

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208261Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹								
NDA # 208261 BLA #	NDA Supplement # 00 BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>						
Proprietary Name: Zepatier Established/Proper Name: elbasvir/grazoprevir Dosage Form: Tablet		Applicant: Merck Sharp & Dohme Corp. Agent for Applicant (if applicable):						
RPM: Nina Mani		Division: Antiviral Products						
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) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: 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.</i></p>						
<p>➤ Actions</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 70%;"> <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 28, 2016</u> • Previous actions <i>(specify type and date for each action taken)</i> </td> <td style="width: 30%; text-align: center;"> <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None </td> </tr> <tr> <td> ❖ 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 _____ </td> <td style="text-align: center;"> <input type="checkbox"/> Received </td> </tr> <tr> <td>❖ Application Characteristics³</td> <td></td> </tr> </table>			<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 28, 2016</u> • Previous actions <i>(specify type and date for each action taken)</i> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None	❖ 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 _____	<input type="checkbox"/> Received	❖ Application Characteristics ³	
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 28, 2016</u> • Previous actions <i>(specify type and date for each action taken)</i> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None							
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❖ Application Characteristics ³								

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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).

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.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|--|---|
| <input 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 |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Information Advisory
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
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) AP, January 28, 2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ 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
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s)	• October 3, 2015
• Review(s) <i>(indicate date(s))</i>	• September 25, 2015
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> July 21, 2015; DMEPA: <input checked="" type="checkbox"/> January 13, 2016; December 12, 2015 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> January 12, 2016 OPDP: <input checked="" type="checkbox"/> January 7, 2016 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> Non-Clinical, January 28, 2016
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	July 21, 2015
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included January 27, 2016
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<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
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>November 4, 2015</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	Grant: April 1, 2015 (2); October 18, 2013 Rescind: April 14, 2015
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	October 14, 2013; March 16, 2015 (2)
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>)	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> February 20, 2015
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> May 22, 2014
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> September 10, 2015
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> November 19, 2015
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> January 28, 2016
Deputy Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> January 15, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> (addendum); January 19, 2016; December 21, 2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> Nine (9)
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	January 19, 2016 (addendum); October 28, 2015
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review 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>)	Clinical Review: October 28, 2015 Pgs. 137-139
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> QT-IRT review: September 22, 2015
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ 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"/> January 23, 2016 (OSE)
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> Review: October 28, 2015 (Review); Letters: October 6, 2015; December 1, 2015; December 10, 2015; December 11, 2015
Clinical Microbiology <input checked="" type="checkbox"/>	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> January 21, 2016 (addendum); October 28, 2015
Biostatistics <input checked="" type="checkbox"/>	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> October 28, 2015
Clinical Pharmacology <input checked="" type="checkbox"/>	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> October 28, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical <input checked="" type="checkbox"/>	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> October 29, 2015
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> October 26, 2015; October 28, 2015
❖ 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 checked="" type="checkbox"/> None Included in P/T review, page _____
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input checked="" type="checkbox"/>	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 30, 2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<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>)	Pg. 93; October 23, 2015
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input checked="" type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable October 23, 2015 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
<ul style="list-style-type: none"> ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input checked="" type="checkbox"/> Done <i>(Send email to CDER OND IO)</i>
<ul style="list-style-type: none"> ❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Ensure Pediatric Record is accurate 	<input checked="" type="checkbox"/> Done
<ul style="list-style-type: none"> ❖ Send approval email within one business day to CDER-APPROVALS 	<input checked="" type="checkbox"/> Done

EXCLUSIVITY SUMMARY

NDA # 208261

SUPPL # 00

HFD #

Trade Name Zepatier

Generic Name grazoprevir/elbasvir

Applicant Name Merck Sharp & Dohme Corp.

Approval Date, If Known

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?

Five (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 NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

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

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

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

YES NO

If yes, explain:

Name of person completing form: Nina Mani
Title: Regulatory Project Manager
Date: January 27, 2016

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

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

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/s/

NINA MANI
01/27/2016

JEFFREY S MURRAY
01/27/2016

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: USPI Revisions
Date: Wednesday, January 27, 2016 10:59:40 AM

Thank you Nina, I will take care of this.

Sincerely,

Tom

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Wednesday, January 27, 2016 10:51 AM
To: Chambers, Thomas
Subject: NDA 208261: USPI Revisions
Importance: High

Hi Tom:

Attached are the word and PDF versions of the USPI. We have a comment in Section 2.1, and minor editorial changes to Section 12.4.

Could you send back the word version as a .docx as it is easier for us to work in that format.

Since these are very minor changes we request that you send back the document by **4:00 pm, today**.

We are in agreement with the USPPi and will use the clean version you provided on Monday, January 25, 2016 as the final version.

Kindly acknowledge receipt of this communication.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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NINA MANI
01/27/2016

From: Mani, Nina
To: ["Chambers, Thomas"](#)
Subject: RE: NDA 208261 - Revised USPI - January 22
Date: Friday, January 22, 2016 7:52:00 PM
Attachments: [NDA 208261 ZEPATIER USPPI-original 1 22 2016 edits.pdf](#)
[NDA 208261 ZEPATIER USPPI-original 1 22 2016 edits.docx](#)

Hi Tom:

My team just cleared the PPI (word and PDF), which I am sending for your team's review. The usual terms apply.

Please provide your response by **Monday, January 25, 2016**.

Sorry for the last minute change!

Regards,
Nina

From: Mani, Nina
Sent: Friday, January 22, 2016 7:37 PM
To: 'Chambers, Thomas'
Subject: RE: NDA 208261 - Revised USPI - January 22

Hi Tom:

Please find attached the word and PDF versions of our latest revisions to the USPI. As usual, please accept all changes you are in agreement with and only leave in track changes those that require further negotiation. Please provide your response by **Monday, January 25, 2016**.

The PPI is still under review and will be sent on Monday.

Kindly acknowledge receipt.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, January 22, 2016 5:20 PM
To: Mani, Nina
Subject: Re: NDA 208261 - Revised USPI - January 20

Thank you Nina.
Tom

Sent from my iPhone

On Jan 22, 2016, at 4:33 PM, Mani, Nina <Nina.Mani@fda.hhs.gov> wrote:

Hi Tom:

I will be sending you the PI and PPI later this evening with a return response requested by Monday.

