

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204384Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 204384

SUPPL # n/a

Division: DAIP

Trade Name Sirturo

Generic Name Bedaquiline Tablets

Applicant Name Janssen Therapeutics, a Division of Janssen Products, LP

Approval Date, If Known 12-28-2012

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

#### 505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

**5 years (NME)**

**7 years (granted orphan status for the indication: pulmonary multi-drug resistant tuberculosis)**

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA

#(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical

investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO



Investigation #1  
!  
! YES  NO   
! Explain: ! Explain:

Investigation #2  
!  
! YES  NO   
! Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

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Name of person completing form: Fariba Izadi, Pharm.D.  
Title: Senior Regulatory Project Manager  
Date: 12-27-2012

Name of Office/Division Director signing form:  
Title:

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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FARIBA IZADI  
01/03/2013

KATHERINE A LAESSIG  
01/03/2013

# ACTION PACKAGE CHECKLIST

| <b>APPLICATION INFORMATION<sup>1</sup></b>  |                                      |  |
|---|--------------------------------------|--|
| NDA # 204384<br>BLA #   | NDA Supplement #<br>BLA Supplement # | If NDA, Efficacy Supplement Type:  |
| Proprietary Name: bedaquiline<br>Established/Proper Name: Sirturo<br>Dosage Form: 100 mg Tablets  |                                      | Applicant: Janssen Therapeutics<br>Agent for Applicant (if applicable): Janssen Research & Development, LLC  |
| RPM: Fariba Izadi, Pharm.D.   |                                      | Division: Anti-Infective Products  |
| <p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)<br/>           Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p> |                                      | <p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.<br/> <input type="checkbox"/> This application relies on literature.<br/> <input type="checkbox"/> This application relies on a final OTC monograph.<br/> <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> |
| <p>❖ <b>Actions</b></p> <ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>December 29, 2012</u></li> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>  |                                      | <p><input checked="" type="checkbox"/> AP   <input type="checkbox"/> TA   <input type="checkbox"/> CR</p> <hr/> <p><input checked="" type="checkbox"/> None</p>  |

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

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|---|--|
| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br/>                 Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>  | <p><input checked="" type="checkbox"/> Received</p>  |
| <p>❖ Application Characteristics <sup>3</sup></p> <p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority<br/>                 Chemical classification (new NDAs only): 1</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch<br/> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch<br/> <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span><br/> <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span><br/> <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span><br/> <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input type="checkbox"/> MedGuide</span><br/> <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 200px;"><input type="checkbox"/> Communication Plan</span><br/> <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 200px;"><input type="checkbox"/> ETASU</span><br/> <span style="margin-left: 200px;"><input type="checkbox"/> MedGuide w/o REMS</span><br/> <span style="margin-left: 200px;"><input type="checkbox"/> REMS not required</span></p> <p>Comments:</p> |  |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>   | <p><input type="checkbox"/> Yes, dates <input checked="" type="checkbox"/> N/A</p>   |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>   | <p><input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A</p>  |
| <p>❖ Public communications (<i>approvals only</i>)</p>  |  |
| <p>• Office of Executive Programs (OEP) liaison has been notified of action</p>   | <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>   |
| <p>• Press Office notified of action (by OEP)</p>   | <p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>   |
| <p>• Indicate what types (if any) of information dissemination are anticipated</p>  | <p><input type="checkbox"/> None<br/> <input checked="" type="checkbox"/> HHS Press Release<br/> <input type="checkbox"/> FDA Talk Paper<br/> <input type="checkbox"/> CDER Q&amp;As<br/> <input type="checkbox"/> Other</p> |

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

|  |  |
|--|--|
| ❖ Exclusivity  |  |
| <ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes  |
| <ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>   | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If, yes, NDA/BLA #          and date exclusivity expires:   |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #          and date exclusivity expires:<br><input checked="" type="checkbox"/> N/A  |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #          and date exclusivity expires:<br><input checked="" type="checkbox"/> N/A  |
| <ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>   | <input type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #          and date exclusivity expires:<br><input checked="" type="checkbox"/> N/A  |
| <ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>  | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes<br>If yes, NDA #          and date 10-year limitation expires:   |
| ❖ Patent Information (NDAs only)   |  |
| <ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>  | <input checked="" type="checkbox"/> Verified<br><input type="checkbox"/> Not applicable because drug is an old antibiotic.   |
| <ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>   | 21 CFR 314.50(i)(1)(i)(A)<br><input type="checkbox"/> Verified<br><br>21 CFR 314.50(i)(1)<br><input type="checkbox"/> (ii) <input type="checkbox"/> (iii)<br><br><input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>   | <input type="checkbox"/> No paragraph III certification<br>Date patent will expire<br><input checked="" type="checkbox"/> N/A  |
| <ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul> | <input checked="" type="checkbox"/> N/A (no paragraph IV certification)<br><input type="checkbox"/> Verified   |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

Yes     No     N/A

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No     N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

Yes     No     N/A

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No     N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

|   |   |
|---|---|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes    <input type="checkbox"/> No    <input checked="" type="checkbox"/> N/A</p> |
|---|---|

**CONTENTS OF ACTION PACKAGE**

|   |  |
|---|--|
| ❖ Copy of this Action Package Checklist <sup>4</sup>  | Included                                     |
| <b>Officer/Employee List</b>  |  |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> ) | <input checked="" type="checkbox"/> Included |
| Documentation of consent/non-consent by officers/employees  | <input checked="" type="checkbox"/> Included |
| <b>Action Letters</b>   |  |
| ❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )   | Action(s) and date(s) Approval<br>12-28-2012 |
| <b>Labeling</b>   |  |
| ❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )  |  |
| <ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>      | June 28, 2012                                |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>  | June 29, 2012                                |
| <ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>  |  |

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

|   |  |
|---|--|
| <p>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</p>   | <p><input checked="" type="checkbox"/> Medication Guide<br/> <input type="checkbox"/> Patient Package Insert<br/> <input type="checkbox"/> Instructions for Use<br/> <input type="checkbox"/> Device Labeling<br/> <input type="checkbox"/> None</p>   |
| <ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>  | <p>12-28-2012</p>  |
| <ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>  | <p>December 10, 2012</p>   |
| <ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>  |  |
| <p>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>  |  |
| <ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>  | <p>December 20, 2012</p>   |
| <p>❖ Proprietary Name</p> <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• <i>Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</i></li> </ul> | <p>Acceptability Letter 10/15/2012<br/> Review 10/10/2012</p>  |
| <p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>   | <p><input checked="" type="checkbox"/> RPM 11/23/2012, 12-04-12<br/> <input checked="" type="checkbox"/> DMEPA 12/03/2012<br/> <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 12/19/2012<br/> <input checked="" type="checkbox"/> OPDP (DDMAC) 12/09/2012, 12/17/2012<br/> <input type="checkbox"/> SEALD<br/> <input type="checkbox"/> CSS<br/> <input checked="" type="checkbox"/> Other reviews Clinical Pharmacology 12/10/2012</p> <p><u>Labeling Meeting Dates:</u></p> <ul style="list-style-type: none"> <li>• 11/16/2012</li> <li>• 11/21/2012</li> <li>• 11/26/2012</li> <li>• 12/03/2012</li> <li>• 12/04/2012</li> <li>• 12/05/2012</li> <li>• 12/06/2012</li> <li>• 12/07/2012</li> <li>• 12/10/2012</li> <li>• 12/14/2012</li> <li>• 12/18/2012</li> <li>• 12/19/2012</li> <li>• 12/20/2012</li> </ul> |

| <b>Administrative / Regulatory Documents</b>   |  |
|--|--|
| <ul style="list-style-type: none"> <li>❖ Administrative Reviews (e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting) (indicate date of each review)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (indicate date)</li> </ul> | Quality Micro 07/16/2012<br>Clinical Micro 07/24/2012<br>Statistics 07/26/2012<br>Pharm/Tox 07/30/2012<br>Clinical Pharmacology 08/02/2012<br>CMC/08/28/12<br>Clinical 09/09/2012<br>RPM Filing Review 12/18/2012,<br>Revised RPM 11/30/2012<br><br><input checked="" type="checkbox"/> Not a (b)(2)<br><input checked="" type="checkbox"/> Not a (b)(2) |
| ❖ NDAs only: Exclusivity Summary (signed by Division Director)   | <input checked="" type="checkbox"/> Included   |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br><a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>   |  |
| <ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>  | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  |
| <ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (indicate date)</li> <li>○ If yes, OC clearance for approval (indicate date of clearance communication)</li> </ul> </li> </ul>                      | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No<br><br><input type="checkbox"/> Not an AP action   |
| <ul style="list-style-type: none"> <li>❖ Pediatrics (approvals only)               <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____<br/>If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (approvals only, must be reviewed by PERC before finalized)</li> </ul> </li> </ul>           | <input type="checkbox"/> Included <input checked="" type="checkbox"/> N/A (orphan designation)   |
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)   | <input checked="" type="checkbox"/> Verified, statement is acceptable  |
| ❖ Outgoing communications (letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)  | Included   |
| ❖ Internal memoranda, telecons, etc.   | Telecon Memo 10/10/2012,<br>12/07/12, 12/13/12, 12/18/12   |
| ❖ Minutes of Meetings  |  |
| <ul style="list-style-type: none"> <li>• Regulatory Briefing (indicate date of mtg)</li> </ul>   | <input checked="" type="checkbox"/> No mtg   |
| <ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (indicate date of mtg)</li> </ul>  | <input checked="" type="checkbox"/> N/A or no mtg  |
| <ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (indicate date of mtg)</li> </ul>   | 10/07/2011   |
| <ul style="list-style-type: none"> <li>• EOP2 meeting (indicate date of mtg)</li> </ul>  | 02/09/2011 (clinical)<br>11/05/2009 (CMC)  |
| <ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)</li> </ul>  | Type C Meeting 09/23/2008<br>Type A Meeting (CMC) 05/21/2012   |
| ❖ Advisory Committee Meeting(s)  | <input type="checkbox"/> No AC meeting   |
| <ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>  | 11/28/2012   |
| <ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available (do not include transcript)</li> </ul>   | N/A  |

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

| <b>Decisional and Summary Memos</b>   |   |
|---|---|
| ❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )  | 12/28/2012  |
| Division Director Summary Review ( <i>indicate date for each review</i> )   | 12/27/2012  |
| Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )  | 12/21/2012  |
| PMR/PMC Development Templates ( <i>indicate total number</i> )  | 9   |
| <b>Clinical Information<sup>6</sup></b>   |   |
| ❖ Clinical Reviews  |   |
| • Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )   | 12/21/2012  |
| • Clinical review(s) ( <i>indicate date for each review</i> )   | 12/28/2012  |
| • Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )   | <input checked="" type="checkbox"/> None  |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )  | 12/28/2012 Clinical Review  |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )   | <input type="checkbox"/> None<br><input checked="" type="checkbox"/> Other: Cardio/Renal 10-16-2012, 12/12/2012 |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )  | <input checked="" type="checkbox"/> Not applicable  |
| ❖ Risk Management <ul style="list-style-type: none"> <li>• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul> | <input checked="" type="checkbox"/> None<br>REMS Review 12/19/2012  |
| ❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )   | 12/21/2012 Summary<br>12/20/2012 (3)-Letters  |
| <b>Clinical Microbiology</b> <input type="checkbox"/> None  |   |
| ❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )  | 12/04/2012  |
| Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )  | 12/04/2012  |
| <b>Biostatistics</b> <input type="checkbox"/> None  |   |
| ❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )  | <input checked="" type="checkbox"/> None  |
| Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )  | 12/04/2012, 12/21/2012  |
| Statistical Review(s) ( <i>indicate date for each review</i> )  | 12/04/2012, 12/21/21  |

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

| <b>Clinical Pharmacology</b> <input type="checkbox"/> None  |  |
|---|--|
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None                                 |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review)   | <input type="checkbox"/> None 12/03/2012, 12/10/2012                     |
| Clinical Pharmacology review(s) (indicate date for each review)   | <input type="checkbox"/> None 11/30/2012, 12/10/2012                     |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)   | <input checked="" type="checkbox"/> None                                 |
| <b>Nonclinical</b> <input type="checkbox"/> None  |  |
| ❖ Pharmacology/Toxicology Discipline Reviews  |  |
| • ADP/T Review(s) (indicate date for each review)   | <input checked="" type="checkbox"/> None                                 |
| • Supervisory Review(s) (indicate date for each review)   | 12/12/2012   |
| • Pharm/tox review(s), including referenced IND reviews (indicate date for each review)   | 12/11/2012   |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)  | <input checked="" type="checkbox"/> None                                 |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)  | <input checked="" type="checkbox"/> No carc                              |
| ❖ ECAC/CAC report/memo of meeting   | <input checked="" type="checkbox"/> None<br>Included in P/T review, page |
| ❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)   | <input checked="" type="checkbox"/> None requested                       |
| <b>Product Quality</b> <input type="checkbox"/> None  |  |
| ❖ Product Quality Discipline Reviews  |  |
| • ONDQA/OBP Division Director Review(s) (indicate date for each review)   | 12/21/2012   |
| • Branch Chief/Team Leader Review(s) (indicate date for each review)  | 11/16/2012, 12/21/2012   |
| • Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)  | 11/16/2012, 12/21/2012 (CMC)<br>11/16/2012, Biopharmaceutics             |
| ❖ Microbiology Reviews  |  |
| <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review)   | 11/02/2012   |
| <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)  |  |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)   | <input checked="" type="checkbox"/> None<br><input type="checkbox"/>     |
| ❖ Environmental Assessment (check one) (original and supplemental applications)   |  |
| <input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population) | 11-16-2012   |
| <input type="checkbox"/> Review & FONSI (indicate date of review)   |  |
| <input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)   |  |

|   |   |
|---|---|
| ❖ Facilities Review/Inspection  |   |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout) ( <i>date completed must be within 2 years of action date</i> ) ( <i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup></i> ) | Date completed: 12/21/2012<br><input checked="" type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation<br><input type="checkbox"/> Not applicable           |
| <input type="checkbox"/> BLAs: TB-EER ( <i>date of most recent TB-EER must be within 30 days of action date</i> ) ( <i>original and supplemental BLAs</i> )   | Date completed:<br><input type="checkbox"/> Acceptable<br><input type="checkbox"/> Withhold recommendation  |
| ❖ NDAs: Methods Validation ( <i>check box only, do not include documents</i> )  | <input checked="" type="checkbox"/> Completed<br><input type="checkbox"/> Requested<br><input type="checkbox"/> Not yet requested<br><input type="checkbox"/> Not needed (per review) |

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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/s/

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FARIBA IZADI  
01/03/2013

**From:** Izadi, Fariba  
**Sent:** Saturday, December 22, 2012 2:07 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Cc:** Keen, Robin [JRDUS]  
**Subject:** Revised PMR

**Importance:** High  
Dear Mr Lewis,

Below, please find our revised version of the PMR dates for developing a patient registry. Please check the time lines and submit the PMR & PMCs officially to the NDA if there are no edits.

2 # 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

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

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/  
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FARIBA IZADI  
12/25/2012

**From:** Izadi, Fariba  
**Sent:** Friday, December 21, 2012 5:45 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384 (bedaquiline)

**Importance:** High

**Attachments:** QT figure.PDF  
[Dear Mr. Lewis,](#)

[Here is the QT figure you have requested yesterday.](#)

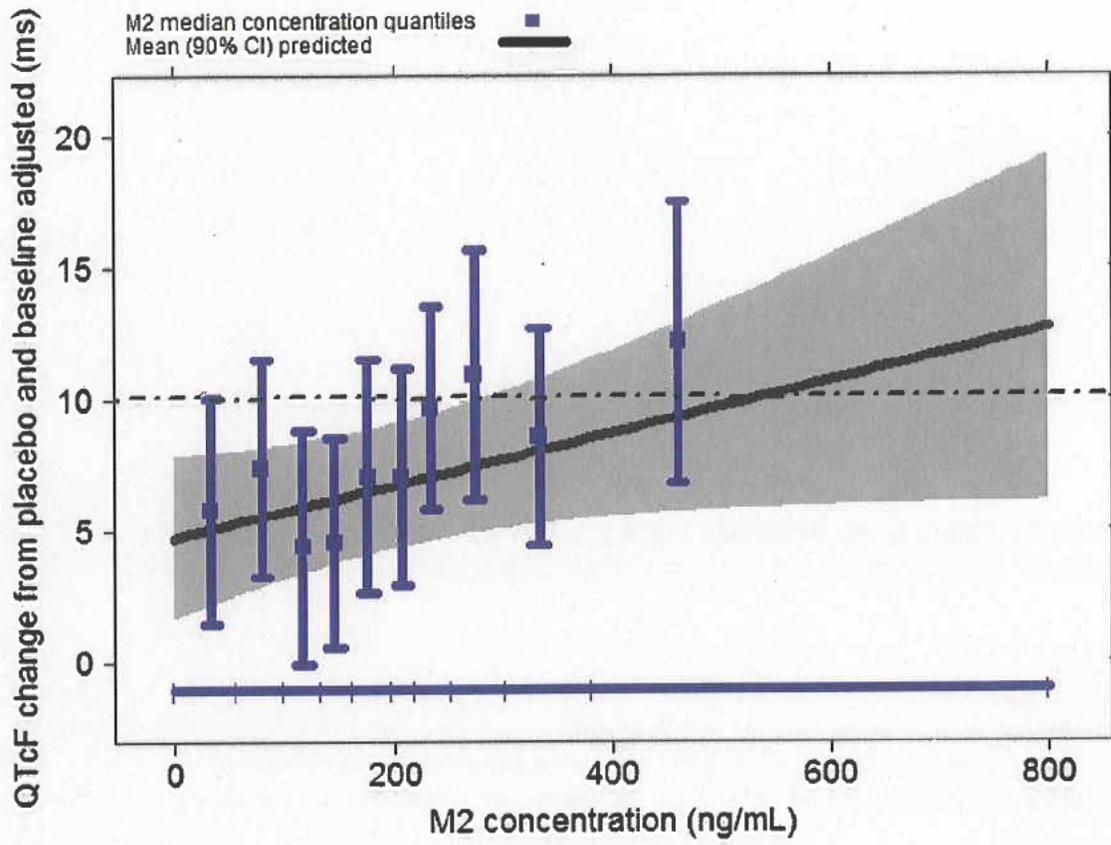
[Best regards](#)

[Fariba](#)



QT figure.PDF (81  
KB)

Figure 3:  $\Delta\Delta$ QTcF vs. M2 Concentration



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/s/  
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FARIBA IZADI  
12/25/2012

**From:** Izadi, Fariba  
**Sent:** Wednesday, December 19, 2012 2:51 PM  
**To:** 'Keen, Robin [JRDUS]'  
**Cc:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384-(bedaquiline) -Referenced Tables

**Importance:** High

Dear Robin,

Below, please find the tables discussed during our teleconference this morning.

