

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205123Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205123

SUPPL #

HFD # 530

Trade Name Olysio™

Generic Name TMC435/simeprevir

Applicant Name Janssen Research & Development, LLC

Approval Date, If Known November 22, 2013

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.

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:

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

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

YES NO

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 <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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 <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

YES
Explain:

!
! NO
! 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:

Name of person completing form: Victoria Tyson
Title: Regulatory Project Manager
Date: November 7, 2013

Name of Office/Division Director signing form: Jeff Murray
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

VICTORIA L TYSON
11/21/2013

JEFFREY S MURRAY
11/21/2013

DEBARMENT CERTIFICATION

TMC435 (SIMEPREVIR)

NDA 205-123

Janssen Research & Development, LLC certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.

Robin A Keen

Robin Keen
Vice-President, Global Regulatory Affairs
Infectious Disease and Vaccines

5 March 2013

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 205123 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Olysio™ Established/Proper Name: TMC435/simeprevir Dosage Form: 150 mg capsules		Applicant: Janssen Research and Development, LLC Agent for Applicant (if applicable):
RPM: Victoria Tyson		Division: DAVP
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) 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><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></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. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>November 28, 2013</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None	

¹ 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.

² 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).

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

³ 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"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (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> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> 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> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III 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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV 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> 	<input type="checkbox"/> N/A (no paragraph IV certification) <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?

Yes No

(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)).

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

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?

Yes No

(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," 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

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>	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	included
Officer/Employee List	
❖ 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
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval-11/22/2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	11/22/2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	3/28/2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ 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>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	11/22/2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	3/28/2013
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	11/21/2013
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</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. 	Sovriad denied-7/11/13 Olysio granted-11/7/13 Reviews-7/11/13, 11/6/13
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 4/26/13 <input checked="" type="checkbox"/> DMEPA 10/17/13(container) <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 10/28/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 10/28/13 <input checked="" type="checkbox"/> SEALD 11/19/13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	Filing Review and memo-4/29/13, 5/7/13 <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>10/30/13</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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 <i>(include certification)</i>	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i>	4/1/13, 4/3/13, 4/10/13, 4/17/13, 4/25/13, 4/29/13 (2), 5/7/13, 5/13/13, 5/15/13, 5/16/13, 5/23/13, 5/28/13, 5/29/13 (2), 6/5/13, 7/16/13 (2), 7/18/13 (2), 7/22/13, 7/25/13, 7/26/13, 7/29/13, 8/1/13, 8/5/13, 8/13/13, 8/14/13 (2), 8/20/13, 8/21/13, 8/27/13, 8/28/13, 8/29/13 (2), 9/5/13 (3), 9/24/13 (2), 9/30/13, 10/3/13, 10/10/13, 10/11/13, 10/18/13, 10/24/13, 10/28/13, 10/29/13, 11/1/13, 11/12/13(2), 11/13/13, 11/15/13 (2), 11/20/13, 11/21/13 (4)
❖ Internal memoranda, telecons, etc.	6/7/13, 9/19/13, 9/30/13, 11/13/13
Minutes of Meetings	
• Regulatory Briefing <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 9/19/ 2013
• If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i>	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 8/2/ 2012 and 1/ 30/2013
• EOP2 meeting <i>(indicate date of mtg)</i>	<input type="checkbox"/> No mtg 10/18/ 2010 and 9/15/2011
• Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i>	EOP1-1/13/09, EOP2b 7/29/11; Type C-CMC 2/6/13, MCC-7/22/13 LCM-10/8/13
Advisory Committee Meeting(s)	
• Date(s) of Meeting(s)	<input type="checkbox"/> No AC meeting October 24, 2013
• 48-hour alert or minutes, if available <i>(do not include transcript)</i>	October 30, 2013
Decisional and Summary Memos	
❖ Office Director Decisional Memo <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 22, 2013
Division Director Summary Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 5, 2013
Cross-Discipline Team Leader Review <i>(indicate date for each review)</i>	<input type="checkbox"/> None October 30, 2013
PMR/PMC Development Templates <i>(indicate total number)</i>	<input type="checkbox"/> None 7
Clinical Information⁶	
Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	
• Clinical review(s) <i>(indicate date for each review)</i>	Filing-4/24/2013 Final-8/ 25/2013

⁶ Filing reviews should be filed with the discipline reviews.

<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR 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> 	Section 3.3-Clinical Review
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> 	<input type="checkbox"/> None Consult Review-DDDP-9/4/13 DRISK-10/21/13
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i> 	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> ❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> • 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> 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i> 	<input type="checkbox"/> None requested 9/26/13
Clinical Microbiology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Filing-4/23/2013 Final-8/28/2013 (2) Addendum-11/21/2013
Biostatistics <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Filing-4/23/2013 Final-8/28/2013 Addendum-11/7/2013
Clinical Pharmacology <input type="checkbox"/> None	
<ul style="list-style-type: none"> ❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None Filing-4/30/2013 Final-8/28/2013 Addendum-11/22/2013
<ul style="list-style-type: none"> ❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i> 	<input type="checkbox"/> None 9/17/2013

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/21/2013
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Filing-4/29/2013 Final-8/ 22/2013 Addendum-11/18/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Biopharm Filing-4/22/2013 Biopharm-Final- 8/ 27/2013 Addendum-9/26/2013 CMC Filing-5/17/2013 CMC-Final-8/28/2013 Addendum-11/4/2013 Methods Validation Report- 8/26/2013
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed Filing-6/24/13 Final-8/13/13
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	8/28/2013
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: 8/20/2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ 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.

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

/s/

VICTORIA L TYSON
11/26/2013

MEMORANDUM of TELECONFERENCE

MEETING DATE: November 13, 2013
TIME: 1:30 PM, EST
LOCATION: WO, Bldg 22, Room 4322
APPLICATION: NDA 205123
DRUG NAME: Sovriad/Olysio (simeprevir)
SPONSOR: Janssen
TYPE OF MEETING: Proprietary Name

FDA ATTENDEES:

Morgan Walker, Acting Team Leader, DMEPA
Todd Bridges, Acting Deputy Director, DMEPA
Danyal Chaudhry, Safety Regulatory Project Manager

SPONSOR ATTENDEES:

Bruce Jaenicke, Sr. Trademark Counsel
Michele Dias, MSc, Manager, NA Regulatory Liaison
Valerie Donnelly, Director, Global Trademark Development
Ronald Kalmeijer, MD, MBA, Sr. Director, Compound Development Leader
Chi Li, PhD, MBA, Director, Global Regulatory Leader
Richard Nettles, VP Medical Affairs, Janssen Therapeutics (Tentative)
Gaston Picchio, PhD, VP, Hepatitis Disease Area
Hilde Walgraeve, PhD, Sr. Director, Global Regulatory Affairs

BACKGROUND:

Sovaldi & Sovriad denied due to similarities with each other. Alternate names (b) (4) & Olysio respectively) submitted by both applicants (Gilead & Janssen) accepted; yet applicants want to pursue primary names submitted

MEETING OBJECTIVES:

FDA requesting teleconference to discuss Janssen's preference to retain primary name, "Sovriad" over the approved alternate name, "Olysio"

DISCUSSION:

FDA reiterated that Janssen's name, Sovriad, is still considered unacceptable at this point because of the potential medication errors (b) (4). FDA also presented the concerns from the Division (b) (4). FDA stated that the Division is trying to finalize labeling for this product and would like to resolve this proprietary name review issue as quickly as possible. Based on the pending name conflict and concerns from the Division, Janssen was informed of the option to move forward with the alternate name, Olysio, or to resolve the proprietary name issue post-approval (if approved). FDA stated that Janssen would have to submit a prior approval supplement labeling supplement in order to submit a request for proprietary name review post-approval, and that the name approval would be on 90 day PDUFA clock and the

labeling supplement would be on a 6 month PDUFA clock. FDA further clarified that if Janssen did not resolve the proprietary name issue, they would have to go to market (if application is approved) with the established name only.

Janssen agreed to provide feedback to the FDA regarding their decision by Monday, November 18, - or Tuesday, November 19th at the absolute latest.

APPEARS THIS WAY ON ORIGINAL

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

/s/

AZEEM D CHAUDHRY
11/15/2013



NDA 205123

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Janssen Research & Development
920 Route 202
Raritan, NJ 08869

ATTENTION: Michele Dias, M.S.
Manager, Global Regulatory Affairs

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) dated and received March 28, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Simeprevir (TMC435) Capsule, 150 mg.

We also refer to your correspondence dated and received August 16, 2013, requesting review of your proposed proprietary name, Olysio. We have completed our review of the proposed proprietary name Olysio, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your August 16, 2013, submission are altered, the name must 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 Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Victoria Tyson at (301) 796-0827.

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

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

/s/

AZEEM D CHAUDHRY
11/07/2013

CAROL A HOLQUIST
11/07/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: November 1, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: Simeprevir, 150 mg capsule
Subject: Information Request-PMCs PMRs

Please refer to NDA 205123, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection in combination with peginterferon and ribavirin, in adults with compensated liver disease, including cirrhosis. As discussed during the Late-Cycle Meeting we are establishing the following postmarketing commitment (PMC) and postmarketing requirements (PMRs). Please provide dates for milestones listed below:

Postmarketing Requirements:

Pediatrics:

- Conduct a trial to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of simeprevir as a component of a combination antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

- Conduct a trial that includes at least ^(b)₍₄₎ years follow-up of pediatric subjects to characterize long-term safety of simeprevir.

Final Protocol Submission: MM/YY
Study Completion: MM/YY
Final Report Submission: MM/YY

Clinical

- Submit the final study report and datasets from the ongoing clinical trial TMC435HPC3005, entitled “A Phase 3, Randomized, Double-Blind, Double Dummy, Placebo-Controlled Study Conducted in the Asia-Pacific Region to Investigate the Efficacy, Pharmacokinetics, Safety and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon alfa-2a and Ribavirin in Treatment-naïve, Genotype 1 Hepatitis C-Infected Subjects.”

Study Completion: MM/YY

Final Report Submission: MM/YY

Virology

- Conduct a study to determine the phenotypic susceptibility of TMC435 against:

L356F, V406I, or V629I expressed in genotype 1a replicon cultures, individually and in combination with Q80K

R24W, K213R, T358F, P574A, P574S, T610I, or V629I expressed in genotype 1b replicon cultures

Final Report Submission: MM/YY

Postmarketing Commitment:

Clinical

- Submit the final study report and datasets for trial HPC3001, entitled, “A Phase 3, Randomized, Double-Blind Trial to Evaluate the Efficacy, Safety and Tolerability of TMC435 versus Telaprevir, both in Combination with PegIFN α -2a and Ribavirin, in Chronic Hepatitis C Genotype-1 Infected Subjects who were Null or Partial Responders to Prior PegIFN α and Ribavirin Therapy.”

Study Completion: MM/YY

Final Report Submission: MM/YY

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
11/01/2013

From: Tyson, Victoria
Sent: Tuesday, October 29, 2013 9:37 AM
To: 'Dias, Michele [JRDUS]'
Subject: NDA 205123-Container labels
Importance: High

Good morning Michele,

The container labels dated and received on October 28, 2013, are not acceptable. Please change "(simeprevir) Capsules" to a darker font color. The (b) (4) is difficult to read with a (b) (4) background. Please submit the revised container labels by noon on November 4, 2013. Thanks Vicky

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

/s/

VICTORIA L TYSON
10/29/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: October 18, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: Simeprevir, 150 mg capsule
Subject: Information Request-Container Labeling

Please refer to IND NDA 205123, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. The Division of Medication Error Prevention and Risk Management reviewed the container labels and package insert submitted on April 12, 2013, for the simeprevir 150 mg capsules and recommend that the following changes to the label be implemented:

1. Ensure that the proposed proprietary name and established name is title case and not in all uppercase lettering for ease of readability.
2. Increase the prominence of the established name so that it is commiserate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printing features per 21 CFR 201.10(g)(2).
3. Move the “Each capsule contains...” statement from the PDP to the side panel and replace with the “Alert...” statement that is currently located on the side panel as this statement provides important information to patients.
4. Relocate the dosage form “capsule” to the established name statement “simeprevir” as the following demonstrates, since the dosage form is part of the established name:

(Simeprevir) Capsules
150 mg

Please provide a response by COB, Monday, October 28, 2013.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
10/18/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: October 10, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: Simeprevir, 150 mg capsule
Subject: Response to Information Request-Clinical Virology PMC

Please refer to IND NDA 205123, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection and the October 8, 2013, Late-Cycle Meeting (LCM). In follow-up to the LCM, we are providing the rationale for inclusion of the selected substitutions in the proposed Clinical Virology PMC.