Thanks,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Thursday, January 21, 2016 4:43 PM
To: Mani, Nina
Subject: RE: NDA 208261 - Revised USPI - January 20

Hello Nina,
Just checking to see whether you think there will be additional labelling comments issued by the Division by tomorrow (Friday).
Sincerely,
Tom

From: Chambers, Thomas
Sent: Wednesday, January 20, 2016 4:48 PM
To: 'Mani, Nina'
Subject: FW: NDA 208261 - Revised USPI - January 20
Importance: High

Dear Nina,

Please find attached the Annotated, Tracked and Clean Word documents of the proposed MK5172A USPI in response to FDA comments received on Jan 15, 2016.

Please note this is for convenience in advance of the Gateway submission that is scheduled for later today.

Sincerely,
Tom
Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

[Annotated USPI](#)

<< File: 07-annotated-uspi-mk5172a-t-original.doc >>

[Tracked USPI](#)

<< File: 07-wrm-uspi-mk5172a-t-original.doc >>

[Clean USPI](#)

<< File: 07-crt-uspi-mk5172a-t-original.doc >>

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NINA MANI
01/22/2016

From: Mani, Nina
To: ["Chambers, Thomas"](mailto:Thomas.Chambers@merck.com)
Subject: RE: NDA 208261: Carton and Container Advice - follow-up
Date: Tuesday, January 19, 2016 11:16:00 AM

Hi Tom:

The review team finds acceptable the revised container label and carton labeling submitted on December 21, 2016 for Zepatier and have no further recommendations at this time.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Tuesday, January 19, 2016 10:51 AM
To: Mani, Nina
Subject: RE: NDA 208261: Carton and Container Advice - follow-up

Hello Nina,

Any update on the timing for the container labelling?

Sincerely,
Tom

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Friday, January 08, 2016 1:54 PM
To: Chambers, Thomas
Subject: RE: NDA 208261: Carton and Container Advice - follow-up

Hi Tom:

I should have comments to you after the middle of next week.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, January 08, 2016 10:44 AM
To: Mani, Nina
Subject: FW: NDA 208261: Carton and Container Advice - follow-up

Hello Nina,

Just following up and checking to see if you know when any additional FDA comments will be issued on the carton and container labelling revisions we submitted on December 21(SN0047)? We are trying to assess how to manage any required changes to the artwork.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Thursday, December 17, 2015 4:08 PM
To: Chambers, Thomas
Subject: NDA 208261: Carton and Container Advice

Hi Tom:

Kindly acknowledge receipt of the attached Advice communication.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
01/19/2016

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: Revised PI and PPI
Date: Friday, January 15, 2016 11:38:42 AM

Hello Nina,

Thank you for sending the revised USPI and PPI.
This is to acknowledge receipt of the documents.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Friday, January 15, 2016 11:12 AM
To: Chambers, Thomas
Subject: NDA 208261: Revised PI and PPI

Hi Tom:

We acknowledge receipt of your January 14, 2016 submission regarding your preference for language in Section 2.1. In turn, we are sending our latest revisions to the PI and PPI (Word and PDF formats).

Please accept all changes you are in agreement with (please let us know via comment bubble or other mechanism), and only keep in track changes those that need negotiating. Also, please make formatting changes as needed to be PLR compliant.

Kindly acknowledge receipt of this communication and submit your response by **COB, Wednesday, January 20, 2016**.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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NINA MANI
01/15/2016

**ELECTRONIC MAIL CORRESPONDENCE**

Date: January 13, 2016

To: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
Merck Sharp & Dohme Corp.

From: Nina Mani, Regulatory Project Manager, Division of Antiviral Products (DAVP)

NDA/Drug: NDA 208261/ Zepatier (elbasvir/grazoprevir)

Subject: **Response to Request for Change in Section 2.1 Language**

Please refer to your New Drug Application (NDA) for Zepatier and your submission received on January 12, 2016, which contains a revised USPI as well as a response document requesting reconsideration of the Division's decision to change the language in Section 2.1 from (b) (4) of screening to "recommendation".

The Division has reviewed the Sponsor's rationale document related to the language in Section 2.1. The Division's view on this issue, as previously outlined, has not changed. The Division has also determined that a teleconference to discuss this issue will not be beneficial. As dosing in GT1a patients in Table 1 is now directly linked to the results of NS5A screening, it is imperative that health care providers are clear that testing should be performed for all GT1a patients. The Division has determined that either of the following two options would adequately address this requirement. Please inform us by **COB on Thursday, January 14, 2016** of your preference for one of these two options. Please note that the use of terms (b) (4) is unacceptable and incongruent with the dosage recommendations in Table 1.

Option 1 (original language):

Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with ZEPATIER to determine the dosage regimen and duration [see Dosage and Administration (2.2)], Table 1. In subjects receiving ZEPATIER for 12 weeks, sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93 [see Microbiology (12.4)], Table 11

Option 2 (acceptable alternative):

Test patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms prior to initiation of treatment with ZEPATIER to determine the dosage regimen and duration [see Dosage and Administration (2.2)], Table 1. In subjects receiving

ZEPATIER for 12 weeks, sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93 [see Microbiology (12.4)], Table 11.

PLEASE REPLY BY EMAIL (nina.mani@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (240) 402-0333 or the Division's main number at (301) 796-1500.

{See appended electronic signature page}

Nina Mani, PhD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
01/13/2016

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: Clinical PMR
Date: Friday, January 08, 2016 4:34:54 PM

Hi Nina,

This is to acknowledge receipt of the message regarding the Clinical PMR.

Sincerely,
Tom

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Friday, January 08, 2016 4:32 PM
To: Chambers, Thomas
Subject: NDA 208261: Clinical PMR

Hi Tom:

Since the 16 week treatment regimen of Zepatier with ribavirin is being recommended in the labeling, the Clinical PMC sent on December 23, 2015 will now be a PMR in order to confirm the results of trial 068, and is below for your consideration:

Conduct a trial in hepatitis C virus genotype 1a infected subjects with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93 to evaluate if treatment with elbasvir/grazoprevir and ribavirin for at least 16 weeks reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations. The trial should have adequate representation of subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy in clinical trials evaluating recommended regimens.

Please provide the following milestone dates for this PMR:

Final Protocol Submission:

Trial Completion:

Final Report Submission:

The Division would like the confirmatory results to be available as soon as possible and requests the final report submission in **2018**. If the Sponsor does not believe this is feasible, please provide your rationale for your proposed submission date.

Kindly acknowledge receipt of this communication and provide your response by **Tuesday, January 12, 2016**.