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

The following analyses of outcome by MIC was conducted by our statistical reviewers and is similar to your Table 18 in the Microbiology summary in Section 2.7.2.4 of the NDA.

**Culture conversion at Week 24 by baseline MIC (Agar proportion method) for TMC207 group in Study C208 Stage 2 in the ITT population and all subjects in Study C209**

| $\mu\text{g/ml}$ | n/N (%)     |
|------------------|-------------|
| 0.0075           | 2/2 (100)   |
| 0.015            | 14/24 (58)  |
| 0.03             | 51/64 (80)  |
| 0.06             | 90/127 (71) |
| 0.12             | 36/48 (75)  |
| 0.24             | 0/1 (0)     |
| 0.48             | 5/6 (83)    |
| >0.48            | 0/1 (0)     |
| Total            | 198/273     |

**Culture conversion at Week 24 by baseline MIC (REMA method) for TMC207 group in Study C208 Stage 2 in the ITT population and all subjects in Study C209**

| $\mu\text{g/ml}$ | n/N (%)     |
|------------------|-------------|
| 0.0039           | 4/6 (67)    |
| 0.0078           | 19/25 (76)  |
| 0.0156           | 38/46 (83)  |
| 0.0313           | 82/108 (76) |
| 0.0625           | 50/73 (68)  |

|       |          |
|-------|----------|
| 0.125 | 3/5 (60) |
| 0.25  | 4/5 (80) |
| 0.5   | 0/1 (0)  |
| Total | 200/269  |

We also refer you to Table 5 in the same Microbiology Summary section that shows the 4 fold shift in MIC in patients whose isolates contained the atp mutation.

Our analysis finds only moderate correlation between the MIC values obtained from the Agar and REMA method in the mITT population (Pearson correlation coefficient was 0.54, p-value < 0.0001).

#### Minimal inhibitory concentration by relapse status at baseline, Week 8, and Week 24

| Visit     | Bedaquiline           |                | Placebo               |                |
|-----------|-----------------------|----------------|-----------------------|----------------|
|           | Subjects with relapse | Other subjects | Subjects with relapse | Other subjects |
| Baseline  |                       |                |                       |                |
| N         | 4                     | 64             | 6                     | 59             |
| Mean (SD) | 0.038 (0.026)         | 0.065 (0.070)  | 0.048 (0.020)         | 0.060 (0.063)  |
| Range     | 0.015, 0.060          | 0.004, 0.480   | 0.015, 0.060          | 0.008, 0.480   |
| Week 8    |                       |                |                       |                |
| N         | 1                     | 11             |                       | 23             |
| Mean (SD) | 0.060 (0)             | 0.094 (0.131)  |                       | 0.052 (0.037)  |
| Range     |                       | 0.015, 0.480   |                       | 0.008, 0.120   |
| Week 24   |                       |                |                       |                |
| N         |                       | 1              |                       | 6              |
| Mean (SD) |                       | 0.240 (0)      |                       | 0.068 (0.044)  |
| Range     |                       |                |                       | 0.015, 0.120   |

#### Culture conversion at Week 24 by baseline MIC (Agar proportion method) for TMC207 group in Study C208 Stage 2 in the ITT population and all subjects in Study C209

| µg/ml  | n/N (%)     |
|--------|-------------|
| 0.0075 | 2/2 (100)   |
| 0.015  | 14/24 (58)  |
| 0.03   | 51/64 (80)  |
| 0.06   | 90/127 (71) |
| 0.12   | 36/48 (75)  |
| 0.24   | 0/1 (0)     |
| 0.48   | 5/6 (83)    |
| >0.48  | 0/1 (0)     |
| Total  | 198/273     |

**Culture conversion at Week 24 by baseline MIC (REMA method) for TMC207 group in Study C208 Stage 2 in the ITT population and all subjects in Study C209**

| $\mu\text{g/ml}$ | n/N (%)     |
|------------------|-------------|
| 0.0039           | 4/6 (67)    |
| 0.0078           | 19/25 (76)  |
| 0.0156           | 38/46 (83)  |
| 0.0313           | 82/108 (76) |
| 0.0625           | 50/73 (68)  |
| 0.125            | 3/5 (60)    |
| 0.25             | 4/5 (80)    |
| 0.5              | 0/1 (0)     |
| Total            | 200/269     |

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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.**  
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/s/  
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FARIBA IZADI  
12/21/2012

**Tele-conference Memo:  
NDA 204384 (TMC 207/Bedaquiline)**

An informal T-con was held between the Division of Anti-Infective products and Janssen on December 07, 2012. The purpose of the T-con was to discuss the details of the Sponsor's proposed risk management program.

**Janssen Attendees**

|                               |                                  |
|-------------------------------|----------------------------------|
| Nyasha Bakare, MD             | Safety Medical Physician         |
| Brian Dannemann, MD           | Clinical Leader                  |
| Robin Keen, VP                | Global Regulatory Affairs        |
| Katia Boven, MD               | Therapeutic Area Head            |
| Chrispin Kambili, MD          | Medical Leader                   |
| Gary Lewis, MS                | North American Regulatory Leader |
| Els Van Beirendonck, Pharm. D | Global Regulatory Leader         |

**Division of Anti-Infective Attendees**

|                                |   |
|--------------------------------|---|
| Edward Cox, MD, MPH            | Office Director                         |
| John Farley, MD, MPH           | Acting Division Director                |
| Katherine A. Laessig, MD       | Deputy Director                         |
| Sumathi Nambiar, MD, MPH       | Deputy Director for Safety              |
| Eileen Navarro-Almario, MD     | Clinical Team Leader                    |
| Ariel Porcalla, MD, MPH        | Medical Officer                         |
| Dakshina Chilukuri, PhD        | Clinical Pharmacology Reviewer          |
| Kerry Snow, MS                 | Clinical Microbiologist                 |
| Daphne Lin, PhD                | Office Director- Statistics             |
| Karen Higgins, PhD             | Statistics Team Leader                  |
| Xianbin Li, PhD                | Statistics Reviewer                     |
| Owen McMaster, PhD             | Pharmacology/Toxicology Reviewer        |
| Cathy Chang, Pharm D Candidate | Student Pharmacist                      |
| David Roeder, MS               | Associate Director of Regulatory Affair |
| Fariba Izadi, PharmD,          | Regulatory Project Manager              |

**Comments & Responses:**

**FDA Question 1:** How do you plan to address/communicate issues with mortality and relevant findings from clinical trials to physicians and other healthcare providers?

**Janssen Response:** We are currently working on a new proposal but this has not yet gone through internal review. We would ideally like to be more descriptive of the Stage 2 trial.

- a. Have you thought about the level at which to communicate it/how best to address this? Possibly a box describing issues with morality and prominently including this in the beginning?

**Janssen Response:** As previously discussed, our initial plans were just to be descriptive, so one idea is to include more information in the clinical trials section.

Would you be comfortable with providing the outline of proposed inclusions of clinical trial section?

**Janssen Response:** Yes, we will provide you with that information.

**FDA Question 2:** In reference to the responsible access and pharmacovigilance – this is conceptually a good idea, but how might this work in practice? Could you elaborate on this?

**Janssen Response:** [REDACTED] (b) (4)

**FDA Question 3:** In terms of managing distribution and implementing responsible access, is there a commercial operation that you've contracted with? Or will CDC be the responsible agency for distribution?

**Janssen Response:** [REDACTED] (b) (4)

What if it's *not* for a MDR-TB patient or through public health authorities?

**Janssen Response:** In TB control programs, there are usually public health pharmacies. [REDACTED] (b) (4)

You have indicated in your risk management program document that bedaquiline [REDACTED] (b) (4)

**Janssen Response:** Should there be a need for discussion or questions regarding bedaquiline. [REDACTED] (b) (4)

**FDA Question 4:** What fraction of patients would end up in registry? How many dispenses do you predict to have on an annual basis?

**Janssen Response:** We estimate about (b) (4) patients with MDR-TB per year in the United States would be eligible for access to bedaquiline. Essentially all of these patients would be included in the registry.

What are your thoughts on the ability of the registry to interface with the public health system?

**Janssen Response:** We are currently exploring this in depth with the CDC.

**FDA Question 5:** Risk management elements are very similar to what's incorporated in REMS. Have there been any thoughts on implementing a REMS?

**Janssen Response:** (b) (4)

**Questions from the FDA regarding Breakpoints:**

**FDA Question 6:** We are trying to establish interpretive criteria for breakpoints based on correlation to clinical efficacy. What is the basis for the (b) (4) breakpoint?

**Janssen Response:** We proposed the critical concentration (95%) to be (b) (4)

We believe that (b) (4) as a susceptible breakpoint would be a plausible place to start.

**FDA Comment:** We are looking at a 76% success rate at the MIC (b) (4) compared to outcomes at other MIC levels and find we do not have enough data to understand this issue.

**Janssen Response:** This is all the available data we have. Based on the distribution based on availability or MIC (b) (4) It is not straight forward to find breakpoint here.

**FDA Question 7:** FDA: We are also concerned about the range of MICs and their correlation with clinical outcome. Looking at the table and the relapses how does all this fit together? The MIC does not explain all the failures. We are also concerned that the clinical efficacy at other MIC values is less than that seen at the proposed susceptibility.

**Janssen Response:** We don't see a PK/PD relationship in response to exposure. We were concerned about having patients excluded due to an MIC value > 0.12 for

example. We didn't see that the data supports efficacy in those subjects up to a <sup>(b) (4)</sup> and also didn't see a trend that would have a *worse* outcome.

**FDA Comment:** We recognize that the Agar proportion method as the gold standard and have questions concerning the comparison of MIC methods (Agar method, REMA).

**Janssen Comment/question:** Do you have any additional analysis or have any suggestions for different analysis.

**FDA Response:** No, we only have the clinical outcomes for c 208- stage II.

**Action Item:** Janssen will provide proposed text on mortality for the labeling

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FARIBA IZADI  
12/17/2012

**From:** Izadi, Fariba  
**Sent:** Tuesday, December 18, 2012 9:26 AM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384-(bedaquiline)-Information request

**Importance:** High  
Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (bedaquiline) and have the following information requests.

Please provide the following information on two mortalities described in Trial C208 Stage 2:

- Patient 208-5067: A complete clinical summary that includes the interval history between the time the patient's serum transaminases increased to the time the patient was diagnosed with peritonitis and probable perforated viscus, medical history, all laboratory evaluations, and a full autopsy report, if available.
- Patient 208-5069: : A complete clinical summary that includes a complete medical history, all laboratory evaluations, and a full autopsy report, if available.

These two patients are from one clinical site in Thailand and there have been inconsistent references in the case narratives submitted for the two patients

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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FARIBA IZADI  
12/18/2012

**From:** Izadi, Fariba  
**Sent:** Monday, December 17, 2012 11:14 AM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384-information requests

**Importance:** High  
Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (bedaquiline) and request response to the following as soon as possible, no later than Tuesday December 18, 2012.

Patient 208-4041, reported as having died from alcohol intoxication, also appears to have developed transient pancreatitis, followed by fever and pruritus. The accompanying case summary does not provide critical details of his hospital course and his autopsy findings. Please provide a complete clinical summary that includes a description of his medical history, baseline and postbaseline labs including all CBC with manual differential counts (including eosinophil counts and platelet counts), hepatic analytes and a full chem 7, with calculated anion gap, BUN, and creatinine, baseline and postbaseline symptoms and physical findings by date, all laboratory and radiographic investigations, all medications and their start and stop dates, and the full autopsy report.

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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FARIBA IZADI  
12/18/2012

**From:** Izadi, Fariba  
**Sent:** Monday, December 17, 2012 4:35 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** PMR-PMC-bedaquiline

**Importance:** High

**Attachments:** Final- Bedaquiline PMRPMC (7).doc  
Dear Mr. Lewis,

Attached, please find our Division's PMR/PMC requests for NDA 204384 (bedaquiline) submitted June 29, 2012. Please review and provide an agreement letter filling in the necessary dates both officially and via e-mail by COB December 18, 2012.

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



Final- Bedaquiline  
PMRPMC (7)....

PMRs:

Clinical:

1. Conduct a confirmatory trial: Randomized double blind placebo controlled 2 arm multicenter phase III trial in subjects with sputum smear-positive pulmonary infection with MDR-TB. This study should assess long term outcome of failure or relapse or death at least 6 months after all MDR-TB treatment is completed.
  - Final Protocol Submission:
  - Trial Completion:
  - Final Report Submission:
  
2. Develop a patient registry for bedaquiline-treated patients that captures the following:
  - a. indication for use
  - b. susceptibility data for baseline and any subsequent isolate
  - c. drug utilization data
  - d. information on the drug distribution mechanisms used
  - e. patient outcomes (clinical and microbiologic)
  - f. safety assessments in bedaquiline-treated patients, including deaths
  - g. Concomitant medications
  - Final Protocol Submission:
  - Trial Completion:
  - Final Report Submission:

Microbiology:

1. Conduct a prospective study over a five-year period after introduction of SIRTURO (bedaquiline) to the market to determine susceptibility of *Mycobacterium tuberculosis* to bedaquiline for the first 5 years from marketing. Provide a detailed protocol describing the study to the Agency for review and comment before commencing the study.
  - Final Protocol Submission:
  - First Interim Report: xxx, and then annually
  - Trial Completion:
  - Final Report Submission:

Clinical Pharmacology:

1. Conduct a drug interaction study of bedaquiline and efavirenz to determine a safe and effective dose regimen of both drugs when they are coadministered in HIV co-infected MDR-TB patients.

- Final Protocol Submission:
- Trial Completion:
- Final Report Submission:

PMC:

1. Conduct an in vitro study to characterize the potential of bedaquiline and M2 as a substrate, inhibitor or inducer of the OATP1B1 and OATP1B3 drug transporters.
  - Final Protocol Submission:
  - Trial Completion:
  - Final Report Submission:
2. Conduct a study to define the Quality Control ranges of bedaquiline for *M. tuberculosis* isolates using standard proportion methods.
  - Final Protocol Submission:
  - Trial Completion:
  - Final Report Submission:
3. Conduct a study to define the Quality Control ranges of bedaquiline for *M. tuberculosis* isolates using MIC methods.
  - Final Protocol Submission:
  - Trial Completion:
  - Final Report Submission:

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FARIBA IZADI  
12/18/2012

**From:** Izadi, Fariba  
**Sent:** Thursday, December 13, 2012 2:11 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384 (bedaquiline)- Information requests

**Importance:** High

Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (bedaquiline) and have the following information requests:

- 1) Please resubmit the data from your phase 2 studies in the format that would accommodate assessment using eDish. the enclosed file provides specifics.
- 2) if available, please submit the PR segment durations for your phase 2 studies.
- 3) Please provide additional clinical detail for the late onset deaths recently reported. Specifically, please clarify whether follow-up for these patients was in line with your described patient follow-up in the protocol for Study C208.

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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FARIBA IZADI  
12/13/2012

**From:** Izadi, Fariba  
**Sent:** Thursday, December 13, 2012 1:12 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384-(bedaquiline)-Information request

**Importance:** High  
Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (bedaquiline) and have the following information request.

Please provide us with a timeline for submission of the definitive Tier II multicenter agar MIC and REMA MIC to support labeling.

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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FARIBA IZADI  
12/13/2012

**From:** Izadi, Fariba  
**Sent:** Tuesday, December 04, 2012 3:10 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384 (bedaquiline)-Information request

**Importance:** High  
Dear Mr. Lewis,

During the Advisory committee meeting held on November 28, 2012 for NDA 204384 (bedaquiline tablets), we believe that we heard Dr. Haxaire-Theeuwes mention that two additional deaths occurred in Study C208 and that they perhaps occurred in subjects who had rolled over onto TMC 207. Could you please clarify if this was the case and, if so, what the subject numbers are for these subjects.

