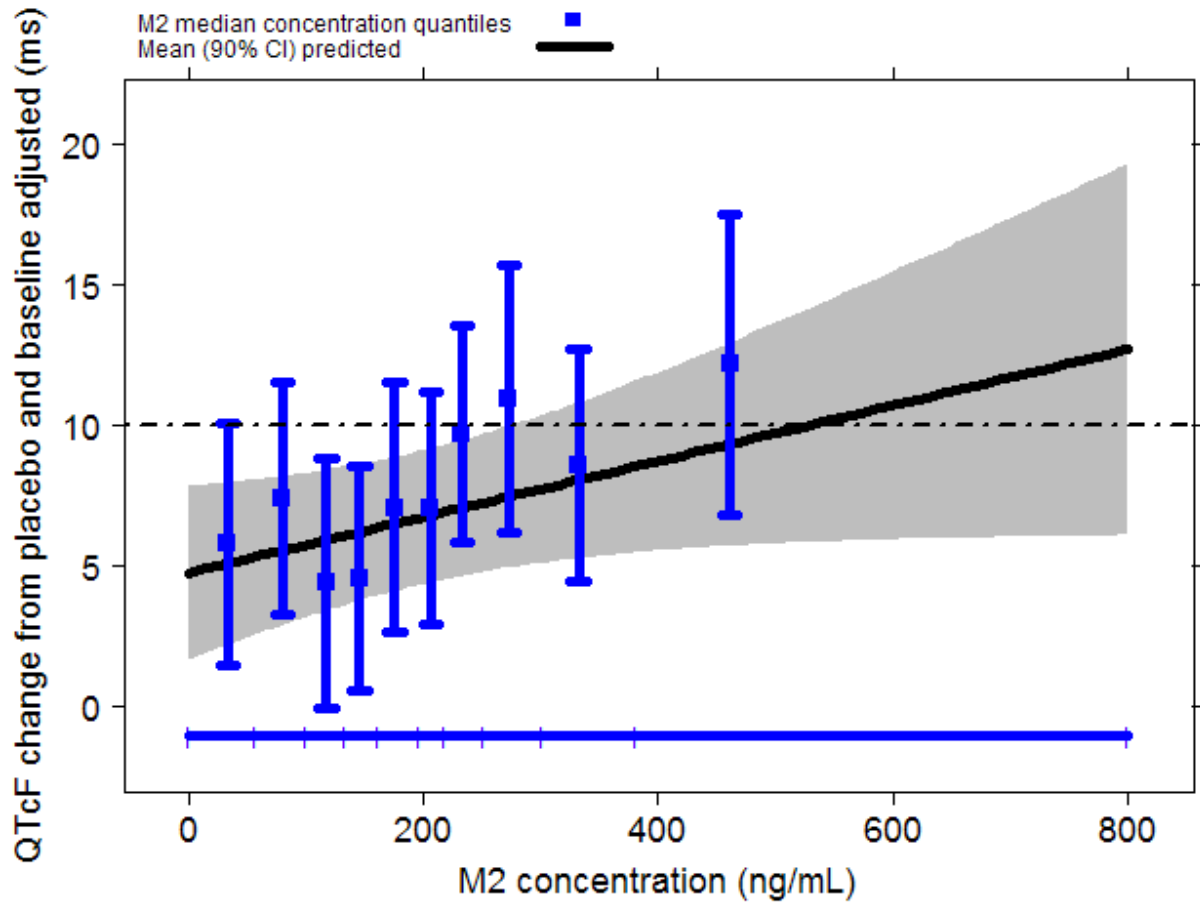
The relationship between $\Delta\Delta$ QTcF and bedaquiline concentrations is visualized in Figure 2 with no evident exposure-response relationship.

Figure 2: $\Delta\Delta$ QTcF vs. Bedaquiline Concentration



Evidence of a trend of increasing $\Delta\Delta$ QTcF with increasing M2 concentration was found. The relationship between $\Delta\Delta$ QTcF and M2 concentrations is visualized in Figure 3. This positive relationship is independently consistent with the observation from the TQT study (see previous IRT review dated 10/16.2012). An effect of M2 concentration on $\Delta\Delta$ QTcF can also explain the contradictory findings from the negative TQT study and C208. These results should be interpreted with caution, however, as these studies were not designed to evaluate specifically the effect of M2 on $\Delta\Delta$ QTcF. It is possible there are confounding factors accounting for the observed trend. To this end, it is worth noting that maximum concentrations of M2 are expected at Week 2, but $\Delta\Delta$ QTcF appears to continue to increase after this time in C208.

Figure 3: $\Delta\Delta\text{QTcF}$ vs. M2 Concentration



ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics only 20% of ECGs were annotated in the primary lead II, and rest in multiple leads (V1 to V6), with less than 0.7% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

Thank you for requesting our input into the development of this product under NDA 204384. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdercpqt@fda.hhs.gov

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/s/

MONICA L FISZMAN
12/06/2012

KEVIN M KRUDYS
12/12/2012

NORMAN L STOCKBRIDGE
12/12/2012

Division of Anti-Infective Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 204384

Name of Drug: Sirturo (bedaquiline) 100 mg Tablet

Applicant: Janssen Pharmaceuticals

Labeling Reviewed

Submission Date: 06-29-12

Receipt Date: 06-29-12

Background and Summary Description:

On January 10 2005, TMC207 (bedaquiline) was granted orphan-drug designation by the Office of Orphan Products Development, FDA, under request # 04-1993 for the treatment of active tuberculosis. In addition, TMC207 (bedaquiline) was granted fast-track designation by FDA on April 22, 2011. In accordance with Section 506(c) of the Federal Food, Drug, and Cosmetic Act and FDA's Guidance for Industry, "*Fast Track Drug Development Programs-Designation, Development, and Application Review*," January 2006, Janssen Research & Development, L L.C. is seeking priority review for this application.

Indication: Multi drug resistant pulmonary Tuberculosis.

Review Status: Priority

Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist.

Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Fariba Izadi

11-29-12

Regulatory Project Manager

Date

Frances LeSane

Chief, Project Management Staff

Date

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/s/

FARIBA IZADI
11/30/2012

FRANCES V LESANE
12/04/2012

**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**

Label, Labeling and Packaging Review

Date:	December 3, 2012
Reviewer:	Aleksander Winiarski, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Todd Bridges, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Sirturo (Bedaquiline) Tablets, 100 mg
Application Type/Number:	NDA 204384
Applicant:	Janssen
OSE RCM #:	2012-1625

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

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1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Sirturo (Bedaquiline) 100 mg Tablets, NDA 204384, for areas of vulnerability that could lead to medication errors.

Sirturo (Bedaquiline) is a new molecular entity (NME) under priority review with a 6 month PDUFA clock.

1.1 PRODUCT INFORMATION

The following product information is provided in the June 29, 2012 submission.

- Active Ingredient: Bedaquiline
- Indication of Use: Multi-Drug Resistant Pulmonary Tuberculosis
- Route of Administration: Oral
- Dosage Form: Tablet
- Strength: 100 mg
- Dose and Frequency: 400 mg daily for 14 days, then 200 mg three time per week for 22 weeks
- How Supplied: Bottle containing 188 tablets
- Storage: Room temperature in original container and protect from light
- Container and Closure Systems: HDPE bottle with child-resistant polypropylene closure with induction seal liner

2 METHODS AND MATERIALS REVIEWED

Sirturo (Bedaquiline) is not an approved product; therefore DMEPA did not search the FDA FAERS database for Sirturo medication error reports. We reviewed the following proposed Sirturo labels and labeling submitted by the Applicant using the principals of human factors and Failure Mode and Effects Analysis¹:

- Container Label submitted June 29, 2012 (Appendix B)
- Insert Labeling submitted June 29, 2012

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 IDENTIFIED DEFICIENCIES

The proposed product is administered over a 24 week treatment schedule.

In addition, the proposed insert labeling, under the Dosage and Administration section, the normal dosing schedule from Week 3 onward [“3 times per week (with at least 48 hours between doses)”] and dosing schedule for missed doses from Week 3 onward (“taken as 3 intakes of 200 mg per day, at least 24 hours apart”) may be confusing and needs further revisions for clarification. Our comments are listed below in section 5.1.

The container label states: “Store in original container to protect from light”. We foresee several situations in which fewer than the 188 Bedaquiline tablets may need to be dispensed, which would require storage or removal from the original container. For example, if the prescription insurance plan does not pay for the entire bottle (24 week supply), when hospitals need to place the drug into blisters for unit-dose dispensing or placement into an automated dispensing cabinet, or when patients are initiated on therapy while in the hospital then are discharged and need to complete the remainder of the 24 week course of therapy at home.

Due to these concerns, an information request was sent to the Applicant asking how they intend to address these potential challenges with the proposed packaging configuration. The Applicant indicated that stability data supports storage of the product outside of the original bottle in a tight, light-resistant container for up to 3 months, and ONDQA confirmed this claim. ONDQA and DMEPA are in agreement that the container label and insert labeling require revisions to reflect this additional storage information and provide recommendations in sections 5.1 and 5.2 of this review.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA.

5.1 COMMENTS TO THE DIVISION

A. Full Prescribing Information Dosage and Administration Section

1. The administration subsection provides information regarding the importance of why the dose should be taken with food. Prescribers need to know this information so that they do not misinterpret the statement “[TRADENAME] should be taken with food.” as optional (e.g. to prevent stomach irritation, as with Ibuprofen). However, as proposed the information is not prominent because it appears at the end of the section and away from the prescribed dose and may be omitted by the prescriber.

To ensure that this important information is not omitted by the prescriber relocate this information to main Dosage and Administration section under the listed dosage and delete the administration subsection, similar to:

- The total duration of treatment with [TRADENAME] is 24 weeks. [TRADENAME] should be taken orally with food, as administration with food increases oral bioavailability [*see Pharmacokinetics (12.3)*]. It is recommended that the [TRADENAME] tablets be swallowed whole with water.
2. To clarify that the total weekly dose (from Week 3 onward) is 600 mg, revise the recommended dosage statement to read as follows:
 - Weeks 3-24: 200 mg (2 tablets of 100 mg) 3 times per week, (with at least 48 hours between doses) for a total of 600 mg per week.
 3. The dosing schedule directions for missed doses (from Week 3 onward) "... (taken as 3 intakes of 200 mg per day, at least 24 hours apart)" are unclear and may be misinterpreted to administer the next 3 doses 24 hours apart. To clarify revise the directions to read as follows:

Missed dose

From Week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose and adjust the dosing schedule to achieve a total dose of 600 mg in the 7 day dosing period. Do not exceed 200 mg per day and separate the missed dose by at least 24 hours from the next scheduled dose.

B. Full Prescribing Information, Storage and Handling

To ensure Sirturo is not stored outside of the original bottle for longer than the three month established stability, revise the storage and handling section to read as follows:

"Keep out of reach of children.

Dispense in original container. Tablets dispensed outside the original container should be stored in a tight light-resistant container with a 3 month expiration date.

Store at 25°C (77°F); Excursions permitted to 15°C - 30°C (59°F - 86°F). [See USP Controlled Room Temperature]."

C. Highlights of Prescribing Information, Dosage and Administration Section

1. The important information regarding why the dose should be taken with food is omitted from this section and may be omitted by the prescriber, because they may misinterpret the statement "Take [TRADENAME] with food..." as optional (e.g. to prevent stomach irritation, as with Ibuprofen). Revise the information in this section to read as follows:

- 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks. Take [TRADE NAME] with food, as administration with food increases oral bioavailability. Swallow [TRADE NAME] tablets whole with water.

5.2 COMMENTS TO THE APPLICANT

A. Container Label

1. Place the proprietary name “Sirturo” in title case, similar to the current place holder (Tradename) in font type, style, and size.