Regards,
Nina

Nina Mani

*Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333*

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/s/

NINA MANI
01/08/2016

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261: USPI Revisions
Date: Friday, January 08, 2016 4:30:00 PM
Attachments: [Rationale for USPI Changes and USPI 1_8_2016.pdf](#)
[NDA 208261 uspi-1_8_2016.docx](#)

Hi Tom:

Kindly acknowledge receipt of the attached latest PI revisions (Word and PDF formats) in the labeling submitted on December 18, 2015.

The first 3 pages of the PDF version also contain our rationale for the changes being recommended in Clinical and Clinical Pharmacology sections in the PI. Please accept all changes you are in agreement with (please let us know via comment bubble or other mechanism), and only keep in track changes those that need negotiating.

The PPI is currently under review and will be sent next week.

Please provide your response by **COB, Tuesday, January 12, 2016**.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

Rationale for the Changes to Sections 2.1 and 2.2

The Division's thinking with respect to the optimal approach to Section 2 has recently evolved. The Division is concerned that the current approach to Sections 2.1 and 2.2 (in the label submitted by the Sponsor on 12/18/2015) could lead to inadvertent, suboptimal treatment of some patients by HCV care providers. This concern is due to the lack of clear guidance in Sections 2.1 and 2.2 for the management of GT1a-infected patients with key baseline NS5A polymorphisms (i.e., polymorphisms at positions 28, 30, 31, and 93). As currently written, the dosing instructions in Table 1 may be misinterpreted by providers as recommending 12 weeks of Zepatier for all GT1a-infected patients irrespective of the presence of baseline NS5A polymorphisms if the footnote referencing Section 2.1 is overlooked. If providers reference only the dosing table in the label highlights, the likelihood of selecting a suboptimal regimen is further compounded as there is no relevant footnote for this table.

The Division has concluded that it is imperative to provide clear direction in Section 2 for the management of GT1a-infected patients both with and without key baseline NS5A polymorphisms. As such, the Division is willing to leverage the available data from Clinical Trial 068 to support a dosing recommendation of Zepatier + RBV for 16 weeks in GT1a-infected patients with key baseline NS5A polymorphisms. This recommendation is contingent on the provision of confirmatory data in this patient population in the form of a PMR. As dosing recommendations in Section 2.2 of the label are now based on the outcome of NS5A screening for GT 1a-infected patients, the language in Section 2.1 with respect to baseline screening for NS5A polymorphisms in GT1a-infected patients has changed from (b)(4) to a recommendation in order to determine the regimen and duration.

Changes to Sections 12.4 and 14 have also been made to incorporate relevant data from the 16 week Zepatier + RBV arm of Clinical Trial 068 based on revisions to Section 2 as discussed above.

CLINICAL PHARMACOLOGY RATIONALE

1. The grazoprevir clinical drug interaction study with pitavastatin, a selective and sensitive in vivo probe substrate of OATP1B, demonstrates that grazoprevir is not an OATP1B inhibitor in humans. Following coadministration of multiple doses of GZR and a single dose of pitavastatin, there was no pharmacokinetic interaction, with a GMR [90% CI] (pitavastatin+GZR/pitavastatin) for pitavastatin AUC_{0-∞} of 1.11 [0.91, 1.34] [Sec. 2.7.2.2.4.1.7]).

FDA Response: *While pitavastatin may be a selective substrate, it may not be a sensitive substrate for some cases. The co-administration of known in vivo OATP1B inhibitors, lopinavir/ritonavir or gemfibrozil, did not significantly increase the exposure of pitavastatin. While it is unknown the reason for this discrepancy, this indicates that no drug interaction with pitavastatin and grazoprevir may not necessarily exclude the possibility of OATP1B inhibition by grazoprevir.*

2. Consistent with clinical data, grazoprevir is not anticipated to be a clinically relevant inhibitor of OATP1B1 or OATP1B3 based on the in vitro IC₅₀ values for OATP1B and the calculated R-values for the 100 mg dose of grazoprevir [Sec. 2.6.4.A.7.2]. The potential for substrate-dependent OATP1B inhibition for grazoprevir or rifampin (a control OATP1B inhibitor) was studied using pitavastatin (0.1 and 1 μM) and atorvastatin (0.1 and 1 μM) as probe substrates in human hepatocytes [Sec. 2.6.4.A.7.4]. Grazoprevir did not demonstrate substrate-dependent inhibition of pitavastatin or atorvastatin in vitro and is not predicted to be a clinically relevant inhibitor of OATP1B using either pitavastatin or atorvastatin [Sec. 2.6.4.A.7.4]. Rifampin showed similar in vitro inhibition for pitavastatin and atorvastatin, and is predicted to be a clinically relevant inhibitor of OATP1B using both substrates [Sec. 2.6.4.A.7.4].

FDA Response: *R-value is a method to predict the presence of a drug interaction using an IC₅₀ value and the theoretical maximum concentration of a perpetrator. It is a useful tool to determine whether in vivo drug interaction studies may be recommended in the absence of in vivo drug interaction trial results. However, it is not a method to definitively determine whether a drug is a clinically relevant OATP1B1 inhibitor or not. In fact, approximately 20% of clinically relevant OATP1B1 inhibitors showed false-negative results based on R-values (cut off 1.25) including the effect of cyclosporine on pitavastatin exposure.*
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/UCM299786.pdf>.

3. Atorvastatin is a substrate of BCRP in addition to OATP1B. Based on pharmacogenetic data, clinical pharmacokinetic exposure of atorvastatin is sensitive to decreased function of OATP1B, P-gp, and BCRP, whereas pitavastatin is only sensitive to decreased function of OATP1B and not P-gp or BCRP {03RV6S}. Grazoprevir and elbasvir are inhibitors of BCRP, as demonstrated by the rosuvastatin DDI study with GZR and GZR+EBR [Sec. 2.7.2.3.4.2.3]. Thus, increases in atorvastatin exposure when co-administered with GZR or GZR+EBR are attributed in part to inhibition of CYP3A (by GZR), intestinal P-gp (EBR), BCRP (by GZR and EBR), and the interplay between BCRP efflux and CYP3A.