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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FARIBA IZADI  
12/10/2012

**From:** Izadi, Fariba

**Sent:** Tuesday, November 20, 2012 1:41 PM

**To:** 'Lewis, Gary [JRDUS]'

**Subject:** RE: NDA 204384 (TMC207) Upcoming Advisory Committee Meeting - Informal Discussion Requested

**Importance:** High

Dear Mr. Lewis,

Below, please find our written responses to your questions submitted on November 19, 2012 regarding the upcoming Advisory Committee Meeting for NDA 204384 (bedaquiline).

1. We have been informed that the sponsor will be allotted 75 minutes for the sponsor presentation. Is it possible for this to be extended to 90 minutes?

**FDA Response:** Yes, but you absolutely must not exceed 90 minutes.

2. A small number of our back up slides reflect the 'final analysis' that was included in the C208 final study report submitted to IND 69,600, but that these will be clearly marked to indicate that this was not data in the NDA file currently under review. Does the Agency agree that it is acceptable to discuss this information during the Q&A session if prompted?

**FDA Response:** Yes.

3. In reviewing FDA's Background materials, we observed that little emphasis is placed on PK. Is it acceptable for the sponsor to present PK with a similar level of detail?

**FDA Response:** We are expecting that you will provide adequate details in your AC presentation to cover the clinical pharmacology program. Particular details regarding in vitro drug metabolism, in-vivo drug-drug interactions, exposure-response, dosing in special populations (hepatic and renal impairment), TQT trial, [REDACTED] (b) (4) [REDACTED]. The FDA presentation will not cover these topics in anticipation that the your presentation will do so.

4. Does the Agency have a preference for how to approach the topic of mortality? **FDA Response:** We plan to have an extensive discussion of the deaths during our safety presentation. We have reviewed the FDA's assessment of mortality in FDA's Background materials and we intend to reflect a similar assessment/adjudication in our opening presentation. Does the FDA agree with this approach? **FDA Response:** Yes.

5. Proposed Phase III trial design – would the Agency like the sponsor in responses to queries from panel members to go into depth regarding the Phase III trial design during the Advisory Committee meeting, or will the FDA indicate to panel members that this is not a focus of the meeting?

**FDA Response:** You may be required to go into some depth about the Phase 3 trial since it is the confirmatory trial but we will request that the chair not let the committee spend an inordinate amount of time on it.

6. Surrogate endpoint and accelerated approval procedure – will FDA confirm agreement of surrogate endpoint and accelerated approval during the opening statement?

**FDA Response:** Yes.

Best regards,

Fariba Izadi, Pharm.D.  
Regulatory Health Project Manager  
Division of Anti-Infective Products  
Phone: (301) 796-0563

Reference ID: 3221882

Fax: (301) 796-9881  
E-mail: Fariba.Izadi@fda.hhs.gov

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**From:** Lewis, Gary [JRDUS] [mailto:GLewis3@its.jnj.com]  
**Sent:** Monday, November 19, 2012 2:31 PM  
**To:** Izadi, Fariba  
**Subject:** RE: NDA 204384 (TMC207) Upcoming Advisory Committee Meeting - Informal Discussion Requested

Hi Fariba:

Thanks for speaking with me today. Per your request, we have re-reviewed the mortality question that was previously provided, and are replacing it with the following question below. Also, per your request, this question and others will be officially submitted to NDA 204-384. Any questions, please let me know.

- We have reviewed the FDA's assessment of mortality in FDA's Background materials and we intend to reflect a similar assessment/adjudication in our opening presentation. Does the FDA agree with this approach?

Kind regards,  
Gary

---

**From:** Lewis, Gary [JRDUS]  
**Sent:** Saturday, November 17, 2012 3:49 PM  
**To:** 'Izadi, Fariba'  
**Subject:** NDA 204384 (TMC207) Upcoming Advisory Committee Meeting - Informal Discussion Requested

Hi Fariba:

As mentioned during our telephone conversation on November 16, 2012, Janssen would like to have a brief teleconference with you and possibly Dr. Navarro (Robin Keen, VP Regulatory Affairs, Els Van Beirendonck, Global Regulatory Affairs and myself on our end) to discuss several topics regarding the upcoming Advisory Committee Meeting. We are proposing **Monday, November 19, 2012**, but will accommodate anytime at your convenience. Below are some talking points to help facilitate the discussion:



Reference ID: 3221882

Kind regards,

Gary

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/s/  
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FARIBA IZADI  
11/27/2012

**From:** Izadi, Fariba  
**Sent:** Thursday, November 08, 2012 2:42 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384 (TMC-207) Additional information requests

**Importance:** High  
Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (TMC-207) and have the following information requests:

For studies 208, Stage 1 and 2, and 209, please provide an analysis of the mean, median, range, and interquartile range of the maximum measured QT interval, and the QT interval prolongation from baseline in milliseconds in patients who received either bedaquiline or placebo in concert with

- No known QT prolonging drug
- 1 drug with QT prolonging potential
- 2 drugs with QT prolonging potential
- 3 drugs with QT prolonging potential
- > 3 drugs with QT prolonging potential

The products we identified to have been used concurrently in C208 are: levofloxacin, moxifloxacin, clofazimine, azithromycin, linezolid, clarithromycin, erythromycin. The products we identified in C209 are: azithromycin, clofazimine, clarithromycin, linezolid, moxifloxacin, levofloxacin, amitriptyline, astemizole, aztreonam, loratadine, domperidone, erythromycin, fluconazole, fluoxetine, haloperidol, hydroxyzine.

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/  
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FARIBA IZADI  
11/14/2012

## Cuff, Althea

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**From:** Cuff, Althea  
**Sent:** Tuesday, October 30, 2012 10:21 AM  
**To:** Cuff, Althea; 'glewis3@its.jnj.com'  
**Cc:** Izadi, Fariba  
**Subject:** NDA 204384 - Information Request

Dear Mr. Lewis,

In reviewing the Chemistry, Manufacturing and Controls section of your NDA, we have the following information request. Please response by Friday November 2, 2012 and be sure to submit officially to the NDA.

1. In your response to Question 8 of Information Request dated 26-Sep-2012, you did not include the (b) (4) for the drug substance batches used in the drug product DoE. Please update your response to include all drug substance batches used for Table 1 in P.2.3, including lots used in the DoE and manufactured at (b) (4).

(b) (4)

Thanks, Althea.

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ALTHEA CUFF  
11/01/2012

**From:** Izadi, Fariba  
**Sent:** Monday, October 22, 2012 3:55 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384 (TMC)-207 Information request

**Importance:** High

Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (TMC 207) and have the following comment and information request:

We note the following statement on your container label [REDACTED] (b) (4)  
[REDACTED] We foresee several situations in which fewer than the 188 bedaquiline tablets may need to be dispensed - in which case the dispensed quantity of drug would not be stored in the original container. Examples of these situations are when the prescription insurance plan will not pay for the entire bottle (24 week supply), when hospitals need to place the drug into blisters for dispensing via unit dose carts or automated cabinets, and when patients are initiated on therapy while in the hospital and discharged home for the remainder of the 24 week course of therapy. Please consider such situations and submit a detailed response stating how you intend to address them. We recommend conducting a risk assessment of those and other potential situations, considering what data, if any, is available to support storage under the different scenarios outlined.

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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FARIBA IZADI  
11/01/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

NDA 204384

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Janssen Research and Development, LLC  
920 U.S. Highway 202  
P.O. Box 300  
Raritan, NJ 08869-0602

ATTENTION: Gary Lewis  
Associate Director, Global Regulatory Affairs

Dear Mr. Lewis:

Please refer to your New Drug Application (NDA), dated and received June 29, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Bedaquiline Tablets, 100 mg. We also refer to:

- your correspondence, dated and received July 20, 2012, requesting review of your proposed proprietary name, Sirturo, and
- your Proprietary Name Amendment dated and received July 25, 2012.

We have completed our review of the proposed proprietary name, Sirturo and have concluded that it is acceptable.

The proposed proprietary name, Sirturo, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. If **any** of the proposed product characteristics as stated in your July 20, 2012 and July 25, 2012 submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Fariba Izadi at (301) 796-0563.

Sincerely,  
*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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CAROL A HOLQUIST  
10/15/2012

**Tele-conference Memo:  
NDA 204384 -(TMC 207/Bedaquiline)**

An informal T-con was held between the Division of Anti-Infective products and Janssen on October 10, 2012. The purpose of the T-con was to informally discuss the upcoming Advisory Committee meeting with the Sponsor. In preparation for AC meeting, Janssen had submitted the questions below and requested advice from the Division:

**Janssen Attendees**

|                               |                                  |
|-------------------------------|----------------------------------|
| Brian Dannemann, MD           | Medical Leader                   |
| Myriam Haxaire-Theeuwes, DDS  | Compound Development Team Leader |
| Robin Keen, VP                | Regulatory Affairs               |
| Gary Lewis, MS                | North American Regulatory Leader |
| Els Van Beirendonck, Pharm. D | Global Regulatory Leader         |

**Division of Anti-Infective Attendees**

|                            |  |
|----------------------------|--|
| John Farley, MD, MPH       | Acting Division Director                       |
| Katherine A. Laessig, MD   | Deputy Director                                |
| Diem-Kieu Ngo, PharmD      | DFO Team Leader, Advisory Committee            |
| Diane Goyette, RPh, JD     | Designated Federal Officer, Advisory Committee |
| Eileen Navarro-Almario, MD | Clinical Team Leader                           |
| Ariel Porcalla, MD, MPH    | Medical Officer                                |
| Fariba Izadi, PharmD       | Regulatory Health Project Manager              |
| Fang Li, PhD               | Pharmacometric Reviewer                        |
| Zhixia Yan, PhD            | Clinical Pharmacology Reviewer                 |
| Xianbin Li, PhD            | Statistics Reviewer                            |
| Karen Higgins, PhD         | Statistics Team Leader                         |
| Cecilia N. Cruz, PhD       | CMC Reviewer                                   |
| Dorota Matedka, PhD        | CMC Team Leader                                |
| Owen McMaster, PhD         | Pharmacology/Toxicology Reviewer               |
| Lynette Berkeley, PhD      | Clinical Microbiology Reviewer                 |

1. Are there any specific issues/challenges or topics that the sponsor should be made aware of?

**FDA response:** Sponsor should discuss the following:

1. Benefits of TMC207
2. Clarifications on definition of relapse
3. Sputum conversion
4. Safety of product
5. Potential drug-drug interactions

2. Can you provide any details on the format and content of the Advisory Committee Meeting as it relates to TMC207 (bedaquiline)?

**FDA response:** The standard format of the Advisory Committee Meeting begins with an introduction/opening remark, applicant's presentation, followed by question session. This is then followed by FDA's presentations, and lastly an open public hearing.

3. Will there be any discussion on the CMC aspects of TMC207 (bedaquiline)?

**FDA response:** There will be no discussions on CMC.

4. Filing with Phase 2 data. Will the FDA address this up front with the Advisory Committee or should we prepare for this?

**FDA response:** Please be prepared to have this discussion. Please consider focusing on how adequate and well-controlled the study is.

5. Is the Agency expecting a discussion on the Phase 3 study design for TMC207 (bedaquiline)?

**FDA response:** Yes, please be prepared to have this discussion.

6. Is it permissible to have external members (such as CDC, WHO, etc) speak on the sponsor's behalf as advocates for the TMC207 (bedaquiline)'s clinical program relative to the Medical Landscape and/or Risk/Benefits associated with this compound?

**FDA response:** As this issue was previously addressed, it is a violation of ethics statutes 18 U.S.C. 203 and 205 for a Federal Employee (including but not limited to full-time and part-time employees of the NIH, CDC, DOD, and VA) to represent a third party before another Agency. Please note that Federal Employees will not be permitted to represent your company at the meeting; however, WHO representatives are acceptable.

**Additional questions from the sponsor:**

1. Sponsor inquired if there will be a discussion regarding non-clinical perspective.

**FDA response:** There will be no non-clinical discussion at this time.

2. Sponsor inquired about the Agency's preference on the investigational drug name, whether TMC207 or bedaquiline, for consistency.

**FDA response:** Agency chooses "bedaquiline" for consistency.

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FARIBA IZADI  
10/24/2012

**From:** Izadi, Fariba  
**Sent:** Friday, October 05, 2012 3:16 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384-(TMC-207)-Information Request

**Importance:** High  
Dear Mr. Lewis:

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (TMC-207) and have the following information requests:

In Table 8 (page 107) of the C208 study report, 18 and 20 subjects in the TMC207 and placebo groups completed the trial, respectively. However, in Table 24 (page 131) only 4 and 16 subjects had Week 120 visit. Please clarify the results from these two tables.

According to the study report, relapse was defined as having a confirmed positive sputum culture after prior confirmed culture conversion. However, according to the MBAD data set it appears that some positive sputum culture results were overruled by subsequent negative sputum culture results (i.e., not considered as relapse). Please explain the definitions of conversion and relapse in detail (i.e. number of negative cultures and number of intermittent positive cultures to be considered a conversion; number of positive cultures and number of intermittent negative cultures to be considered a relapse; whether resolution or recurrence of signs and symptoms are also considered to determine conversion or recurrence, respectively) . In addition, please clarify why some subjects (such as 4280, 4385) who had one positive sputum culture result at the last visit were not considered as relapse.

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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FARIBA IZADI  
10/09/2012



NDA 204384

**METHODS VALIDATION  
MATERIALS RECEIVED**

Janssen Therapeutics, a Division of Janssen Products, LP  
Attention: Gary Lewis  
920 Route 202  
South Raritan, NJ 08869

Dear Gary Lewis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bedaquiline tablets, 100 mg and to our August 21, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on October 5, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email ([Michael.Trehy@fda.hhs.gov](mailto:Michael.Trehy@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
10/05/2012

**From:** Izadi, Fariba  
**Sent:** Thursday, September 27, 2012 11:25 AM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384-TMC207-Information Request

**Importance:** High  
Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 and have the following information request from our non-clinical team.

Please provide us with the historical control fertility data of Sprague-Dawley (CrI:CD<sup>®</sup>) rats at the (b) (4) site.

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/  
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FARIBA IZADI  
09/27/2012



NDA 204384

**INFORMATION REQUEST**

Janssen Research and Development, LLC  
Attention: Gary Lewis  
Associate Director, Global Regulatory Affairs  
920 U.S. Highway 202  
P.O Box 300  
Raritan, NJ 08869-0602

Dear Mr. Lewis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC 207.

We also refer to your June 28, 2012, New Drugs Application submission.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. In order to meet internal review goal dates, please provide the response on or before October 26, 2012.

**Drug Product**

1. (b) (4) appears to be critical to finished product quality as it is the main point of control for initial tablet (b) (4)  
Therefore,
  - a. Include (b) (4) as a critical in-process control in Table 1 in section P.3.4.
  - b. Propose an adequate acceptance criteria based on your development data.
  - c. Verify and align the acceptance criteria among the manufacturing process description, the Kemwell master batch record, and P.3.4.

2. (b) (4)

3.  (b) (4)

4.  (b) (4)

5.  (b) (4)

6. For validation of dissolution method AD-TM-R403323-F001-TAB-DL-006222-V0.1
- a. Provide reproducibility test results at 10, 15, 20, and 30 minute dissolution time points, if available. The validation report only contains results for the 45 minute sampling time. Time point data would facilitate evaluation of the proposed Q at 30 minutes and the reproducibility of the dissolution profile.
  - b. Submit the main conclusions for robustness study referenced to AD-IN-ROBUST-R403323-TAB-DISS-00173-V1.0.

7.  (b) (4)

8. We refer to your amendment received 12 September 2012, specifically the response to FDA Question #2. The method verification studies requested by the FDA in this question were for the microbial enumeration studies, specifically the method verification studies for USP<61> and <62> assays. Please submit the method verification studies which support your planned release test for microbiological purity.

9. Regarding the post-approval stability commitment proposals in 3.2.P.3.8, please address the following:
  - a. For the first three commercial drug product batches, test each batch for microbiological purity; please update Table 1 of 3.2.P.3.8.2 accordingly.
  - b. Clarify if the protocol for annual stability monitoring will include 5 °C, 25 °C/60% RH, and 30 °C/ 75% RH, as shown in Table 1 of 3.2.P.3.8.2.1, otherwise, please clarify the stability conditions in section 3.2.P.3.8.2.2. Update to show that microbiological purity will be performed on every batch tested on annual stability for the long term conditions.
10. We were not able to locate “Figure 1” of the pXRD method description containing the scan for the tablet formulation (3.2.P.3.8). Please submit information to locate the reference scan, or provide a copy.

Drug Substance:

1. Although (b) (4) was consistently observed below (b) (4) in all tested drug substance batches, for genotoxicity control over product life cycle, we recommend inclusion of a limit for (b) (4) in the specification of the starting material (b) (4) or drug substance..
2. Address the following comments related to the (b) (4) process:
  - a. (b) (4)
  - b. Provide a detailed description, including process parameters, for the (b) (4) in Section 3.2.S.2.2.
3. (b) (4)
4. (b) (4)
5. (b) (4)

(b) (4)

6. (b) (4)

7. (b) (4)

8. Regarding the drug substance particle size distribution,

a. (b) (4)

b. Clarify if the same particle size distribution testing method was used for clinical and commercial batches.