Remove the italic formatting from “*bedaquiline*” tablets”. The established name should have a prominence commensurate with the prominence of the proprietary name including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
2. The statement of quantity “188 Tablets” competes for prominence with the statement of strength 100 mg. To decrease the prominence of the net quantity statement, decrease the size of the statement “188 Tablets”, remove the bold formatting, and relocate it to the bottom portion of the label. Additionally, remove the bolded line that appears below the statement “188 Tablets”.
3. To decrease clutter and ensure that the proprietary name, established name and strength are prominently displayed on the principal display, relocate the statement “Each tablet contains bedaquiline fumarate equivalent to 100 mg of bedaquiline” to the side panel.
4. To ensure Sirturo is not stored outside of the original bottle for longer than the three month established stability, revise the storage statement to read as follows and relocate it to the principal display panel.

Attention Pharmacist: Dispense in original container. Tablets dispensed outside the original container should be stored in a tight light-resistant container with a 3 month expiration date. Store at 25°C (77°F); Excursions permitted to 15°C-30°C (59°F - 86°F).[See USP Controlled Room Temperature].

If you have questions or need clarifications, please contact Karen Townsend, OSE project manager, at 301-796-5413.

APPENDICES

Appendix A. Database Description

Federal Adverse Event Reporting System (FAERS)

The Federal Adverse Event Reporting System (FAERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses FAERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of FAERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonization. Adverse events in FAERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

FAERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: CONTAINER LABEL



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/s/

ALEKSANDER P WINIARSKI
12/03/2012

TODD D BRIDGES
12/03/2012

CAROL A HOLQUIST
12/03/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 204384

Application Type: New NDA

Name of Drug: TMC 207 (bedaquiline) 100 mg Tablet

Applicant: Janssen Therapeutics

Submission Date: 06-29-12

Receipt Date: 06-29-12

1.0 Regulatory History and Applicant's Main Proposals

On January 10 2005, TMC207 (bedaquiline) was granted orphan-drug designation by the Office of Orphan Products Development, FDA, under request # 04-1993 for the treatment of active tuberculosis. In addition, TMC207 (bedaquiline) was granted fast-track designation by FDA on April 22, 2011. In accordance with Section 506(c) of the Federal Food, Drug, and Cosmetic Act and FDA's Guidance for Industry, "*Fast Track Drug Development Programs-Designation, Development, and Application Review*," January 2006, Janssen Research & Development, L.L.C. is seeking priority review for this application.

Indication:: Multi drug resistant pulmonary Tuberculosis.
Review Status: Priority

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

N/A

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

N/A

14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A

17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

YES

Selected Requirements of Prescribing Information (SRPI)

30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A

31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES

32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES

33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES

34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES

35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES

36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES

37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES

38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- N/A** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- N/A** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

FARIBA IZADI
11/15/2012

FRANCES V LESANE
11/23/2012

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	204384
Brand Name	Bedaquiline
Generic Name	TMC207
Sponsor	Janssen Therapeutics
Indication	Multi- Drug Resistant Pulmonary Tuberculosis
Dosage Form	Tablet
Drug Class	Mycobacterial ATP synthase inhibitor
Therapeutic Dosing Regimen	400 mg p.o., q.d., for 2 weeks followed by 200 mg p.o., t.iw for 22 weeks.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Maximum dose tested 700 mg single dose, 400 mg q.d., over 15-day treatment.
Submission Number and Date	001, 11 Jul 2012
Review Division	DAIP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of TMC207 was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between TMC207 and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 9, indicating that assay sensitivity was established.

In this randomized, double-blinded, parallel study, 88 subjects with tuberculosis received either TMC207 or a single oral dose of moxifloxacin 400 mg, and placebo. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for TMC207 and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
TMC207 800 mg	16	2.7	(0.2, 5.2)
Moxifloxacin 400 mg*	10	12	(10.0, 14.0)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 9.3 ms.

The single-dose administration study design was insufficient to achieve exposures of the major metabolite that cover the high-exposure scenario in the clinical setting. Exposure-response data from both study c208 and this dedicated QT study combined with the time course of QTcF compared with the time course of TMC207 and M2 concentrations suggest that an exposure-QTcF relationship exists for the metabolite M2. No exposure-QTcF relationship was evident with TMC207 exposure. The clinically relevant exposure of M2 occurs after 14 days of 400 mg q.d. dosing, owing to the long terminal half-life of the metabolite (5.3 months). QTcF assessment in the dedicated QT study was following a single dose of TMC207 and the C_{max} and AUC values for M2 were 1/5.4- and 1/6.4-fold of the exposures to M2 observed in tuberculosis patients in the phase 2 study c208.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- This single-dose TQT study was insufficient to characterize the potential of TMC207 to prolong the QTc interval. Since this was single dose study, M2 exposures never achieved clinically relevant concentrations. The finding of a positive concentration-QTc relationship, suggest that M2 concentrations are responsible for the QTc prolongation observed in the registration trials.

2 PROPOSED LABEL



3 BACKGROUND

3.1 PRODUCT INFORMATION

TMC207 (formerly known as R207910, and also referred to as “J”14) is a diarylquinoline selected for clinical development as an oral treatment of TB. It has a novel mode of action for TB drugs (specific inhibition of mycobacterial ATP synthase). Thus, TMC207 introduces a new class of anti-TB drugs.

3.2 MARKET APPROVAL STATUS

TMC207 is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From QT-IRT protocol review (October 1st 2010)

Reviewer's comments: TMC207 inhibits hERG currents in a concentration-dependent manner. A 42% reduction in the hERG current was achieved with a concentration 40% of the C_{max} exposure for a proposed therapeutic regime of 400 mg q.d. for 10 days. In the 6-month dog study QTc prolongation and increase in troponin I levels were observed. Although it is stated in the IB that cardiac toxicity was reached at high doses, we cannot reach a conclusion about the cardiotoxicity potential of TMC207 at the proposed human exposures because of the lack of drug exposure data in the study.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4. Page 269, TMC207 and QT interval Effect

In C208 Stage 1 in MDR-TB infected subjects, mean QTcF increases were observed in both groups during the 8-week Investigational Treatment phase but were more pronounced in the TMC207 group (Section 4.1.1.4). Mean increases in the TMC207 group were observed from the first assessment after Day 1 (i.e., Week 1) and increases > 10 ms were observed from Week 6 onwards. During the Investigational Treatment phase, the largest mean increase from reference at a predose time point was 17.6 ms (Week 6) in the TMC207 group and 8.6 ms (at Week 7) in the placebo group. After the end of the TMC207 dosing period (Week 8), mean QTcF fluctuated with increases and decreases observed in both treatment groups.

In the controlled trial C208 Stage 2, the incidence of QTcF abnormalities was higher in the TMC207 group than in the placebo group.

At prespecified time points in C208 Stage 2, triplicate ECGs were taken at predose and 5 h postdose (i.e., at TMC207 t_{max}). In the TMC207 group, the mean changes from reference in QTcF were comparable between the 5 h postdose assessments and the respective predose assessments, but were greater than the respective predose assessments in the placebo group. This suggests there is no direct relationship between TMC207 C_{max} and QTcF prolongation.

In the subset of subjects undergoing full pharmacokinetic profiling in C208 Stage 2, triplicate ECGs were recorded at each time point a blood sample was taken for pharmacokinetics (i.e., predose and 1, 3, 5, 6, 8, 12, and 24 h after dosing). This full day ECG profile showed little fluctuation throughout the day in mean QTcF values in the TMC207 group, either at Week 2 or at Week 24, suggesting that there was no increase in QTcF interval coinciding with TMC207 t_{max} (i.e., 5 h after dosing). Similar observations were made in the placebo group.

In the TMC207 group in C208 Stage 2, a mean increase from reference in QTcF was observed from the first assessment after Day 1 (9.9 ms at Week 1). Mean increases from reference in QTcF grew gradually larger over the first 8 weeks of TMC207 treatment and then remained more or less stable until Week 24. The largest mean increase in QTcF at a predose time point in the first 24 weeks was 15.7 ms in the TMC207 group (at Week 18). In the placebo group, mean changes from reference were generally < 10 ms. The largest mean increase in QTcF at a predose time point in the first 24 weeks was 6.2 ms in the

placebo group (at Week 18). After Week 24, QTcF increases in the TMC207 group gradually became less pronounced.

In general, no clear relationship between TMC207 or M2 plasma concentration up to Week 2 (400 mg q.d.) and after Week 3 (200 mg t.i.w.) and corresponding changes in QTcF was observed in male or female subjects in C208 Stage 2.

During the Investigational Treatment phase in C208 Stage 2, QTcF values of more than 500 ms were observed in 1 subject in the TMC207 group (505 ms) and no subjects in the placebo group.

QTcF values between 450 and 480 ms, and QTcF increases from reference of 30 to 60 ms and > 60 ms were observed more frequently in the TMC207 group than in the placebo group.

During the Investigational Treatment phase in C208 Stage 2, no AEs identified by the SMQ for Torsade de Pointes/QT prolongation were reported as SAE, led to permanent discontinuation of the investigational medication, or were considered grade 3 or 4 in severity. No AEs with preferred term torsade de pointes were reported during the Investigational Treatment phase. Adverse events identified by the SMQs for Torsade de Pointes/QT prolongation were observed for 5.1% of subjects in the TMC207 group and 4.9% of subjects in the placebo group.

In the C209 trial, mean increases from reference in QTcF were observed from the first assessment after Day 1 (9.3 ms at Week 2) with mean increases from reference of more than 10 ms observed from Week 8. The largest mean change from reference in QTcF at a predose time point was 14.2 ms at Week 24. After Week 24, QTcF increases were less pronounced. After Week 36, data were only available for 52 subjects in this ongoing trial. Mean changes from reference for QTcF at the 5-hour assessment time points were comparable to those at predose time points. A trend towards greater QTcF changes with higher TMC207 or M2 plasma concentrations was observed in both male and female subjects in C209 (Module 5.3.5.2/TMC207-C209-CSR-W24).

During the Investigational Treatment phase in C209, a QTcF value of more than 500 ms was observed in 1 subject (514 ms). QTcF increases from reference of more than 60 ms were noted in 9 (3.9%) subjects and resulted in QTcF values above 450 ms in 5 of those 9 subjects (including the subject with QTcF > 500 ms). QTcF increases from reference of 30 to 60 ms were noted in 84 (36.7%) subjects and resulted in QTcF values above 450 ms in 18 of those 84 (21.4%) subjects.

During the Investigational Treatment phase in C209, one grade 3 AE of ECG QT prolonged was reported as SAE and led to permanent discontinuation of TMC207. No other AEs identified by the Torsade de Pointes/QT prolongation SMQ were considered serious or led to discontinuation of investigational medication. No AEs with preferred term torsade de pointes were reported during the Investigational Treatment phase. Adverse events identified by the SMQ for Torsade de Pointes/QT prolongation were observed in 2.6% of subjects.

Reviewer's comments: In studies C208 1 and 2 and C-209 mean post-baseline QTcF increases between 15 and 18 ms were reported. In all studies the number of subjects with QTcF changes > 60 ms was higher in the TMC207-treated group than in the active

control group. Very few subjects had a QTcF > 500 ms during the studies (1 subject in each study). Neither Torsade de pointes nor sudden cardiac death were reported in these studies. In the C209 trial, mean increases from reference in QTcF were larger in subjects with concomitant clofazimine use (Week 24, 0 h: 32 ms) than in subjects without concomitant clofazimine use (Week 24, 0 h: 12 ms).

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of bedaquiline's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 69600 and NDA 204384. The sponsor submitted the study report TMC207TBC1003 for TMC207, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

"A double-blind, randomized, placebo- and positive-controlled, parallel-group trial to evaluate the effect of single-dose TMC207 on the QT/QTc interval in healthy subjects."

4.2.2 Protocol Number

TMC207TBC10003

4.2.3 Study Dates

21 February 2011 - 12 May 2011

4.2.4 Objectives

The primary objective was to evaluate the effect of single-dose administration of 800 mg TMC207 versus placebo on the QT and QTc interval in healthy subjects.

The secondary objectives were:

- to evaluate the effect of single-dose TMC207 800 mg on non-QT interval ECG-parameters (RR interval, heart rate [HR], PR, and QRS interval) in healthy subjects;
- to evaluate the pharmacokinetics of TMC207 and M2 after single-dose administration of TMC207 800 mg in healthy subjects;
- to explore the concentration-effect relationship for QT/QTc for TMC207, M2, and moxifloxacin in healthy subjects;
- to evaluate trial sensitivity (i.e., to evaluate the effect of a positive control, a single 400-mg dose of moxifloxacin on the QT/QTc interval in healthy subjects);
- to evaluate the short-term safety and tolerability of single-dose TMC207 800 mg in healthy subjects.