Several viruses expressing novel NS3 substitutions emerged in subjects who received simeprevir + P/R, did not achieve SVR, and did not have detectable levels of known simeprevir-resistant variants. A subset of these emergent variants expressed substitutions at highly conserved sites, indicating that they may have been selected in the presence of simeprevir. These variants included:

- HCV GT1a expressing L356F that emerged in two subjects (C208-0047 and HPC3007-6152).
- HCV GT1a expressing V406I emerged at Week 2 in Subject C208-0383.
- HCV GT1b expressing R24W emerged in Subject C208-0007.
- HCV GT1b expressing T358F emerged in Subject C206-0569.
- HCV GT1b expressing P574A/S in subjects C206-0022 (P574A) and C206-0470 (P574S), which were detected in the next-generation genotypic analysis of C205 and C206.

- HCV GT1 expressing V629I emerged in two subjects, C206-0042 (GT1a) and C206-0137 (GT1b), which were detected in the next-generation genotypic analysis of C205 and C206.

In addition, subjects infected with HCV GT1b viruses expressing K213R or T610I at baseline appear to have experienced reduced SVR rates relative to the overall HCV GT1b-infected population.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
10/10/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: October 3, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: Simeprevir, 150 mg capsule
Subject: Advice/Information Request-Clinical Pharmacology PMC/R

Please refer to IND NDA 205123, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection and the Late-Cycle Meeting Background Package that was issued on Monday, September 30, 2013. Following further consideration, the review team would like to clarify our current thinking regarding dosing in patients of East Asian ancestry or patients with moderate or severe hepatic impairment:

The Division plans to propose a postmarketing requirement in which the pharmacokinetics and safety of simeprevir 100 and 150 mg QD are evaluated in patients of East Asian ancestry.

In addition, the Division plans to propose a postmarketing commitment in which the requisite chemistry and manufacturing data are submitted [REDACTED] (b) (4) [REDACTED] should the results of the above trial deem a lower dose advisable in patients of East Asian ancestry.

With regard to patients with moderate or severe hepatic impairment, the Division would like you to evaluate simeprevir pharmacokinetics in and identify an appropriate dose for these patient populations during your ongoing development of simeprevir-containing interferon-free regimens.

The Division intends to present the observations of higher exposures in patients of East Asian ancestry compared to the Phase 3 population and higher exposures in subjects with moderate or severe hepatic impairment relative to healthy controls at the upcoming Advisory Committee Meeting as part of the overall clinical pharmacology findings.

We look forward to a productive discussion on October 8, 2013, during the Late-Cycle Meeting.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
10/03/2013

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 30, 2013
Application Number: 205123
Product Name: simeprevir
Sponsor/Applicant Name: Janssen Research and Development, LLC
Subject: AC Background Document

FDA Participants :

Jeff Murray, MD, MPH, Deputy Director, DAVP
Mary Singer, MD, Ph.D., Medical Team Leader
Adam Sherwat, MD, Medical Officer
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer
Islam Younis, Ph.D., Clinical Pharmacology Team Leader
John Lazor, PharmD., Director, Office of Clinical Pharmacology 4
Kellie Reynolds, PharmD., Deputy Director, Office of Clinical Pharmacology 4
Jiang Liu, Ph.D., Pharmacometrics Reviewer
Jeff Florian, Ph.D., Pharmacometrics Reviewer
Victoria Tyson, Regulatory Project Manager

Applicant Participants :

Maria Beumont-Mauviel, MD, Sr. Director, Medical Leader
Katia van Boven, MD, Sr. Director, Global Clinical Development
Michele Dias, Manager, NA Regulatory Liaison
Ronald Kalmeijer, M.D., Sr. Director, Compound Development Team Leader
Chi Li, Ph.D., M.B.A., Director, Global Regulatory Affairs
Gaston Picchio, Ph.D., Disease Area Stronghold Leader

1.0 BACKGROUND:

This teleconference was scheduled to advise Janssen to remove all safety and efficacy data from ongoing trials in HIV/HCV-coinfected and HCV genotype 4 subjects, as well as data from the COSMOS trial from their AC Background package. In addition, Janssen's request to revise the Division's AC Background package and defer discussion of Questions 4a and 4b (regarding the appropriate simeprevir dose for chronic hepatitis C (CHC) patients with moderate or severe hepatic impairment or patients of East Asian ancestry) until after the Advisory Committee meeting was discussed.

2.0 DISCUSSION:

Dr. Murray advised Janssen to remove the safety and efficacy data from ongoing trials in HIV/HCV-coinfected and HCV genotype 4 subjects and data from the COSMOS trial from their AC Background package because preliminary data from these trials will not be open to discussion at the AC Meeting. Janssen is free to discuss their clinical development plans for the future including their ongoing trials, but not to provide details with respect to the preliminary data from those trials.

The Division asked Janssen whether they had any concerns about including the preliminary data from the COSMOS trial given the withdrawal of their meeting request submitted to discuss the clinical development of the simeprevir/sofosbuvir combination, specifically if that request was withdrawn because of the lack of a Right of Reference to sofosbuvir data from Gilead. Janssen stated that interim COSMOS data has already been presented at the CROI meeting earlier this year, and that they are waiting for a response from Gilead regarding their ability to provide us with later interim analyses. Janssen asked whether they could discuss the data from the COSMOS trial related to the subgroup of subjects with the Q80K baseline viral polymorphism if they are specifically queried on this topic. The Division responded that data from this trial (which is still preliminary, has not been fully reviewed by the Division, and is not directly related to the proposed indication) should not be discussed.

Janssen asked if the Division's position has changed since the Type C Pre-NDA meeting on the inclusion of safety data in the label from the ongoing HIV/HCV coinfection trial. The Division responded that our position has changed somewhat, in that only information related to significant or serious safety concerns in this patient population will be included in the label at this time.

The Division informed Janssen that our AC Background package has been finalized and includes information regarding increased exposures in patients with moderate or severe hepatic impairment and those of East Asian ancestry, as well as a discussion regarding the advisability of a reduced dose for the treatment of chronic hepatitis C virus infection in these patient populations, although specific references to the 100 mg dose have been removed. This issue will be further discussed at the Late-Cycle Meeting (LCM) scheduled for October 8, 2013 and may also be addressed at the AC meeting. The Division plans to request postmarketing commitments and/or requirements to assess the need for a reduced dose strength for patients of East Asian ancestry or patients with moderate or severe hepatic impairment.

The LCM Background package will be sent to Janssen on September 30, 2013. During the LCM teleconference Janssen should be prepared to discuss how they plan to address the issues outlined in the LCM background package.

3.0 ACTION ITEMS:

- After this teleconference the Division consulted with the AC Staff and asked Janssen to submit the revised AC Background Package by 10:00 am on Wednesday, October 2, 2013. Janssen agreed to submit the revised backgrounder by this time.

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

/s/

VICTORIA L TYSON
10/02/2013

Informational Center Director Briefing Minutes
September 19, 2013 11:00 a.m. to 12:00 p.m.

Topic: Simeprevir

CDER Staff Contact: Debra Birnkrant, Director, Division of Antiviral Products (DAVP)

CDER Executive Operations Staff Contact: Arlethia Royster

Invitees: Janet Woodcock, John Jenkins, Edward Cox, David Roeder, John Farley, Debra Birnkrant, Jeffrey Murray, Sarah Connelly, Mary Singer, Poonam Mishra, Adam Sherwat, Damon Deming, Julian O'Rear, Stephen Miller, Rapti Madurawe, Linda Onaga, Victoria Tyson, Hanan Ghantous, Karen Winestock, Elizabeth Thompson, George Lunn, Fuqiang Liu, Krishnakali Ghosh, Mahesh Ramanadham, Christopher Leptak, Michael Pacanowski, Guoxing Soon, Tara Gooen, Don Henry, David Doleski, Dionne Price, Fraser Smith, Yanming Yin, Janice Lansita, Christopher Ellis, Jeffry Florian, Vipul Dholakia, Lisa LaVange, Minerva Hughes, Carmelo Rosa, Alicia Mozzachio, Lawrence Yu

Background: The purpose of this briefing was to inform the Center Director of the current status of two NME NDA applications for the treatment of hepatitis C virus. For simeprevir, efficacy and companion diagnostic issues were discussed.

Simeprevir

Summary of Discussion:

- The proposed indication of simeprevir is for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.
- The NDA for simeprevir has been granted priority review status and an Advisory Committee meeting is scheduled for October 24, 2013.
- In the subgroup of subjects with HCV genotype 1a (GT1a) virus bearing the NS3 Q80K polymorphism, a substantial impact on the efficacy of simeprevir in combination with pegylated interferon and ribavirin was observed.
- Given the high frequency of GT1a virus with the Q80K polymorphism in the HCV-infected U.S. population and its significant impact on SVR rates, the Division of Antiviral Products (DAVP) plans to include a statement in the Indications and Usage section of the label strongly recommending that all GT1a-infected patients undergo screening for this baseline polymorphism prior to treatment with simeprevir and that alternative treatment options be considered for patients found to be infected with this polymorphic variant.
- Dr. Woodcock agreed that Q80K testing was not “essential” in terms of triggering a need for simultaneous approval/clearance of a companion diagnostic and also

Informational Center Director Briefing Minutes
September 19, 2013 11:00 a.m. to 12:00 p.m.

Topic: Simeprevir

agreed with DAVP's proposed approach to including a strong labeling recommendation for screening subjects infected with GT1a virus for the presence of the Q80K polymorphism. She requested that CDRH be informed of DAVP's recommended revisions to the Indications and Usage section of the label.

APPEARS THIS WAY ON ORIGINAL

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

/s/

VICTORIA L TYSON
09/26/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: September 4, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: Simeprevir, 150 mg capsule
Subject: Information Request-Clinical

Please refer to IND NDA 205123, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following request for additional information:

Assuming that information with respect to drug allergies was collected on subjects in the Phase 3 trials (C208, C216, and HPC3007), please perform an analysis to assess for the presence (or absence) of an association of grouped rash AEs, grouped photosensitivity AEs, and combined grouped rash & photosensitivity AEs with a documented history of sulfa allergy.

Please provide a response by COB, Friday, September 13, 2013.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
09/05/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: September 5, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: Simeprevir, 150 mg capsule
Subject: Advice/Information Request-Clinical

Please refer to IND NDA 205123, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. The Division has reviewed your proposal dated 27 August 2013 and we do not find it acceptable. The Division strongly recommends (for the reasons outlined in our communication of 5 August 2013) that all ongoing and future clinical trials involving TMC435 include sun protection measures consistent with those used in the pivotal phase 3 trials.

As noted in our communication of 5 August 2013, a significant degree of overlap was apparent between adverse events strictly categorized as rash, and adverse events strictly categorized as photosensitivity. The use of narrow pooling for photosensitivity events may underestimate the actual rate of occurrence of photosensitivity events as some of these events which were consistent with photosensitivity were reported under the more general pooled term of rash. Grade 3 AEs of photosensitivity and/or rash were reported only in the TMC435 group. There was an increased rate of discontinuation of TMC435 due to AEs secondary to 'rash' (some of which strongly appeared to be consistent with photosensitivity reactions) compared to the Control group. One of the two SAEs which occurred due to photosensitivity was a grade 3 AE and should have led to discontinuation of TMC435 per protocol. Both photosensitivity SAEs resulted in hospitalization and one subject required systemic corticosteroid therapy. We agree that the majority of photosensitivity and rash AEs were Grade 1 or Grade 2 in severity. However, the Division considers Grade 2 rash and photosensitivity events clinically relevant as they were responsible for approximately half of the discontinuations of TMC435 related to rash/photosensitivity in pooled trials C205, C206, C208, C216, and HPC3007.

In addition to these concerns stemming from the clinical trials, the Division notes the following with respect to the dedicated photosensitivity study C125:

Immediate photosensitivity was exhibited by 33% of subjects in the TMC435 group and in no subjects in the ciprofloxacin or placebo groups. We consider these findings to be clinically significant and do not agree

that they are nullified by the results from retesting or that any ultimate study conclusions should rely on the results from the retesting.

It is unclear why the investigators would discount the immediate phototoxicity responses observed with TMC435. The provided explanation was that immediate erythema may have represented an artifact of the testing method. However, the investigators do not explain why only subjects in the TMC435 group were susceptible to this “artifact.” That is, the explanation that the immediate erythema was an artifact of the testing method would not explain why the reaction was observed only in the TMC435 group and only at wavelengths that correspond to absorption wavelengths of TMC435 in the UVA range.