9. Address the following comments related to the drug substance manufacturing process description:

a. (b) (4)

b. (b) (4)

c. (b) (4)

If in the future you propose a reduction in microbial limits testing we recommend that you have a microbial specification for the drug substance at that time.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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RAPTI D MADURawe  
09/26/2012

**From:** Izadi, Fariba  
**Sent:** Friday, September 21, 2012 12:16 PM  
**To:** 'Lewis, Gary [JRDUS]'  
**Subject:** NDA 204384 (TMC 207) -Information Requests

Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (TMC 207) and have the following information requests:

For Study C208, we are able to replicate the time-to-conversion analysis results in Display EFF.21, Display EFF.23, and Display EFF.24 in Section 6.4.1, using variables T24CON, T24CONMF, and T24CON2 and their corresponding censoring variables. However, we could not find a time-to-conversion variable to exactly replicate the results in Display EFF.1, although we have obtained similar results based on the information provided in the Study Report. This variable is different for at least two subjects from variable T24CON used to generate Display Eff.21, according to the Study Report. Please direct us to the variable and corresponding censoring variable to replicate the analysis results in Display Eff.1. In addition, please describe the differences between this time-to-conversion variable and T24CON in detail.

In the NDA submission, a Statistical Analysis Plan for Study C208, issued on 9/14/2011, is included. Please clarify the database lock time for the primary efficacy analysis in Study C208.

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/  
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FARIBA IZADI  
09/27/2012



NDA 204384

**FILING COMMUNICATION**

Janssen Research and Development, LLC  
Attention: Gary Lewis  
Associate Director, Global Regulatory Affairs  
920 U.S. Highway 202  
P.O Box 300  
Raritan, NJ 08869-0602

Dear Mr. Lewis:

Please refer to your New Drug Application (NDA) dated June 28, 2012, received June 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for bedaquiline.

We also refer to your amendments(s) dated July 20, 24, 25, and 31, August 14 and 24, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by December 01, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Please provide site-specific individual subject data (“line”) listings for each investigator listed in the table below. The data listings should contain:
  - Listing for each subject/number screened and reason(s) for subjects who did not meet eligibility requirements
  - Subject listing for treatment assignment (randomization)
  - Subject listing of drop-outs and subjects that discontinued with date and reason
  - Evaluable subjects/ non-evaluable subjects and reason not evaluable
  - By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
  - By subject listing of AEs, SAEs, deaths and dates
  - By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
  - By subject listing of the primary efficacy parameters. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
  - By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
  - By subject listing of laboratory tests performed for safety monitoring

| Site # (Name,Address, Phone number, email, fax#)  | Protocol ID | Number of Subjects           | Indication |
|---|-------------|------------------------------|------------|
| ZA00023<br><b>Andreas Diacon</b><br>Brooklyn Chest Hospital<br>Stanberry Road<br>Ysterplaat, Cape Town 7405<br>South Africa<br>Telephone 021 949 7751<br>Cell (b) (6)<br>Fax 021 918 1378<br>Email ahd@sun.ac.za                  | C208        | Stage 1 – 5<br>Stage 2 – 20  | MDRTB      |
|   | C 209       | ITT 38<br>mITT 32            |            |
| ZA00052<br><b>Alexander Pym</b><br>King George V Hospital<br>Stanley Copely Drive<br>Durban<br>4001<br>South Africa<br>Telephone 27 0 31 203 4771<br>Fax 27 0 31 203 4702<br>Cell (b) (6)<br>Email apym@mrc.ac.za                 | C208        | Stage 1 – 11<br>Stage 2 – 18 | MDRTB      |
| ZA00059<br><b>Francesca Conradie</b><br>Sizwe Hospital<br>Modderfontein Road<br>Sandringham, Johannesburg<br>2131<br>South Africa<br>Tel 011 276 8800<br>Cell (b) (6)<br>Fax 011 482 2130<br>Email<br>f.conradie@witshealth.co.za | C208        | Stage 1 – 2<br>Stage 2 – 14  | MDRTB      |
| CN00022<br><b>QIU, LIHUA</b><br>SHANDONG<br>PROVINCIAL<br>CHEST HOSPITAL TB<br>DEPT<br>Lishan Rd N 46<br>Jinan 250013<br>China  | C209        | ITT 10<br>MITT 10            | MDRTB      |

|  |      |                   |       |
|--|------|-------------------|-------|
| Tel 8613969085108<br>No fax, no cell<br>Qiu-lh@163.com   |      |                   |       |
| CN00019<br><b>TANG, SHENJIE</b><br>SHANGHAI<br>PULMONARY<br>HOSPITAL<br>Zhengmin Rd No 507<br>Shanghai 200433<br>China<br>Tel 8621 65115006-2022<br>Fax 8621 65111298<br>Email tangsj1106@sina.com | C209 | ITT 17<br>MITT 17 | MDRTB |

2. Provide the verification studies that support the proposed microbiological test methods.

3.



Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager, at (301) 796-0563.

Sincerely,

*{See appended electronic signature page}*

Katherine A. Laessig, MD  
Deputy Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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KATHERINE A LAESSIG  
08/28/2012



NDA 204384

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Janssen Therapeutics  
Attention: Gary Lewis  
920 Route 202 South  
Raritan, NJ 08869

Dear Gary Lewis:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bedaquiline Tablets, 100 mg.

We will be performing methods validation studies on Bedaquiline Tablets, 100 mg, as described in NDA 204384.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method, current version**

LC-005327-V1 Bedaquiline Fumarate Tablet HPLC method

**Samples and Reference Standards**

100 Bedaquiline Fumarate Tablets, 100 mg

(b) (4)

**Equipment**

1 (b) (4)  
10 (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: Michael L. Trehy, Ph.D.  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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MICHAEL L TREHY  
08/21/2012

**From:** Izadi, Fariba  
**Sent:** Monday, July 30, 2012 4:35 PM  
**To:** Lewis, Gary [JRDUS]  
**Subject:** NDA 204384- (TMC 207)- Information request

**Importance:** High  
Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (TMC 207) and have the following information requests:

- 1) Please provide a table listing the current and previously used code numbers/names, along with the chemical names and structures for all compounds referenced in the NDA, including starting materials, reagents, intermediates, drug substance and drug product impurities and degradation products, and impurities in the starting materials.
- 2) Please provide information on the fate and control levels of (b) (4) starting material, and fate of (b) (4) during the manufacturing process, as requested at the EOP2 meeting on November 5, 2009. Include available literature on the genotoxic potential for (b) (4). If this information has been submitted in the NDA, please indicate the relevant sections of the NDA.
- 3) Please provide us with the bioanalytical reports for the following clinical trials. If you have provided this information in the NDA submission, please provide where the information is located.
  1. R207910-CDE-101 (CDE-101)
  2. R207910-CDE-102 (CDE-102)
  3. TMC207-C208 (C208, both stages)
  4. TMC207-C209 (C209)
  5. R207910BAC1003 (BAC1003)

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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FARIBA IZADI  
08/07/2012

**From:** Izadi, Fariba  
**Sent:** Wednesday, July 25, 2012 3:38 PM  
**To:** Lewis, Gary [JRDUS]  
**Subject:** NDA 204-384 (TMC207) -Information Request

**Importance:** High  
Dear Mr Lewis,

We are reviewing your submission for NDA 204-384 ( TMC-207) and request respond to the following information requests as soon as possible.

1. The dissolution method development report is incomplete. Provide the complete dissolution profile data (individual values, mean, RSDs, and plots) for all variables tested (i.e., apparatus, media, agitation speed, etc.) to support the selection of the proposed dissolution test method as optimal for your product. FDA was unable to locate the dissolution data using USP Apparatus<sup>(b)(4)</sup> as referenced in Section 3.2.P.2.2, and summary statistics (i.e., mean and RSDs) were not reported for all other conditions evaluated. In addition, FDA recommends dissolution testing under mild test conditions (i.e., basket method at 100 rpm). To support the faster paddle speed of 150 rpm, provide the dissolution profile data evaluating intermediary paddle speeds (e.g., 110, 125, 140, etc.).
2. Provide the complete dissolution profile data (individual values, mean, RSDs and plots) for all the clinical F001 lots used in the Clinical Phase IIb and Relative Bioavailability studies.
3. Provide the complete dissolution profile data (individual values, means, RSDs and plots) for the <sup>(b)(4)</sup> batches and Phase IIb reference batches supporting the f2 similarity values reported in Table 29 of Section 3.2.P.2.3.

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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FARIBA IZADI  
08/07/2012

**From:** Izadi, Fariba  
**Sent:** Tuesday, July 24, 2012 2:58 PM  
**To:** Lewis, Gary [JRDUS]  
**Subject:** NDA 204384- (TMC 207) Inquiry Regarding Number of Patients Enrolled In  
The Investigation Sites for Trial No. C208 and C209

**Importance:** High  
Dear Gary,

Please provide an updated list of investigation sites, investigators, and current number of subjects enrolled in each investigation site for Study C208 (Stages 1 and the ongoing Stage 2) and the ongoing Study C209. If you have provided this information in the NDA submission, please provide where the information is located.

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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FARIBA IZADI  
08/07/2012

**From:** Izadi, Fariba  
**Sent:** Thursday, July 19, 2012 2:10 PM  
**To:** Lewis, Gary [JRDUS]  
**Subject:** RE: NDA 204-384 TMC207 Efficacy Sub-Group Analysis by Age, Gender, and Race

**Importance:** High

Dear Mr. Lewis,

We are reviewing your submission sent on June 29, 2012 for NDA 204384 (TMC 207) and have the following information request.

Please conduct efficacy sub-group analyses by age, gender, and race for stage 2 of the study 208. Please let me know if you think you will be unable to submit this by July 25th.  
Best regards

Fariba

---

**From:** Lewis, Gary [JRDUS] [mailto:GLewis3@its.jnj.com]  
**Sent:** Thursday, July 19, 2012 9:21 AM  
**To:** Izadi, Fariba  
**Subject:** NDA 204-384 TMC207 Efficacy Sub-Group Analysis by Age, Gender, and Race

Dear Fariba:

Reference is made to your 17 July 2012 phone call to inquire about efficacy sub-group analyses by age, gender, and race. Specifically you wanted to know where this information could be found in the NDA for TMC207.

In the TMC207 NDA, the subgroup analyses by age, gender, and race were conducted for safety only. For efficacy, the subgroup analyses by age, gender, and race were not performed. For efficacy, limited pooling was done, because of the limited number of studies and differences in trial design (placebo controlled versus open label and the shorter duration of TMC207 dosing in C208 Stage 1 ) with a focus in the ISE on individual study results. For these studies, the subgroup analyses focused primarily on the disease characteristics/microbiologic status and less on demographical data.

Should you have any questions or need more information regarding this subject matter, please do not hesitate to contact me. I will also give you a quick call today to follow up.

Kind regards,

Gary

Mobile: (b) (6)

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FARIBA IZADI  
08/07/2012



NDA 204384

**NDA ACKNOWLEDGMENT**

Janssen Research and Development, LLC  
Attention: Gary Lewis  
Associate Director, Global Regulatory Affairs  
920 U.S. Highway 202  
P.O Box 300  
Raritan, NJ 08869-0602

Dear Mr. Lewis:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: TMC 207

Date of Application: June 28, 2012

Date of Receipt: June 29, 2012

Our Reference Number: NDA 204384

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 28, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Infective Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Fariba Izadi, Pharm.D., Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

*{See appended electronic signature page}*

Frances V. Le Sane  
Chief, Project Management Staff  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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/s/  
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FRANCES V LESANE  
07/10/2012



IND 69,600

**MEETING PRELIMINARY COMMENTS**

Janssen Research & Development, L.L.C  
Attention: Gary Lewis  
Associate Director, Global Regulatory Affairs  
920 U.S. Highway 202, P.O. Box 300  
Raritan, NJ 08869-0602

Dear Mr. Lewis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TMC207 (bedaquiline).

We also refer to your April 16, 2012, correspondence, received April 16, 2012, requesting a meeting to discuss optimized manufacturing process conditions and controls that will reflect the manufacture conditions of a subset of the Design of Experiments (DoE) batches at [REDACTED] (b) (4) for which passing f2 similarity factors were achieved against the three chosen clinical reference batches..

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 21, 2012, 1:00 – 2:00 pm, EST between Janssen Pharmaceutical and the Division of New Drug Quality Assessment. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

Question:

Does the FDA agree that if the Sponsor limits manufacturing at (b) (4) to the conditions for which the f2 criterion has been demonstrated to meet acceptance limits when compared to all 3 clinical phase IIb reference batches (i.e., (b) (4) (b) (4) coupled with the proposed IPCs on tablet appearance, hardness and weight, then a waiver of a bioequivalence study between tablets from the Janssen R&D development site and those manufactured at the (b) (4) commercial site will be granted?

**Agency Response:**

*Yes, the biowaiver can be granted if similarity of the drug product manufactured at the two sites is supported by dissolution profile comparison and f2 testing using the dissolution method that is deemed Acceptable by the Agency. As biowaivers are generally granted during the NDA review, please include the request and its supporting data in the NDA.*

*The proposal above seems like a reasonable approach. Please plan to include the following information in your NDA.*

- *A comparative description of equipment, scale and process differences between Janssen R&D and the (b) (4) commercial site.*
- *Batch analysis for three drug product lots manufactured at (b) (4) with drug substance manufactured by (b) (4)*
- *A description of the factors, ranges, and results for the drug product process design of experiments; for example, a graphical or tabular summary of input data that shows the multivariate combinations used and the statistical analysis relating the process inputs to the responses. A description of scale for the experiments should also be included.*
- *A description of the statistical analysis and conclusions used to establish the in-process controls for tablet hardness.*
- *A complete description of the commercial scale drug substance and drug product manufacturing processes is required and should include all process parameters. Therefore, include a master batch record and/or a detailed manufacturing process description in section S.2.2 (drug substance) and P.3.3 (drug product) of the application for each site (if processes are different). The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.*
- *At the time of NDA submission, a complete stability data package representative of the final commercial manufacture process train and based on previous communications with the FDA:*
  - *At least 6-months stability data from accelerated and 12-months long-term conditions for 3 drug substance batches from (b) (4) (b) (4)*
  - *In addition to the drug product primary stability data from Janssen R&D, at least 6 months accelerated and long-term stability data from 3 batches*

manufactured at (b) (4) using drug substance manufactured by (b) (4)  
(b) (4)

*Please note that stability updates provided during the NDA review cycle may or may not be reviewed depending on available resources.*

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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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.**  
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/s/  
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RAPTI D MADURAWA  
05/17/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 69600

**MEETING MINUTES**

Tibotec, Inc.  
Attention: Gary Lewis, MS  
Associate Director, Global Regulatory Affairs  
920 Route 202  
P.O. Box 300  
Raritan, NJ 08869-0602

Dear Mr. Lewis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TMC 207.

We also refer to the meeting between representatives of your firm and the FDA on October 7, 2011. The purpose of the meeting was to discuss the content and format of an accelerated New Drug Application (NDA) for the use of TMC207 in the treatment of Multi Drug Resistant Tuberculosis (MDR-TB).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Fariba Izadi, PharmD, Regulatory Health Project Manager at (301) 796-0563.

Sincerely,

*{See appended electronic signature page}*

John Farley, MD, MPH  
Acting Division Director  
Division of Anti-Infective Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** October 7, 2011  
1:00 PM.-2:00 PM (EST)

**Meeting Location:** Food and Drug Administration  
Building #22, Conference Room #1311  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

**Application Number:** IND 69600  
**Product Name:** TMC 207  
**Indication:** Treatment of Multi Drug Resistant Pulmonary Tuberculosis  
**Sponsor/Applicant Name:** Tibotec

**Meeting Chair:** John Farley, MD, MPH  
**Meeting Recorder:** Fariba Izadi, Pharm.D

**FDA ATTENDEES**

Edward Cox, MD MPH Director, Office of Antimicrobial Products  
John Farley, MD MPH Acting Division Director  
Sumati Nambiar, MD MPH Deputy Director for Safety  
Eileen Navarro-Almario, MD Clinical Team Leader  
Anne Purfield, Ph.D Clinical Microbiology Reviewer  
Lynette Berkley, Ph.D Clinical Microbiology Reviewer  
Karen Higgins, Sc.D Statistics Team Leader  
Xianbin Li, Ph.D Statistics Reviewer  
Dakshina Chilukuri, Ph.D Acting Clinical Pharmacology Team Leader  
Seong Jang, Ph.D Clinical Pharmacology Reviewer  
Rapti Madurawe, Ph.D ONDQA, Branch Chief  
Fariba Izadi, Pharm.D Regulatory Health Project Manager  
Balajee Shanmugam, Ph.D Product Quality Reviewer  
Deepika Arora Lakani, Ph.D Biopharmaceutics Reviewer  
Caroline Fukuda Regulatory Health Project Manager

Dorota Mateka, Ph.D  
Manizheh Siahpoushan, Pharm.D

Product Quality Team Leader  
Safety Evaluator, Division of Medication Error Prevention  
and Analysis

Zachary Oleszczuk, Pharm.D

Team Leader, Division of Medication Error Prevention and  
Analysis

**TIBOTEC ATTENDEES**

Koen Andries, DVM, PhD

Microbiology Leader, TMC207

Lindsay Cobbs

Associate Director Regulatory Affairs, FDA Liaison

Brian Dannemann, MD

Medical Leader, TMC207

Tine De Marez, PhD, MBA

Clinical Project Management Leader, TMC207

Robin Keen

VP, Global Regulatory Affairs

Ruud Leemans, MSc

Chem Pharm Leader

Gary Lewis, MS

North American Regulatory Leader, TMC207

Nacer Lounis, PhD

Clinical Microbiology Expert, TMC207

Paul Meyvisch, MS

Statistics Leader, TMC207

Thomas Pituk, Ph

CMC Regulatory Affairs

Ilham Smyej, PhD

Preclinical Development Leader, TMC207

Els Van Beirendonck, PharmD

Regulatory Leader, TMC207

Rudolf Van Heeswijk, PharmD, PhD Clinical Pharmacology Leader, TMC207

Representative from (b) (4) for TB Drug Development

Daniel Everitt, MD

Senior Director, Clinical Development

**BACKGROUND**

On July 28, 2011, Tibotec submitted a Pre-NDA meeting request. The briefing package was submitted on September 01, 2011 and contained the questions noted below in **bold type**. Additional CMC information was emailed to Division on September 03, 2011. The Division provided preliminary comments to the questions, via email on September 04, 2011. These are identified as "**FDA Response**" below. Tibotec responded to the Division's preliminary responses via email on October 06, 2011. These are identified as Sponsor Response to FDA comments. In addition, the Sponsor provided slides to facilitate the discussions. Discussion that took place during the meeting is captured under "*Meeting Discussion*" in italics.