Source: Sponsor's study report, page 27.

4.2.5 Study Description

4.2.5.1 Design

This is a randomized, double-blinded, 2-treatment-arm parallel design with one dosing occasion.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

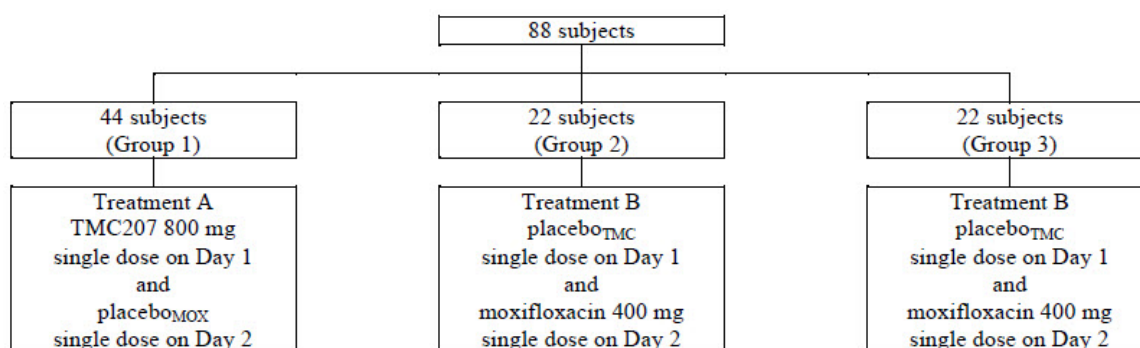
The positive (moxifloxacin) control was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were enrolled in one of two treatment arms (A or B). Subjects assigned to Treatment B were randomly assigned to one of two groups (2 or 3) for later use in investigating the placebo effect.

Figure 1: Sponsor's Treatment Arms



Source: Sponsor's study report, page 29.

4.2.6.2 Sponsor's Justification for Doses

A single dose of 800 mg TMC207 will be tested. To date, a total of 150 healthy subjects have received single doses of TMC207. TMC207 was generally well tolerated up to single doses of 700 mg (highest dose studied to date). The 800-mg single dose to be tested in this study is slightly higher but does not represent any new or safety concerns. In the limited number of repeated dose trials in healthy subjects, TMC207 was also considered generally safe and well tolerated. The safety data of the TMC207-TiDP13-C208 trial in MDR-TB-infected subjects also demonstrated that the selected dose regimen of TMC207 (400 mg q.d. for the first 2 weeks followed by 200 mg t.i.w. for additional 6 weeks) was generally safe and well tolerated when added to a 5-drug background regimen of MDR-TB therapy. A single dose of 800 mg TMC207 is expected to result in a mean maximum plasma concentration which is about two-fold higher than the maximum concentration observed in MDR-TB infected patients after 400 mg TMC207 q.d. for 14 days, thus providing supratherapeutic exposure which is expected to

cover the range of exposures observed in MDR-TB infected patients even when a CYP3A4 inhibitor is coadministered with TMC207.

In this trial, to characterize the effects on QT/QTc interval for TMC207, single-dose treatment and a parallel-group design were chosen, in view of the cationic amphiphilic drug (CAD) characteristics of TMC207 and its M2 metabolite with extensive tissue distribution and a long terminal elimination half-life (which is currently estimated at about 5.5 months for TMC207 and 5.3 months for M2).

Reviewer's Comment: The dose selected was sufficient to cover the high-exposure scenario for TMC207. The C_{max} and AUC values of TMC207 after administration of a single 800 mg dose were 3.0- and 2.2-fold the exposures of TMC207 after 14 days of multiple dose 400 mg administration in the phase 2 trial c208. However, the single dose administration was not sufficient to cover the high-exposure scenario for the metabolite M2. The metabolite's long half-life (5.3 months) led to that were 5.4 and 6.4 times those seen C_{max} and AUC values after 400 mg q.d. dosing for 14 days compared to after a single administration of 800 mg TMC207. Exposures achieved in the phase 2 study c208 are expected to be the high-exposure scenario for the metabolite.

4.2.6.3 Instructions with Regard to Meals

TMC207, moxifloxacin, placeboTMC, and placeboMOX were taken orally between 7 and 9 a.m., at approximately the same time each morning. Study medication was taken together with approximately 240 mL of water per intake. All intakes were within 10 min after completion of a standardized breakfast.

Reviewer's Comment: The C_{max} and AUC with food were 2.6- and 2.0-fold values seen fasted. Therefore, administration with food is acceptable.

4.2.6.4 ECG and PK Assessments

PK Assessments:

Blood samples for determination of study medication concentrations were taken at: 24 h after start of 24-hour Holter ECG recording on Day -1/0.5 h predose and 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 h after start of 24-hour Holter ECG recording on Day 1 (TMC207 and M2 only)

ECG Assessments:

Twelve-lead time-matched triplicate ECGs were extracted from the Holter monitoring at predefined time points: at 0.5 h predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h postdose.

Reviewer's Comment: The time of the ECGs are acceptable to capture the PK and ECG effects within a 24 hour period. However, collecting these samples after a single-day administration is not appropriate for a metabolite with a half-life of 5.3 months.

4.2.6.5 Baseline

The sponsor used a time-matched baseline.

4.2.7 ECG Collection

Holter ECG monitoring was performed continuously for 72 h (3 x 24 h) for each subject on Days -1, 1 and 2 of Treatments A and B. Twelve-lead time-matched triplicate ECGs were extracted from the Holter monitoring at predefined time points.

The ECG reader of the Holter recordings was blinded for subject ID, gender, time, day and treatment. Review of ECGs from a particular subject had to be performed by a single reader.

For safety monitoring, 12-lead time-matched ECGs were performed at predefined time points.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

The trial population consisted of 88 healthy subjects, randomized to Group 1 (N = 44), Group 2 (N = 22) or Group 3 (N = 22).

Most subjects (78 [88.6%] subjects) were White. Each gender was represented by at least 40% (36 [40.9%] subjects were female) as according to the design. Overall, the median (range) age was 36.0 (19-55) years, weight was 68.5 (49-92) kg, and BMI was 24.90 (19.4-27.9) kg/m².

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

Mean and 90% CIs were estimated from a mixed effects model fitted to changes from baseline at each time point as the dependent variable and treatment (TMC207 or placebo), baseline interval, time and the interaction of time and treatment as fixed effects and subject as a random effect, using Day 1 data.

The largest upper limit of the 90% CIs of the differences between TMC207 and placebo in time-matched changes from baseline in QTcF was observed 16 h after intake of TMC207 (mean difference: 5.19 ms, 90% CI: [1.46, 8.92]). This value is below the threshold of 10 ms, indicating this thorough QT study is negative.”

Table 2: Sponsor's 90% CI for $\Delta\Delta$ QTcF TMC207 800 mg

QTcF Computed Time Point	Group 1 TMC207 Minus Placebo ^a		
	Mean (ms)	Lower 90% CL	Upper 90% CL
-0.5 h	0.63	-3.11	4.37
1 h	1.81	-1.92	5.53
2 h	2.59	-1.13	6.32
3 h	1.48	-2.24	5.21
4 h	0.23	-3.50	3.96
5 h	2.68	-1.05	6.41
6 h	-0.98	-4.71	2.74
8 h	1.78	-1.94	5.50
10 h	2.67	-1.06	6.40
12 h	3.71	-0.02	7.44
16 h	5.19	1.46	8.92
24 h	2.64	-1.08	6.37

Source: Sponsor's study report, page 68.

Reviewer's Comments: Our independent analysis agrees with the sponsor's conclusions. See section 5.2.

4.2.8.2.2 Assay Sensitivity

Mean and 98% CI was estimated from a mixed effects model fitted to the changes from baseline as dependent variable and the interaction between treatment (moxifloxacin or placebo) and group (Group 2 or 3), baseline interval, time and the interaction of time, treatment and group as fixed effects and subject as a random effect, using only data of Groups 2 and 3.

For 4 out of 5 predefined time points of interest, the lower limit of the 98% CIs of the differences between moxifloxacin and placebo in time-matched changes from baseline in QTcF was above 5 ms with the largest value observed at 3 h (mean difference: 10.86 ms, 98% CI: [8.41, 13.31]). Therefore, the criterion for trial sensitivity was met."

Source: Sponsor's study report, page 69.

Table 3: Sponsor's 98% CI for $\Delta\Delta$ QTcF Moxifloxacin 400 mg

QTcF Computed Time Point	Group 2 + 3 Moxifloxacin Minus Placebo ^a		
	Mean (ms)	Lower 98% CL	Upper 98% CL
-0.5 h	-1.43	-3.88	1.02
1 h	0.66	-1.81	3.12
2 h	5.16	2.71	7.61
3 h	10.86	8.41	13.31
4 h	9.59	7.14	12.04
5 h	7.80	5.34	10.26
6 h	8.32	5.86	10.78
8 h	9.26	6.80	11.73
10 h	12.08	9.59	14.58
12 h	3.60	1.14	6.07
16 h	9.61	7.16	12.06
24 h	5.45	3.01	7.90

Source: Sponsor's study report, page 70.

Reviewer's Comments: Our independent analysis agrees with the sponsor's conclusions. See section 5.2.

4.2.8.2.3 Categorical Analysis

The sponsor conducted a categorical analysis.

Table 4: Sponsor's Categorical Analysis

Parameter Abnormality, n (%)	Group 1		Group 2 + 3	
	TMC207	Placebo	Placebo	Moxifloxacin
HR (bpm)				
Abnormally low	3 (6.8)	3 (6.8)	3 (6.8)	2 (4.5)
PR Interval (ms)				
Abnormally high	0	0	2 (4.5)	2 (4.5)
QTc Linear (ms)				
]450 ms, 480 ms]	1 (2.3)	1 (2.3)	0	0
Change from baseline [30; 60] ms	0	0	0	2 (4.5)
Change from baseline > 60 ms	0	0	0	0
QTc Nonlinear (ms)				
]450 ms, 480 ms]	1 (2.3)	1 (2.3)	0	0
Change from baseline [30; 60] ms	0	0	0	2 (4.5)
Change from baseline > 60 ms	0	0	0	0
QTc Sagie (ms)				
]450 ms, 480 ms]	1 (2.3)	0	0	0
Change from baseline [30; 60] ms	0	0	0	2 (4.5)
Change from baseline > 60 ms	0	0	0	0
QTcB (ms)				
]450 ms, 480 ms]	3 (6.8)	3 (6.8)	1 (2.3)	2 (4.5)
Change from baseline [30; 60] ms	3 (6.8)	1 (2.3)	2 (4.5)	7 (15.9)
Change from baseline > 60 ms	0	0	0	0
QTcF (ms)				
]450 ms, 480 ms]	1 (2.3)	0	0	0
Change from baseline [30; 60] ms	0	0	0	1 (2.3)
Change from baseline > 60 ms	0	0	0	0

Source: Sponsor's study report, page 75.

4.2.8.3 Safety Analysis

At least 1 AE was reported in 5 (11.4%) subjects who received TMC207, 2 (4.5%) subjects who received placebo(TMC), 7 (15.9%) subjects who received placebo(MOX), and 2 (4.5%) subjects who received moxifloxacin.

No deaths or AEs leading to trial discontinuation were reported during the trial. Two (2.3%) subjects in the trial had an SAE after receiving TMC207: 1 subject had grade 3 headache during the TMC207 treatment phase and 1 subject had grade 1 anxiety during follow-up. No other SAEs or AEs of at least grade 3 were reported.

During the treatment phase, AEs considered at least possibly related to study medication by the investigator were reported in 4 (9.1%) subjects for TMC207, 2 (4.5%) subjects for placebo(TMC), 2 (4.5%) subjects for moxifloxacin, and 5 (11.4%) subjects for placebo(MOX).