Additionally, subjects who exhibited immediate phototoxicity during screening (i.e. prior to any study treatment) were considered to be screening failures and were not enrolled in the study. Therefore, subjects who were apparently predisposed to immediate erythema from the testing methods were excluded from the study. Thus, it is unclear why the reactions observed under study treatment were deemed to be not significant, since the reactions were induced in subjects who had not exhibited the response, under the same UVL exposures, when they were not receiving TMC435 treatment.

We note also that the results of retesting do not reflect evaluation of a specified endpoint, since the study endpoint was “presence or absence of an immediate photosensitivity response” (not the outcomes from retesting of subjects with immediate photosensitivity). The exact meaning of “physiological irradiances” used in the retesting is unclear, and we are not aware that this category of UVL exposures has been defined. Phototoxicity studies, and other special safety studies of this sort, are intended to be provocative, and the testing methods that yielded the positive findings in this study appeared to be acceptable. The validity and meaningfulness of the retesting results are unclear.

It is also unclear why delayed erythema was designated as the reaction of primary significance. Immediate erythema seems to be considered equal to delayed erythema in representing a type of phototoxicity response. That is, it is not clear that delayed erythema is the more meaningful measure of phototoxicity. For example, amiodarone and chlorpromazine are reported to cause immediate phototoxicity.

Importantly, subjects who had the highest TMC435 plasma levels in this study exhibited immediate phototoxicity reactions. TMC435 exposures (AUC) in subjects with hepatitis C are anticipated to be approximately 2-3 times higher than what they are in healthy subjects. This provides additional support for the recommendation of communication of the risk of photosensitivity in the TMC435 label and for sun-protection measures in all ongoing and current trials involving TMC435.

In summary, the results from study C125, performed in healthy subjects in the absence of pegylated interferon and ribavirin, add to the body of evidence that indicates that TMC435 is a photosensitizer.

We request an affirmative response by 9 September 2013 to our original recommendation of 5 August 2013 (i.e. that all ongoing and future clinical trials involving TMC435 include sun protection measures consistent with those used in the pivotal phase 3 trials) to avoid regulatory action.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
09/05/2013

August 29, 2013

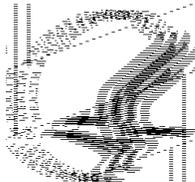
NDA 205123-Container Labeling Comments

- Please change the storage statement on the bottle from (b) (4)
[REDACTED] to "Store TRADENAME capsules
below 30 °C (86 °F) "

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

/s/

VICTORIA L TYSON
08/29/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: August 29, 2013

To: Michele Dias, MS, Manager, Global Regulatory Affairs

From: Victoria Tyson, Regulatory Project Manager

Sponsor: Janssen Research & Development, LLC

NDA: 205123

Drug: Simeprevir, 150 mg capsule

Subject: Advice/Information Request-Clinical-Treatment Algorithm

Please refer to IND NDA 205123, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. This correspondence consists of our recommended treatment algorithm for simeprevir + peginterferon alfa and ribavirin. This treatment algorithm has been tailored to patients who are either infected with HCV GT1a non-Q80K or HCV GT1b and is based on the additional recommendations in the August 27, 2013, Advice/Information Request; specifically comments 1a, 1b, and 1c. Please find below the details of the treatment algorithm including the recommended stopping rules:

Recommended Treatment Algorithm:

All patients in the treatment-naïve and relapser populations will receive a fixed 24 week course of pegylated interferon and ribavirin (PR) in conjunction with 12 weeks of simeprevir.

All patients in the partial- and null-responder populations will receive a fixed 48 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of simeprevir.

Stopping Rules for all populations (treatment-naïve, relapser, partial, and null responders):1. Week 4:

HCV RNA < 25 IU/mL: Continue treatment

HCV RNA ≥ 25 IU/mL: Discontinue all treatment (simeprevir and PR)

2. Week 12:

HCV RNA < 25 IU/mL: Continue Treatment

HCV RNA \geq 25 IU/mL: Discontinue all treatment (i.e. PR)

3. Week 24 (only applies to partial and null populations):

HCV RNA < 25 IU/mL: Continue Treatment

HCV RNA \geq 25 IU/mL: Discontinue all treatment (i.e. PR)

Please provide a response by COB, Friday, September 6, 2013.

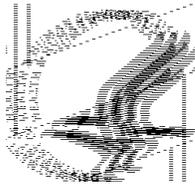
PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
08/29/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: August 27, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Advice/Information Request-Clinical

Please refer to IND NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C virus infection. We have reviewed the amendment dated and received August 14, 2013, consisting of your response to Question 1 in the Post-MidCycle Communication. We have taken your response under consideration and have proposed the following:

Clinical

In lieu of an Indication requiring Q80K screening prior to the use of simeprevir + peginterferon alfa and ribavirin, we are willing to consider the following alternative consisting of three parts (numbers 1, 2, and 3 below):

1. Maintain the currently proposed Indication (including naïve, relapser, and partial and null responder populations) as requested and including all of the following as points to consider under the Indication:
 - a. Simeprevir efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in patients with hepatitis C virus genotype 1a with Q80K polymorphism at baseline.
 - b. Screening for baseline Q80K polymorphism in patients with HCV genotype 1a is recommended in all patients.
 - c. Alternative therapy should be considered for all patients with the Q80K polymorphism at baseline.

AND

2. Include detailed information on the impact of the baseline Q80K polymorphism on treatment outcome (i.e. SVR12) in the Clinical Studies section of the prescribing information.

AND

3. Revise and simplify the currently proposed treatment algorithm. Based on the recommended guidance to be provided under the indication (see #1 above), the treatment algorithm should be tailored to patients who are either infected with HCV G1a non-Q80K or HCV G1b. We are in the process of drafting a revised treatment algorithm and will share this with you as soon as it is available.

Please note the recommendation outlined in number 1 above has already been included in the revised prescribing information the Division will be providing to you on August 28, 2013.

Please provide a response by close of business on September 3, 2013.

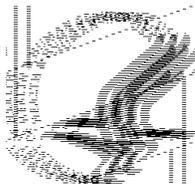
PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
08/27/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: August 21, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Advice/Information Request-Clinical Pharmacology

Please refer to IND NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We reviewed the amendment dated and received August 20, 2013, that consists of your response to the clinical pharmacology comments in the Post-MidCycle Communication and have the following advice/information requests:

Clinical Pharmacology

You suggest that in Asian patients, a dose of 100 mg QD may significantly decrease liver concentrations compared to the 150 mg QD dose, thereby reducing efficacy. Please conduct deterministic simulations of simeprevir liver concentrations at steady state using your PBPK model in:

- HCV-infected Asian patients following administration of 100 mg QD and 150 mg QD.
- HCV-infected Caucasian patients following administration of 100 mg QD and 150 mg QD

These simulations will support further review of simeprevir dose selection in Asian patients but may not be sufficient to fully alleviate the Division's concerns regarding the safety of the 150 mg dose in this population.

Please provide a response by COB, Friday, August 23, 2013.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
08/21/2013

Thompson, Elizabeth

From: Thompson, Elizabeth
Sent: Wednesday, August 14, 2013 10:49 AM
To: MDias5@its.jnj.com
Cc: Thompson, Elizabeth; Tyson, Victoria
Subject: NDA 205123 - New Pharmtox IR for Labeling Section 8.1

Importance: High

Michelle-

Please see the request below from our nonclinical reviewer. Please reply to confirm receipt and let me know if you have any questions.

Nonclinical Information Request

The totality of the reproductive toxicity effects of TMC435 in maternal animals (mortality and post-implantation loss), the fetus (adverse body weight decreases, kinked tail, skeletal variations), and developing offspring (adverse body weight decrease, small size, motor activity decrease) at exposures similar to clinical exposures lead us to conclude that a Pregnancy Category C would be more appropriate (b) (4). Although not all of the findings need to be communicated in labeling, please provide revised labeling for Section 8.1 to adequately communicate the potential pregnancy risks.

Please submit a response to this request by August 21, 2013.

Regards,

Beth

Elizabeth Thompson, M.S.
LCDR, U.S. Public Health Service
Chief, Project Management Staff
FDA/CDER/OND/DAVP
10903 New Hampshire Avenue
Bldg #22, Rm 6334
Silver Spring, MD 20993
301-796-0824 (office); 301-796-9883 (fax)
elizabeth.thompson@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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

/s/

ELIZABETH G THOMPSON
08/14/2013

From: [Dias, Michele \[JRDUS\]](#)
To: [Cuff, Althea](#)
Subject: RE: NDA 205123
Date: Friday, August 02, 2013 12:37:23 PM

Hi Althea,

I confirm receipt of the below.

KR,
Michele

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Thursday, August 01, 2013 7:36 PM
To: Dias, Michele [JRDUS]
Subject: NDA 205123

Dear Michelle,

In response to the information provided on 7/24/2013:

Please establish yearly production batch microbial limits testing and specification as part of the stability protocol and continue to accumulate data from the commitment and primary stability batches to demonstrate product stability through its expiry period. For example, informational data (b) (4) coupled with microbial limits test results throughout this period would be beneficial. After product approval and accumulation of data from the commitment and validation batches on the stability protocol (b) (4)

Please provide a response by Monday August 9, 2013

Thanks, Althea

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

/s/

ALTHEA CUFF
08/14/2013

From: [Thompson, Elizabeth](#)
To: MDias5@its.jni.com
Cc: [Tyson, Victoria](#); [Thompson, Elizabeth](#)
Subject: NDA 205123 (TMC435): Pending NDA Information Request
Date: Monday, August 12, 2013 4:47:53 PM
Importance: High

Michelle-

I am covering for Vicky while she is on leave. The medical reviewer has the following queries and would like to receive responses by August 19, 2013.

1. Please provide any available follow-up information on the pregnancy outcome (i.e. condition of baby at birth, etc.) of Subject 208-0409.

2. If available, please provide the relative Study Day for resolution of the following AEs in the following subjects:

Subject 205-0505; AE 'dermatitis exfoliative'

Subject 205-0085; AE 'rash'

Subject 205-0371; AE 'cutaneous vasculitis'

Subject 206-0426; AE 'rash'

3. We appreciated your response to our Information Request of 22 July 2013. We would request the following additional information on Subject 3004-31-073 with 'erythema multiforme': 1) Please provide any available photographs from this episode; 2) Please provide the biopsy report translated into English and the original report in Japanese. If a translated report is not available by 19 August 2013 this may be provided at a later time; 3) Please comment on whether this subject had mucosal (oral, eye, genital) involvement; 4) Please comment on the reported maximum body surface area of involvement of the rash; 5) Please comment on the presence or absence of desquamation; 6) Please comment on whether this subject was hospitalized related to this AE.

4. Please comment on whether there have been any subjects (apart from Subject 3004-31-073) receiving TMC435 in any study who have been diagnosed with any of the following during the study period: erythema multiforme, Stevens Johnson, toxic epidermal necrolysis, or DRESS (drug reaction with eosinophilia and systemic symptoms). If affirmative, please provide information related to their clinical course (including biopsy reports, photographs, etc.).

Please let me know if you have any questions.

Regards,

Beth

Elizabeth Thompson, M.S.

LCDR, U.S. Public Health Service

Chief, Project Management Staff

FDA/CDER/OND/DAVP

10903 New Hampshire Avenue

Bldg #22, Rm 6334

Silver Spring, MD 20993

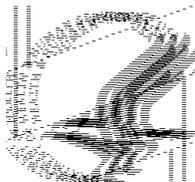
301-796-0824 (office); 301-796-9883 (fax)

elizabeth.thompson@fda.hhs.gov

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

/s/

ELIZABETH G THOMPSON
08/13/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: August 5, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
IND: 75391
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Advice/Information Request

Please refer to IND 75391 and NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your NDA application and have the following advice/information requests:

Clinical

Our review demonstrated that a safety signal was present with respect to photosensitivity/rash events in the phase 2b (C205 & C206) and pivotal phase 3 trials (C208, C216, and HPC3007). This included an increased frequency and severity of photosensitivity/rash adverse events and serious adverse events, as well as an increase in rates of discontinuation of TMC435 due to photosensitivity/rash related adverse events. A significant degree of overlap was noted between adverse events strictly categorized as rash, and adverse events strictly categorized as photosensitivity. The use of narrow pooling for photosensitivity events may underestimate the actual rate of occurrence of photosensitivity events as some of these events which were consistent with photosensitivity were reported under the more general pooled term of rash. It was also noted that all of the subjects in these phase 2b and pivotal phase 3 trials completed treatment with TMC435 prior to the discontinuation of sun protection measures specified per protocol. Additionally, the interpretation of the dedicated photosensitivity study (C125) is limited by the patient population enrolled. This study was performed in healthy subjects and the anticipated drug exposure for TMC435 is 2 to 3-fold lower in a healthy population than in the intended treatment population (i.e. patients with chronic hepatitis C infection).