**DISCUSSION**

**Question 1**

For background drugs we will provide sensitivity results (Sensitive [S]/Resistant [R]) for all clinical isolates of *M. tuberculosis* on 7H11 solid agar medium.

As it is premature to establish critical concentrations for TMC207, we will provide MICs (minimal inhibitory concentrations) for all clinical isolates of *M. tuberculosis*, and calculate the

MIC<sub>50</sub> and MIC<sub>90</sub> values. MIC data were generated by two methods:

1. liquid medium (REMA method in 7H9 broth)
2. solid agar medium (7H11 agar).

Our results indicate that the REMA method is the most reliable and, therefore REMA results will be used in the appropriate section of the label. Does the Agency concur with this approach?

#### **FDA Response**

We recommend that analysis data sets for all susceptibility tests by both the Resazurin Microtiter Assay Plate (REMA) and the agar medium methodologies be sent to FDA. Analysis data sets contain raw and derived variables that represent the analyses performed by the sponsor and can be used by the FDA reviewers to replicate and validate those analyses. We advise you to use susceptibility test methods that have been validated by the Clinical and Laboratory Standards Institute (CLSI) M24-A2 document. If the test methodology has not been validated by the CLSI please include test parameters for our review. All susceptibility test results must be accompanied by quality control results for each batch of tests.

#### **Sponsor Response to FDA comments**

We recently identified the root cause of the increased MICs of TMC207 when using the 7H11 agar method and we have also learned that the quality control reference strain (H37Rv) was not included in all the REMA testing.

We are now repeating both the REMA method and the agar proportion method. For TMC207 we intend to only include these repeated agar and REMA MICs in the submission. Assuming the performance of the two methods is consistent, we propose to only describe the REMA results of TMC207 in the C208 and C209 study reports. Detailed description of the test parameters and results of both methods will be discussed in the Clinical Microbiology Reports and Microbiology Summary.

#### **Meeting Discussion:**

*The Division asked that the test parameters for only the REMA method be submitted before submission of the study reports.*

*The Division also asked Tibotec to provide detailed results of both REMA and agar proportion testing so that the Division can determine if both methods provide equivalent results. The Division agreed that if the performance of both the REMA method and the agar proportion method are equivalent that only REMA results can be provided in the C208 and C209 study reports.*

#### **Question 2**

The Applicant has no intentions to mention the doses for TMC207 in the summary of drug-drug interaction trials in Sections 7 and 12.3 of the USPI, to avoid any potential confusion regarding dosing requirements. Misinterpretation of this information could lead to overdosing of TMC207

during the intermittent dosing period (Weeks 3 to 24). Does the Division agree with the proposed format for the presentation of the drug-drug interaction trials?

**FDA Response:**

Your proposal for the presentation of drug-drug interaction information in the label is a review issue. Based on the current information that you have provided, we agree that the TMC207 doses may not need to be mentioned in the summary of drug-drug interaction trials in Section 7. However, we may require that you describe the essential results of the drug-drug interaction trials with the TMC207 doses used in each trial in Section 12.3.

**Sponsor Response to FDA comments**

Agreed

**Meeting Discussion:** *No further discussion was necessary.*

**Question 3**

The Company plans to provide narratives for all SAEs; all AEs leading to discontinuations; all grade 3 and 4 Standardized MedDRA Queries (SMQs) of special interest; and treatment-emergent QTcF > 500 ms. CRFs will be provided for these subjects. Does the Agency agree?

**FDA Response:**

The Agency agrees with the proposed plan to submit narratives for the listed items.

**Sponsor Response to FDA comments**

No comments

**Meeting Discussion:** *No further discussion was necessary.*

**Question 4**

If the Division requests additional CRFs during the NDA review, Tibotec can usually provide them within 2-10 days depending on the number of CRFs requested. Does the Agency agree with the proposal for the timeline of submission of requested CRFs during the NDA review period?

**FDA Response:**

The Agency agrees with the proposed timeline of 2-10 days for submission of requested CRFs during the NDA review period.

**Sponsor Response to FDA comments**

No comments

**Meeting Discussion:** *No further discussion was necessary.*

**Question 5**

In accordance with the FDA guidance for providing regulatory submissions in electronic format, Tibotec plans to submit electronic datasets as SAS transport files (.xpt) and corresponding data definition files (.xml files). Is this proposal acceptable to the Agency?

**FDA Response:**

You have proposed to submit electronic datasets as SAS transport files (.xpt) and corresponding data definition files (.xml files). In addition, on page 42 of the briefing document, the following additional detail was provided:

- Phase 1 studies: tabulations in CDISC SDTM format, no ADaM datasets
- Phase 2 and thorough QT study: tabulations in CDISC SDTM format and analysis data in ADaM format
- Pooled safety analysis: analysis data in ADaM format

The above proposal is acceptable to the Agency.

**Sponsor Response to FDA comments**

No comments.

Please note, however, that our submission will be based on the current dataset, and not on the dataset on which the topline 24 week analysis was done (database cut-off: March 2010). Please confirm that this is acceptable.

**Meeting Discussion:** *The Sponsor stated that they have not changed the locked database; they have built on the locked database and added the new information to it. They stated that the most recent 24- week analysis is identical to the previously conducted primary efficacy analysis.*

**Question 6**

Tibotec plans to submit annotated ECG (aECG) waveforms only for the two Phase II trials (C208 and C209), and the Phase I QT/QTc study (TBC1003). Does the Agency agree?

**FDA Response:**

The Agency agrees with the submission of annotated ECGs for trials C208, C209 and TBC1003.

**Sponsor Response to FDA comments**

No comments

Meeting Discussion: *No further discussion was necessary*

**Question 7**

The Summary of Clinical Safety (SCS) in the MDR-TB NDA will include safety data from completed Phase I trials and safety data from Phase II trials in subjects with MDR-TB. Safety data from the 2 Phase II trials, C208 and C209, will be pooled. Details on the plans for the integration of safety data are provided in the draft Phase I safety pooling SAP and the draft Phase II safety pooling SAP. The draft Phase II safety pooling SAP includes plans for summaries of demographic and baseline characteristics of the trial population, completion/withdrawal information, and extent of exposure to study drug therapy. Summaries of treatment-emergent adverse events, clinical laboratory tests (hematology and serum chemistry), cardiovascular safety and vital sign measurements will be presented by treatment group. Summaries of the key safety measures by subgroups of interest will also be included. The draft Phase I safety pooling SAP includes plans for pooled safety data from 8 Phase I trials in healthy volunteers. The Phase I safety pooling will be limited to summaries of demographic and baseline characteristics of the trial population, completion/withdrawal information, adverse events and extent of exposure to study drug therapy. Is the proposed plan for summarizing the clinical safety as described in the draft Phase I safety pooling SAP and the draft Phase II safety pooling SAP acceptable to the Agency?

**FDA Response:**

The draft Phase 2 safety pooling SAP describes the pooling of the studies in which TMC207 was administered in combination with a background regimen (C208, both Stage 1 and 2; C209). Not included is trial C202, a phase IIa EBA trial which will be summarized separately in the SCS. The Agency agrees that safety data for C208 and C209 can be pooled as one presentation of safety data. However, we also request that the safety data for C208 and C209 be presented separately for two reasons. First, C208 was a double blind trial in patients with newly diagnosed MDR-TB, while C209 was an open label trial of non-newly diagnosed MDR-TB patients. These differences in design and study population may result in differences in the safety profile. Second, with respect to the package insert, safety information from controlled trials would be presented separately from safety information obtained from uncontrolled trials, and therefore it would be useful to present and analyze the information separately in anticipation of how safety information would be presented in the package insert.

We understand the 96 week follow up for trials C208 and C209 are ongoing, please clarify the duration of safety follow-up data that will be reported for both C208 and C209 at the time of NDA submission in Feb 2012.

The draft Phase I safety pooling SAP includes the following phase I trials: Single TMC207 dose trials: CDE-101 (first and second part), CDE-103, C108, C110, and C111. Multiple TMC207 dose trials: CDE-102, C104, C109. Excluded are trials which studied special populations (moderate hepatic impairment, HIV infected subjects). Also excluded is trial TBC1003, a iTQ trial which will be discussed separately.

The Agency agrees with the proposed plan for summarizing the clinical safety as described in the draft Phase I Safety Pooling SAP.

**Sponsor Response to FDA comments**

Agreed. However, we would like to briefly discuss how we plan to present the safety data in the SCS to ensure that this meets the Agency's requirements at the 7 October 2011 meeting.

To clarify, the investigational treatment phase was 24 weeks in C208 and C209. In the datasets on which the submission is based, the total duration of time in the study from baseline is at least 72 weeks in C208 and at least 24 weeks in C209. In the C208 study, the median duration of time in the study from baseline is 94 weeks (range 2-125). In the C209 study, the median duration of time in the study from baseline is 38 weeks (range 1-81). Does this information address the Division's concerns?

**Meeting discussion:**

*To facilitate the discussion, Tibotec presented slides (Slides 2, 3, 4, 5) for the key safety data tables C208 (Stage 1 and Stage 2) and C209. Tibotec indicated that the data will be presented separately for C208 and C209 studies. They also stated that the safety data from C208 Stage 2 will be presented in separate columns in the pooled safety analysis tables in the SCS. Tibotec indicated that the incidence of adverse events were considerably lower in C209 compared to C208 (during the investigational period).*

*The Division stated that it is their understanding that the 96-week follow-up period for trials c208 and c209 is ongoing but expressed that Tibotec needs to clarify how much of safety follow-up data information will actually be reported beyond treatment. The Division recommended that the treatment results (up to 24 weeks and all data beyond the 24 weeks) be presented.*

*In response to Division's question, Tibotec clarified that the total duration of time in the study is at least 72 weeks for C208, and that all subjects would have at least 72 weeks of data or up to the time of discontinuation of study participation for those lost to follow-up.*

**Question 8**

The SCS in the MDR-TB NDA will include a detailed safety update with 17 November 2011 cut-off for all ongoing Tibotec trials and will include high level safety information limited to SAEs and pregnancies for trials of TMC207 conducted by other sponsors (i.e. (b) (4) and NIH). Is this acceptable to the Agency?

**FDA Response:**

The SCS will include safety information up to 17 Nov 2011 for all ongoing Tibotec trials. In your position statement on page 46 of the briefing document, you have stated that "a summary of enrollment, completions, and trial discontinuations due to AEs that occur prior to cut-off 17 November 2011" will also be included.

The Agency agrees with above proposal.

**Sponsor Response to FDA comments**

No comment.

**Meeting Discussion:** *No further discussion was necessary.*

**Question 9**

Tibotec intends to submit a NDA for TMC207 for the indication of MDR-TB in February 2012. Provided that a priority review is granted for the MDR-TB NDA, based on the fast track status of TMC207, Tibotec proposes to provide a 4 Month Safety Update (4MSU) for the MDR-TB NDA in June 2012. Does the Agency agree that this is acceptable?

**FDA Response:**

You are proposing to submit a NDA for TMC207 for the indication of MDR-TB in February 2012 and the later submission of a 4 Month Safety Update (4MSU) in June 2012. Assuming that a priority review is granted as you have stated above, the Agency's action date would be in Aug 2012 with a probable Advisory Committee meeting in July 2012 (see response to Question 13). To meet these deadlines and yet ensure the complete and timely review of safety data submitted in June 2012, this data cannot be submitted as cumulative listings. The 4MSU data must be analyzed and summarized in the context of the safety profile established at the time of NDA submission in Feb 2012. Any newly identified safety signals should be clearly brought forth and worked up as thoroughly as possible (e.g. looking at nonclinical data, post marketing data).

**Sponsor Response to FDA comments**

**Clarification:**

In addition to the cumulative listings, we agree that in the 4MSU, we will analyze and summarize this additional safety data from November 17, 2011 through March 09, 2012 in the context of the safety profile established at the time of the NDA submission. The 4MSU will be submitted in June 2012.

Please note that in C208 and C209, all subjects have completed the 24 wk investigational period. Enrollment in the phase 3 C210 study is anticipated to start in 2Q2012.

**Meeting Discussion:** *Any new safety signal and analysis of all the ADRs 7-15 day reports should be completed and submitted to FDA.*

**Question 10**

The 4MSU will include a cumulative listing of pregnancies, deaths, SAEs, and a summary of enrollment, completions, and trial discontinuations due to AEs for all Tibotec sponsored trials

that are ongoing at the time of the NDA submission. CIOMS I reports will be provided for the ongoing Tibotec sponsored trials. Given that the 4MSU will be provided in June 2012, the safety data contained in the 4MSU will summarize these events reported after the NDA cut-off date of 17 November 2011 through 09 March 2012 (i.e, the same date of data cut-off as (b) (4) IND Annual Report). For ongoing trials of TMC207 conducted by the (b) (4) we propose to refer to the (b) (4) IND Annual Report through 09 March 2011. For ongoing trials of TMC207 conducted by the NIH we will include high level safety information limited to SAEs and pregnancies. Does the Agency agree that this is acceptable?

**FDA Response:**

You are proposing to submit 4MSU data which will consist of safety data as described above collected from 17 Nov 2011 through 9 Mar 2012. Please see our response to Question 9 regarding the submission of this data in an analyzed and summarized format. The Agency agrees with your proposal to refer to the (b) (4) IND annual report for ongoing trials of TMC207 conducted by the (b) (4). For ongoing trials of TMC207 conducted by the NIH, you have indicated you will include "high level safety information limited to SAEs and pregnancies". Please include deaths and a summary of discontinuations due to AEs as well.

**Sponsor Response to FDA comments**

We acknowledge the Division's request to also include deaths and a summary of discontinuations due to AEs for ongoing trials of TMC207 conducted by the NIH. We will work with the NIH to make sure that these data are available.

**Meeting Discussion:** *No further discussion was necessary*

**Question 11**

The SCE in the MDR-TB NDA will include efficacy data from the primary and key secondary analyses from C202, C208, Stage 1, and from the pivotal 24 week analysis in C208, Stage 2. In addition, the SCE will include follow-up efficacy data beyond 24 weeks of C208, Stage 2 which will be jointly presented with the efficacy data collected on C209 in order to allow comparison of efficacy results across trials. Due to the differences in trial design and population, efficacy data will not be presented in a pooled fashion. Sub-group analyses will be presented to examine the following variables in relation to efficacy by extent of lung cavitation, HIV status, region, and by baseline resistance to background medication. Is this acceptable to the Agency?

**FDA Response:**

You propose to present efficacy data from three Phase II trials, namely C202, C208 and C209. You have stated "the SCE will include follow-up efficacy data beyond 24 weeks of C208, Stage 2". Clarify the total duration of Stage 2 efficacy data that will be submitted at the time of NDA submission in Feb.2012.

We refer you back to FDA's faxed comments (dated Feb 7, 2011) for the end of phase 2 meeting held on Feb 9, 2011. FDA agreed that an NDA submission under the accelerated approval regulations could consist of complete efficacy data from Stage 1 of Study C208 (i.e., 96 weeks off TMC207 therapy), and 24 week data from interim analysis from Study C209. In addition, we requested the following additional data at the time of NDA submission:

- Sensitivity analyses on Stage 1, week 24 efficacy results
- Explanation regarding the lack of observed "dose-response" for Stage 2 week 24
- Clinical data from Studies C208 and C209
- 36 week efficacy data for Study C208 Stage 2

Please ensure that the above information is included in your SCE at the time of NDA submission.

Regarding the last bullet point listed above, we had asked for Study C208 Stage 2 week 36 efficacy data to ensure durability of effect. This would be 12 weeks (3 months) off study drug. The Division's thinking on the optimal timing of endpoints is still evolving, and we believe a more appropriate time point to consider durable effect for MDR-TB may be 48 weeks (6 months) off study drug. We understand this may affect your anticipated NDA submission in Feb 2012; to better understand how to best proceed, we ask that you project how many patients will have 48 week efficacy data as a proportion of the total number of eligible patients enrolled in Study C208 Stage 2 at the time of planned NDA submission.

The planned subgroup analyses according to extent of lung cavitation, HIV status, region and by baseline resistance to background medication is acceptable.