During the treatment phase, the most frequently (> 1 subject) reported AEs following a single dose of TMC207 were nausea, dizziness, and headache in 2 (4.5%) subjects each. During the placebo(TMC) phase, 1 subject reported dizziness and 1 subject reported headache; no subjects in this phase reported nausea.

Reviewer's comments: No AEs of concern as per ICHE14 guidance were reported.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The single-dose administration PK results are presented in Table 5 (TMC207) and Table 6 (M2) and Figure 2. The multiple-dose PK results from the phase 2 PK study (-c208) in patients with tuberculosis are shown in Table 7 (TMC207) and Table 8 (M2) and Figure 3. C_{\max} and AUC values of TMC207 in the thorough QT study were 3.0- and 2.2-fold values seen following administration of 800 mg bedaquiline with 400 mg drug after 2 weeks of q.d. administration in study c208, the intended clinical dose. Whereas, C_{\max} and AUC values of M2 in the thorough QT study were 5.4- and 6.4-fold lower following single-dose administration of 800 mg bedaquiline compared with 400 mg drug after 2 weeks of q.d. administration in study c208, the intended clinical dose.

The terminal-half life of M2 is reported to be 5.3 months.

Table 5. Pharmacokinetic Results of TMC207 after a Single-Dose Administration of 800 mg TMC207 (Day 1)

Pharmacokinetics of TMC207 (mean \pm SD, t_{\max} : median [range])	A single dose of 800mg TMC207 under fed conditions
n	44
C_{\max} , ng/mL	8,275 \pm 3,753
t_{\max} , h	5.12 (4.13-8.13)
AUC _{24h} , ng.h/mL	71,700 \pm 25,000

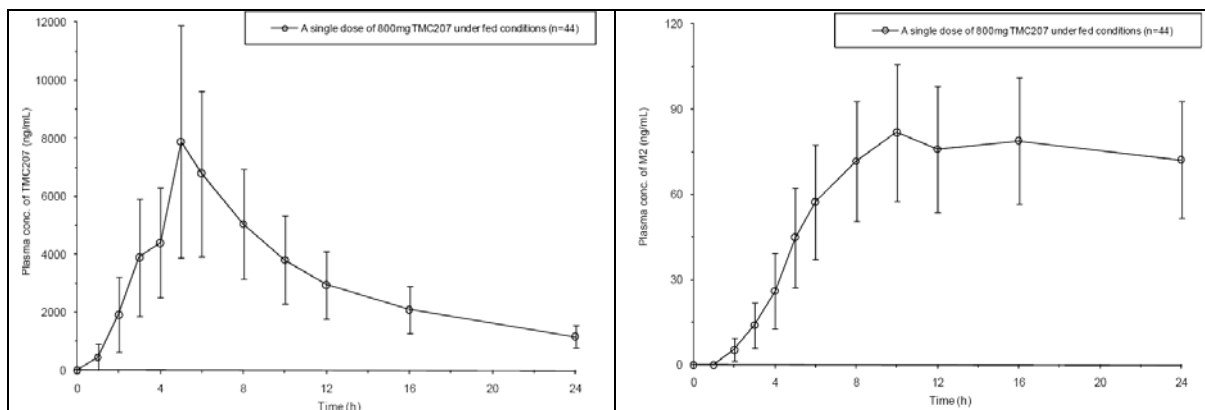
Source: Sponsor's Clinical Study Report, Table 11

Table 6. Pharmacokinetic Results of M2 after a Single-Dose Administration of 800 mg TMC207 (Day 1)

Pharmacokinetics of M2 (mean \pm SD, t_{\max} : median [range])	A single dose of 800mg TMC207 under fed conditions
n	44
C_{\max} , ng/mL	86.68 \pm 23.69
t_{\max} , h	12.12 (8.12-23.62)
AUC _{24h} , ng.h/mL	1,436 \pm 393.0

Source: Sponsor's Clinical Study Report, Table 12

Figure 2. Pharmacokinetic Time Course of TMC207 (left panel) and M2 (right panel) after a Single-Dose Administration of 800 mg TMC207 (Day 1)



Source: Sponsor's Clinical Study Report, Figure 8 and Figure 9

Table 7. Pharmacokinetic Results of TMC207 after Administration of TMC207 at 400 mg q.d. for 2 Weeks, Followed by Administration of TMC207 at 200 mg t.i.w. for 22 Weeks (week 24).

Pharmacokinetics of TMC207 mean \pm SD, t_{max} : median (range)	400 mg TMC207 q.d. (Week 2)	200 mg TMC207 t.i.w. (Week 24)
n	26 ^a	17 ^b
C _{0h} , ng/mL	792.0 \pm 263.9	453.5 \pm 295.2
C _{min} , ng/mL	727.9 \pm 256.6	355.2 \pm 169.5
C _{max} , ng/mL	2763 \pm 1185	1267 \pm 434.5
t _{max} , h	5.00 (2.33 - 6.17)	5.05 (3.07 - 6.77)
AUC _{τ} , ng.h/mL	32960 \pm 12720	28010 \pm 9408
C _{ss,av} , ng/mL	1371 \pm 528.8	584.1 \pm 196.5
FI, %	139.4 \pm 48.42	160.0 \pm 55.18
CL/F, L/h	14.68 \pm 8.521	8.058 \pm 3.510

τ = 24 h for Week 2 and 48 h for Week 24

^a n = 30 for C_{0h} and C_{min}, n = 29 for C_{max} and t_{max}

^b n = 18 for C_{0h} and C_{min}, n = 19 for C_{max} and t_{max}

Source: Sponsor's Clinical Study Report, Trial c208, Table 25

Table 8. Pharmacokinetic Results of M2 after Administration of TMC207 at 400 mg q.d. for 2 Weeks, Followed by Administration of TMC207 at 200 mg t.i.w. for 22 Weeks (Week 24).

Pharmacokinetics of M2 mean \pm SD, t_{max} : median (range)	400 mg TMC207 q.d. (Week 2)	200 mg TMC207 t.i.w. (Week 24)
n	26 ^a	17 ^b
C _{0h} , ng/mL	426.5 \pm 135.1	162.4 \pm 70.72
C _{min} , ng/mL	331.6 \pm 121.7	120.3 \pm 56.98
C _{max} , ng/mL	466.9 \pm 156.8	177.9 \pm 70.70
t _{max} , h	6.15 (1.10 - 24.17)	12.08 (5.00 - 48.08)
AUC _{τ} , ng.h/mL	9217 \pm 3151	7270 \pm 2532
C _{ss,av} , ng/mL	383.0 \pm 129.9	151.6 \pm 52.81
FI, %	40.63 \pm 17.96	42.18 \pm 18.21
Ratio AUC _{τ} M2/TMC207, %	31.08 \pm 14.30	26.14 \pm 4.494

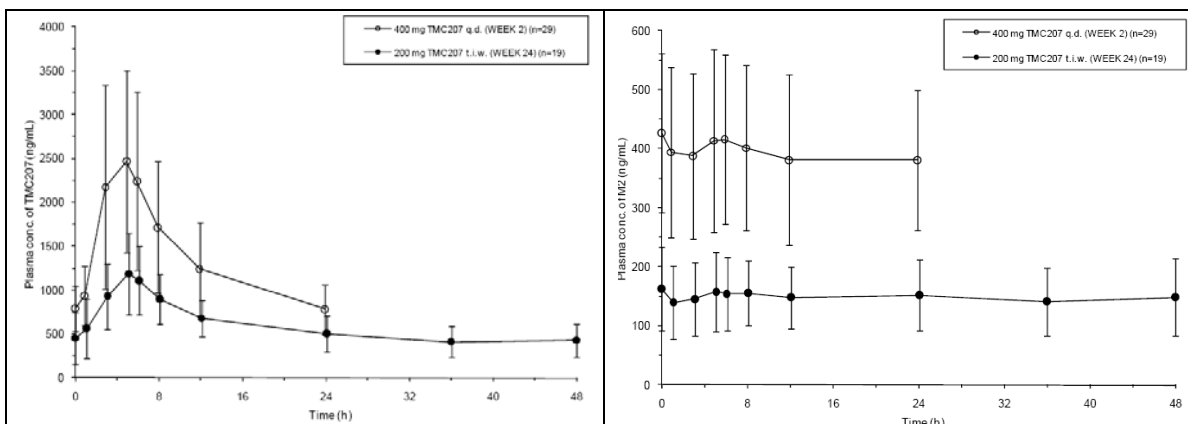
τ = 24 h for Week 2 and 48 h for Week 24

^a n = 30 for C_{0h} and C_{min}, n = 29 for C_{max} and t_{max}

^b n = 18 for C_{0h} and C_{min}, n = 19 for C_{max} and t_{max}

Source: Sponsor's Clinical Study Report, Trial c208, Table 26

Figure 3. Mean Plasma Concentration-Time Curve of TMC207 (left panel) and M2 (right panel) after Administration of TMC207 at 400 mg q.d. for 2 Weeks, Followed by Administration of TMC207 at 200 mg t.i.w. for 22 Weeks (Week 24).



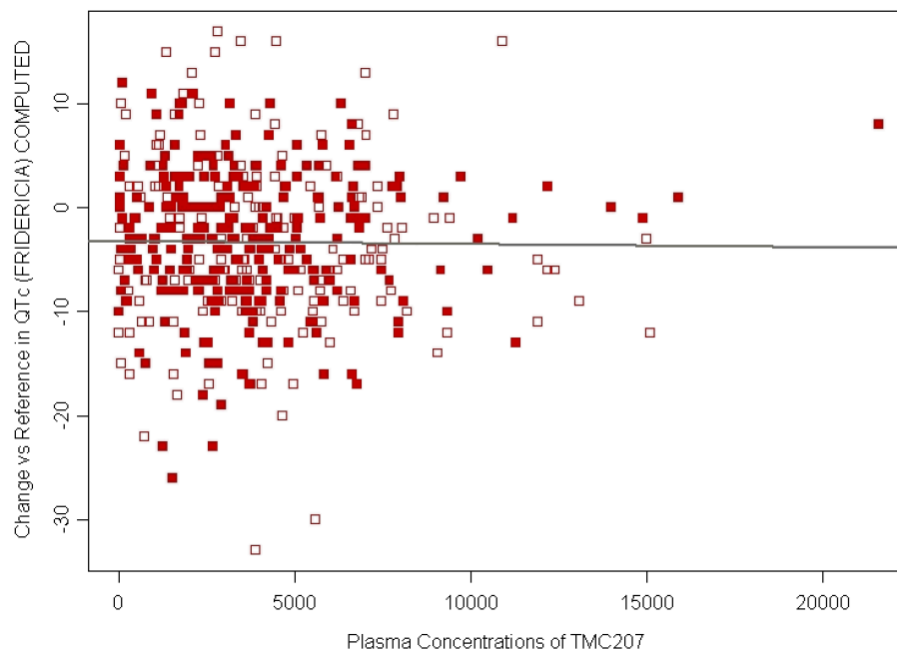
Source: Sponsor's Clinical Study Report, Trial c208, Figure 5 and Figure 6

4.2.8.4.2 Exposure-Response Analysis

Results from the dedicated thorough QT study:

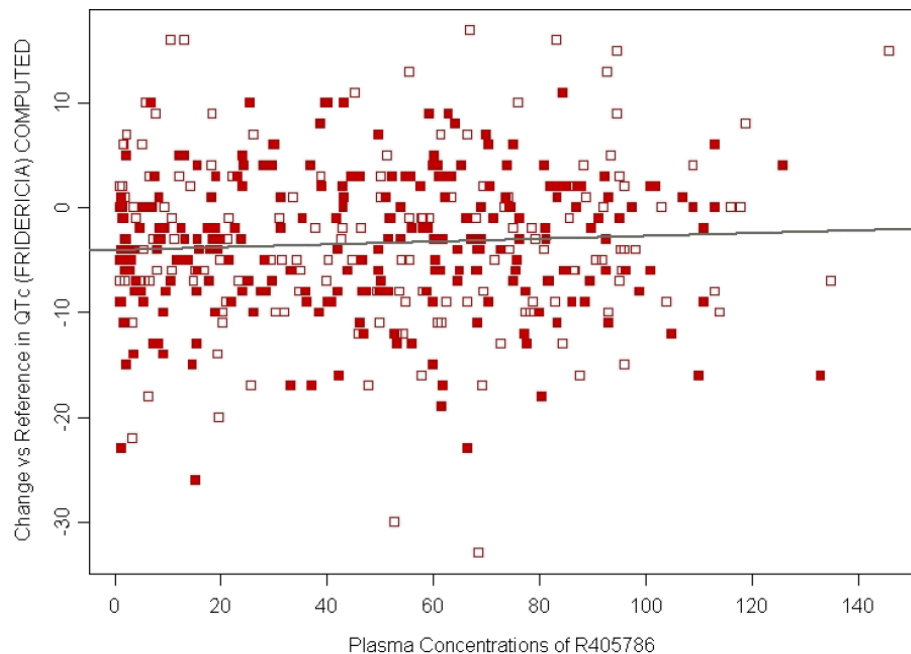
Based on data from study 1003 alone (dedicated QT study) the sponsor claimed, "No clear relationship was observed between the time-matched change from baseline in QTcF and the plasma concentration of TMC207 or M2." Their results are shown in Figure 4 and Figure 5.