Based on the above findings, we strongly recommend that all ongoing and future clinical trials involving TMC435 include sun protection measures consistent with those used in the pivotal phase 3 trials.

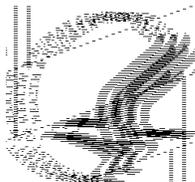
PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
08/05/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: July 29, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Pediatrics

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following information request in regard to your pediatric plan:

Clinical

Please provide the timeframe (month and year) for the anticipated protocol submission and study results submission of your proposed Phase 3 protocol in children ≥ 3 to < 18 years of age. Although we appreciate the difficulty in providing an accurate assessment of these dates, this information is required when we present your pediatric plan to our Pediatric Review Committee.

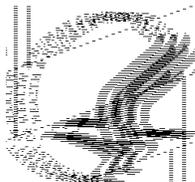
PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
07/29/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: July 26, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Clinical and Nonclinical

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We refer to the response are reviewing your application and have the following information requests:

Clinical

1. As discussed during the Post-MidCycle teleconference, we are considering a recommendation to screen all patients for the genotype 1a Q80K polymorphism with the objective of excluding patients from treatment if the polymorphism is present. In the setting of Q80K screening, we are also considering a simplification of the treatment regimen in the naïve and relapser populations in which patients would receive a fixed 24 week course of peginterferon alfa and ribavirin in conjunction with 12 weeks of TMC435. Patients in the partial and null responder populations would receive a fixed 48 week course of peginterferon alfa and ribavirin in conjunction with 12 weeks of TMC435.
 - a. Please propose alternative stopping rules which assume utilization of Q80K screening at baseline. Separate stopping rules may be provided for treatment-naïve patients and relapser patients and partial and null responders.

Nonclinical

We reviewed the July 23, 2013, amendment that consists of a response to our July 18, 2013, information request and have the following requests for additional information. **Please provide a response as soon as possible.**

2. Please provide the historical data for the exencephaly and protruding tongue findings observed in the pilot mouse embryofetal study (Study No. TMC435350-TiDP16-NC187/TOX8576). Include historical data from both the testing facility that conducted the pilot mouse embryofetal study, Global Preclinical Development, Beerse site, as well as the testing facility that conducted the pivotal mouse embryofetal study (Study No. TMC435350-TiDP16-NC189/TOX8692), (b) (4)
3. Comment on any differences between the pilot and pivotal mouse embryofetal studies (e.g., source of animals) beyond dose volume that may explain why the teratogenic findings were not reproduced in the pivotal study.
4. Please provide the historical data for the kinked tail deformity observed in the rat peri- post-natal study (Study No. TMC435350-TiDP16-NC224/TOX9448) in the male and female F1 offspring. Also provide an interpretation and risk-benefit assessment.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
07/26/2013



NDA 205123

MID-CYCLE COMMUNICATION

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC435 (simeprevir), 150 mg Capsules.

We also refer to the teleconference between representatives of your firm and the FDA on July 22, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Victoria Tyson, Regulatory Project Manager at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Mary Singer, M.D., Ph.D.
Medical Team Leader
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: July 22, 2013, 3:00-4:30

Application Number: 205123

Product Name: TMC435 (simeprevir)

Indication: Treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

Applicant Name: Janssen Research & Development, LLC

Meeting Chair: Mary Singer, MD, PhD, Clinical Team Leader

Meeting Recorder: Victoria Tyson, RPM

FDA Participants:

Adam Sherwat, MD, Clinical Reviewer

Leslie Chinn, PhD, Clinical Pharmacology Reviewer

Jiang Liu, PhD, Pharmaometrics Reviewer

Jeffrey Kraft PhD, Pharmacogenomics Reviewer

Damon Deming, PhD, Clinical Virology Reviewer

Eric Donaldson, PhD, Clinical Virology Reviewer

Jules O'Rear, PhD, Clinical Virology Team Leader

Janice Lansita, PhD, Nonclinical Reviewer

Stephen Miller, PhD, CMC-Lead, ONDQA

Kareen Riviere, PhD, Biopharmaceutics Reviewer, ONDQA

Yanming Yin, PhD, Biometrics Reviewer

Fraser Smith, PhD, Biometrics Reviewer

Elizabeth Thompson, MS, CPMS

Nina Mani, PhD, RPM

Brantley Dorch, Pharm D, RPM, Patient Labeling Team

Morgan Walker, Pharm D, Safety Evaluator, Office of Surveillance and Epidemiology (OSE)

Alfred Sorbello, DO, MPH, Division of Pharmacovigilance, OSE

Xikui Chen, PhD, Reviewer, Office of Compliance, OSI

David Roeder, Associate Director of Regulatory Affairs

Sarah Connelly, MD, Clinical Reviewer

Poonam Mishra, MD, Clinical Reviewer

Linda Lewis, MD, Medical Team Leader

Kim Struble, Pharm D, Medical Team Leader

Kendall Marcus, MD, Deputy Director for Safety
Jeff Murray, MD, MPH, Deputy Director
Debra Birnkrant, MD, Director

(b) (4)

Janssen Research & Development, LLC Participants:

Maria Beumont-Mauviel, MD, Sr. Director, Medical Leader
Katia Boven, MD, Sr. Director, Medical Department Head
Anne Brochot, Chem Eng, Senior Scientist, MBDD
Guy De La Rosa, MD, Global Medical Affairs Leader
Michele Dias, MSc, Manager, NA Regulatory Liaison
Wolfgang Jessner, MD, Director, Study Physician
Ronald Kalmeijer, MD, MBA, Sr. Director, Compound Development Leader
Dawn Kracht, Director, Global CMC Regulatory Affairs
Ward Lemaire, MSc, Data Management Leader
Oliver Lenz, PhD, Sr. Principal Scientist, Clinical Virology
Chi Li, PhD, MBA, Director, Global Regulatory Leader
Lilian Li, PhD, Associate Scientific Director, Global Regulatory Affairs
Richard Nettles, VP Medical Affairs, Janssen Therapeutics
Sivi Ouwerkerk-Mahadevan, PhD, Scientific Director, Clinical Pharmacology Leader
Monika Peeters, MSc, Director, Statistical Leader
Gaston Picchio, PhD, VP, Hepatitis Disease Area
Ilham Smyej, PhD, Principal Scientist, Preclinical Leader
An Thyssen, PhD, Global Labeling Product Leader
Veerle Van Loock, MPharm, Director, Program Management Leader
Hilde Walgraeve, PhD, Sr. Director, Global Regulatory Affairs

1.0 INTRODUCTION

NDA 205123 (TMC435, simeprevir), an NME, was received on March 28, 2013, and is being managed under PDUFA V-The Program. It was assigned a Priority 8 month review with an Action due date is November 28, 2013.

The proposed indication is for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin. The proposed dosing regimen is a 150 mg capsule, administered once-daily with food, in combination with peginterferon alfa and ribavirin for 12 weeks followed by additional 12 or 36 weeks of peginterferon alfa and ribavirin depending on on-treatment viral response and prior treatment status.

The purpose of the Post MidCycle Communication (PMCC) is to give you preliminary notice of issues that have been identified before we complete our review of the entire application; including the status of the review, significant issues identified, information requests, safety concerns, the proposed date for the Late-Cycle Meeting, an update on the Advisory Committee Meeting and other projected timelines. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES/MAJOR SAFETY CONCERNS

As stated, earlier, the purpose of this meeting is not to discuss the issues identified, but in the spirit of transparency to provide a status update on the review of your application. The application is still under review and no regulatory decisions have been determined. The Division informed Janssen that this is not a PDUFA Meeting but we will issue meeting minutes within 30 days.

The following issues were discussed with Janssen Research and Development.

Clinical Safety:

A safety signal was noted with respect to rash and/or photosensitivity events in the Phase 2b (C205 & C206) and pivotal Phase 3 trials (C208, C216, and HPC3007). This included an increased frequency and severity of rash and/or photosensitivity adverse events and serious adverse events, as well as an increase in rates of discontinuation of TMC435 due to rash and/or photosensitivity related adverse events. A significant degree of overlap was noted between adverse events strictly categorized as rash, and adverse events strictly categorized as photosensitivity. The use of narrow pooling for photosensitivity events may underestimate the actual rate of occurrence of photosensitivity events as some of these events which were consistent with photosensitivity were reported under the more general pooled term of rash. It was also noted that all of the subjects in these Phase 2b and Phase 3 trials completed treatment with TMC435 prior to the discontinuation of the sun protection measures specified per protocol. We are currently considering including a discussion of rash and photosensitivity events in the Warnings and Precautions section of the label, and including a recommendation that sun protection measures (consistent with those used in the pivotal trials) be initiated in all patients receiving TMC435.

Clinical Efficacy/Clinical Virology:

Subjects in the pivotal Phase 3 studies who were infected with the HCV genotype 1a, Q80K variant at baseline were less likely to benefit from TMC435 in combination with peginterferon

alfa and ribavirin than subjects infected with other HCV genotype 1 variants. Given the high prevalence of the Q80K polymorphism in genotype 1a patients in the U.S. population, and given concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures (i.e., R155K), we are considering a recommendation to screen all patients infected with HCV genotype 1a Q80K with the objective of excluding patients from treatment if the polymorphism is present.

Utilization of Q80K screening might allow for the following:

1. Extension of the indication to include cirrhotic, partial-responder, and null-responder populations, as the current data are insufficient to allow us to evaluate the efficacy of TMC435 + peginterferon alfa and ribavirin in cirrhotic, partial-, and null-responders infected with the Q80K variant.
2. Simplification of the treatment algorithm as follows:
 - a. All patients in the naïve and relapser populations would receive a fixed 24 week course of peginterferon alfa and ribavirin in conjunction with 12 weeks of TMC435.
 - b. All patients in the partial- and null-responder populations would receive a fixed 48 week course of peginterferon alfa and ribavirin in conjunction with 12 weeks of TMC435.

We assessed your proposed treatment algorithm and have a number of concerns related to using this approach in place of Q80K screening. (b) (4)



We will issue an Information Request (IR) for you to propose alternative stopping rules which assume utilization of Q80K screening at baseline. Separate stopping rules may be provided for 1) treatment-naïve patients and relapser patients and 2) partial and null responders.

Discussion:

Janssen asked if the Division will provide feedback and/or schedule a teleconference to discuss screening for and excluding patients with the Q80K variant and the request to modify [REDACTED] (b) (4)

[REDACTED] The FDA asked Janssen to submit a proposal to the NDA for review and the Division will respond in writing.

Clinical Pharmacology:

In Phase 1 studies of healthy subjects, the exposure of TMC435 after five days of daily dosing with 100 mg of TMC435 was higher in Japanese and Chinese subjects compared with Caucasian subjects. The mean AUC_{24h} of TMC435 was 2.3 and 1.9-fold higher in Japanese (US) and Chinese (Hong Kong) subjects, respectively. In the pivotal Phase 3 trials (C208, C216, and HPC3007), the mean AUC_{24} was 3.4-fold higher in Asian subjects receiving a TMC435 dose of 150 mg daily compared to the pooled subjects as a whole. These differences in exposure appear to be a function of physiological characteristics as opposed to environmental influences (e.g. diet).

Analyses assessing the correlation between TMC435 exposure (based on subjects' AUC_{24} values) with adverse event frequency in the pooled Phase 3 trials demonstrated an increased frequency of anemia, dyspnea, increased bilirubin, pruritus, rash and photosensitivity events with increasing drug exposures. The limited number of Asian subjects in the pivotal Phase 3 trials who received TMC435 (N=14) does not allow for a meaningful assessment of safety in this population at the proposed 150 mg dose.

Similar to Asian subjects, HCV-uninfected subjects with moderate hepatic impairment demonstrated C_{max} and AUC_{24h} values for TMC435 which were 1.7 and 2.4-fold higher respectively at Day 7 as compared to matched control subjects with normal hepatic function.