FDA Response: *We agree that there is a potential role of intestinal BCRP for this interaction. However, CYP3A4 inhibition by GZR is unlikely contributing to the increased exposure of atorvastatin. Atorvastatin metabolism was not altered by the co-administration of GZR in in vitro and in vivo studies.*

4. The reported shorter apparent terminal half-life and reduction in the apparent volume of distribution during the terminal phase (V_z/F) should be interpreted with caution. Due to the assay limits of quantification, the atorvastatin apparent terminal half-life may not have been completely captured in all subjects when coadministered with GZR+EBR. A difference in half-life is less obvious in subjects with a more complete characterization of the terminal phase. In addition, the decrease in the apparent volume of distribution may be the result of an increase in atorvastatin oral bioavailability through GZR+EBR inhibition of CYP3A, P-gp, and BCRP.

FDA Response: *A decrease in an apparent volume of distribution and a shorter apparent terminal half-life appear to be the key characteristics of a drug interaction mediated by the inhibition of hepatic transporters. In both of your drug interaction studies with atorvastatin, the half-lives of atorvastatin were clearly decreased in the presence of GZR. A difference in half-life may be less obvious in subjects with a more complete characterization of the terminal phase, but the difference still exists in both studies.*

An increase in oral bioavailability cannot explain 1) differential changes in V_z/F and CL/F of atorvastatin in the drug interaction studies and 2) changes in the compartment model of atorvastatin (1 compartment without GZR and 3 compartments with GZR).

Overall, the existing data suggest that GZR is possibly an inhibitor of OATP1B1/3. However, we agree that definitive conclusions may not be made due to conflicting data regarding pitavastatin and the potential contribution of intestinal BCRP. Therefore, we recommend removing any statements regarding the inhibition of OATP1B1/3 by GZR.

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NINA MANI
01/08/2016

From: Mani, Nina
To: "[Chambers, Thomas](#)"
Subject: RE: NDA 208261: Carton and Container Advice - follow-up
Date: Friday, January 08, 2016 1:54:00 PM

Hi Tom:

I should have comments to you after the middle of next week.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, January 08, 2016 10:44 AM
To: Mani, Nina
Subject: FW: NDA 208261: Carton and Container Advice - follow-up

Hello Nina,

Just following up and checking to see if you know when any additional FDA comments will be issued on the carton and container labelling revisions we submitted on December 21(SN0047)? We are trying to assess how to manage any required changes to the artwork.

Sincerely,
Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Thursday, December 17, 2015 4:08 PM
To: Chambers, Thomas
Subject: NDA 208261: Carton and Container Advice

Hi Tom:

Kindly acknowledge receipt of the attached Advice communication.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
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NINA MANI
01/08/2016

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: Re: NDA 208261: SVR Follow-up IR
Date: Wednesday, January 06, 2016 3:34:16 PM

Great, thank you.

Sent from my iPhone

On Jan 6, 2016, at 3:21 PM, Mani, Nina <Nina.Mani@fda.hhs.gov> wrote:

That is correct Tom. Thanks.

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Wednesday, January 06, 2016 3:17 PM
To: Mani, Nina
Subject: Re: NDA 208261: SVR Follow-up IR

Hi Nina, for the "relevant polymorphisms", you are referring to positions 28, 30, 31, 93, correct?

They all achieved SVR 24. We are checking the baseline NS5A RAPs.

Tom

Sent from my iPhone

On Jan 6, 2016, at 2:24 PM, Mani, Nina <Nina.Mani@fda.hhs.gov> wrote:

Hi Tom:

Our review team requests the following information:

Please provide the SVR24 status of the following 6 subjects who received 16 weeks of Zepatier plus RBV and had the relevant baseline NS5A polymorphisms: 5172-068_143100003, 5172-068_143500007, 5172-068_143700002, 5172-068_143800018, 5172-068_146200006, and 5172-068_151000006. This information is critical in facilitating the labeling process.

Kindly acknowledge receipt of this request, and provide your response by **COB, January 7, 2016.**

Regards,
Nina

*Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP*

Bldg 22, Room 6317
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From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: Re: NDA 208261: SVR Follow-up IR
Date: Wednesday, January 06, 2016 2:34:15 PM

Thank you Nina, this is to acknowledge receipt.
Sincerely,
Tom

Sent from my iPhone

On Jan 6, 2016, at 2:24 PM, Mani, Nina <Nina.Mani@fda.hhs.gov> wrote:

Hi Tom:

Our review team requests the following information:

Please provide the SVR24 status of the following 6 subjects who received 16 weeks of Zepatier plus RBV and had the relevant baseline NS5A polymorphisms: 5172-068_143100003, 5172-068_143500007, 5172-068_143700002, 5172-068_143800018, 5172-068_146200006, and 5172-068_151000006. This information is critical in facilitating the labeling process.

Kindly acknowledge receipt of this request, and provide your response by **COB, January 7, 2016.**

Regards,
Nina

*Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333*

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/s/

NINA MANI
01/06/2016

From: Mani, Nina
To: ["Chambers, Thomas"](#)
Subject: RE: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR - Follow-up Question
Date: Wednesday, January 06, 2016 12:52:00 PM

Hi Tom:

We cannot agree to removal of the PMCs since we have not received the documents, and even if you submit them by the date you note below we will be unable to review the data by the PDUFA date. Hence the PMCs will stand.

But, do submit the documents ASAP.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Tuesday, January 05, 2016 3:59 PM
To: Mani, Nina
Subject: RE: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR - Follow-up Question

Hello Nina,

To follow-up on the below VIROLOGY Postmarketing Commitments, the trials (PN048, PN061, PN068) are completed and the final study reports are available. In addition, I think we can also submit the data sets in advance of the NDA PDUFA date. In that case, can we arrange to have these items removed from the list of Postmarketing Commitments?

I will follow-up with specific submission dates for these reports/data sets as soon as we have those available. I believe they will be ready around January 21.

Sincerely,
Tom
Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Wednesday, December 30, 2015 8:57 AM

To: Chambers, Thomas
Subject: RE: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR - Follow-up Question

Hi Tom:

Yes, these meet our data set requirements.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, December 25, 2015 10:43 PM
To: Mani, Nina
Cc: Chambers, Thomas
Subject: RE: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR - Follow-up Question

Hello Nina,

Just following up with a clarification regarding the below VIROLOGY PMR study report request for Trials 068, 048, and 061.