**Sponsor Response to FDA comments**

- Please note that the primary efficacy analysis in Stage 1 was a treatment comparison at week 8. Additional efficacy analyses to week 24 have been conducted on the Stage 1 data to be consistent with the efficacy analyses of Stage 2. Please clarify that this addresses your question.
- Explanation regarding the lack of observed "dose-response" for Stage 2 week 24
- We agree to discuss this in the NDA.
- Clinical data from Studies C208 and C209 Agreed. See below.
- 36 week efficacy data for Study C208 Stage 2 Agreed. See below.

To clarify, the investigational treatment phase was 24 weeks in C208, Stage 2. In the dataset on which the submission is based, the total duration of time in the study from baseline is at least 72 weeks. The median duration of time in the study from baseline is 94 weeks (range 2-125). To address the durability of the treatment effect observed at wk 24, a comparison of the responder rates at wks 36, 48, 60, and 72 will be provided in the submission.

**Meeting Discussion:** *No further discussion was necessary.*

**Question 12**

Tibotec proposes to present a summary of the microbiology data in the Clinical Study Reports (CSRs) of the C208 and C209 trials, and in the Microbiology section of the SCE. The individual subject results are intended to be reported in the Clinical Microbiology Reports for C208 and C209. In addition, a summary of all the nonclinical and clinical microbiology studies is intended to be provided in the Microbiology Summary Report. Does the Agency agree with this proposal?

**FDA response**

The "Guidance for Industry-M4E: The CTD-Efficacy" recommends the placement of Microbiology information in two sections of the eCTD. These sections include the summary reports which describe the results and applicant proposals regarding the Microbiology section of product labeling and the study reports that are the scientific basis of the summary reports. Both of these sections should be cross referenced to each other.

1. In Module 2, Section 2.7 Clinical Summary, subsection 2.7.2.4 Special Studies; provide the Microbiology summary report containing the subheadings described in the proposed Microbiology guidance document "Guidance for Industry Microbiological Data for Antibacterial Drug Products-Development, Analysis, and Presentation". This section will contain the summary report formerly submitted in Item 7 of the NDA. Thus it contains the information used to justify the Microbiology information placed in the product package insert.
2. Provide the nonclinical and clinical study reports used in the construction of the summary information provided in subsection 2.7.2.4 above in Module 5 Clinical Study Reports, subsection 5.3.5.4 Other Study Reports. All of the study reports used to construct the summary report presented in Section 2.7.2.4 should be cross-linked to the summary report.

**Sponsor Response to FDA comments**

No comment.

**Meeting Discussion:** *No further discussion was necessary.*

**Question 13**

Recognizing that the decision regarding a need for an FDA Advisory Committee Meeting prior to the approval of an NDA will be addressed during the review, does the Division anticipate that the TMC207 NDA will be the subject of an FDA Advisory Committee Meeting based on the data presented in this package supporting the NDA?

**FDA Response:**

As TMC207 represents a new chemical entity, the Division anticipates that the TMC207 NDA will be the subject of an FDA Advisory Committee meeting.

**Sponsor Response to FDA comments**

No comment.

*Meeting Discussion: No further discussion was necessary.*

**Question 14**

Tibotec intends to provide Financial Disclosure information in Module 1.3.4 only for the following clinical trials: Thorough QT trial TBC1003 and the Phase IIb trials C208 and C209. Does the Division agree with Tibotec's proposal regarding the provision of financial disclosure information?

**FDA Response:**

Disclosure of financial interests and arrangements is required only for covered clinical studies, specifically those studies relied upon to provide support for the effectiveness of a product (21 CFR 54.2(e) and 54.3).

The Agency agrees with the submission of financial disclosure information for trials TBC1003, C208 and C209. If the division determines that other studies will be relied upon to provide support for the effectiveness of a product, we may request the submission of financial disclosure information at a later time.

**Sponsor Response to FDA comments**

No comment.

*Meeting Discussion: No further discussion was necessary.*

**Question 15**

The sponsor plans to submit SAS transport files, some of which could be up to 400 MB in size. Is this acceptable to the Agency?

**FDA Response:**

Up to 400 MB in size is acceptable. Please refer to the Study Data Specifications (pg. 3) for additional information:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>.

**Sponsor Response to FDA comments**

No comment

**Meeting Discussion:** *No further discussion was necessary.*

**Question 16**

The applicant intends to include a second drug substance manufacturer, (b) (4) (b) (4) in the NDA. Does the Agency agree that the data and information that we propose to include in the NDA is sufficient to support the approval of (b) (4) as an additional drug substance manufacturer?

**FDA Response**

The approaches proposed and the data planned to be submitted seem reasonable. In addition to this, 6-months stability data from accelerated and 12-months long-term conditions for 3 batches should be submitted. Additionally, release data of three drug product lots manufactured using drug substance manufactured by (b) (4) should be submitted. In referring to the various manufacturing facilities, the Pre-NDA package is random addressing a few by the name of the manufacturer and some by the location. To minimize confusion, it is requested that you please follow a uniform system in referring to the various manufacturers.

**Sponsor Response to FDA comments**

- We wish to clarify that the NDA will include two commercial manufacturers of drug substance, and the intent is to be able to use drug substance from either source to manufacture commercial drug product.
- The two drug substance sources are as follows:
  - (b) (4)
  - (b) (4)
- As requested, to minimize confusion, a uniform system will be used in the NDA to refer to these manufacturers.
- The NDA will include 18 month primary stability data, including long term and accelerated data, on 3 batches of drug substance manufactured by (b) (4). The 3 validation batches manufactured by (b) (4) will be placed on long term and accelerated stability.
- Equivalency between sites is assured by the use of the same synthesis process and manufacturing equipment (apart from some minor differences as explained in the Company Position), the use of the same raw materials, and applying the same control strategy throughout the synthesis process (same process parameter ranges, same quality of raw materials, same specifications for starting materials, intermediates, and final drug substance).
- Batch release data on (b) (4) drug substance (including 3 validation batches) and 3 validation batches of (b) (4) drug substance will be included in the NDA, to demonstrate that they are equivalent and comply with the proposed commercial drug substance specification covering all critical quality attributes of the drug substance, including the impurity profile and relevant physical properties such as particle size and polymorphism.

Drug product manufactured using (b) (4) drug substance will not be available at time of NDA submission.

**Meeting Discussion**

*The Division stated that since Tibotec has asked for priority review of this NDA, it is important to have a complete package at the time of the NDA submission. The Division expressed that since this is a new molecular entity and there is very limited data about its manufacturing history, it is essential to have more data at the time of submission. The Division clarified that Tibotec needs to provide 6 month accelerated data and 6 month stability data for the new manufacturers at the time of the submission. The Division further explained that this will reduce the possible complications if there is a change or a need for retesting and that the quality of the data will play an important role in the review process.*

*The Division suggested adding (b) (4) as a post approval change and stated that usually this is considered a 4 month review period. Tibotec stated that it is important for them to have approval of all proposed sites and the post approval process in some of the countries could be complicated.*

*Tibotec clarified that the existing drug substance facilities (b) (4) would be phased out and that (b) (4) would be the sole commercial drug substance manufacturing facility.*

*The Division reminded Tibotec that all facilities must be ready for inspection at the time of NDA submission to which Tibotec agreed.*

*The sponsor asked if it would be acceptable to provide 3 months stability data on (b) (4) batches in the original NDA and a 6 month data during the review. The Division expressed that this would be very difficult and reiterated that their policy is for the NDA package to be complete at the time of the submission.*

**Question 17**

The applicant has developed a new dissolution method (b) (4) as the regulatory method for this product. The NDA will include the method description and validation data for this new method, along with data and information on the development and discriminating capabilities of this method. Does the Agency agree that the new proposed method is appropriate for its intended use?

**FDA Response:**

The approach seems reasonable. During the NDA submission, please include:

a) Detailed description of the dissolution method's developmental parameters (i.e., selection of the apparatus, in vitro dissolution media, agitation/rotation speed (e.g., sink conditions, etc.) used to select the proposed dissolution method as the most appropriate. The testing conditions used for each test should be clearly specified.

b) The testing conducted to demonstrate the discriminating capability of the selected dissolution test. Include the dissolution data for the variables. To demonstrate the discriminating capability of the selected test, provide the similarity f2 values for each tested variable, using the target formulation as the reference.

c) The complete dissolution profile data (e.g., individual, mean, RSD, profiles) that were collected during the development and validation of the dissolution test. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim)."

**Sponsor Response to FDA comments**

- a) We agree that the requested information will be included in the NDA.
- b) We agree to provide the requested information in the NDA.
- c) We agree to provide the requested information in the NDA.

**Meeting Discussion:**

*The Division found that acceptable.*

**Question 18**

The manufacture of the drug product primary stability batches is done by Janssen Research & Development (Beerse, Belgium), a Johnson & Johnson company. The commercial manufacturer for this product will be (b) (4). Does the Agency agree that the data and information that we propose to include in the NDA are sufficient to support the approval of the commercial drug product manufacturer?

**FDA Response:**

**CMC:**

Data and information proposed to be included in the NDA is acceptable. Since (b) (4) is the proposed commercial manufacturer, we expect at least 6-months accelerated and long-term stability data from 3 batches manufactured at (b) (4) using drug substance manufactured by (b) (4).

The robustness of the manufacturing process at both facilities should be unequivocally demonstrated by tested for polymorphic stability, blend uniformity etc among other attributes and supported by data to show no change during manufacture and over the shelf-life of the product.

**Biopharmaceutics:**

From a Biopharmaceutics standpoint, in vitro bridging studies will be needed to demonstrate similarity in the dissolution profiles from the two manufacturing sites (f2 similarity factor calculations). Your proposal of not assessing the f2 similarity factor and only considering the acceptability of the dissolution profiles by compliance to the acceptance criterion and visual comparison is not acceptable. The high variability that is being observed between-batches seem to be arising primarily because of the difference in the type of (b) (4) used in manufacturing

that batch [REDACTED] (b) (4) The within-batch variability is very low. Hence, F2 comparison is recommended to support the approval of the drug product manufacturer.

Please note that suitability of the acceptance criterion will be subject of NDA review

**Sponsor Response to FDA comments**

To be discussed at the 7 October 2011 meeting

- To clarify, as noted in Sponsor's Response to FDA's Comment on Question 16, the NDA will include two commercial manufacturers of drug substance, and the intent is to be able to use drug substance from either source to manufacture commercial drug product.
- The NDA will include 12 month primary stability data on 3 primary stability batches of drug product manufactured at [REDACTED] (b) (4) drug substance. Additionally, as requested by FDA, the NDA will contain 3 month stability data on 3 commercial scale drug product batches produced by [REDACTED] (b) (4) the intended commercial manufacturer. The [REDACTED] (b) (4) batches also use [REDACTED] (b) (4) drug substance. No data on drug product manufactured using [REDACTED] (b) (4) drug substance will be included in the NDA. We believe that equivalence of the drug substance produced by both of the drug substance manufacturers will be demonstrated at the drug substance level, and therefore, no stability data for drug product using [REDACTED] (b) (4) drug substance should be needed.
- The manufacturing process at [REDACTED] (b) (4) is being evaluated extensively by a full scale full factorial design of experiments for the following [REDACTED] (b) (4) homogeneity and tableting studies have been performed at [REDACTED] (b) (4) and will be reported in the NDA.
- The first batch after completion of the validation campaign at [REDACTED] (b) (4) with drug substance from [REDACTED] (b) (4) (b) (4) drug substance) will be produced [REDACTED] (b) (4) and put on post marketing stability.
- Please note that our original proposal of considering the acceptability of the dissolution profiles by compliance to the acceptance criterion and visual comparison is our preferred approach.
- We agree that the between-batches variability, which is related to the high discriminative capabilities of the dissolution method, is attributed to variation in the [REDACTED] (b) (4) which we consider to be typical process variation, and which is taken into account for establishing the [REDACTED] (b) (4) process design space.
- F2 calculations were performed for [REDACTED] (b) (4) batches (EX-TMC100TI-04, EX-TMC100TI-05, EX-TMC100T-06) vs. batches used in the pivotal Phase 2b clinical studies:

a) [REDACTED] (b) (4)

(b) (4)

b) (b) (4)

c) (b) (4)

The sponsor is willing to accept FDA's proposal to do the comparison based on the f2 calculations. However, it should be noted that the f2 comparisons between the (b) (4)

(b) (4)

**Meeting Discussion:**

Tibotec presented slides to compare the Dissolution profiles of the (b) (4) batches (EX-TMC100T1-004, EX-TMC100T1-005, EX-TMC100T1-006) with the dissolution profiles of all batches used in the phase IIb clinical studies which were produced at a smaller scale in Janssen Beerse (presented in Figure 5 of the Briefing Package and repeated hereafter). The dissolution profiles of the (b) (4) stability batches all fall within the range of batches used in the phase IIb clinical studies although the f2 criterion is not met. Tibotec stated that this demonstrates that the (b) (4) stability batches are comparable to relevant batches produced by Janssen and that no further comparison needs to be undertaken.

The Division stated that the visual comparison of dissolution profiles does not qualify for batch comparability. The Division suggested that Tibotec should attempt to justify the f2 failures by providing clinical data that may support the similarity of the batches. The Division stated that this can be done by performing subgroup analyses on clinical batches. Tibotec responded that it is very difficult to trace back multiple batches since some patients may have received drug product manufactured at more than one facility. The Division stated that they will provide further guidance. (Please see Post-Meeting Comments below).

The Division stated that the various dissolution profiles could be due to process variability and the discriminative capabilities of the dissolution method used. Tibotec indicated that the process variability is being evaluated and that the design space will be submitted in the NDA.

The Division requested the polymorph stability to be evaluated for the drug product.

The Division asked if the facilities have been inspected by the FDA. Tibotec stated that (b) (4) has been inspected, but (b) (4) has only been inspected by European authorities, not the FDA.

**Additional comments**

The Division asked if Tibotec intends to conduct a PK study in patients with severe hepatic impairment. Tibotec stated that currently they are not planning to do a study. The Division recommended excluding the subjects with severe hepatic impairment.

In response to Division's question, Tibotec stated that they will include a PK-PD analysis of TMC-207 in the NDA.

**Post-Meeting Comments:**

Please note that if similarity of drug product manufactured at the two sites cannot be supported using f2 comparison, the approval of the site change must be supported by data generated from an in vivo BE study comparing the drug products manufactured at the two sites. We recommend that the (b) (4) drug substance/ (b) (4) drug product be used in the BE study.

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/s/  
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JOHN J FARLEY  
11/04/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 69,600

Tibotec, Inc.  
Attention: Gary Lewis, MS  
Associate Director, Global Regulatory Affairs  
920 Route 202  
PO Box 300  
Raritan, NJ 08869-0602

Dear Mr. Lewis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TMC207.

We also refer to the end-of-phase 2 meeting between representatives of your firm and the FDA on February 9, 2011. The purpose of the meeting was to discuss the proposed overall development program for TMC207 and to discuss the results of Stage 2 analysis from the ongoing Phase 2 trial TMC207-TiDP13-C208, "A randomized, double-blind, placebo-controlled Phase 2 trial to evaluate the antibacterial activity, safety, and tolerability of treatment when TMC207 is added to a background regimen of MDR-TB therapy, compared to placebo, in subjects with newly diagnosed sputum smear positive pulmonary MDR-TB infection."

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Hyun Son, Pharm.D.  
Safety Regulatory Project Manager  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

Reference ID: 2923873

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** February 9, 2011  
**TIME:** 3:00 – 4:30 PM EST  
**LOCATION:** FDA/CDER  
10903 New Hampshire Ave  
Building 22, Room 1419  
Silver Spring, MD 20993  
**APPLICATION:** IND 69,600  
**DRUG NAME:** TMC-207  
**TYPE OF MEETING:** EOP2

**MEETING CHAIR:** Joette Meyer, Pharm.D.

**MEETING RECORDER:** Hyun Son, Pharm.D.

### FDA ATTENDEES: (Title and Office/Division)

|                                   |  |
|-----------------------------------|--|
| Edward Cox, M.D., MPH             | Director, Office of Antimicrobial Products |
| Renata Albrecht, M.D.             | Division Director                          |
| Eileen Navarro, M.D.              | Acting Deputy Director                     |
| Joette Meyer, Pharm.D.            | Clinical Team Leader                       |
| Owen McMaster, Ph.D.              | Pharmacology/Toxicology Reviewer           |
| Lynette Berkeley, Ph.D.           | Microbiology Reviewer                      |
| Karen Higgins, Sc.D.              | Statistics Team Leader                     |
| Xianbin Li, Ph.D.                 | Statistics Reviewer                        |
| Philip Colangelo, Pharm.D., Ph.D. | Clinical Pharmacology Team Leader          |
| Dakshina Chilukuri, Ph.D.         | Clinical Pharmacology Reviewer             |
| Hyun Son, Pharm.D.                | Senior Regulatory Management Officer       |

### EXTERNAL CONSTITUENT ATTENDEES:

|                                   |   |
|-----------------------------------|---|
| Koen Andries, DVM, PhD.           | Microbiology Expert, TMC207                                   |
| Myriam Haxaire-Theeuwes, D.D.S.   | Compound Development Team Leader, TMC207                      |
| Robin Keen                        | VP, Global Regulatory Affairs                                 |
| Lindsay Cobbs                     | Associate Director Regulatory Affairs, FDA Liaison            |
| Gary Lewis, M.S.                  | North American Regulatory Leader, TMC207                      |
| David McNeeley, MD                | Medical Leader, TMC207  |
| Paul Meyvisch, Msc.               | Lead Biostatistician, TMC207                                  |
| Ilham Smyej, PhD.                 | Preclinical Development Leader, TMC207                        |
| Rudolf Van Heeswijk, PharmD, PhD. | Human PK Expert, TMC207                                       |
| Brian Woodfall, MD                | Sr. Director, Global Clinical Development and Medical Affairs |
| Tina De Mauz, Ph.D. MBA           | (Clinical) Project Management Leader, TMC207                  |
| Els Van Beirendonck, Pharm.D.     | Regulatory Leader, TMC207                                     |

(b) (4)

## Development

### **BACKGROUND:**

Tibotec submitted the protocol for a Phase 2 study on November 9, 2006: TMC207-C208 (randomized, double-blind, placebo-controlled trial to evaluate the antibacterial activity, safety, and tolerability of treatment when TMC207 is added to a background regimen of MDR-TB therapy, compared to placebo, in subjects with newly diagnosed sputum smear positive pulmonary MDR-TB infection). This ongoing trial is being conducted in 2 consecutive stages: an exploratory stage of 8 weeks of treatment with TMC207 (Stage 1) and a proof-of-efficacy stage with 6 months of TMC207 treatment (Stage 2). Both stages are to be analyzed separately. On June 30, 2008, Tibotec requested a Type C meeting to discuss the results of the Stage 1 primary analysis. The meeting was held on September 23, 2008.