In our view, the dose strength of TMC435 should be reduced to 100 mg daily in Asian patients as well as in patients with moderate hepatic insufficiency. During labeling negotiations it will be important to determine how best to address this in the package insert [REDACTED] (b) (4)

Nonclinical:

Potential TMC435-related reproductive toxicity findings have been noted in the nonclinical toxicity studies. These reproductive toxicity findings are currently not described in the proposed product labeling. These findings may need to be included in labeling (Sections 8.1, Sections 13.1 and 13.2), and the proposed Pregnancy Category may need to be changed, based on our review of your response to the nonclinical IRs regarding the reproductive toxicity findings in the general toxicology studies, embryofetal studies, the peri-, post-natal study, and the fertility study.

CMC:

Janssen confirmed receipt of the CMC/Biopharm/Product-Micro IR issued on July 18, 2013. Janssen will submit a response to all issues in the IR as well as those sent for simeprevir drug substance under DMF 026864, except for the dissolution issue, by July 24, 2013.

Inspectional activities for the manufacturing sites submitted in the NDA for simeprevir are ongoing.

3.0 RISK MANAGEMENT

At this time we have not determined whether a risk management plan will be established.

4.0 MILESTONES IN THE REVIEW CYCLE

PMR/PMC/Labeling Goal-August 28, 2013.

5.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The Late-Cycle Meeting (LCM) is scheduled for October 8, 2013. The purpose of the LCM is to share information on the plans for the Advisory Committee Meeting and to discuss plans for the remainder of the review cycle. We will send you the background package for the LCM by secure email by October 4, 2013.

6.0 ADVISORY COMMITTEE MEETING

An Advisory Committee (AC) Meeting is scheduled for October 24, 2013. At this time, we have not determined if the Advisory Committee Meeting will be held here on the White Oak campus or at another location.

Your background package is due to the AC Staff by September 23, 2013.

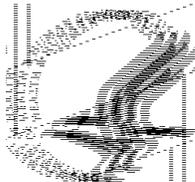
Discussion:

Janssen asked the Division if we are planning to include an update on the current status of drug development for treatment of CHC during the introduction at the AC Meeting. The Division is not planning on doing an extensive update on the current status of drug development for treatment of CHC during the introduction of the AC Meeting and deferred such a presentation to Janssen.

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

/s/

MARY E SINGER
07/25/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: July 22, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Clinical

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following information requests:

Clinical

1. Please explain why study drug was not discontinued in Subject 3007-6189 who experienced a Grade 3 photosensitivity reaction categorized as an SAE. Per protocol, it appears that a Grade 3 cutaneous adverse event would trigger permanent discontinuation of all study medications. Was this judged a protocol deviation?
2. Based on the toxicity grading scale for cutaneous AEs used in Studies C208, C216, and HPC3007, one of the defining criteria for a Grade 4 event is “mucous membrane involvement.” The following subjects had mucous membrane related adverse events reported in close proximity to their cutaneous AEs:

Subject 208-0416: Rash beginning on study day (SD) 67; Aphthous Stomatitis on SD 75

Subject 216-3022: Rash beginning on SD 52; Mouth Ulceration on SD 57

Subject 216-3475: Maculo-papular Rash beginning on SD 32; Conjunctivitis on SD 23 and Aphthous Stomatitis on SD 42

- The cutaneous AEs were reported as Grade 2, Grade 2, and Grade 3 events for these subjects respectively. Please provide your rationale for why these cutaneous events temporally associated with mucosal findings were not categorized as Grade 4 events.
3. Based on the toxicity grading scale for cutaneous AEs used in Study C205, one of the defining criteria for a Grade 4 event is “exfoliative dermatitis.” Subject 205-0505 experienced a Grade 3 cutaneous AE termed “dermatitis exfoliative.” Please provide your rationale for why this event was not categorized as a Grade 4 event.
 4. Please provide narratives for the following two subjects who discontinued study drugs in Study HPC3004:
 - HPC3004-10-082 (interstitial lung disease); and
 - HPC3004-31-073 (erythema multiforme).

Please provide a response by 29 July 2013.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
07/22/2013



NDA 205123

INFORMATION REQUEST

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC435(simeprevir), 150 mg Capsules.

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 by July 24, 2013, in order to continue our evaluation of your NDA.

1. Based on the mean *in-vitro* dissolution profile data from the clinical and primary stability batches at release and under long term stability (12 months), the following dissolution acceptance criterion is recommended: $Q = (b) (4)$ at 25 minutes. Revise the dissolution acceptance criterion accordingly and submit an updated table of specifications for the drug product.
2. We conclude that the primary and supportive stability data support a drug product shelf life $(b) (4)$ when stored at less than 30 °C.
3. Based on the totality of the primary stability and physicochemical characterization data submitted, we agree with your proposal $(b) (4)$
 $(b) (4)$ Please update NDA section P.8.2 to reflect the following commitments:
 $(b) (4)$
 - Inclusion of reporting of end-to-end stability studies A16429 and A16432.
4. Include a test $(b) (4)$ $(b) (4)$ for final drug product, to be tested as part of the protocol for commitment batches and annual monitoring of stability. Alternatively, the $(b) (4)$ critical quality attribute could be monitored on stability as follows:



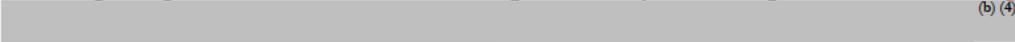
(b) (4)

5. We acknowledge that the (b) (4) method (b) (4) is adequately defined and validated based on the description and validation results reported in the NDA. However, we advise the following points for future maintenance of this analytical method:



(b) (4)

6. FDA considers the particle size distribution (b) (4) as critical. We acknowledge the adequacy of the proposed proven acceptable ranges (b) (4) and the observed consistency of the particle size distribution based on process performance. However, we request that any future changes to the (b) (4) process be evaluated against the range of particle sizes that has been proven to yield acceptable clinical/PK performance:



(b) (4)

7. We acknowledge that the development data supports the (b) (4) PARs as defined in your response and the adequacy of the in-process controls for weight (b) (4). However, we were not able to confirm the stated PARs in P.3.3 or in the master batch record. Please confirm that the stated PARs (b) (4) are reflected in the manufacturing batch record or in the documents referenced (e.g. P/CR-LAT-12/011).

8. Please include microbial limits testing in the stability protocol for one production batch of the drug product per year. We note the microbial limits test results for samples on the different stability protocols, but please provide the microbial limits specifications for the ongoing primary stability batches, the first 3 Latina validation batches as well as the requested yearly monitoring batches that are to be added to the stability protocol.

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

Sincerely,

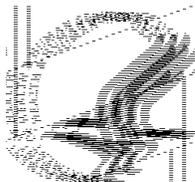
{See appended electronic signature page}

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

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

/s/

RAPTI D MADURawe
07/18/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: July 18, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Nonclinical

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. **Please submit a response to the following information request as soon as possible:**

Nonclinical

Please provide the historical reference data for the insufficient sperm, 100% static sperm finding observed in the male and female rat fertility study (Study No. TMC435350-TiDP16-NC190/TOX8714) in 2/24 male rats at the low-dose and 1/24 male rats at the high-dose. This finding was associated with small testes and epididymides (unilateral and bilateral) and had a negative impact on pregnancy outcome in 2/3 of the female mating partners. Although there is not a clear dose-dependent relationship and the incidence is low, testicular findings were also seen in the 6-month rat and dog toxicity studies which may elevate the level of concern for this finding. Also provide an interpretation and risk-benefit assessment for this finding with regard to patient clinical safety.

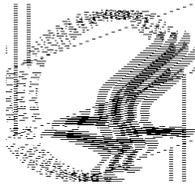
PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
07/18/2013

**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: July 15, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Nonclinical

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. Please submit the following information as soon as possible/**no later than COB July 23, 2013:**

Nonclinical

1. A summary of the potential mechanisms that could explain the reduction in exposure with repeat doses of TMC435 observed across species. Although this effect was most marked in mice following repeat doses, it also appears to be observed in high dose females in the 9-month dog study (Study No. TMC435-TiDP16-NC207/TOX9256), as well as in high dose males in the 3 month rat dietary feed study (Study No. TMC435-TiDP16-NC244/TOX9170) and to a lesser degree in other repeat dose rat studies.
2. Historical data for the osteosarcoma (1/10 males) and sparse corpora lutea (4/10 females) findings observed in the 3-month dietary feed CD-1 mouse study (Study No. TMC435-TiDP16-NC253/TOX9258). Please also provide an interpretation and risk-benefit assessment for each of these findings with regard to clinical safety.
3. Scientific rationale to explain why test article-related maternal toxicity was observed in the pivotal mouse embryofetal study (Study No. TMC435350-TiDP16-NC189/TOX8692) but not in the pilot mouse embryofetal study (Study No. TMC435350-TiDP16-NC187/TOX8576).
4. Scientific rationale for not including potential test article-related findings observed in the pilot mouse embryofetal study (Study No. TMC435350-TiDP16-NC187/TOX8576), the pivotal mouse embryofetal study (Study No. TMC435350-TiDP16-NC189/TOX8692), as

well as the rat peri-postnatal study (Study No. TMC435350-TiDP16-NC224/TOX9448) in Section 8.1 of the proposed simeprevir labeling.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
07/16/2013

From: [Dias, Michele \[JRDUS\]](#)
To: [Cuff, Althea](#)
Subject: RE: NDA 205123 (TMC 435 simeprevir) Information Request
Date: Tuesday, July 16, 2013 10:27:52 AM
Attachments: [emfalert.txt](#)

Hi Althea,

I confirm receipt of this email.

KR,
Michele

From: Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]
Sent: Monday, July 15, 2013 11:37 AM
To: Dias, Michele [JRDUS]
Subject: NDA 205123 (TMC 435 simeprevir) Information Request

Dear Ms. Dias,

Please commit to monitoring product stability and include yearly batches of the product from the proposed Latina manufacturing site on the stability protocol. We note the microbial limits test results for samples on the different stability protocols, but please provide the microbial limits specifications for the ongoing primary stability batches, the first 3 Latina validation batches as well as the requested yearly monitoring batches that are to be added to the stability protocol.

Please confirm receipt of this e-mail.

Thanks,

Althea Cuff, MS
Regulatory Health Project Manager
Food & Drug Administration, CDER
Office of New Drugs Quality Assessment II
301-796-4061

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

/s/

ALTHEA CUFF
07/16/2013



NDA 205123

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Janssen Research & Development
920 Route 202
Raritan, NJ 08869

ATTENTION: Michele Dias, M.S.
Manager, Global Regulatory Affairs

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) dated and received March 28, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Simeprevir Capsules, 150 mg.

We also refer to your correspondence dated and received April 12, 2013, requesting review of your proposed proprietary name, Sovriad. We have completed our review of this proposed proprietary name and have concluded that the proposed proprietary name Sovriad could result in medication errors (b) (4)

(b) (4)

(b) (4) you will be requested to submit another name.

We note that you have not proposed an alternate proprietary name for review. If you wish to withdraw the proposed proprietary name at this time based on the aforementioned risk (b) (4) and avoid delay in finding an acceptable proprietary name for your product, please submit an alternate proprietary name for review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Victoria Tyson at 301-796-0827.

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

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

/s/

FRANKLIN T STEPHENSON
07/11/2013

CAROL A HOLQUIST
07/11/2013



NDA 205123

FILING COMMUNICATION

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) dated and received March 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for TMC435 (simeprevir), 150 mg Capsules.

We also refer to your amendments dated March 28, 2013, March 29, 2013, April 4, 2013, April 12, 2013, April 23, 2013, April 29, 2013, May 2, 2013, May 9, 2013, May 13, 2013, May 24, 2013 and May 28, 2013.

In addition, the planned date for our internal mid-cycle review meeting is July 9, 2013. We are currently planning to hold an advisory committee meeting to discuss this application. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to:

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>

During our filing review of your application, we identified the following potential review issue:

Clinical

Please provide a “coding dictionary” or, if already provided, indicate its location in the submission. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

We are providing the above clinical comment to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we identified the following labeling format issues:

Contraindications:

The Package Insert (PI) did not indicate any contraindications for simeprevir and only lists contraindications for the coadministered products. Please update the Contraindications section in the Full Prescribing Information and the Highlights sections of the PI by including the statement “None” if there are no known contraindications to simeprevir. If there is more than one contraindication to simeprevir, please bullet each one.

We request that you resubmit labeling that addresses these issues by June 17, 2013. The resubmitted labeling will be used for further labeling discussions.