Figure 4. Time-Matched Change from Baseline in QTcF versus TMC207 Plasma Concentrations after Single-Dose Administration in Healthy Subjects.



Source: Sponsor's Clinical Study Report, Figure 11

Figure 5. Time-Matched Change from Baseline in QTcF versus M2 Plasma Concentrations after Single-Dose Administration in Healthy Subjects.

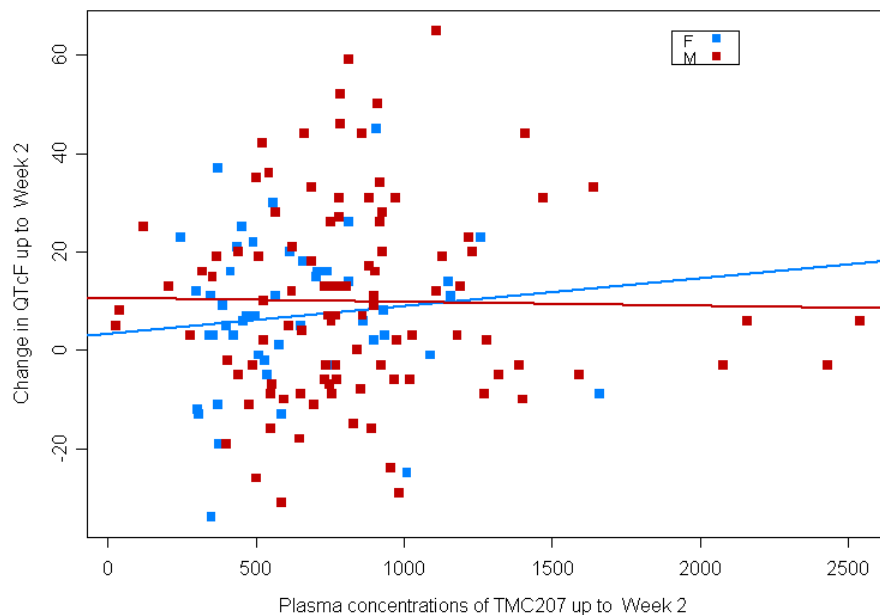


Source: Sponsor's Clinical Study Report, Figure 11

Results from study c208:

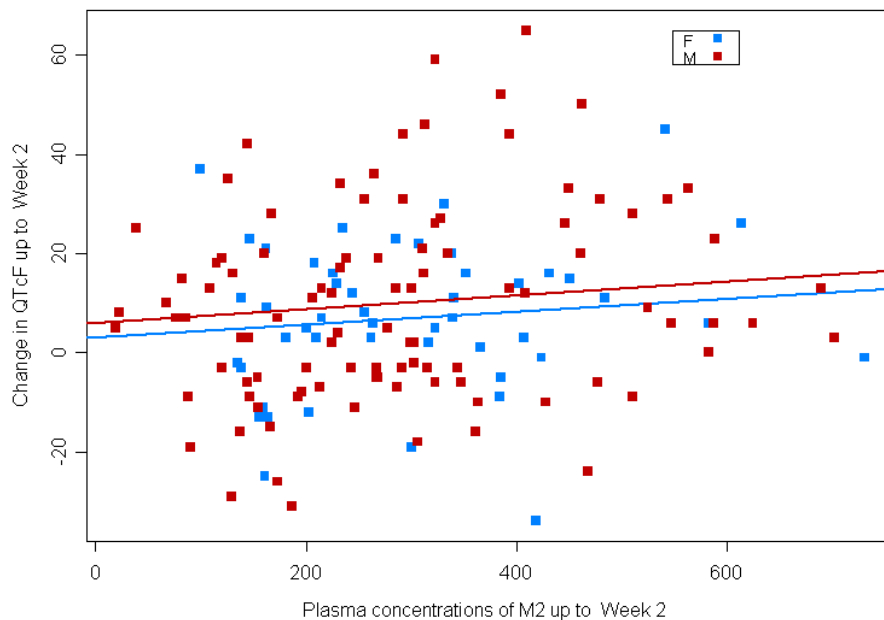
The sponsor also claimed for study c208 that there were no clear relationships between TMC207 or M2 and QTcF. Their results are shown in Figure 6 and Figure 7.

Figure 6. Scatterplot of TMC207 Plasma Concentration up to Week 2 vs. Change in QTcF up to Week 2 for Male and Female Subjects.



Source: Sponsor's Clinical Study Report, Trial c208, Figure 29

Figure 7. Scatterplot of M2 Plasma Concentration up to Week 2 vs. Change in QTcF up to Week 2 for Male and Female Subjects.



Source: Sponsor's Clinical Study Report, Trial c208, Figure 31

Reviewer's Comments:

- 1) The C_{max} and AUC of the Metabolite M2 were 5.4- and 6.4-fold higher in the phase 2 trial (c208) where QT-prolongation was evidenced as a concern. The reason for this is likely due to accumulation of the metabolite.
- 2) Half-life of the metabolite M2 is 5.3 months. The QT study was done as a single-dose administration which does not account for accumulation of the metabolite concentrations.
- 3) The sponsor's analysis considers only baseline corrected QTcF. The reviewer's analysis (Section 5.3) gives results for both baseline and placebo corrected QTcF data.
- 4) The sponsor's exposure-response analysis for metabolite in the dedicated QT study uses a limited range of exposures compared to the data available from the phase 2 trial (c208).
- 5) Despite claiming no relationship for TMC207 or M2 in either study, the sponsor's regression model produced a consistent relationship for both males and females for M2 in trial c208.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcB distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcB), and the interaction term of RR and correction type. The slopes of QTcF and QTcB versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 9, it appears that QTcF had smaller absolute slopes than QTcB. Therefore, QTcF is a better correction method for the study data.

Table 9: Comparison of QTcF and QTcB Using the Mixed Model

Treatment Groups	Slope of QTcB	Slope of QTcF	P-value
TMC207 800 mg	-0.0819	-0.0105	0.0000
Moxifloxacin 400 mg	-0.0650	0.0094	0.0000
Placebo (TMC)	-0.0785	-0.0085	0.0000
Placebo (moxifloxacin)	-0.0759	-0.0052	0.0000

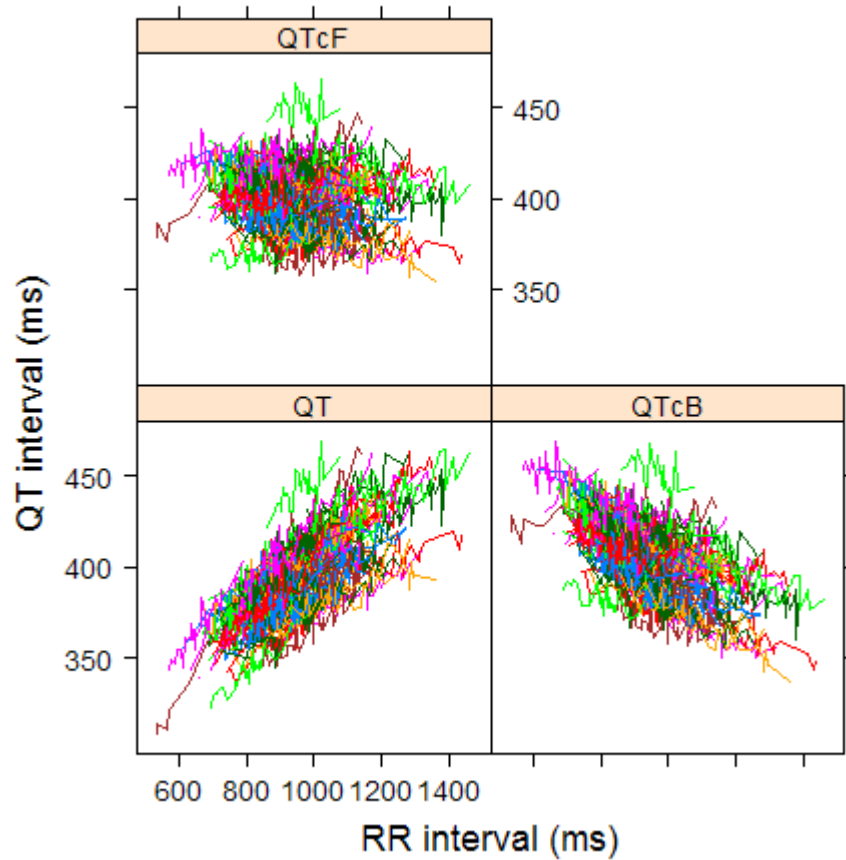
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 10, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 10: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcB		QTcF	
	N	MSSS	N	MSSS
TMC207 800 mg	44	0.0089	44	0.0016
Moxifloxacin 400 mg	44	0.0090	44	0.0073
Placebo (TMC)	44	0.0069	44	0.0012
Placebo (moxifloxacin)	44	0.0079	44	0.0012
All	88	0.0074	88	0.0012

The relationship between different correction methods and RR is presented in Figure 8.

Figure 8: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for TMC207

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment and sex as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in Table 11.

**Table 11: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Treatment Group A:
TMC207 800 mg x 1 day**

	Δ QTcF: TMC207 (ms)			Δ QTcF: Placebo (ms)			$\Delta\Delta$ QTcF (ms)		
Time (h)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
1	44	-3.2	1.0	44	-2.9	1.0	44	-0.3	(-2.6, 2.0)
2	44	-1.5	1.0	44	-2.1	1.0	44	0.6	(-1.6, 2.9)
3	44	-3.5	0.9	44	-2.4	0.9	44	-1.1	(-3.3, 1.1)
4	44	-5.1	1.0	44	-3.0	1.0	44	-2.0	(-4.4, 0.4)
5	44	-1.1	1.0	44	-1.2	1.0	44	0.0	(-2.3, 2.4)
6	44	-3.4	1.1	44	-0.3	1.1	44	-3.1	(-5.7, -0.5)
8	44	-5.6	1.0	44	-5.7	1.0	44	0.1	(-2.3, 2.5)
10	44	-5.6	1.0	43	-6.0	1.0	43	0.4	(-1.8, 2.7)
12	44	-2.0	1.0	44	-3.7	1.0	44	1.7	(-0.6, 4.1)
16	44	2.8	1.1	44	0.1	1.1	44	2.7	(0.2, 5.2)
24	44	0.3	0.7	44	-1.2	0.7	44	1.5	(-0.2, 3.2)

The largest upper bound of the 2-sided 90% CI for the mean difference between TMC207 800 mg and placebo was 5.2 ms.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model and included group as a fixed effect to analyze moxifloxacin and placebo data. The results are presented in Table 12. The largest unadjusted 90% lower confidence interval is 10.0 ms. When considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.3 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 12: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Moxifloxacin