On September 30, 2010, Tibotec requested a Type B (end-of-phase 2) meeting to discuss the proposed overall development program for TMC207 for the treatment of MDR-TB, in combination with other anti-TB agents and also to discuss the results of Stage 2 analysis from Study TMC207-TiDP13-C208.

On January 5, 2011, Tibotec submitted a meeting package. On February 7, 2011, the Division sent preliminary comments to the questions posed in the meeting package. On February 9, 2011, Tibotec sent responses to the Division's preliminary comments (attached) and noted they primarily wished to focus on Questions 11 and 12, relative to the design of the proposed Phase 3 trial (Study C210), which was designed to support traditional approval. During the meeting, Tibotec presented slides to facilitate the meeting discussion (attached).

### **MEETING OBJECTIVES:**

- To discuss the adequacy of the Phase 2 trial TMC207-TiDP13-C208 and anticipated safety database to support accelerated approval of TMC207 for the treatment of MDR-TB
- To discuss the proposed human PK, microbiology and nonclinical package to support accelerated approval TMC207
- To discuss the design of the planned Phase 3 trial TMC207-TiDP13-C210.

### **DISCUSSION POINTS:**

Tibotec began the discussion with presentation of their slides to address the Division's responses to Questions 11 and 12 (see attached document containing Tibotec's questions and the Division's preliminary responses).

#### **Discussion of Question #11**

Tibotec discussed the rationale for the design of their proposed Phase 3 trial (C210) and explained that there is limited or no information available based on the literature and/or trials in MDR-TB that could be used to establish a non-inferiority (NI) margin. Specifically, there are no published randomized, placebo-controlled trials for MDR-TB. The Division acknowledged that prospective, randomized, placebo-controlled trials may not be available, but stated they are willing to consider other data which

may be available, including data gathered across studies. The Division also suggested Tibotec consider identifying unpublished databases. In particular, the Division requested Tibotec attempt to identify information which supports the need for 18 months of treatment instead of 12 months of treatment, i.e., identify outcome differences between 12 months versus 18 months of treatment and include any clinical findings observed at these time points.

Tibotec questioned whether they could initially design Study C210 as a superiority trial and then switch to a NI design, if they were able to support a margin (M1) for the determination of NI in the future. The Agency stated that a superiority trial with a potential switch to a NI design would be acceptable as long as the Division agrees to the NI margin and the data to justify M1 is based on information from outside of the trial. Tibotec questioned whether, in the absence of M1, there would be a robust way to process M2. The Division clarified that for the demonstration of efficacy and safety M2 needs to be as small as or smaller than M1; therefore M1 is a pre-requisite for the determination of M2.

The discussion turned to whether it would be possible to consider a superiority design using the proposed Arm C as the test arm and an Arm D as control, preferably in a blinded randomized study. Arm D would be added as another arm in the trial to act as a control to Arm C, i.e., similar to Arm C but without TMC207. The Division agreed that this could also be considered as a superiority trial to show efficacy for traditional approval of TMC207, using the proposed endpoint of failure/relapse. The Division noted that the sponsor would first need to be able to support the selection of the control regimen as standard of care in the country(ies) in which the study would be conducted.

The Division stated that they agreed with Tibotec's definition of the primary endpoint of failure/relapse in Study C210.

The Division also asked Tibotec if they have any data available on clinical responses. Tibotec replied that they did not collect clinical information in Stage 1 of Study C208, but are currently analyzing the clinical data from Stage 2. In addition, they are collecting additional clinical data in Study C209 using a PRO instrument. A PRO instrument will also be used in Study C210.

### **Discussion of Question #12**

The discussion proceeded to Question 12b. Tibotec indicated that they expect to have a high drop-out rate in Study C210, as in Study C208, and the differential treatment free follow-up period and imputation of all dropouts as failures will introduce substantial bias if both the test and control arms need to be followed for the same amount of time from randomization, since the treatment in the test arm is of shorter duration. They estimate that the majority of the relapses will likely occur in first six month after treatment and then more drop-out than relapse would be expected thereafter. The Division indicated that if the same time point from randomization is not used, then the study will be biased against the control arm (Arm A), since the control arm will have the longer duration of follow-up.

The Division indicated that sensitivity analyses could be conducted which would handle missing data differently; however, differential rates of missing data across treatment arms would be difficult to analyze. The protocol should have methods in place to maximize data collection and minimize missing data as much as possible. Tibotec assured the Agency that they will do everything they can to try and retain the patients in the study using creative methods of follow-up (e.g., collection of data by telephone). Tibotec wanted to clarify if the Division would be willing to accept clinical data (patient

doing well) in the absence of microbiological data. The Division encouraged Tibotec to collect follow-up data using any available means and will consider any, and all, data available.

Tibotec indicated some patients withdraw informed consent during Study C208 because it is difficult for them to comply with the study visits. Tibotec will continue to explore possible ways to retain patients in the study (e.g., by using social workers to go out to do the follow visits) and have already started employing drivers to bring patients to the clinical trial site for their visits in some areas.

In closing Tibotec noted they estimate to submit accelerated package in the first quarter of 2012 if the study design for Study C210 can be agreed upon.

The Division requested additional follow-up information to what was noted in the meeting package:

- The complete referenced publication discussing sterilization by TMC207 in the guinea pig model.
- Additional information on the patient who died from relapsed MDR-TB in the TMC207 arm of Study C208.

**ACTION ITEMS:**

1. Follow-up meeting within 3 months
2. Tibotec will a copy of the article on the sterilizing activity of TCM207 in guinea pigs
3. Tibotec will provide a summary on the patient in Study C208 that died from relapsed MDR-TB.
4. Tibotec will evaluate the need for *in vivo* drug interaction studies involving CYP1A1, 2C8, 2C18, 2C19 and 3A5.

**ATTACHMENTS/HANDOUTS:**

Tibotec Handout  
Tibotec Power Point slides

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HYUN J SON  
03/25/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

IND 69,600

MEETING MINUTES

Tibotec, Inc.  
Attention: Jenny Z. Lin, Pharm.D.  
Associate Director, Global Regulatory Affairs  
1020 Stony Hill Road, Suite 300  
Yardley, PA 19067

Dear Ms. Lin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TMC207.

We also refer to the meeting between representatives of your firm and the FDA on November 5, 2009. The purpose of the meeting was an End-of-Phase 2 discussion on specific Chemistry, Manufacturing, and Controls (CMC) aspects of the pharmaceutical development of TMC207.

A copy of the official minutes of the face-to-face meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Stephen P. Miller, Ph.D.  
Acting Chief, Branch IV  
Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment

Enclosure



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT**

|                                  |   |
|----------------------------------|---|
| <b>Sponsor Name:</b>             | Tibotec, Inc.   |
| <b>Application Number:</b>       | IND 69,600  |
| <b>Product Name:</b>             | TMC207  |
| <b>Meeting Requestor:</b>        | Jenny Lin, Pharm.D.<br>Associate Director/Global Regulatory Leader, Tibotec, Inc. |
| <b>Meeting Type:</b>             | Type B End-of-Phase 2 Meeting   |
| <b>Meeting Category:</b>         | Chemistry, Manufacturing and Controls (CMC)                                       |
| <b>Meeting Date and Time:</b>    | Thursday, November 5, 2009, 11:00 AM – 12:00 PM EST                               |
| <b>Meeting Location:</b>         | Food and Drug Administration,<br>White Oak Campus, Silver Spring, MD              |
| <b>Received Briefing Package</b> | October 2, 2009   |
| <b>Meeting Chair:</b>            | Rapti Madurawe, Ph.D.   |
| <b>Meeting Recorder:</b>         | Jeannie David, M.S.   |

**FDA ATTENDEES:**

**CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)**

*Office of Pharmaceutical Science/Office of New Drug Quality Assessment (ONDQA)*

Mark Seggel, Ph.D.                      Review Chemist  
Rapti Madurawe, Ph.D.                Pharmaceutical Assessment Lead  
Stephen Miller, Ph.D.                 Acting Chief, Branch IV  
Jeannie David, M.S.                  Regulatory Health Project Manager

*Division of Special Pathogens and Transplant Products (DSPTP)*

Hyun Sun, Pharm.D.                  Regulatory Health Project Manager

**EXTERNAL ATTENDEES:**

**TIBOTEC, INC. AND ASSOCIATES**

[REDACTED] (b) (4)

|                            |   |
|----------------------------|---|
| Ruxandra Govoreanu         | Senior Scientist/Analytical Development,<br>Johnson & Johnson Pharmaceutical Research and Development |
| Mahender Korapati, M.S.    | Program Manager/GPSG,<br>Johnson & Johnson Pharmaceutical Research and Development                    |
| Jenny Lin, Pharm.D.        | Associate Director/Global Regulatory Leader, Tibotec, Inc.  |
| Thomas Pituk, Ph.D., R.Ph. | Senior Director/Global CMC Regulatory Affairs, Tibotec, Inc.  |
| Laurent Schueller          | Senior Manager/ChemPharm Leader, Tibotec BVBA   |
| Guy Smans                  | Principal Scientist, Pharmaceutical Development   |

## BACKGROUND

Tibotec, Inc. requested a Type B meeting, letter dated August 19, 2009, to discuss specific Chemistry, Manufacturing and Controls (CMC) aspects of the pharmaceutical development of TMC207 as part of their End-of-Phase 2 discussions. A separate, clinical guidance meeting for this IND was held between Tibotec, Inc. and the Division of Special Pathogens and Transplant Products on September 23, 2008 (FDA Meeting Minutes dated November 6, 2008, briefing package dated August 22, 2008). The sponsor has not yet started their Phase 3 clinical trials.

The briefing package for this meeting was received on October 2, 2009, and the FDA's initial responses to Tibotec, Inc.'s questions in the briefing package, and the minutes captured during the meeting discussion are listed below.

## Sponsor Questions and FDA Response:

### Question 1:



(b) (4)

**FDA POST-MEETING COMMENT:**

We now concur with Tibotec regarding testing only for *E.coli*.

**CONCURRENCE:**

*{See appended electronic signature page}*

**Jeannie David, M.S.**  
**Regulatory Project Manager**  
**Division of Pre-Marketing Assessment II**  
**Office of New Drug Quality Assessment**

*{See appended electronic signature page}*

**Rapti Madurawe, Ph.D.**  
**Pharmaceutical Assessment Lead**  
**Division of Pre-Marketing Assessment II**  
**Office of New Drug Quality Assessment**

**ATTACHMENTS AND HANDOUTS:**

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

IND-69600

GI-1

TIBOTEC INC

TMC207

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/s/

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JEANNIE C DAVID  
12/04/2009

RAPTI D MADURAWA  
12/04/2009  
(for Steve Miller)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 69,600

Tibotec, Inc.  
Attention: Jenny Lin, Pharm.D.  
Senior Manager, Global Regulatory Affairs  
1020 Stony Hill Road, Suite 300  
Yardley, PA 19067

Dear Dr. Lin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for TMC207.

We also refer to the meeting between representatives of your firm and the FDA on September 23, 2008. The purpose of the meeting was to discuss results of Stage 1 analysis for study TMC207-C208, "A randomized, double-blind, placebo-controlled Phase 2 trial to evaluate the antibacterial activity, safety, and tolerability of treatment when TMC207 is added to a background regimen of MDR-TB therapy, compared to placebo, in subjects with newly diagnosed sputum smear positive pulmonary MDR-TB infection."

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Hyun Son, Pharm.D.  
Regulatory Project Manager  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** September 23, 2008  
**TIME:** 1:00 PM-2:30 PM EST  
**LOCATION:** FDA/CDER  
10903 New Hampshire Ave  
Building 22, Room 1415  
Silver Spring, MD 20993  
**APPLICATION:** IND 69,600  
**DRUG NAME:** TMC-207  
**TYPE OF MEETING:** Type C Meeting

**MEETING CHAIR:** Steven Gitterman, MD, PhD

**MEETING RECORDER:** Hyun Son, Pharm.D.

### **FDA ATTENDEES:** (Title and Office/Division)

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| Renata Albrecht, M.D.             | Division Director                    |
| Steven Gitterman, M.D., Ph.D.     | Deputy Director                      |
| Joette Meyer, Pharm.D.            | Acting Clinical Team Leader          |
| Tafadzwa Vargas-Kasambira, M.D.   | Medical Officer                      |
| Leonard Sacks, M.D.               | Medical Officer                      |
| William Taylor, Ph.D.             | Pharmacology/Toxicology Team Leader  |
| Owen McMaster, Ph.D.              | Pharmacology/Toxicology Reviewer     |
| Shukal Bala, Ph.D.                | Microbiology Team Leader             |
| Simone Shurland, Ph.D.            | Microbiology Reviewer                |
| Karen Higgins, Sc.D.              | Statistics Team Leader               |
| Xianbin Li, Ph.D.                 | Statistics Reviewer                  |
| John Lazor, Pharm.D.              | Director, OTS/OCP/DCP4               |
| Philip Colangelo, Pharm.D., Ph.D. | Clinical Pharmacology Team Leader    |
| Dakshina Chilukuri, Ph.D.         | Clinical Pharmacology Reviewer       |
| Rapti Madurawe, Ph.D.             | Pharmaceutical Assessment Lead       |
| Hyun Son, Pharm.D.                | Senior Regulatory Management Officer |

### **EXTERNAL CONSTITUENT ATTENDEES:**

|                                   |   |
|-----------------------------------|---|
| Koen Andries, DVM, PhD.           | Microbiology Expert, TMC207                                   |
| Karel De Beule, PharmD, MBA       | Compound Development Team Leader, TMC207                      |
| Robin Keen                        | VP, Global Regulatory Affairs                                 |
| Jenny Lin, PharmD                 | Regulatory Leader, TMC207                                     |
| David McNeeley, MD                | Medical Leader, TMC207  |
| Paul Meyvisch, Msc.               | Lead Biostatistician, TMC207                                  |
| Araz Raouf, PhD.                  | Preclinical Development Leader, TMC207                        |
| Rudolf Van Heeswijk, PharmD, PhD. | Human PK Expert, TMC207                                       |
| Brian Woodfall, MD                | Sr. Director, Global Clinical Development and Medical Affairs |
| Tina De Mauz, Ph.D.               | Global Clinical Research                                      |

**BACKGROUND:**

Tibotec submitted a Phase 2 study TMC207-C208 (randomized, double-blind, placebo-controlled trial to evaluate the antibacterial activity, safety, and tolerability of treatment when TMC207 is added to a background regimen of MDR-TB therapy, compared to placebo, in subjects with newly diagnosed sputum smear positive pulmonary MDR-TB infection) on November 9, 2006.

This ongoing trial is conducted in 2 consecutive stages, an exploratory stage (Stage 1) and a proof-of-efficacy stage (Stage 2). Both stages are analyzed separately. On June 30, 2008, Tibotec requested a Type C meeting to discuss the results of the primary Stage 1 analysis of trial TMC207-C208, which was performed when all subjects in Stage 1 had completed 8 weeks double-blind treatment or discontinued earlier.

On August 21, 2008, Tibotec submitted a meeting package. On September 19, 2008, the division sent preliminary comments to the questions posed in the meeting package. At the beginning of the meeting, Tibotec pointed out that they would like to discuss questions 4, 5, 3, 10, 7, and 6 (in this order) and indicated that they agreed with the preliminary comments with regard to the remaining questions. Tibotec presented slides to facilitate the meeting discussion.

**MEETING OBJECTIVES:**

- To discuss the adequacy of the Phase 2 trial TMC207-C208 and anticipated safety database to support accelerated approval of TMC207 for the treatment of MDR-TB
- To discuss the proposed human PK, microbiology and nonclinical package to support accelerated approval TMC 207
- To discuss the timing and approach for additional program to be initiated for TMC207

**DISCUSSION POINTS:**

Tibotec began the discussion with presentation of the slides for question 4. The FDA Preliminary Responses (sent September 19, 2008) are in **bold** and discussion are in *italics*.