1. For the data sets to be included in these reports, we assume you are referring to the standard SDTM (study data tabulation model) data, which will be SAS transport files containing our raw data. And since these are virology requests, we expect to provide the data in the format as noted in the "Guidance for Submitting HCV Resistance Data". We will base these Virology data sets on those previously submitted to the NDA which required some customization as you may recall (Response to Information Request on Virology Data Sets, submitted July 2, 2015 [SN0010]).
2. We are not planning to submit statistical review aid packages for these studies, so we are not planning to include analysis datasets or other specially-formatted datasets.

Please let me know if this will meet the needs of the data set requests or if additional discussion is required.

Sincerely,
Tom
Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, December 23, 2015 1:39 PM
To: Chambers, Thomas
Subject: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR

VIROLOGY PMRs: In my e-mail sent on November 20, 2015, these two Virology PMRs had been in one PMR, but they are now two separate PMRs. Please confirm that you concur with the information below.

1. Please conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors.

Final Protocol Submission:	<u>03/31/2016</u>
Study/Trial Completion:	<u>12/30/2016</u>
Final Report Submission:	<u>01/27/2017</u>

2. Please conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.

Final Protocol Submission:	<u>03/31/2016</u>
Study/Trial Completion:	<u>12/30/2016</u>
Final Report Submission:	<u>01/27/2017</u>

Kindly acknowledge receipt of this communication and let me know if you have any comments or questions on these PMCs/PMRs .

Please submit your response by **January 7, 2016**.

Happy Holidays!

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
01/06/2016

From: Mani, Nina
To: ["Chambers, Thomas"](#)
Subject: RE: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR - Follow-up Question
Date: Wednesday, December 30, 2015 8:57:00 AM

Hi Tom:

Yes, these meet our data set requirements.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, December 25, 2015 10:43 PM
To: Mani, Nina
Cc: Chambers, Thomas
Subject: RE: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR - Follow-up Question

Hello Nina,

Just following up with a clarification regarding the below [VIROLOGY PMR](#) study report request for Trials 068, 048, and 061.

1. For the data sets to be included in these reports, we assume you are referring to the standard SDTM (study data tabulation model) data, which will be SAS transport files containing our raw data. And since these are virology requests, we expect to provide the data in the format as noted in the *"Guidance for Submitting HCV Resistance Data"*. We will base these Virology data sets on those previously submitted to the NDA which required some customization as you may recall (Response to Information Request on Virology Data Sets, submitted July 2, 2015 [SN0010]).
2. We are not planning to submit statistical review aid packages for these studies, so we are not planning to include analysis datasets or other specially-formatted datasets.

Please let me know if this will meet the needs of the data set requests or if additional discussion is required.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Wednesday, December 23, 2015 1:39 PM
To: Chambers, Thomas
Subject: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR

Hi Tom:

Below are **5 PMCs** for your consideration.

- For the Virology PMCs, please propose the Final Report Submission milestone dates
- For the Clinical PMC, please propose Final Protocol Submission, Study/Trial Completion, and Final Report Submission, and
- Provide your concurrence on the Genomics PMC milestone dates.

The Virology PMR that had been sent earlier is now two separate PMRs (see below).

VIROLOGY

1. Please submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 068 (C-EDGE TE).
2. Please submit the final report and datasets, including the SVR24 data, for Phase 2 Trial 048 (C-SALVAGE).
3. Please submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 061 (C-EDGE CO-INFECTION).

CLINICAL

4. Conduct a trial or study in hepatitis C virus genotype 1a infected subjects with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93 to evaluate if a longer duration of treatment with elbasvir/grazoprevir and the addition of ribavirin reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations. The trial or study should have adequate representation of subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy in clinical trials evaluating recommended regimens.

GENOMICS

5. Evaluate the effect of SLCO1B1 genotype on grazoprevir pharmacokinetics and response to elbasvir/grazoprevir treatment in patients with chronic hepatitis C virus infection. To evaluate this effect, either conduct a prospective clinical trial with pharmacokinetic and pharmacodynamic endpoints or a retrospective analysis of previously conducted clinical trials with pharmacokinetic data for which stored biospecimens are available. The trial should be enriched or have sufficient numbers of subjects who are homozygous for reduced function alleles (i.e., N130D and V174A), respectively, to adequately assess whether there are differences in PK and treatment responses.

Final Protocol Submission:

05/30/2016

Study/Trial Completion:

(b) (4)

Final Report Submission:

06/30/2017

VIROLOGY PMRs: In my e-mail sent on November 20, 2015, these two Virology PMRs had been in one PMR, but they are now two separate PMRs. Please confirm that you concur with the information below.

1. Please conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors.

Final Protocol Submission:	<u>03/31/2016</u>
Study/Trial Completion:	<u>12/30/2016</u>
Final Report Submission:	<u>01/27/2017</u>

2. Please conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.

Final Protocol Submission:	<u>03/31/2016</u>
Study/Trial Completion:	<u>12/30/2016</u>
Final Report Submission:	<u>01/27/2017</u>

Kindly acknowledge receipt of this communication and let me know if you have any comments or questions on these PMCs/PMRs .

Please submit your response by **January 7, 2016**.

Happy Holidays!

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
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/s/

NINA MANI
12/30/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers_Thomas.(thomas_chambers2@merck.com))
Subject: NDA 208261: Labeling IR
Date: Wednesday, December 23, 2015 5:39:00 PM

Hi Tom:

Kindly acknowledge receipt of the following request from our Clinical team:

In Section 6.1 under Adverse Reactions with ZEPATIER with or without Ribavirin in Treatment-Experienced Subjects, we note the following text:

Median increase in CD4+ T-cell counts of 32 cells/mm³ was observed at the end of 12 weeks of treatment with ZEPATIER alone. In subjects treated with ZEPATIER with ribavirin for 16 weeks, CD4+ T-cell counts decreased a median of (b)(4) cells per mm³ at the end of treatment.

- 1. Please verify if the median increase of 32 cells/mm³ includes only the 12w arm from P068. If so, please provide the USUBJID, baseline CD4+ cell count, and TW16 CD4+ cell count for the subjects used to calculate this number.*
- 2. Please verify if the median decrease of (b)(4) cells/mm³ includes only the 16w/RBV arm from P068. If so, please provide the USUBJID, baseline CD4+ cell count, and TW16 CD4+ cell count for the subjects used to calculate this number.*

Please submit your response by **January 7, 2016**.