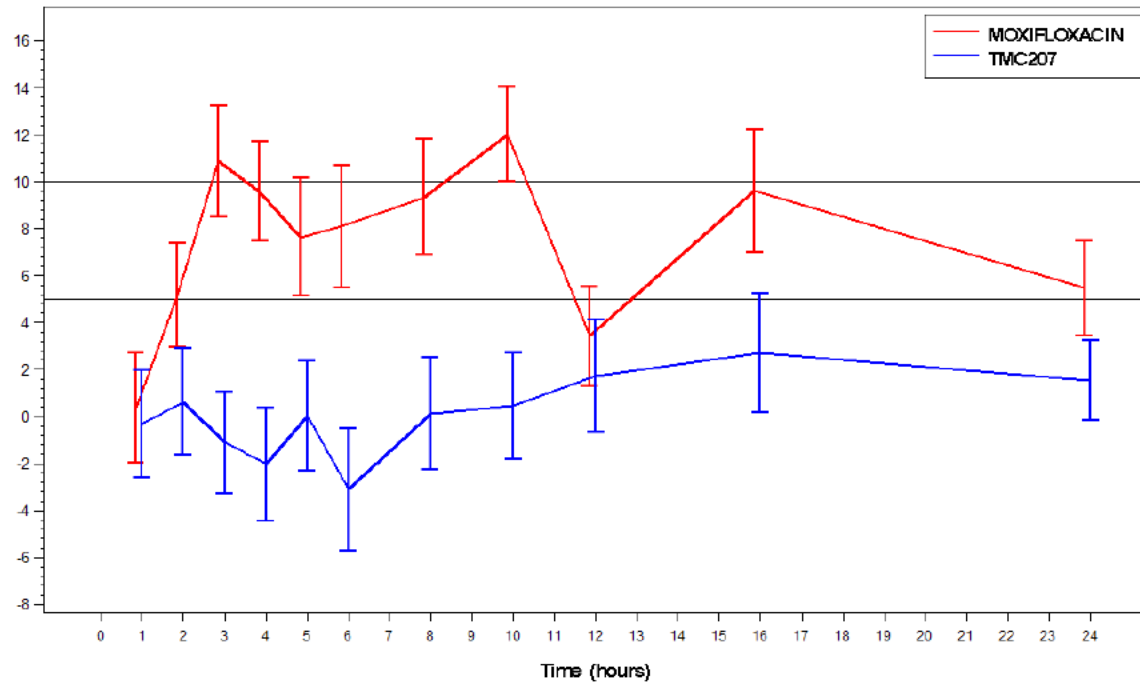
	Δ QTcF: moxifloxacin (ms)			Δ QTcF: placebo (ms)			$\Delta\Delta$ QTcF (ms)			
Time (h)	N	Mean	SD	N	Mean	SD	N	Mean	Unadjusted 90% CI	Adjusted* 90% CI
1	43	-2.6	1.0	44	-3.0	1.0	43	0.4	(-1.9, 2.7)	(-2.8, 3.6)
2	44	3.2	0.9	44	-1.9	0.9	44	5.2	(2.9, 7.4)	(2.1, 8.2)
3	44	9.2	1.0	44	-1.7	1.0	44	10.9	(8.5, 13.2)	(7.6, 14.1)
4	44	7.1	0.9	44	-2.5	0.9	44	9.6	(7.5, 11.7)	(6.7, 12.5)
5	43	7.2	1.1	43	-0.4	1.1	43	7.6	(5.1, 10.2)	(4.2, 11.1)
6	43	8.4	1.1	44	0.3	1.1	43	8.1	(5.5, 10.7)	(4.5, 11.7)
8	43	4.3	1.1	44	-5.1	1.0	43	9.3	(6.9, 11.8)	(6.0, 12.7)
10	42	6.3	0.9	44	-5.7	0.9	42	12.0	(10.0, 14.0)	(9.3, 14.8)
12	43	0.7	0.9	44	-2.8	0.9	43	3.4	(1.3, 5.5)	(0.5, 6.3)
16	44	10.1	1.1	44	0.5	1.1	44	9.6	(7.0, 12.2)	(6.0, 13.2)
24	44	4.5	0.9	44	-0.9	0.9	44	5.5	(3.4, 7.5)	(2.7, 8.2)

* Bonferroni correction was applied for multiple endpoint adjustment for 4 time points.

5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 9: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse



All CIs are unadjusted, including moxifloxacin.

5.2.1.4 Categorical Analysis

Table 13 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 13: Categorical Analysis for QTcF

Treatment Group	N	Value \leq 450 ms	450 ms < Value \leq 480 ms
TMC207 800 mg	44	43 (97.7%)	1 (2.3%)
Moxifloxacin 400 mg	44	44 (100%)	0 (0.0%)
Placebo (TMC)	44	44 (100%)	0 (0.0%)
Placebo (moxifloxacin)	44	43 (97.7%)	1 (2.3%)

Table 14 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 14: Categorical Analysis of $\Delta QTcF$

Treatment Group	N	Value ≤ 30 ms	30 ms < Value ≤ 60 ms
TMC207 800 mg	44	44 (100%)	0 (0.0%)
Moxifloxacin 400 mg	44	43 (97.7%)	1 (2.3%)
Placebo (TMC)	44	44 (100%)	0 (0.0%)
Placebo (moxifloxacin)	44	44 (100%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 15. The largest upper limit of 90% CI for the HR mean differences between TMC207 800 mg and placebo is 5.5 bmp.

Table 15: Analysis Results of ΔHR and $\Delta\Delta HR$ for Treatment Group A: TMC207 800 mg x 1 day

Time (h)	ΔHR : TMC207 (bpm)			ΔHR : Placebo (bpm)			$\Delta\Delta HR$ (bpm)		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
1	44	1.4	0.7	44	2.0	0.7	44	-0.6	(-2.3, 1.1)
2	44	2.0	0.6	44	2.1	0.6	44	-0.0	(-1.4, 1.4)
3	44	3.4	0.7	44	2.5	0.7	44	0.9	(-0.7, 2.6)
4	44	2.0	0.6	44	1.7	0.6	44	0.2	(-1.3, 1.7)
5	44	4.5	0.8	44	1.4	0.8	44	3.1	(1.1, 5.0)
6	44	4.5	0.8	44	4.1	0.8	44	0.4	(-1.5, 2.2)
8	44	4.0	1.0	44	2.1	1.1	44	1.9	(-0.5, 4.4)
10	44	3.0	0.9	44	0.6	0.9	44	2.4	(0.4, 4.5)
12	44	1.5	0.8	44	2.1	0.9	44	-0.6	(-2.5, 1.4)
16	44	3.9	1.0	44	0.8	1.0	44	3.1	(0.7, 5.5)
24	44	1.1	0.8	44	1.0	0.8	44	0.1	(-1.7, 1.8)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the PR mean differences between TMC207 800 mg and placebo is 5.6 ms.

The outlier analysis results for PR are presented in Table 17.

Table 16: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group B: TMC207 800 mg X 1 day

	Δ PR: TMC207 800 mg (ms)			Δ PR: Placebo (ms)			$\Delta\Delta$ PR (ms)		
Time (h)	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
1	44	-2.2	1.1	44	-2.7	1.1	44	0.5	(-2.1, 3.1)
2	44	-0.5	1.2	44	-0.8	1.2	44	0.4	(-2.5, 3.2)
3	44	2.2	0.9	44	-1.2	0.9	44	3.4	(1.2, 5.5)
4	44	1.6	0.9	44	-0.2	0.9	44	1.8	(-0.5, 4.0)
5	44	2.6	1.2	44	-0.2	1.2	44	2.8	(0.1, 5.6)
6	44	1.7	1.3	44	0.3	1.3	44	1.4	(-1.7, 4.4)
8	44	2.5	1.6	44	2.3	1.6	44	0.2	(-3.6, 3.9)
10	44	0.7	1.7	43	3.0	1.8	43	-2.3	(-6.4, 1.7)
12	44	0.3	1.6	44	3.9	1.6	44	-3.6	(-7.4, 0.2)
16	44	0.8	1.7	44	4.6	1.7	44	-3.8	(-7.8, 0.1)
24	44	-0.2	1.2	44	1.1	1.2	44	-1.3	(-4.1, 1.4)

Table 17: Categorical Analysis for PR

Treatment Group	N	PR < 200 ms	PR \geq 200 ms
TMC207	44	43 (97.7%)	1 (2.3%)
Placebo (TMC)	44	39 (88.6%)	5 (11.4%)
Placebo (moxifloxacin)	44	43 (97.7%)	1 (2.3%)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 18. The largest upper limits of 90% CI for the QRS mean differences between TMC207 800 mg and placebo is 1.9 ms.

There are no subjects who experienced QRS interval greater than 110 ms in the TMC207 800 mg group.

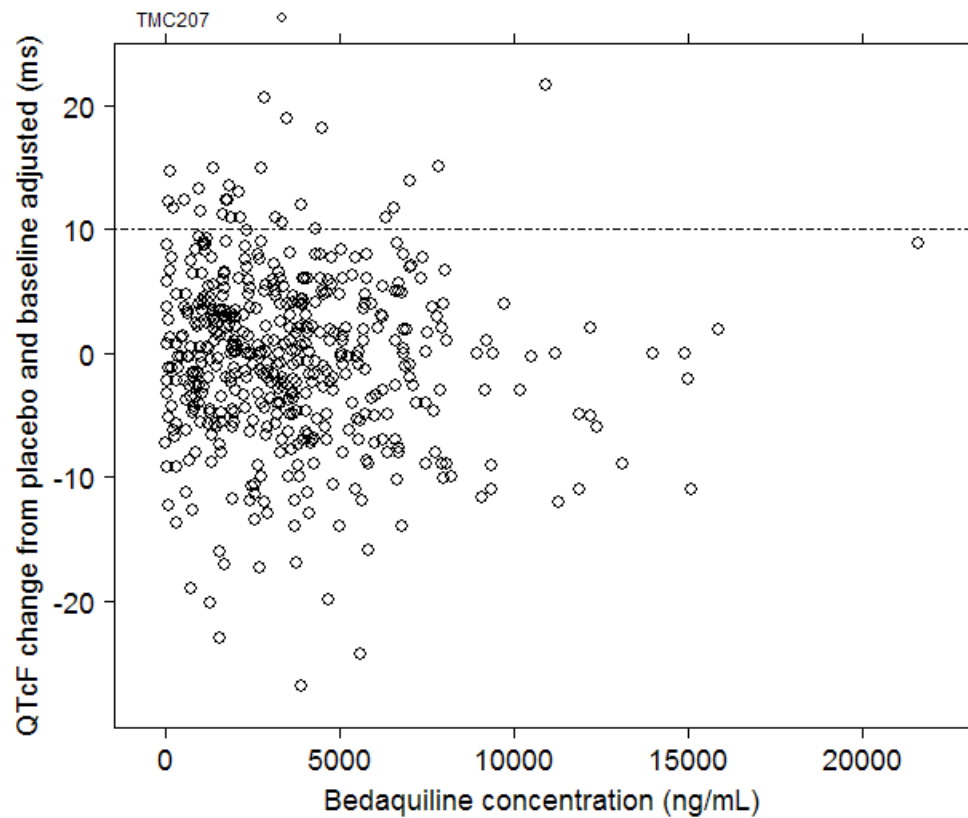
Table 18: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group A: TMC207 800 mg X 1 day

Time	Δ QRS: TMC207 (ms)			Δ QRS: Placebo (ms)			$\Delta\Delta$ QRS (ms)		
	N	Mean	SD	N	Mean	SD	N	Mean	90% CI
1	44	-0.0	0.5	44	-0.1	0.5	44	0.1	(-1.0, 1.2)
2	44	-0.2	0.4	44	-0.5	0.4	44	0.3	(-0.6, 1.3)
3	44	0.2	0.4	44	-0.1	0.4	44	0.3	(-0.6, 1.2)
4	44	0.1	0.3	44	0.1	0.3	44	0.0	(-0.7, 0.7)
5	44	0.5	0.4	44	-0.3	0.4	44	0.8	(-0.1, 1.7)
6	44	0.1	0.4	44	-0.7	0.4	44	0.8	(-0.2, 1.9)
8	44	0.2	0.4	44	0.1	0.4	44	0.1	(-0.9, 1.1)
10	44	-0.1	0.3	43	-0.4	0.3	43	0.3	(-0.4, 1.1)
12	44	0.1	0.4	44	-0.7	0.4	44	0.8	(-0.1, 1.8)
16	44	0.7	0.5	44	0.1	0.5	44	0.6	(-0.6, 1.8)
24	44	-0.5	0.3	44	-0.6	0.3	44	0.1	(-0.7, 0.8)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