**Question 4:**

Pending the primary efficacy analysis at Week 24 for Stage 2 of trial TMC207-TiDP13-C208 demonstrating statistically superior antibacterial activity of TMC207 compared to placebo, does the Division consider TMC207-TiDP13-C208 constitutes a single adequate and well-controlled study to support the accelerated approval of TMC207 for the treatment of MDR-TB?

**FDA Preliminary Response:**

As discussed in Question #2, we agree to accept the Week 24 data evaluating time to sputum clearance to support accelerated approval. In addition, **the Stage 2 portion of Study 208 can be considered an adequate and well-controlled trial in support of your application.** The data from Stage 1 of Study 208 can be considered supportive evidence of efficacy.

**In terms of reliance on a single study to support approval, you will have to consider the risk in selecting this approach. If efficacy relies on a single study the effect should be robust and clinically meaningful.**

The “*Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*” ([www.fda.gov/cder/guidance/1397fnl.pdf](http://www.fda.gov/cder/guidance/1397fnl.pdf)) states the following:

*“A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.”*

We note that the clinical endpoints for Stage 2 are microbiological in nature. **It would be valuable to have evidence that the patient’s clinical condition improves concomitantly with the microbiological endpoint. Clinical endpoints of interest include survival, resolution of cough, weight gain, a patient reported outcome (PRO) measure of clinical improvement.** Other endpoints such as such as improvement in of chest radiograph appearance may also be valuable. The ability to show that patients who received TMC207 had improvement in such parameters compared to placebo patients would provide important additional supportive evidence for the microbiological results of your trial.

**A regulatory decision on whether or not a single adequate and well-controlled trial will be sufficient for accelerated approval can only be made upon review of the data. Please note that prior to making any decision, it is likely that we would hold an open public advisory committee meeting to discuss the application.**

In addition, we note that you are proposing to use TMC207 for the initial 24 weeks of treatment for MDR-TB and then continue only the background regimen for the remaining duration of treatment of 12-18 months (or a minimum of 12 months following sputum conversion). **You do not state the reason for stopping TMC207 therapy at 24 weeks. Please explain why TMC207 would not be continued along with the background regimen for a period of time after sputum conversion, i.e., please provide the justification for the specific treatment regimen you have proposed.**

#### *Discussion*

*Tibotec agreed that clinical endpoints, in addition to microbiologic endpoints, are of interest in this study and stated that they would add secondary endpoints based upon clinical findings on chest x-ray, patient’s weight and hemoglobin levels. They also stated that they plan to only use TMC-207 for the first 24 weeks of treatment because they expect a “good response” by that time point. They have no plans to study any longer durations of therapy or to conduct any additional clinical trials.*

*The Division stated that if TMC207 is effective, it would be anticipated that in clinical practice use would be extended beyond 6 months. Tibotec stated that ultimately they envision decreasing the total duration of treatment of MDRTB to 6 months if TMC207 is found effective. Tibotec also stated that their nonclinical animal data shows that the duration of therapy can be decreased significantly.*

*The Division replied that it will be important for Tibotec to address the question of how to best use TMC207 in clinical practice in their NDA submission.*

**Question 5:**

Is the anticipated safety database considered adequate to support accelerated approval for TMC207 for the treatment of MDR-TB?

**FDA Preliminary Response:**

Your proposed safety database contains up to 237 TB patients treated with TMC207 at the proposed clinical dose:

- 14 patients with susceptible TB who received TMC207 at a dose of 400 mg a day for 7 days
- 23 patients with MDR-TB treated with the proposed clinical regimen for 8 weeks in Stage 1 of Study 208
- 200 patients with MDR-TB treated with the proposed regimen for 24 weeks (i.e., approximately 75 TMC207-treated patients from Stage 2 of Study 208 and approximately 125 patients from the open-label study 209).

The ICH E1A guideline for industry “*The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-life-Threatening Conditions,*” ([www.fda.gov/cder/guidance/iche1a.pdf](http://www.fda.gov/cder/guidance/iche1a.pdf)) discusses a safety database of **at least 300 patients to rule out possible adverse events that may occur at an incidence of 1%**. Although, we recognize that TMC207 is intended to treat a life-threatening disease, **we still ask that you meet this standard for safety. Therefore, we do not consider your proposed safety database to be adequate to support approval for TMC207.**

In addition, your submission is unclear regarding how you made the determination that you will have data on 200 patients with MDR-TB treated for 24 weeks. Stage 2 of Study 208 will enroll 150 patients, 75 of whom are randomized to TMC 207 and may not remain on drug for the entire duration of therapy, and another 75 placebo-treated patients who have the opportunity to roll over into Study 209, but only if they fail after the first 12 months. Please clarify if study 209 enroll additional patients who have not previously participated in Study 208. **We should note that it would be extremely helpful to have laid out clearly the number of safety patients anticipated in an NDA filing and the duration of exposure to TMC207 they will have had at the time of data locking. The amount of safety information available at the time of NDA submission will be a critical issue during review of the application.**

We further note that you plan to conduct drug interaction studies with protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Given that many patients with MDR-TB are infected with HIV and receiving concomitant antiretroviral therapy (ART), **please discuss your plans for evaluating the safety of TMC207 in patients on ART as part of your overall drug development plan.**

***Discussion***

*Tibotec stated that Safety Study 209 would be open-label and would include approximately 225 new MDR patients as well as roll-over patients from study 208. TMC207 would be administered for the first 24 weeks only along with optimum background therapy (OBT). Tibotec informed the Agency that study 209 is still a virtual trial, i.e., not yet designed, and Tibotec intends to submit the protocol once finalized. Tibotec outlined the challenges of getting a trial started, ongoing recruitment and retention*

*of subjects. They explained that they are dealing with trial sites without clinical trial experience, addressing the different logistics and regulatory requirement of national TB boards in different countries, and the co-morbid conditions and complex social backgrounds of their study patients. Tibotec also stated there was up to a 40% dropout rate from Stage 1 in study 208 by week 60, not for adverse events, but withdrawal of consent (e.g., patients are often suspicious of the need for ongoing/repeated blood work). Tibotec expects to have about 225 patients with an estimated 8 weeks of exposure to TMC207 in the NDA database and to submit the NDA in 3Q2011. Increasing the size of the safety database would involve increasing the enrollment in study 209 and delay NDA submission by one year.*

*The Division discussed various ways in which Tibotec could increase the size of their safety database in a timely manner. The Division asked if study 209 would include only patients that are rifampin and isoniazid resistant, as in study 208. Tibotec replied that the patients would be resistant to quinolones, however as the study is not yet fully designed, they are not able to give a complete response at this time. The Division suggested Tibotec consider relaxing the inclusion criteria in study 209 in various ways, such as including patients with a range of drug-resistance (from resistance to a single drug, like rifampin, to multi-drug resistance with drugs other than both rifampin and isoniazid) or including patients with CD4 counts of 250 and above. In addition, the Division said another possibility to increase the size of the safety database would be to include multiple dose drug-interaction studies in HIV positive patients. However, the Division also cautioned Tibotec that the overall number of patients and duration of exposure is a critical issue and suggested that it might be valuable to discuss the drug development of TMC207 during a closed session with the Anti-Infectives Advisory Committee. The Division stated that they would internally discuss the possibility of holding such a meeting and get back to Tibotec.*

**Question 3:**

Does the Division agree with the proposed rollover of placebo-treated subjects in Stage 2 of the trial TMC207-TiDP13-C208, who meet the proposed criteria into an open-label trial with TMC207, provided that the subject has completed the first 12 month treatment phase of Stage 2?

**FDA Preliminary Response:**

**In Stage 2 of your protocol for Study 208, you state that you anticipate that a certain proportion of placebo-treated subjects will meet the definition of treatment failure after completing the first 12 months of MDR-TB treatment. You propose to allow a subset of these subjects to roll over into an open-label safety trial TMC207-TiDP13-C209 (in non-newly diagnosed MDR-TB subjects) for treatment with TMC207 for a maximum duration of 24 weeks. Specifically, you propose to roll over those placebo-treated subjects in Study 2 who have completed 12 months of MDR-TB treatment and who meet the criteria for treatment failure.**

**We agree that your proposed rollover of placebo-treated subjects who meet the criteria for treatment failure following 12 months of treatment is acceptable. However, please explain why you chose 12 months as the point at which a patient is deemed to have failed treatment. Please also submit the proposed protocol for Study 209 for review.**

***Discussion***

*The Division asked Tibotec if they thought it was ethical to wait until 12 months to determine a patient as a failure and had they considered an earlier time point to declare failures. Tibotec stated that if the*

*study was unblinded early, there may be bias. Tibotec also clarified that the DSMB has accepted the rollover of patients at 12 months, although with some reservations, and that they are monitoring the trial for safety. Tibotec will reconsider rolling over patients remaining sputum positive at an earlier time point. Tibotec asked the Division for ideas as to how to protect the integrity of the data and still allow treatment of placebo subjects who did not convert. The Division stated that Tibotec could consider keeping all subjects blinded by randomizing all subjects to a sequence of treatments, TMC207 followed by placebo for those who did not convert or placebo followed by TMC207 for those who did not convert. There would need to be discussion on at what time point subjects who did not convert would be treated with the second drug in their sequence, since that would be the last point in which a comparison of rate of conversion between TMC207 and placebo could be easily assessed.*

**Question 10:**

Given the overall risk-benefit profile for TMC207 in healthy subjects, does the Division consider the intensive ECG monitoring implemented as part of the Phase II trial TMC207-TiDP13-C208 sufficient to evaluate the effect on QT interval and that a thorough QT/QTc trial in healthy subjects can be waived?

**FDA Preliminary Response:**

**We note that you have amended Study 208 to include ECG assessments on days of intensive pharmacokinetic sampling during Stage 2 of the trial and we agree with this approach: it will provide ECG data from patients at steady state, which is important given the long half life of the drug and the time to reach equilibration within tissues. However, we do not agree that intensive ECG monitoring in Study 208 is sufficient to evaluate the effect of TMC207 on the QT interval. Given that TMC207 is an NME and is indicated for chronic use in patients who receive many concurrent medications, it is important to understand the cardiovascular safety profile (QT prolongation potential) of the drug prior to its approval. Thus we recommend that a Thorough QT study be performed to characterize the QT prolongation potential of TMC207 and M2. Please submit a protocol for a Thorough QT study for review. Please refer to the Guidance for Industry E14 “Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” (<http://www.fda.gov/cder/guidance/6922fnl.htm>).**

*Discussion*

*Tibotec stated that they acknowledge the need to characterize the effect of TMC207 on the QT interval. Tibotec has previously concluded that it is unacceptable to use healthy volunteers in multiple dose studies of TMC207. The Division acknowledged that given the pharmacokinetic properties of TMC207, it may be challenging to design a Thorough QT Study that meets the criteria listed in the ICH E14 Guidance and agreed to consult with the QT-IRT team regarding an appropriate study design. The Division stated that the QT-IRT would require a tabular listing of the PK and QT data collected on TMC207 to date. Tibotec acknowledged that they have provided similar tables for other drugs they have in development and would prepare a submission with the Division’s assistance.*

*The Division inquired about the contribution of the metabolite M2 to the overall TB activity of the parent compound (TMC-207). Tibotec stated that M2 is about 3-5 times less active than the TMC207 and the exposure is about 20-30% in humans. Overall, M2 contributes about 5% of the activity. Study 208 will provide additional information on M2.*

*The Agency recommended that a drug interaction study and hepatic impairment study be conducted as well.*

**Question 7:**

Does the Division consider the completed and planned human pharmacokinetic trials adequate to support an application for accelerated approval of TMC207 for the treatment of MDR-TB?

**FDA Preliminary Response:**

We note your completed and planned human pharmacokinetic (PK) trials that you discuss in your briefing package. **We do not consider your current proposal adequate to support an approval of TMC207. We have the following comments and requests for clarification. Please note that if you have not already obtained the following information you should obtain it prior to an NDA submission:**

- a) **Pharmacokinetic (PK) data in females:** We have noted that in table 2 of your background package (page 18), all of the PK studies have been conducted in males. It is important to characterize the PK of TMC207 in females, in addition to males. Please provide a clarification of whether you have obtained PK data in females.
- b) **Characterization of the PK in patients with MDR-TB:** In your future clinical trials (including Studies 208 and 209), we recommend that you obtain blood samples in patients to obtain systemic PK profiles of TMC207 and M2 in a subset of MDR-TB patients.
- c) **Potential Drug Interactions with Anti-Retroviral Agents (ARVs):** We agree with your proposal to evaluate *in vivo* drug interactions of TMC207 with ARVs. Please specify and provide a rationale for the choice of protease inhibitors and non-nucleoside reverse transcriptase inhibitors that you are planning to use in the studies. We also recommend that you conduct a population based screen for potential drug interactions with HIV drugs if you are including patients that are on ARVs.
- d) **Characterization of the PK in Elderly Subjects/Patients:** From your meeting package it is unclear if the PK of TMC207 and M2 has been evaluated in elderly subjects/patients. Please provide clarification if elderly subjects/patients have been included in the clinical studies conducted to date and if any PK differences were observed between young vs. elderly subjects/patients.
- e) **Exposure-Response Analysis:** In all future clinical trials please design the studies to enable evaluation of exposure-response relationships for both effectiveness and adverse events of both TMC207 and M2.
- f) ***In vitro* Transport:** We recommend that you evaluate the effects of transporters on the *in vitro* transport of TMC207 and M2.

**Discussion**

After going over the slides for question 7, Tibotec acknowledged the Division's request to obtain PK data in females. They stated that women have not yet been included in the clinical trials for TMC207, but that their intent is to include about 20-25% females in study 208. They also acknowledged the Division's request to obtain PK profiles of TMC207 and M2 in a subset of patients with MDRTB. Tibotec stated they plan to obtain full PK data from Stage 1 of study 208 and include a PK substudy in Stage 2. Study 209 will include sparse sampling. Tibotec also acknowledged the Division's request to evaluate *in vivo* drug interactions between TMC207 and antiretroviral agents. Tibotec stated they are planning studies with Kaletra (lopinavir/ritonavir) and nevirapine; in addition, they are in the planning stages with the (b) (4) for an interaction study between TMC207 and efavirenz.

**Question 6:**

Does the Division consider that relapse data to be generated during the treatment-free follow-up period (minimum of 24 weeks) in Stage 2 of trial TMC207-TiDP13-C208 are adequate for traditional approval requirements?

**FDA Response:**

Approval under Subpart H (CFR 314.510) is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit in relation to an ultimate outcome, such as survival. Studies to support traditional approval requirements must also be adequate and well-controlled. **Please explain how you plan to confirm the clinical benefit of TMC207 in order to support traditional approval requirements.**

We agree that data on relapse generated during the 24 week treatment-free follow-up period in Stage 2 of Study 208 is important to assess the rate of relapse. **However at this time, we can not agree that by itself it is adequate to support traditional approval requirements. In addition, in the setting of susceptible TB, most relapses occur within the first year off therapy. In order for us to determine the appropriate follow-up period off therapy in patients with MDR-TB to assess relapse, please submit a rationale for your proposal supported by literature data.**

**Finally, please address whether it is anticipated that TMC207 will be used for longer than 24 weeks of treatment in patients with MDR-TB and your plan to address the efficacy of TMC207 in a setting of prolonged use.**

*Discussion*

*Tibotec explained that because the long-term drop-out rates are so high there is a reluctance to prolong the study even longer than proposed (6 month relapse data); in addition, they considered that given the long half-life of TMC207, 6 months of follow-up off therapy would be sufficient to capture safety data. They also stated that the timing of relapse is dependent on the length of therapy and that the optimal duration of therapy for MDRTB has not been determined. The Division stated that the duration of follow-up and type of data needed for full approval could also be discussed during a closed session of the Advisory Committee*

*Additional Discussion*

*The Division expressed its concern regarding TMC207 and hepatic impairment. The Division stated that a study performed at a TMC207 dose of 400 mg QD for 14 days would be ideal. The Division would like to review the results of the single dose hepatic impairment study and then make a determination if a multiple dose study is needed to characterize the PK in hepatic impaired patients.*

**ACTION ITEMS:**

1. Tibotec will submit the protocol for Study 209 once finalized.
2. Tibotec accepted the Division's requests for additional human pharmacokinetic data for the NDA.
3. The Division will consult the QT/IRT team for the QT studies. Tibotec will provide the necessary background documents with the Division's assistance.

4. Tibotec will take the Division's recommendation regarding the need for additional studies and number of patients in the safety database. They are not planning any other studies at this time, but if they revise study 208, they will submit the protocol amendment for review. They also acknowledge that if they do conduct additional clinical studies, they will not be completed at the time of NDA submission.
5. Tibotec will include information regarding the contribution of M2 in study 208.
6. The Division will internally discuss the possibility of a closed AC session to provide feedback to Tibotec regarding their development plans.
7. Tibotec agreed to consider rolling over patients earlier from study 208 into study 209, and investigate how to do this without compromising the integrity of the trial.
8. The Division agreed to an ongoing dialog with Tibotec and asked them to consider writing a White Paper regarding their drug development issues.

**ATTACHMENTS/HANDOUTS:**

Tibotec Power Point Presentation, 9/23/08

19 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Linked Applications

Sponsor Name

Drug Name

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IND 69600

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TIBOTEC INC

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TMC207

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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.**  
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/s/  
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11/06/2008