Regards,
Nina

*Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333*

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NINA MANI
12/23/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: Re: NDFA 208261: Virology, Clinical and Genomics PMCs, and Virology PMR
Date: Wednesday, December 23, 2015 2:43:59 PM

Thank you Nina. This is to acknowledge receipt of your PMR requests.
Sincerely,
Tom

Sent from my iPhone

On Dec 23, 2015, at 1:39 PM, Mani, Nina <Nina.Mani@fda.hhs.gov> wrote:

APPEARS THIS WAY ON ORIGINAL

Hi Tom:

Below are **5 PMCs** for your consideration.

- <!--[if !supportLists]-->• <!--[endif]-->For the Virology PMCs, please propose the Final Report Submission milestone dates
- <!--[if !supportLists]-->• <!--[endif]-->For the Clinical PMC, please propose Final Protocol Submission, Study/Trial Completion, and Final Report Submission, and
- <!--[if !supportLists]-->• <!--[endif]-->Provide your concurrence on the Genomics PMC milestone dates.

The Virology PMR that had been sent earlier is now two separate PMRs (see below).

VIROLOGY

- <!--[if !supportLists]-->**1.** <!--[endif]-->Please submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 068 (C-EDGE TE).
- <!--[if !supportLists]-->**2.** <!--[endif]-->Please submit the final report and datasets, including the SVR24 data, for Phase 2 Trial 048 (C-SALVAGE).
- <!--[if !supportLists]-->**3.** <!--[endif]-->Please submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 061 (C-EDGE CO-INFECTION).

CLINICAL

- <!--[if !supportLists]-->**4.** <!--[endif]-->Conduct a trial or study in hepatitis C virus genotype 1a infected subjects with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93 to evaluate if a longer duration of treatment with elbasvir/grazoprevir and the addition of ribavirin reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations. The trial or study should have adequate

representation of subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy in clinical trials evaluating recommended regimens.

GENOMICS

5. Evaluate the effect of SLCO1B1 genotype on grazoprevir pharmacokinetics and response to elbasvir/grazoprevir treatment in patients with chronic hepatitis C virus infection. To evaluate this effect, either conduct a prospective clinical trial with pharmacokinetic and pharmacodynamic endpoints or a retrospective analysis of previously conducted clinical trials with pharmacokinetic data for which stored biospecimens are available. The trial should be enriched or have sufficient numbers of subjects who are homozygous for reduced function alleles (i.e., N130D and V174A), respectively, to adequately assess whether there are differences in PK and treatment responses.

Final Protocol Submission:	05/30/2016
Study/Trial Completion:	(b) (4)
Final Report Submission:	06/30/2017

VIROLOGY PMRs: In my e-mail sent on November 20, 2015, these two Virology PMRs had been in one PMR, but they are now two separate PMRs. Please confirm that you concur with the information below.

1. Please conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors.

Final Protocol Submission:	03/31/2016
Study/Trial Completion:	12/30/2016
Final Report Submission:	01/27/2017

2. Please conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.

Final Protocol Submission:	03/31/2016
Study/Trial Completion:	12/30/2016
Final Report Submission:	01/27/2017

Kindly acknowledge receipt of this communication and let me know if you have any comments or questions on these PMCs/PMRs .
Please submit your response by **January 7, 2016**.

Happy Holidays!

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
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/s/

NINA MANI
12/23/2015



ELECTRONIC MAIL CORRESPONDENCE- NDA INFORMATION REQUEST

Date: December 17, 2015

To: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
Merck Sharp & Dohme Corp.

From: Nina Mani, Regulatory Project Manager, Division of Antiviral Products (DAVP)

NDA/Drug: NDA 208261/ Zepatier (elbasvir/grazoprevir)

Subject: Proposed Container Label and Carton Labeling

Please refer to your New Drug Application (NDA) dated and received May 28, 2015. We have the following recommendations regarding the container label and carton labeling.

Container Label

1. Proposed Container Label (blister sleeve of the dosepak)
 - a. The lot number and expiration date are required on the immediate container per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Add both to the back (outer) panel of the blister sleeve.
 - b. On the outer blister sleeve, place the proprietary name, established name, strength, lot number, expiration date, and manufacturer so that the information appears on each segment panel, ensuring this important information is available in the event the sleeve is removed or torn at the fold. The strength should describe the milligram amount of drug per single unit so that there is no confusion as to how much product is contained in a single unit. We recommend the product strength appear as follows: 50 mg /100 mg per tablet.
 - c. Ensure the directions to take one tablet daily are available on each segment panel in case the sleeve is removed or torn at the fold.

d.  (b) (4)

 (b) (4). We recommend you propose an alternate solution to address the risk for this type of medication error. Consider whether labeling  (b) (4)  (b) (4) may help to mitigate the risk for this error. We recognize you conducted a packaging comprehension study; however, your response to the

information request that described your testing suggests that this particular hazard was not investigated during your testing.

Carton Labeling

1. Proposed Carton Labeling

- a. Change the following statement (b) (4) to read as follows: “This carton contains a total of 28 tablets packaged within 2 dose packs. Each dose pack contains 14 blister units with one-50mg/100 mg tablet per unit.”

Please submit revised container label and carton labeling by **December 21, 2015**.

PLEASE REPLY BY EMAIL (nina.mani@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (240) 402-0333 or the Division’s main number at (301) 796-1500.

{See appended electronic signature page}

Nina Mani, PhD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
12/17/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: Labeling Comments - Clarification
Date: Monday, December 14, 2015 4:40:47 PM

Thank you Nina,
This is very helpful.

Sincerely,
Tom

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Monday, December 14, 2015 3:39 PM
To: Chambers, Thomas
Subject: RE: NDA 208261: Labeling Comments - Clarification

Hi Tom:

Yes, our request is for removal of (b) (4) 16-week data should be retained. However, we defer to you whether you wish to retain or remove (b) (4). Though an (b) (4) is not a recommended duration, inclusion is acceptable and appropriate from a safety perspective.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Monday, December 14, 2015 2:17 PM
To: Mani, Nina
Subject: RE: NDA 208261: Labeling Comments - Clarification

Hello Nina,

Just seeking clarification regarding the below FDA comments on deleting (b) (4) week data from several sections of the USPI.

Sincerely,
Tom

OUR QUESTION: In all cases we assume you mean that numbers from 16 (b) (4) regimens can be included in addition to 12 weeks; it is only (b) (4) weeks that you request not be included?

-

Your comments:

Section 5.1:

“Please verify that the denominators do not include subjects from (b) (4) week treatment arms. Because an (b) (4) week treatment duration is not a recommended regimen and because elevations generally occurred at or after (b) (4), subjects who received a planned (b) (4) treatment course in clinical trials should not be included in the denominator.”