PHARMACOVIGILANCE PLAN

FDA encourages sponsors to submit a pharmacovigilance plan designed to detect new safety risks and to further evaluate identified safety risks with simeprevir following market approval. The pharmacovigilance plan can be included in Module 5 of the Electronic Common Technical Document (eCTD). Currently, submission of a pharmacovigilance plan is voluntary and is not subject to specific regulatory or statutory requirements.

PROMOTIONAL MATERIAL

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) and patient PI. 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) and patient PI, 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.

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827 or (301) 796-1500.

Sincerely,

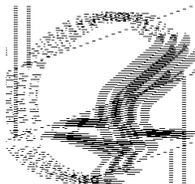
{See appended electronic signature page}

Debra Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

JEFFREY S MURRAY
06/05/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: May 29, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Clinical

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following comments and requests for information:

Clinical

In the pooled Phase 3 studies (C208, C216, and HPC3007) there were 92 subjects with dyspnea and/or exertional dyspnea reported in the first 12 weeks of the study in the TMC435 group. Of those 92 subjects, 9 subjects were in the AE outcome category of "Not Recovered/Not Resolved" based on the ISS datasets. Please provide any available follow-up information on those 9 subjects. We are particularly interested in whether any of these subjects were re-categorized as resolved at a later visit or if any of the AEs worsened in severity at subsequent follow-up visits. Also, any available information with respect to the clinical assessment of these subjects including diagnostic procedures performed (e.g. chest radiography, spirometry, etc.) would be appreciated.

The ID numbers of the participants in question include the following: 208-0071, 208-0089, 208-0278, 208-0104, 3007-6034, 3007-6048, 3007-6099, 3007-6152, and 3007-6238.

Please provide a response by 12 June 2013.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
05/29/2013



NDA 205123

INFORMATION REQUEST

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC435(simeprevir), 150 mg Capsules.

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 by June 26, 2013, in order to continue our evaluation of your NDA.

To facilitate timely review, you can submit official responses to groups of questions, as information becomes available.

Biopharmaceutics

1. Provide the complete dissolution profile data (raw data and mean values) from the pivotal clinical batches supporting your selection of the proposed dissolution acceptance criterion of $Q = \text{(b) (4)}$ at 30 minutes for your proposed product.

Drug Substance

2. Include a drug substance section in Module 3 of the NDA with appropriate reference to the Drug Master File. At a minimum, include the molecular structure, nomenclature, drug substance manufacturing/testing facility addresses (with contact information) and drug substance specifications in the NDA.

Drug Product

3. In P.2.1, provide the following:
 - a. Solubility of simeprevir (b) (4)

- b. The observed range of times taken to dissolve drug substance with a particle size (b) (4).
4. It is our observation that some parameters were considered to be "non-critical" based on pre-selection of narrow operating ranges or on the observed magnitude of product quality response (i.e., drug product CQAs). However, future changes from the selected targets/ranges could have a minor, moderate or substantial potential to adversely affect product quality. The Agency's expectation is that the potential impact of changes to process parameters, including those designated as non-critical process parameters as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.
5. We do not agree that the (b) (4) steps are "non-critical" and that the CQAs of the drug product are not impacted by the process parameters in these manufacturing steps. An experimental study which queries a reasonable range of operation may yield an acceptable range of operation, but this does not mean that the variables have no impact on the CQA.
 - a. As the (b) (4) (b) (4) is critical for the (b) (4) identity CQAs, include a minimum temperature and a range for mixing rate and/or time in Table 1 of P.3.3..
 - b. In your design of experiments, you have shown that (b) (4) (b) (4) have a significant impact on (b) (4) particle size (b) (4). Therefore, the proposed range for these process parameters should be considered critical and these ranges should provide reasonable assurance that the process will yield a particle size distribution in the justified range, as discussed in P.2.3.3 and P.2.2.
 - c. Propose a specification for particle size distribution (b) (4). The acceptance criteria proposed should take into consideration the particle size range (b) (4) that assures drug product performance. Also, include an adequate analytical method.
6. To understand the variance (b) (4) (b) (4) provide the actual (b) (4) corresponding to the (b) (4) batches reported in the characterization data. Also, include the (b) (4) (b) (4) corresponding to the (b) (4) measurement meeting the ICH limit (b) (4).
7. According to ICH Q3C (R5), (b) (4) (b) (4)
8. To further evaluate the risk of form changes upon storage, please provide the following:
 - a. (b) (4)

- f. A commitment to conduct post-approval (first three commercial batches) and annual monitoring of (b) (4) stability at the long terms conditions.
11. Provide data on the limit of detection (b) (4)
12. Please provide a table with the particle size (b) (4) used to manufacture (b) (4) as included in P.2.3 discussion for (b) (4) development.
13. Please justify your practice of adjusting the amount of (b) (4) material (b) (4)
- a. Please submit a clarification of which “API assay” is used (b) (4), as stated in the master batch record.
14. The critical process parameters identified in P.2.3 (b) (4) are not reflected in P.3.3, please update accordingly.
15. (b) (4) Please discuss the mitigation plans to address this risk during manufacturing and handling of the intermediate and drug produc (b) (4)
16. In your 12-month stability data package, methods LC-007440-V2 and LC-007440-V3 have been used as the assay and chromatographic purity method for capsules. Please summarize the differences between these versions (a tabular format preferred) and provide the bridging study conclusions for these two methods to support the stability study.

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

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

/s/

RAPTI D MADURawe
05/29/2013



NDA 205123

**METHODS VALIDATION
MATERIALS RECEIVED**

Janssen Research & Development, LLC
Attention: Michele Dias
920 Route 202 South Raritan, NJ 08869

Dear Michele Dias:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Simeprevir capsules, 150 mg and to our April 29, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on May 23, 2013, 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).

Sincerely,

{See appended electronic signature page}

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

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

/s/

MICHAEL L TREHY
05/28/2013

From: Tyson, Victoria
Sent: Thursday, May 23, 2013 9:12 AM
To: mdias5@its.jnj.com
Subject: NDA 205123-Trial TMC435-C112
Importance: High

Good morning Michele,

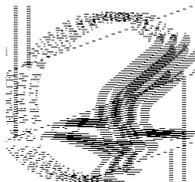
For study TMC435-C112, the bioanalytical study summary for citalopram was included twice and the bioanalytical study summary for simeprevir was not submitted. Please submit the bioanalytical study summary for simeprevir within 5 business days.

Thank you, Vicky

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

/s/

VICTORIA L TYSON
05/23/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: May 16, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Clinical

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following comments and requests for information:

Clinical

1. There appears to be a discrepancy in the narrative for the death of Subject 206-0278. Per narrative demographics, the subject is on treatment arm TMC435 150 mg/12 weeks, but the date of first dose of TMC435 is reported as 22 January 2010 and date of last dose of TMC435 as 28 August 2010 (calculated based on narrative text). Please reconcile and provide the actual date (and study day) of discontinuation of TMC435 (which was left blank in the narrative demographics section).
2. Please provide any available photographs of rashes and/or photosensitivity events that were either reported as SAEs, grade 3/4 AEs, or that led to discontinuation of TMC435.

Please provide a response by COB, Thursday, May 23, 2013.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
05/16/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: May 13, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Clinical

Please refer to your NDA 205123, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following comments and requests for information:

Clinical

1. Please provide the cutoff date for data included in the Study C212 datasets.
2. Please provide the criteria used for the cutoff values (in msec) for "Abnormally low PR interval" and "Abnormally high PR interval" as pertains to the Phase 3 trials (C208, C216, and HPC3007).
3. Please provide a typewritten translation for the two derm-pathology reports (one in French and one in Hebrew) provided on May 2, 2013.
4. With respect to use of the ISE datasets, please provide a clarification of the default timeframe for analyses (if a specific timeframe or phase is not specified as an analysis variable). As an example, included is the Clinical Reviewer's output using the "standard disposition" variable for the ITT population in pooled trials C208 and C216. A specific time-based variable was not applied to this analysis. In this case, what is the default timeframe (e.g. Week 60 analysis, other) for events falling under the various standard disposition terms (e.g. "adverse event," "completed," "lost to follow-up," etc)?

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
05/13/2013



NDA 205123

PRIORITY REVIEW DESIGNATION

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) dated and received March 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for TMC435(simeprevir), 150 mg Capsules.

We also refer to your submissions dated March 29, 2013, April 4, 2013, April 12, 2013, April 23, 2013, April 29, 2013 and May 2, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is November 28, 2013.

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, mid-cycle, 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 August 28, 2013.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before June 10, 2013.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

JEFFREY S MURRAY
05/07/2013



NDA 205123

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Janssen Research & Development, LLC
Attention: Michele Dias
920 Route 202
South Raritan, NJ 08869

Dear Michele Dias:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Simeprevir capsules, 150 mg.

We will be performing methods validation studies on Simeprevir capsules, 150 mg, as described in NDA 205123.

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

Method, current version

Simeprevir Test method HPLC AD-TM-R494617-DS-LC-006634-V4.0

Samples and Reference Standards

- 2 x 250 mg R494617 reference material
- 2 x 250 mg R494617 drug substance
- 2 x 50 mg R494617 selectivity batch

Equipment

- 1 Acquity UPLC BEH-C18 column (b) (4)

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

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
1114 Market Street, Room 1002
St. Louis, MO 63101

You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

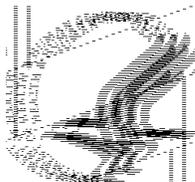
{See appended electronic signature page}

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

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

/s/

MICHAEL L TREHY
04/29/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: April 29, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request-Clinical Pharmacology

Please refer to your NDA 2051323, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following requests for information:

Clinical Pharmacology

1. Please provide adequate justification for the exclusion of P-gp in the final PBPK model. Such justification may include the results of simulations of drug-drug interactions (e.g. cyclosporine) that suggest similar simeprevir pharmacokinetics regardless of whether or not the PBPK model incorporated P-gp.
2. Please provide pharmacokinetic profiles of simeprevir in the following populations:
 - a. HCV-infected Asian patients;
 - b. HCV-infected Asian patients with severe hepatic impairment; and
 - c. HCV-infected Caucasian patients with severe hepatic impairment.

These profiles may be based on data from relevant clinical trials and/or predicted using PBPK modeling and simulation.

3. Please provide the files used to generate the final PBPK simulations (e.g. drug model files, population files, and workspace files). These files may be submitted via CD.

Please provide a response by COB, Monday, May 13, 2013.

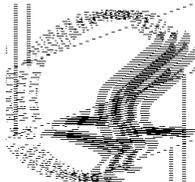
PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
04/29/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: April 25, 2013
To: Michele Dias, MS, Manager, Global Regulatory Affairs
From: Victoria Tyson, Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435, simeprevir, 150 mg capsule
Subject: Information Request

Please refer to your NDA 2051323, TMC435, simeprevir, for the treatment of genotype 1, chronic hepatitis C infection. We are reviewing your application and have the following comments and requests for information:

Clinical

1. Please explain how the "Medical History" and "Concurrent Conditions" are defined in the Subject Narratives. For example, are conditions listed under "Medical History" those that occurred and resolved before screening or enrollment? Are "Concurrent Conditions" those that arose before screening or enrollment but continued into the study period?
2. Please clarify whether sun-protection measures were recommended for subjects during either the Phase 2b studies (C205 and C206) or the Phase 3 studies (C208, C216, HPC3007). If yes, please provide an explanation of these measures. If these measures were only in place for part of one or more of these studies, please provide the number (and percentage) of subjects who completed treatment with TMC435 in each of these studies prior to the discontinuation of these measures.
3. Please explain the process that was undertaken to select the MedDRA PTs that were pooled to provide the derived variable "rash" as reported in Table 2 of the draft product insert.
4. The Narratives for Study C205 appear incomplete. Please provide subject narratives for all SAEs as well as all AEs that led to discontinuation of study drug(s). Please prioritize drafting the narratives for Subjects 205-0085 and 205-0512 and submit them as soon as possible.

5. Please provide a copy of the skin biopsy report, dermatology consult, and specialized labs (e.g. porphyria assessment) for Subject 3007-6189. Please provide a copy of the skin biopsy report and dermatology consult for Subject 206-0292.
6. Please provide the most recently updated CIOMS reports for the following subjects:

216-3063, 3007-6128, 3007-6189, 208-0019, 208-0066, 208-0243, 208-0416, 208-0340, 216-3022, 216-3475, 205-0049, 206-0426, 206-0485, 205-0505, 205-0085, 205-0455, 206-0292, 205-0512, and 205-0371.
7. Please provide additional information about your Phase variable option "TMC/placebo + PR". For example, if this variable is selected for an assessment of studies C205 and C206 will it appropriately select the subjects who received TMC435/placebo for either 12 weeks, 24 weeks or 48 weeks and only select for abnormalities (e.g. AEs or laboratory abnormalities) for each of those subjects during the time when TMC435 was received.