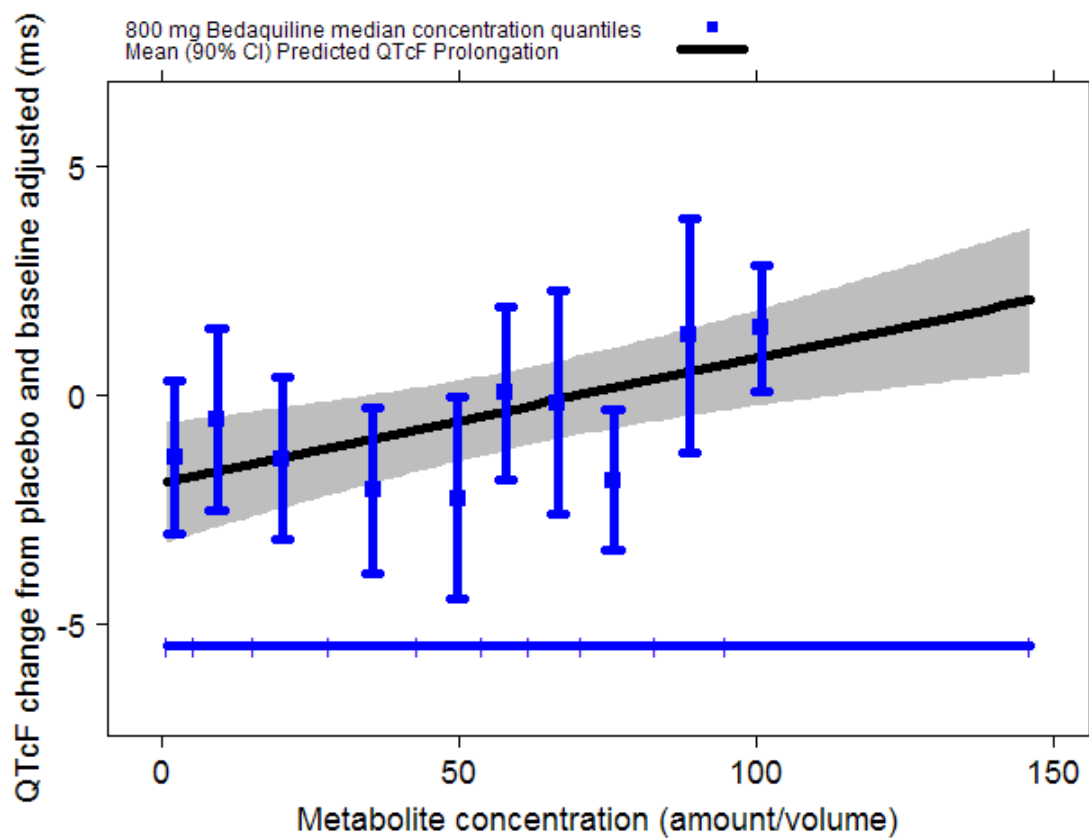
The relationship between $\Delta\Delta$ QTcF and bedaquiline concentrations is visualized in Figure 10 with no evident exposure-response relationship.

Figure 10: $\Delta\Delta$ QTcF vs. bedaquiline concentration



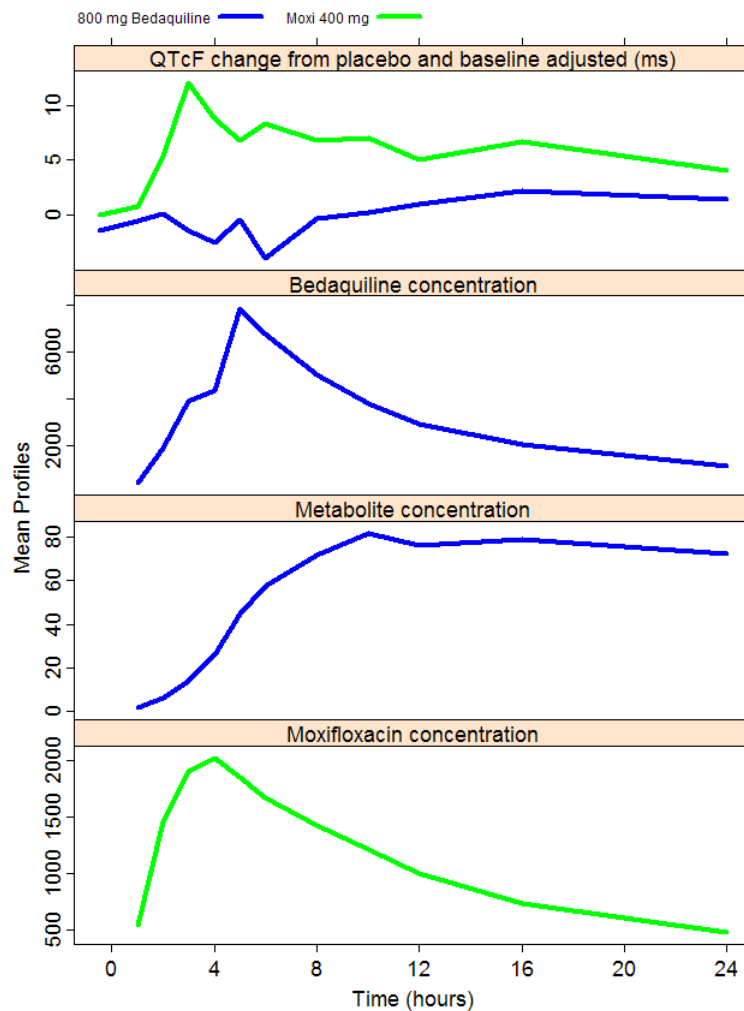
Whereas, evidence of an exposure-response relationship was determined for M2. The relationship between $\Delta\Delta$ QTcF and M2 concentrations is visualized in Figure 11.

Figure 11: $\Delta\Delta$ QTcF vs. M2 concentration.



Further, the time course of the QTcF appears to more closely follow the time course of metabolite M2 exposure when compared to the time course of TMC207 exposure (Figure 12).

Figure 12. Time Course of $\Delta\Delta$ QTcF, Bedaquiline Concentration (TMC207), Metabolite Concentration (M2), and Moxifloxacin.



Data from the thorough QT study alone cannot inform of the QTcF prolongation at the clinically relevant concentrations of M2. Since this was single dose study, M2 exposures never achieved clinically relevant concentrations for the high-exposure scenario. Based on the sponsor's analysis after multiple dosing of 400 mg TMC207 q.d. for two weeks, a prolongation of ~10 ms may be expected for the mean C_{\max} of 467 ng/mL for patients with tuberculosis.

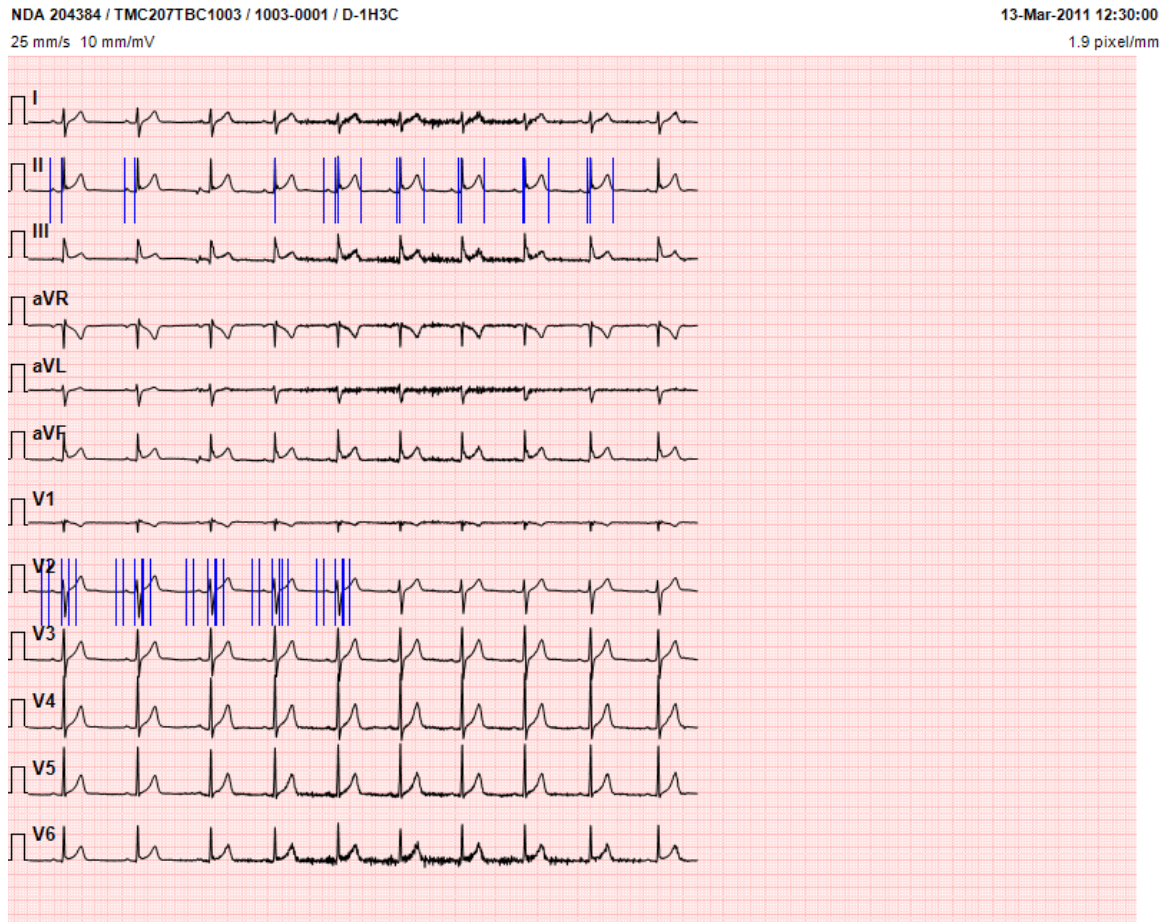
5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 99% of the ECGs were annotated in multiple leads (mainly PR and QT annotated in lead II and QRS in V2, see below), with less than 0.07 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.