Section 6.1:

Clinical Trials Experience

“Please update these numbers to include only trials and/or subjects in treatment arms consisting of TRADEMARK with or without RBV for at least 12 weeks (recommended regimens). Zepatier is not indicated for an (b) (4) week treatment course and should not be included.”

Serum late ALT elevations:

“Because an (b) (4) week treatment duration is not a recommended regimen and because elevations generally occurred at or after (b) (4), subjects who received a planned (b) (4) treatment course in clinical trials should not be included in the denominator.”

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/s/

NINA MANI
12/16/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261: Labeling Comments
Date: Friday, December 11, 2015 5:22:00 PM
Attachments: [NDA 208261 USPI 12 11 2015.pdf](#)
[NDA 208261 USPI 12 11 2015.docx](#)

Hi Tom:

Kindly acknowledge receipt of the attached USPI revisions made by the Division (word and PDF).

When sending back your revised version on **Friday, December 18, 2015**, please accept all changes you are in agreement with and make a note of it in a comment or by some other mechanism. Only leave in tracked changes those that require negotiation.

Also, due to our extensive comments and editing some reformatting of sections may be required, and we encourage you to use the approved proprietary name when sending back the labeling.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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

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/s/

NINA MANI
12/11/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261 November 30 Label submission-NS5A
Date: Monday, December 07, 2015 12:59:52 PM

Thank you Nina for the information.

It does not sound like we will be needing to plan any teleconference for this week.

I look forward to receiving further updates as this goes forward.

Sincerely,

Tom

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Monday, December 07, 2015 10:23 AM
To: Chambers, Thomas
Subject: RE: NDA 208261 November 30 Label submission-NS5A

Hi Tom:

We will be providing revised labeling in the coming weeks which will include detailed, explanatory comments for any substantive revisions (including but not limited to labeling issues related to NS5A screening).

Regards,

Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, December 04, 2015 11:42 AM
To: Mani, Nina
Subject: NDA 208261 November 30 Label submission

Hello Nina,

Just following up on the recent submission of the revised labelling.

We are interested to know if there will be written feedback on our proposal regarding which NS5A Resistance Polymorphisms should be included in baseline screening, or does the Division think a teleconference will be necessary to go into this in further detail.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

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/s/

NINA MANI
12/07/2015

**PeRC Meeting Minutes
November 4, 2015**

PeRC Members Attending:

Lynne Yao

Wiley Chambers **NON-RESPONSIVE**

Gettie Audain

Meshaun Payne

George Greeley

Tom Smith

Daiva Shetty

Lily Mulugeta (Did not review Zepatier, **NON-RESPONSIVE**)

Kevin Krudys

Shrikant Pagay

Greg Reaman (Did not review Zepatier, **NON-RESPONSIVE**)

Linda Lewis

Hari Cheryl Sachs

Michelle Roth Kline

Dionna Greene

Maura O Leary

Dianne Murphy

Lisa Faulcon

Barbara Buch

Adrienne Hornatko-Munoz **NON-RESPONSIVE**

Agenda

NON-RESPONSIVE

NDA 208261	Zepatier (grazoprevir/elbasvir) (Partial Waiver/ Deferral/Plan) with Agreed iPSP	DAVP	Nina Mani	Treatment of genotype 1, 4 and 6 HCV infection
---------------	--	------	-----------	--

NON-RESPONSIVE

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RESPONSIVE

NON-RESPONSIVE

Grazoprevir/Elbasvir Partial Waiver/Deferral/Plan with agreed iPSP

- Indication: Treatment of genotype 1, 4 and 6 HCV infection
- The division clarified that the adult approval will not include patients with genotype 6

(b) (4)

- *PeRC Recommendations:*

The division confirmed that the pediatric plan is consistent with the plan as presented in the Agreed iPSP (with the exception that genotype 6 patients will not be included in pediatric studies). The PeRC concurred with the pediatric plan.

NON-RESPONSIVE

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/s/

MESHAUN L PAYNE
11/23/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: Re: NDA 208261: Clinical Virology PMR
Date: Friday, November 20, 2015 6:38:02 PM

Thank you Nina,
This is to acknowledge receipt of your request.
Sincerely,
Tom
Thomas Chambers
Merck & Co., Inc.
TEL: (267) 305-6722

Sent from my iPhone

On Nov 20, 2015, at 3:56 PM, Mani, Nina <Nina.Mani@fda.hhs.gov> wrote:

Hi Tom:

Please propose milestone dates for the following Clinical Virology PMR:

1. Please conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.
2. Please conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors.

Please propose dates for the following:

Final Protocol Submission:
Study/Trial Completion:
Final Report Submission:

Kindly acknowledge receipt of this communication and submit your response by **Monday, November 30, 2015**.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
11/23/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: PREA PMRs
Date: Monday, November 09, 2015 6:00:40 PM

Dear Nina,

This is to confirm receipt of your request regarding the PSP timelines.

Sincerely,

Tom

Thomas Chambers
Merck and CO., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Monday, November 09, 2015 5:06 PM
To: Chambers, Thomas
Subject: NDA 208261: PREA PMRs

Hi Tom:

Based on the Agreed iPSP submitted with your NDA application the following two PREA PMRs are planned. Kindly confirm the scheduled milestones for each PMR and provide your response by **Monday, November 16, 2015**.

1. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of elbasvir and grazoprevir in pediatric subjects 3 to 17 years of age with chronic hepatitis C infection.
Final Protocol submission: March 31, 2016
Final Study completion: December 31, 2019
Final Study submission: January 4, 2021
2. Collect and analyze long-term safety data for subjects enrolled in the pediatric elbasvir and grazoprevir safety, pharmacokinetic and efficacy study. Data should be collected for at least 3 years following the end of treatment in order to characterize the long-term safety of elbasvir and grazoprevir including growth assessment, sexual maturation and characterization of elbasvir and grazoprevir resistance associated substitutions in viral isolates from subjects failing therapy.
Final Protocol submission: March 31, 2016
Final Study completion: December 31, 2022
Final Study submission: July 20, 2023

Kindly acknowledge receipt of this communication.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
11/10/2015

From: [Mani Nina](#)
To: "Chambers Thomas"
Subject: RE: NDA 208261- Late Cycle Meeting
Date: Friday, November 06, 2015 12:33:56 PM

Hi Tom:

Yes, you are correct, no revised USPI at this time. When you read the issues mentioned in the package you will see that they all affect the USPI. Hence, till we reach resolution on those we cannot move forward with labeling.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, November 06, 2015 12:26 PM
To: Mani, Nina
Subject: RE: NDA 208261- Late Cycle Meeting

Thank you Nina,

If I understand correctly, you will not be providing a revised USPI at this time. Will that be provided prior to the LCM, or only after our meeting negotiations?