Please provide a response by COB, Thursday, May 2, 2013.

PLEASE REPLY BY EMAIL (victoria.tyson@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0827). We are providing the above information via electronic mail for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.**

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

VICTORIA L TYSON
04/25/2013

From: Tyson, Victoria
Sent: Wednesday, April 17, 2013 9:04 AM
To: mdias5@its.jnj.com
Subject: NDA 205123-Clinical Virology Information Request
Importance: High

Good morning Michele,

Please provide a response to the information request listed below as soon as possible. Thanks Vicky (301) 796-0827

Several isolates in the "GENOTYPE" databases for C208, C216, and HPC3007 contain two or three distinct amino acid sequence entries for the same time point. For example, Subject TMC435-C208-0007 has three rows devoted to the Week 28 isolate collected on 2011-10-24 at 7:15:00, M766235, and each row contains a distinct substitution pattern. Please clarify the significance of each row. If the multiple rows are independent RT-PCR amplifications or sequence runs of the same sample, please consolidate the substitution changes into a single row for each isolate.

APPEARS THIS WAY ON ORIGINAL



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

/s/

VICTORIA L TYSON
04/17/2013

From: Tyson, Victoria
Sent: Tuesday, April 09, 2013 9:20 AM
To: 'mdias5@its.jnj.com'
Subject: NDA 205123-Simeprevir-Acknowledgement Letter. Information Request
Importance: High

Good morning Michelle,

I am the RPM assigned to NDA 205123, Simeprevir, TMC435, for the treatment of chronic hepatitis C, genotype 1infection, in combination with pegylated interferon and ribavirin, in treatment-naïve and treatment-experienced adults with compensated liver disease, including cirrhosis. I am including my contact information and a copy of the acknowledgement letter for NDA 205123. If you have not received the acknowledgement letter as yet you will soon.

Please submit the following the information as soon as possible:

1. Please provide an updated "List of Investigators and Clinical Sites" that includes telephone and/or fax contact information.
2. Please clarify whether Tibotec or Janssen currently has possession of the clinical trial data from Studies C208, C216, and HPC3007. In addition, please provide the dates Janssen acquired the studies from Tibotec and the dates that Janssen merged with J& J.

Thanks and have a nice day! Vicky



Who to call
Please contact:



See the acknowledgement letter for
the site information

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

/s/

VICTORIA L TYSON
04/10/2013



NDA 205123

NDA ACKNOWLEDGMENT

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

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

Name of Drug Product: TMC435 (simeprevir), 150 mg Capsules

Date of Application: March 28, 2013

Date of Receipt: March 28, 2013

Our Reference Number: 205123

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 May 27, 2013, 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 Antiviral 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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-0827 or (301) 796-1500.

Sincerely,

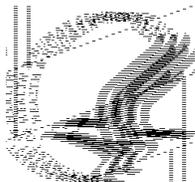
{See appended electronic signature page}

Victoria Tyson
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

VICTORIA L TYSON
04/03/2013



**ELECTRONIC MAIL CORRESPONDENCE-INFORMATION
REQUEST/ADVICE**

Date: April 1, 2013
To: Michele Dias, MS, Manager Global Regulatory Affairs
From: Sammie Beam, RPh., Regulatory Project Manager
Sponsor: Janssen Research & Development, LLC
NDA: 205123
Drug: TMC435 (simeprevir)
Subject: Information Request

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC435 (simeprevir). We have the following information request:

1. The Clinical Study Reports for C208, C216, and HPC3007 each provide a link under Section 4.4 (Protocol Deviations) to a "Listing of Major Protocol Deviations" (LSIDV01). Those listings provide a CRF ID for each Protocol Deviation but do not include an identification of the site and Primary Investigator for each occurrence. Please provide a document which identifies the site and Primary Investigator for each of the major protocol deviations in Study C208 (14 deviations), Study 216 (25 deviations), and Study HPC3007 (20 deviations).
2. Please explain the differences between the SDTM and Legacy datasets provided for studies C205 and C206. Which dataset (SDTM or Legacy) was used to create the analysis datasets for these studies?

Please provide this information with 48 hours

PLEASE REPLY BY EMAIL (sammie.beam@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (301-796-0080). We are providing the above information via electronic mail for your convenience.

Sammie Beam, R.Ph.
CAPT, U.S. Public Health Service
Regulatory Project Manager

Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

SAMMIE G BEAM
04/01/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 205123

LATE-CYCLE MEETING MINUTES

Janssen Research and Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) dated March 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TMC435 (simeprevir) 150 mg Capsules.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 8, 2013.

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

If you have any questions, call Victoria Tyson, Regulatory Project Manager at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Mary Singer, MD, PhD
Medical Team Leader
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: October 8, 2013, 10:30-11:20 pm

Application Number: 205123
Product Name: TMC435 (simeprevir), 150 mg Capsules
Applicant Name: Janssen Research & Development, LLC

Meeting Chair: Mary Singer, MD, PhD, Medical Team Leader
Meeting Recorder: Victoria Tyson, Regulatory Project Manager

FDA PARTICIPANTS

Adam Sherwat, M.D., Medical Officer
Leslie Chinn, Ph.D., Clinical Pharmacology Reviewer
Islam Younis, Ph.D., Clinical Pharmacology Team Leader
Jiang Liu, Ph.D., Pharmacometrics Reviewer
Jeffry Florian, Ph.D., Pharmacometrics Reviewer
Janice Lansita, Ph.D., Nonclinical Reviewer
Damon Deming, Ph.D., Clinical Virology Reviewer
Eric Donaldson, Ph.D., Clinical Virology Reviewer
Julian O'Rear, Ph.D., Clinical Virology Team Leader
Yanming Yin, Ph.D., Biometrics Reviewer
Fraser Smith, Ph.D., Biometrics Reviewer
Greg Soon, Ph.D., Biometrics Team Leader
Dionne Price, Ph.D., Biometrics Branch Chief
Celia Cruz, Ph.D., Product Quality Reviewer
Kareen Riviere, Ph.D., Biopharmaceutics Reviewer
Stephen Miller, Ph.D., CMC Lead
Krishnakali Ghosh, Ph.D., CMC Facility Reviewer
Morgan Walker, Pharm D, DMEPA
Kemi Asante, Pharm D. OPDP Reviewer
Neha Gada, Pharm D., Safety Evaluator
Carolyn Yancey, M.D., Medical Officer, OSE
Sarah Connelly, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Linda Lewis, M.D., Medical Team Leader
Kellie Reynolds, Pharm D., Deputy Director, Division of Clinical Pharmacology 4
Elizabeth Thompson, MS, Chief, Project Management Staff
Jeffrey Murray, M.D., MPH, Deputy Director, Division of Antiviral Products (DAVP)
Debra Birnkrant, M.D., Director, DAVP
John Jenkins, M.D., Director, Office of New Drugs

JANSSEN PARTICIPANTS

Maria Beumont-Mauviel, MD, Sr. Director, Medical Leader
Kim Boue, Associate Director, Global CMC Regulatory Affairs
Katia Boven, MD, Sr. Director, Medical Department Head
Guy De La Rosa, MD, Global Medical Affairs Leader
Michele Dias, MSc, Manager, NA Regulatory Liaison
Stephanie Dincq, Director, Program Management
Wolfgang Jessner, MD, Director, Study Physician
Ronald Kalmeijer, MD, MBA, Sr. Director, Compound Development Leader
Robin Keen, VP, Global Regulatory Affairs
Oliver Lenz, PhD, Sr. Principal Scientist, Clinical Virology
Chi Li, PhD, MBA, Director, Global Regulatory Leader
Lilian Li, PhD, Associate Scientific Director, Global Regulatory Affairs
Richard Nettles, VP Medical Affairs, Janssen Therapeutics
Sivi Ouwerkerk-Mahadevan, PhD, Scientific Director, Clinical Pharmacology Leader
Monika Peeters, MSc, Director, Statistical Leader
Gaston Picchio, PhD, VP, Hepatitis Disease Area
Ilham Smyej, PhD, Principal Scientist, Preclinical Leader
Ivan Somers, Scientific Director, Portfolio Management
An Thyssen, PhD, Global Labeling Product Leader
Veerle Van Loock, MPharm, Director, Program Management Leader
Ellen Vloeberghs, Sr. Manager, Program Management
Hilde Walgraeve, PhD, Sr. Director, Global Regulatory Affairs

1.0 BACKGROUND

NDA 205123 was submitted and received on March 28, 2013, to provide TMC435 (simeprevir), 150 mg capsules, an NS3/4A protease inhibitor, for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease, including cirrhosis. Simeprevir is an NME being managed under The Program. The Late-Cycle Meeting (LCM) was held to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. An AC meeting is planned for October 24, 2013 and the PDUFA goal date for this NDA is November 28, 2013.

2.0 DISCUSSION

LCM AGENDA

1. Introductory Comments

This is the LCM for NDA 205123, TMC435, simeprevir, 150 mg capsules, an NS3/4A protease inhibitor, with a proposed indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis.

The purpose of the LCM is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

We issued the LCM Background Package to you on September 30, 2013, and an update on the Clinical Pharmacology Postmarketing Commitments/Requirements regarding dosing in patients of East Asian ancestry and patients with moderate to severe hepatic impairment on October 3, 2013.

If you submit any new information in response to the issues identified in the background package prior to this LCM or the AC meeting, we may not be prepared to discuss that new information at this meeting.

2. Discussion of Substantive Review Issues

The Division of Antiviral Products (DAVP) and Janssen have reached consensus on the following major substantive issues outlined in LCM Background Package:

- Clinical Efficacy-to include a recommendation to screen all genotype 1a chronic hepatitis C patients for the Q80K polymorphism prior to treatment with simeprevir in combination with peginterferon alfa and ribavirin.
- Clinical Pharmacology-to include language regarding the substantial increases in mean simeprevir exposures in patients of East Asian ancestry compared to the Phase 3 population and higher exposures in subjects with moderate or severe hepatic impairment compared to healthy controls who received the 150 mg dose.
- Pharmacology-Toxicology-to categorize simeprevir as a Pregnancy Category C drug in labeling based on reproductive toxicities in the rat and mouse that indicate potential adverse effects in the pregnant animal, the fetus, and the developing offspring.
- Clinical Safety-to include a discussion of photosensitivity reactions (including sun-protection language) in the Warnings and Precautions section of the product label.

N.B. DAVP is currently discussing whether it would be appropriate to include a separate discussion of rash in the Warnings and Precautions section of the product label. DAVP intends to raise this question at the simeprevir AC Meeting. If a decision is made on this issue prior to the AC, we will inform you in writing of our decision (including our rationale for the decision and the proposed language for the W&P).

3. Discussion of Upcoming Advisory Committee Meeting

The AC Meeting is scheduled October 24, 2013, from 8:00 am to 5:00 pm, at the Sheraton Silver Spring Hotel, in the Cypress Ballroom, 8777 Georgia Avenue, Silver Spring, MD. The potential questions and discussion topics for the AC meeting were outlined in the LCM Background package. We received your AC Meeting Background package on October 3, 2013, and the Divisions AC Meeting Background package was sent to you on October 4, 2013.

The Division plans to summarize our analyses of efficacy, safety and clinical pharmacology, and to focus on the questions for the AC committee. In order to avoid repeating the same information during presentations at the AC meeting the Division will issue our final slides to you as soon as they are available and asked Janssen to submit their final slides to the Division as soon as possible.

Discussion:

- Janssen will submit their AC slides by October 16, 2013 and asked if the AC meeting will still be held because of the government shutdown. The Division should know by October 17, 2013, if the AC meeting will be held.
- The Division agreed to remove Question 3 for discussion at the AC meeting. Question 3 addressed the advisability of the 150 mg dose for:
 - a. patients of East Asian ancestry due to higher simeprevir exposures observed in this subgroup of chronic hepatitis C subjects compared to the pooled Phase 3 population; and
 - b. patients with moderate or severe hepatic impairment due to higher simeprevir exposures observed in HCV-uninfected subjects with moderate or severe hepatic impairment compared to healthy controls.

The Division will present the data from the clinical trials in these subgroups at the AC meeting.