5.4.3 PR and QRS Interval

Five subjects had postbaseline PR > 200 ms that were not clinically relevant (between 203 to 215 ms). No subject had a QRS > 110 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	<p>Include maximum proposed clinical dosing regimen.</p> <p>The selected therapeutic dose for TMC207 is 400 mg p.o. q.d. for 2 weeks followed by 200 mg p.o. t.i.w for 22 weeks (total treatment duration of 24 weeks).</p>	
Maximum tolerated dose	<p>Include if studied or NOAEL dose</p> <p>The maximum tolerated dose in humans has not been established. A maximum dose of 700 mg has been studied after single-dose administration in healthy subjects. In studies of repeated administration of TMC207 a maximum dose of 400 mg q.d. has been evaluated over a 15-day treatment period in healthy subjects. TMC207 was generally well tolerated in these studies.</p>	
Principal adverse events	<p>Include most common adverse events; dose limiting adverse events</p> <p>The most common adverse events have been nausea, diarrhea, headache, postural dizziness, hyperuricemia, arthralgia, hemoptysis, deafness. Many of these side effects are associated with drugs administered together with TCM207. The only AE associated with TMC207 that might be dose-limiting is nausea.</p>	
Maximum dose tested	Single Dose	<p>Specify dose:</p> <p>700 mg (R207910-CDE-101, Part 1)</p>
	Multiple Dose	<p>Specify dosing interval and duration:</p> <p>400 mg q.d. for 15 days in healthy subjects (TMC207-C104)</p> <p>400 mg q.d. for 14 days followed by 200 mg t.i.w for 6 weeks in patients with MDR-TB (TMC207-C208, Stage 1)</p>
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Mean (%CV) C_{max} and AUC:</p> <p>Data from trial R207910-CDE-101, 700 mg dose:</p> <p>Mean C_{max} ± SD: 6747 ± 2210 ng/mL (%CV 32.8)</p> <p>Mean AUC_{144h} ± SD: 97816 ± 38074 ng.h/mL (%CV 38.9)</p> <p>Mean AUC_∞ ± SD: 133125 ± 44913 ng.h/mL (%CV 33.7)</p>
	Multiple Dose	<p>Mean (%CV) C_{max} and AUC:</p> <p>Data from trial TMC207-C104 (PK after 10 days of TMC207 400 mg q.d. in healthy subjects, n=22):</p> <p>Mean C_{max} ± SD: 4408 ± 1532 ng/mL (%CV 34.8)</p> <p>Mean AUC_{24h} ± SD: 51360 ± 15750 ng.h/mL (%CV 30.7)</p> <p>Data from trial TMC207-C109 (PK after 11 days of TMC207 400 mg q.d. in healthy subjects, n=15):</p> <p>Mean C_{max} ± SD: 6400 ± 2096 ng/mL (%CV 32.8)</p> <p>Mean AUC_{24h} ± SD: 77740 ± 26770 ng.h/mL (%CV 34.4)</p> <p>Data from trial TMC207-C208 (PK after 14 days of TMC207 400 mg q.d. in patients with MDR-TB, n=21)</p> <p>Mean C_{max} ± SD: 3270 ± 1144 ng/mL (%CV 35.0)</p> <p>Mean AUC_{24h} ± SD: 42500 ± 16810 ng.h/mL (%CV 39.6)</p>
Range of linear PK	<p>Specify dosing regimen:</p> <p>10-700 mg after single-dose administration in healthy subjects</p> <p>50-400 mg q.d. after repeated administration in healthy subjects</p>	
Accumulation at steady state	<p>Mean (%CV); specify dosing regimen</p> <p>Data from trial R207910-CDE-101, Part 2</p> <p>After 14 days of dosing TMC207 at a dose of 400 mg q.d., the mean AUC_{24h} increased 1.9 to 2.4-fold compared to Day 1.</p> <p>Due to the long terminal half-life, however, steady-state was not achieved after 14 days of once-daily dosing. In the ongoing Phase II trial, TMC207 is administered as 400 mg q.d. during the first 14 days followed by a reduced dose of 200 mg t.i.w. afterwards.</p>	
Metabolites	<p>Include listing of all metabolites and activity</p> <p>The metabolism of TMC207 was investigated in liver subcellular fractions and hepatocytes of different species, including humans and in vivo in mice, rats and dogs. From these data it was clear that oxidative phase I metabolism was of primary importance in the elimination of TMC207.</p>	

	<p>The mono-<i>N</i>-demethylation of TMC207, leading to the formation of the metabolite M2, was the major metabolic pathway in all species in vitro. In patients with MDR-TB, the ratio of the AUC_{24h} of M2 over TMC207 was 22.9 ± 6.2% after 14 days of TMC207 400 mg q.d. and 31.2 ± 12.7% after another 6 weeks of TMC207 200 mg t.i.w. The activity of metabolite M2 against <i>M. tuberculosis</i> is 3-6 times less than the parent compound TMC207.</p> <p>In the liver subcellular fractions and/or hepatocytes of most species, M2 was further <i>N</i>-demethylated to form the <i>N</i>-didesmethyl metabolite M3. Additionally M2 could also be further oxidized leading to the formation of metabolite M4. A minor metabolic pathway was the oxidation of TMC207 to form metabolite M1. The glucuronidation of TMC207 to form metabolite M5 was observed in rabbit hepatocytes only.</p>	
Absorption	Absolute/Relative Bioavailability	<p>Mean (%CV)</p> <p>The absolute bioavailability of TMC207 in humans has not been established.</p>
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent <p>Median T_{max} of TMC207 is 5.0h (range 2.0-8.0h).</p> <ul style="list-style-type: none"> • Median (range) for metabolites <p>Median T_{max} of the M2 metabolite 6-8h (range 0-24 h).</p>
Distribution	Vd/F or Vd	<p>Mean (%CV)</p> <p>The mean Vd/F was 1315 L after single-dose administration of 700 mg (based on R207910-CDE-101).</p>
	% bound	<p>Mean (%CV)</p> <p>TMC207 was extensively bound to plasma proteins in mice, rats, dogs, monkeys, rabbits, and humans. At a concentration of 5.00 µg/mL, plasma protein binding appeared to be >99.9% in all animal species and man.</p>

Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated <p>Metabolism and excretion studies were performed in rats, dogs and monkeys upon single oral administration of 14C-labeled TMC207 (10 mg/kg in dogs and monkeys and 6 mg/kg in rats). In all species a small percentage of the radioactivity (1.35% in dogs, 2% to 4% in rats and 2.5% in monkeys) was recovered in urine. The radioactivity was excreted very slowly and predominantly in the feces. The overall recovery of radioactivity was 56% in dogs and 71% in monkeys at 2 weeks after dosing, and 90% in male rats and 72% in female rats at 216 hours. The dose not yet excreted at 216 hours in rats was recovered in the carcass. In rats, 5% to 7% of the dose was recovered in the bile over 24 hours after single oral administration of 14C-labeled TMC207 (6 mg/kg). The amount of unchanged TMC207 recovered was negligible (about 0.1%).</p> <ul style="list-style-type: none"> • Other routes <p>The urinary excretion of unchanged TMC207 was 0.01% of the dose administered, indicating that renal clearance of unchanged TMC207 was insignificant in humans (R207910-CDE-101, Part 2).</p>
	Terminal t½	<ul style="list-style-type: none"> • Mean (%CV) for parent <p>After single-dose administration, TMC207 concentrations declined tri-exponentially with time. The mean half-life of the 3rd (terminal) phase, ranged from 117 to 172 hours (%CV ≈20) across the dose range of 10-700 mg (R207910-CDE-101).</p> <p>In healthy subjects who received TMC207 400 mg q.d. for 15 days (last 5 days in combination with isoniazid and pyrazinamid) the mean terminal half-life of TMC207 was 132 days (%CV 43) (TMC207-C104).</p> <ul style="list-style-type: none"> • Mean (%CV) for metabolites <p>In healthy subjects who received TMC207 400 mg q.d. for 15 days (last 5 days in combination with isoniazid and pyrazinamid) the mean terminal half-life of M2 was 112 days (%CV 99) (TMC207-C104).</p>
	CL/F or CL	<p>Mean (%CV)</p> <p>The mean Cl/F was 5.26 L/h after single-dose administration of 700 mg (based on R207910-CDE-101).</p>

Intrinsic Factors	Age	Specify mean changes in Cmax and AUC The effect of age on the pharmacokinetics of TMC207 has not yet been evaluated.																											
	Sex	Specify mean changes in Cmax and AUC The effect of sex on the pharmacokinetics of TMC207 has not yet been evaluated.																											
	Race	Specify mean changes in Cmax and AUC The effect of race on the pharmacokinetics of TMC207 has not yet been evaluated.																											
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC A study to evaluate the pharmacokinetics of TMC207 and M2 in patients with hepatic impairment is planned.																											
Extrinsic Factors	Drug interactions	<div>Include listing of studied DDI studies with mean changes in Cmax and AUC</div> <div>Summary of Drug-Drug Interactions: the Effect of Coadministered Drugs on the Pharmacokinetics of TMC207.</div> <table><tr><th rowspan="2">Coadministered drug</th><th rowspan="2">Dosage</th><th rowspan="2">n</th><th colspan="3">Ratio^a (90% confidence interval) of the pharmacokinetic parameters of TMC207 with/without coadministered drug</th></tr><tr><th>C_{max}</th><th>AUC_{24h}</th><th>C_{min}</th></tr><tr><td>Rifampin^b</td><td>600 mg q.d.</td><td>16</td><td>0.57 (0.48-0.67)</td><td>0.48 (0.43-0.54)^c</td><td>NA</td></tr><tr><td>Ketoconazole</td><td>400 mg q.d.</td><td>15</td><td>1.09 (0.98-1.21)</td><td>1.22 (1.12-1.32)</td><td>1.33 (1.24-1.43)</td></tr><tr><td>Isoniazid/Pyrazinamide</td><td>0.3/2 g q.d.</td><td>22</td><td>0.94 (0.89-1.00)</td><td>0.87 (0.84-0.91)</td><td>0.92 (0.88-0.96)</td></tr></table> <div>n = number of volunteers; AUC_{24h} = AUC over the dosing interval; NA = not applicable.</div> <div>^aRatio of the least square means (a ratio of 1.00 indicates absence of an interaction)</div> <div>^bsingle-dose administration of TMC207</div> <div>^cAUC_{0-336h}</div>	Coadministered drug	Dosage	n	Ratio ^a (90% confidence interval) of the pharmacokinetic parameters of TMC207 with/without coadministered drug			C _{max}	AUC _{24h}	C _{min}	Rifampin ^b	600 mg q.d.	16	0.57 (0.48-0.67)	0.48 (0.43-0.54) ^c	NA	Ketoconazole	400 mg q.d.	15	1.09 (0.98-1.21)	1.22 (1.12-1.32)	1.33 (1.24-1.43)	Isoniazid/Pyrazinamide	0.3/2 g q.d.	22	0.94 (0.89-1.00)	0.87 (0.84-0.91)	0.92 (0.88-0.96)
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	Food Effects	<div>Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)</div> <div>Data from trial TMC207-C108:</div> <div>TMC207 Pharmacokinetic Parameters Following a Single Oral Dose of 100 mg TMC207 as Tablet With and Without Food (standard breakfast) in Healthy Subjects</div> <table><tr><th>(N=12)</th><th>Fasted</th><th>With Food^b</th><th>Ratio (90% CI)^a</th></tr><tr><td>C_{max} (ng/mL)</td><td>282.5 ± 90.2</td><td>732.8 ± 108.7</td><td>2.63 (2.23-3.09)</td></tr><tr><td>AUC_{240h} (ng.h/mL)</td><td>9361 ± 3604</td><td>17580 ± 4944</td><td>1.95 (1.67-2.26)</td></tr></table> <div>mean ± SD, for t_{max}; median (range); N = number of subjects; NA = not applicable</div> <div>^aRatio of least square means after intake with food to intake without food (ratio of 1 indicates absence of food effect) + 90% confidence interval (CI)</div> <div>^bThe standardized breakfast consisted of 4 slices of bread, 2 slices of ham or cheese, butter, jam, and two cups of decaffeinated coffee or tea with milk and/or sugar.</div>	(N=12)	Fasted	With Food ^b	Ratio (90% CI) ^a	C _{max} (ng/mL)	282.5 ± 90.2	732.8 ± 108.7	2.63 (2.23-3.09)	AUC _{240h} (ng.h/mL)	9361 ± 3604	17580 ± 4944	1.95 (1.67-2.26)															
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Expected High Clinical Exposure Scenario	<div>Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</div> <div>TMC207 is primarily metabolized by CYP3A4. It is, therefore, anticipated that exposure to TMC207 may be increased during co-administration of potent inhibitors of this metabolic enzyme. In a drug-drug interaction study with the established CYP3A4 inhibitor ketoconazole at a dose of 400 mg q.d. for 3 days, the TMC207 AUC_{24h} increased by a modest 22% (90% CI 1.12-1.32).</div> <div>With the selected dosing regimen of TMC207, i.e. 400 mg q.d. for 2 weeks followed by 200 mg t.i.w. for another 22 weeks, the highest exposure will be achieved after 14 days. After switching the dose to 200 mg t.i.w. the average exposure to TMC207 will be about 50% lower compared to Day 14, based on Stage 1 results of TMC207-C208. Given the modest effect of ketoconazole on the pharmacokinetics of TMC207, the exposure on Day 14 can thus be considered supra-therapeutic for the remainder of the TMC207 treatment period.</div> <div>The intensive ECG monitoring in Stage 2 of the C208 trial together with the PK sampling is therefore expected to allow a detailed analysis of the effect of TMC207 on the QTcF interval across a wide range of exposures.</div>																												

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