4. Postmarketing Requirements/Postmarketing Commitments

Pediatrics

The Division modified the following pediatric PMRs to be less specific with regard to the treatment regimen:

- Conduct a trial to evaluate the safety and treatment response (using sustained virologic response as a measure) of simeprevir as a component of a combination antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.
- Conduct a trial that includes at least ^(b)₍₄₎ years follow-up of pediatric subjects to characterize long-term safety of simeprevir.

Requirements:

- Submit the final study report and datasets from the ongoing clinical trial TMC435HPC3005, entitled “A Phase 3, Randomized, Double-Blind, Double Dummy, Placebo-Controlled Study Conducted in the Asia-Pacific Region to Investigate the Efficacy, Pharmacokinetics, Safety and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon alfa-2a and Ribavirin in Treatment-naïve, Genotype 1 Hepatitis C-Infected Subjects,” to fulfill the PMR that will be established to determine if a lower dosage strength is needed for chronic hepatitis C patients of East Asian ancestry.
- Conduct a study to determine the phenotypic susceptibility of TMC435 against:
 - L356F, V406I, or V629I expressed in genotype 1a replicon cultures, individually and in combination with Q80K
 - R24W, K213R, T358F, P574A, P574S, T610I, or V629I expressed in genotype 1b replicon cultures

Commitments:

- Submit the final study report and datasets for trial HPC3001, entitled, “A Phase 3, Randomized, Double-Blind Trial to Evaluate the Efficacy, Safety and Tolerability of TMC435 versus Telaprevir, both in Combination with PegIFN α -2a and Ribavirin, in Chronic Hepatitis C Genotype-1 Infected Subjects who were Null or Partial Responders to Prior PegIFN α and Ribavirin Therapy,” as confirmatory evidence of efficacy of simeprevir in conjunction with PegIFN α -2a and ribavirin in the partial and null responder patient populations.
- Should the results from the ongoing trial in chronic hepatitis C patients of East Asian ancestry or the hepatic impairment trials indicate that a reduced dose strength of simeprevir is warranted, a postmarketing commitment will be established ^(b)₍₄₎

Discussion

- Janssen agreed to submit the final study report and datasets for trial HPC3001, and asked if it would be acceptable to submit the Week 60-SVR data at the time of filing and Week-72 SVR data during the review cycle from trial HPC3001. The Division stated this approach may be acceptable but will require further discussion ^(b)₍₄₎

- Janssen asked if a PMC could be established instead of a PMR for submission of the data from clinical trial HPC3005 evaluating simeprevir safety, efficacy, and pharmacokinetics in Asian subjects. The Division explained that a PMR would be established to address this safety-related issue, i.e. higher simeprevir exposures (which were associated with a higher frequency of adverse events in Phase 3 trials) in this subgroup of subjects. Janssen will submit the protocol to IND 75391 for review. Janssen also stated that 79% of the subjects enrolled are IL28B CC genotypes.
- A PMC/R will not be established to evaluate a simeprevir interferon-free regimen in patients with moderate to severe hepatic impairment at this time. Janssen will evaluate an interferon-free treatment regimen for this subgroup of patients under IND. Janssen asked for more specifics on the focus of the trial and the number of patients required. The specifics and the design of the trial will be discussed under IND.
- Following the LCM, the Division provided the rationale for the mutations selected for the Clinical Virology PMR.

5. Major Labeling Issues

Apart from the potential inclusion of a Warning and Precaution related to rash, at this time the Division has not identified any major remaining labeling issues. The response to our last labeling proposal dated September 30, 2013, and received on October 1, 2013, is currently under review. We plan to issue the revised labeling to you during the week of October 14, 2013. The revised labeling will include the Division's preliminary comments on the Patient Package Insert. In addition, we consulted the Patient Labeling Team in the Office of Medical Policy Initiatives, the Division of Risk Management, the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology and the Office of Prescription Drug Promotion and will have additional revisions to the PPI.

The container labels received on October 1, 2013, are acceptable to the Office of New Drug Quality and Assessment.

Discussion:

- Janssen would prefer that rash not be included in the Warnings and Precautions section of the PI. The Division informed Janssen this issue is still under discussion internally and will be discussed during the AC Meeting, before a final decision is made.

6. Review Plans

The request for review of the proprietary names SOVRIAD and OLYSIO are under review. DMEPA plans to complete the review of the proposed trade name by November 14, 2013.

The Division plans to issue an Information Request later in the review cycle to formally establish the Postmarketing Commitments and Requirements that includes the timelines/milestones for the submission of the final protocol, study completion and final report submission. The IR will be issued after the AC meeting.

The Division plans to complete the review of NDA 205123 on or before the November 28, 2013, PDUFA Action date.

Discussion:

- Janssen asked if the Division has any updates on the review of the trade name SOVRIAD since the last correspondence was issued on July 11, 2013. DMEPA will issue an Information Request or schedule a teleconference to discuss the trade name at a later date.

7. Wrap-up and Action Items

The minutes of this meeting will be issued to you within 30 days of today.

This application has not yet been fully reviewed by the signatory authority, Division Director and Cross-Discipline Team Leader (CDTL) and therefore, this meeting will not address the final regulatory decision for the application.

APPEARS THIS WAY ON ORIGINAL



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

/s/

MARY E SINGER
10/28/2013



NDA 205123

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC435 (simeprevir), 150 mg Capsules.

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 8, 2013. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: October 8, 2013, 10:30 am to 12:00 pm
Meeting Location: White Oak, Building 22, Room 1309

Application Number: 205123
Product Name: TMC435 (simeprevir)
Indication: Treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease (including cirrhosis) who are treatment naïve or who have failed previous interferon therapy (pegylated or non pegylated) with or without ribavirin. (1)

Applicant Name: Janssen Research & Development, LLC

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans, and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, Division Director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

The following substantive review issues have been identified to date:

Clinical Efficacy:

In the subgroup of subjects infected with genotype 1a virus with the NS3 Q80K polymorphism at baseline, a substantial impact on the efficacy of simeprevir was observed. Given the high frequency of the genotype 1a virus with the Q80K polymorphism in the U.S. HCV-infected population and its significant impact on rates of SVR12, the Division of Antiviral Products (DAVP) is recommending that all genotype 1a virus-infected patients undergo screening for this polymorphism prior to treatment with simeprevir and that alternative treatment options be considered for patients found to be infected with this polymorphic variant. Please refer to the FDA's Advisory Committee (AC) Background Package for NDA 205123 for additional details.

Clinical Pharmacology:

Subjects with moderate or severe hepatic impairment and subjects of East Asian ancestry had substantial increases in mean simeprevir exposures compared to healthy subjects and compared to the pooled Phase 3 population, respectively. Based on 1) the paucity of safety data in a subjects having mean simeprevir exposures 2- to 5-fold higher than the mean observed in Phase 3 trials; and 2) the positive relationship between simeprevir exposures and the incidence of adverse events including rash and photosensitivity, DAVP recommends a reduced simeprevir dose for patients with moderate or severe hepatic impairment or patients of East Asian ancestry. However, as no reduced dose strengths are currently available, definitive dose recommendations and labeling for these populations will likely need to be accomplished as postmarketing requirements or commitments. Please refer to the FDA's AC Background Package for NDA 205123 for additional details.

Pharmacology/Toxicology:

Simeprevir will be categorized as a Pregnancy Category C drug in labeling based on reproductive toxicities in the rat and mouse that indicate potential adverse effects in the pregnant animal, the fetus, and the developing offspring. Please refer to the FDA's AC Background Package for NDA 205123 for additional details.

Clinical Safety:

The major safety signal identified in the review involved rash and/or photosensitivity events. This included an increased frequency and severity of rash/photosensitivity adverse events and serious adverse events, as well as an increase in rates of discontinuation of simeprevir due to rash/photosensitivity related adverse events. DAVP intends to include a warning related to photosensitivity in the prescribing information including a recommendation for sun protection measures for all patients receiving simeprevir. Please refer to the FDA's AC Background Package for NDA 205123 for additional details.

ADVISORY COMMITTEE MEETING

Date of AC meeting: October 24, 2013

Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management: September 26, 2013

Potential questions and discussion topics for AC Meeting are as follows:

1. Please comment on the safety profile of simeprevir focusing on rash and photosensitivity events reported during the clinical trials.
 - a. Does the committee agree that a discussion of the photosensitivity events should be included in the Warnings and Precautions section of the simeprevir prescribing information?
 - b. Based on the available data, does the committee agree that sun-protection measures should be recommended for all patients receiving simeprevir?
 - c. Does the committee believe it appropriate and/or necessary to include a discussion of rash events (separate from that for photosensitivity) in the Warnings and Precautions section of the prescribing information?
2. Considering the overall risks and benefits, do the available data support approval of simeprevir in combination with pegylated interferon and ribavirin for treatment of HCV infection?
 - a. DAVP intends to recommend screening all HCV genotype 1a-infected patients for virus with the NS3 Q80K polymorphism prior to initiation of simeprevir (in combination with pegylated interferon and ribavirin), and that alternative treatment options be considered for those patients infected with virus bearing this polymorphism. Does the committee agree with DAVP's proposed approach to managing the reduction in efficacy apparent in the setting of infection by genotype 1a virus with the Q80K polymorphism?
3. At the proposed dose of simeprevir 150 mg once daily, mean exposures were approximately 3.4-fold higher in individuals of East Asian ancestry compared to the pooled Phase 3 population. Similarly, simeprevir 150 mg once daily provided 2.4- and 5.2-fold higher exposures in subjects with moderate or severe hepatic impairment, respectively, compared to healthy controls. Considering the lack of safety data in patients with mean exposures that are 2- to 5-fold higher compared to those observed in the Phase 3 population, as well as the positive relationship between simeprevir exposures and the incidence of adverse events (including rash, photosensitivity, pruritus, dyspnea, and increased bilirubin), should the dose strength of simeprevir be reduced in the following patient subgroups:
 - a. Patients of East Asian ancestry
 - b. Patients with moderate or severe hepatic insufficiency

4. Are there postmarketing studies that should be conducted to further define risks or to optimize use of simeprevir?

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes (Victoria Tyson/Mary Singer, MD, Ph.D.)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 30 minutes

- Clinical Efficacy
- Clinical Pharmacology
- Pharmacology-Toxicology
- Clinical Safety

3. Discussion of Upcoming Advisory Committee Meeting – 10 minutes

4. Postmarketing Requirements/Postmarketing Commitments – 15 minutes

Pediatric Postmarketing Requirement:

- Conduct a trial to evaluate the safety and treatment response (using sustained virologic response as a measure) of simeprevir as a component of an interferon-free direct acting antiviral treatment regimen in pediatric subjects 3 through 17 years of age. This trial should include at least ^(b)₍₄₎ years follow-up of pediatric subjects to characterize long term safety of simeprevir.

Postmarketing Requirements:

- Conduct a clinical trial to evaluate the pharmacokinetics and safety of simeprevir 150 mg and 100 mg once daily in patients of East Asian ancestry.
- Conduct a clinical trial to evaluate the pharmacokinetics of simeprevir 100 mg once daily in HCV-infected patients with moderate hepatic impairment.

Postmarketing Commitments:

- Provide the final study report for trial HPC3001, entitled, “A Phase 3, Randomized, Double-Blind Trial to Evaluate the Efficacy, Safety and Tolerability of TMC435

versus Telaprevir, both in Combination with PegIFN α -2a and Ribavirin, in Chronic Hepatitis C Genotype-1 Infected Subjects who were Null or Partial Responders to Prior PegIFN α and Ribavirin Therapy,” as confirmatory evidence of efficacy of simeprevir in conjunction with PegIFN α -2a and ribavirin in the partial and null responder patient populations.

- Conduct a trial to evaluate the pharmacokinetics of a reduced dose of simeprevir in HCV-infected patients with decompensated cirrhosis.
- Should the results from the Asian or hepatic impairment trials indicate that a reduced dose strength of simeprevir is warranted, submit the requisite chemistry and manufacturing and controls data (b) (4)
- Conduct a study to determine the phenotypic susceptibility of TMC435 against:
L356F, V406I, or V629I expressed in genotype 1a replicon cultures, individually and in combination with Q80K
R24W, K213R, T358F, P574A, P574S, T610I, or V629I expressed in genotype 1b replicon cultures

5. Major labeling issues – 10 minutes

6. Review Plans – 10 minutes

7. Wrap-up and Action Items – 10 minutes

APPEARS THIS WAY ON ORIGINAL

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

/s/

JEFFREY S MURRAY
09/30/2013