Sincerely,
Tom

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Friday, November 06, 2015 12:15 PM
To: Chambers, Thomas
Subject: RE: NDA 208261- Late Cycle Meeting

Hi Tom:

Kindly acknowledge receipt of the attached courtesy copy of the LCM Briefing Package.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Thursday, October 29, 2015 2:04 PM
To: Mani, Nina
Subject: RE: NDA 208261- Late Cycle Meeting

Dear Nina,

This is to acknowledge receipt of your message regarding the November 19 Late Cycle Meeting.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Thursday, October 29, 2015 1:37 PM

To: Chambers, Thomas
Subject: RE: NDA 208261- Late Cycle Meeting

Tom:

This is a reminder to send me the names of the November 19 meeting participants.

One week prior to the meeting e-mail me any updates to your attendees. For each foreign visitor, complete and email me the attached Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access. Foreign visitors must bring their passport with them for the meeting.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Nina Mani, Regulatory Project Manager, (240) 402-0333; Michael Stanfield, Regulatory Information Specialist, (301) 796- 4145.

Please refer to the following link for visiting the White Oak Campus:
<http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/ucm241748.htm>

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Kindly acknowledge receipt of this communication.

Thanks,
Nina

Nina Mani, PhD, MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/s/

NINA MANI
11/06/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261- Late Cycle Meeting
Date: Thursday, October 29, 2015 2:04:35 PM

Dear Nina,

This is to acknowledge receipt of your message regarding the November 19 Late Cycle Meeting.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Thursday, October 29, 2015 1:37 PM
To: Chambers, Thomas
Subject: RE: NDA 208261- Late Cycle Meeting

Tom:

This is a reminder to send me the names of the November 19 meeting participants.

One week prior to the meeting e-mail me any updates to your attendees. For each foreign visitor, complete and email me the attached Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access. Foreign visitors must bring their passport with them for the meeting.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Nina Mani, Regulatory Project Manager, (240) 402-0333; Michael Stanfield, Regulatory Information Specialist, (301) 796- 4145.

Please refer to the following link for visiting the White Oak Campus:
<http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/ucm241748.htm>

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Kindly acknowledge receipt of this communication.

Thanks,
Nina

Nina Mani, PhD, MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Merck Sharp & Dohme Corp.
MEETING START DATE AND TIME	November 19, 2015 2:30 PM
MEETING ENDING DATE AND TIME	November 19, 2015 4:00 PM
PURPOSE OF MEETING	Late Cycle Meeting
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	Debra Birnkrant, MD Division Director, DAVP White Oak, Bldg 22 , Rm 6332 301-796-1500
ESCORT INFORMATION (If different from Hosting Official)	Nina Mani, PhD, MPH White Oak, Bldg 22, Rm 6137 (240) 402-0333

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/s/

NINA MANI
10/29/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261
Date: Wednesday, October 28, 2015 10:51:15 AM

Thank you Nina,
Tom

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, October 28, 2015 10:13 AM
To: Chambers, Thomas
Subject: RE: NDA 208261

Hi Tom:

We will not be providing any comments in advance of the LCM Briefing Package.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Tuesday, October 27, 2015 8:12 PM
To: Mani, Nina
Subject: RE: NDA 208261

Hello Nina,

Just checking if you can comment. Should we expect any additional Label comments or other feedback on our response, in advance of the Late Cycle briefing package?

Sincerely,
Tom

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Monday, October 26, 2015 4:40 PM
To: Chambers, Thomas
Subject: RE: NDA 208261: NGS

Thanks Tom.

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Monday, October 26, 2015 4:38 PM
To: Mani, Nina
Subject: RE: NDA 208261: NGS

Hello Nina,

The password is (b) (4)

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Monday, October 26, 2015 2:52 PM
To: Chambers, Thomas
Subject: NDA 208261: NGS

Hi Tom:

Can you provide the password for the drive you have submitted.

Thanks,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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NINA MANI
10/29/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: Re: NDA 208261 IR P067- Suicide
Date: Monday, October 12, 2015 10:55:26 AM

Hello Nina,
This is to acknowledge the two safety information requests. I will get back to you with timelines after discussion with the team.

Sincerely,
Tom
Thomas Chambers
Merck and Co., Inc.
(267) 305-6722

Sent from my iPhone

On Oct 12, 2015, at 10:22 AM, Mani, Nina <Nina.Mani@fda.hhs.gov> wrote:

There is one request for information;

The Safety Update Report includes a new death for subject 607770 in Study P052. The report states that the subject died from sensory impairment which was unrelated to study medication. Please provide additional details regarding the subject's sensory impairment and how it led to the subject's death.

Thanks,
Nina

From: Mani, Nina
Sent: Monday, October 12, 2015 10:21 AM
To: Chambers, Thomas (thomas_chambers2@merck.com)
Subject: NDA 208261 IR P067- Suicide

Hi Tom:

Please acknowledge receipt of the following information request, and let me know when we can expect the requested information.

Death by suicide was reported in P067 in the Safety Update Report (AN 106831). Please provide additional information as it becomes available, including but not limited to: (1) unblinded treatment assignment; GZR/EBR versus placebo, and (2) any details that may explain the onset of suicidal ideation and completion of suicide.

Regards,
Nina
Nina Mani
Regulatory Project Manager

*FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333*

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/s/

NINA MANI
10/12/2015



NDA 208261

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Merck Sharp & Dohme Corp.
351 N. Sumneytown Pike
P. O. Box 1000, UG2D-68
North Wales, PA 19454

ATTENTION: Thomas J. Chambers, M.D.
Director, Global Regulatory Affairs

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) dated and received May 28, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Elbasvir and Grazoprevir Tablets, 50 mg/100 mg.

We also refer to your correspondence dated and received July 16, 2015, requesting review of your proposed proprietary name, Zepatier. We have completed our review of the proposed proprietary name Zepatier, and have concluded it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 16, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Nina Mani, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

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

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/s/

AZEEM D CHAUDHRY
09/30/2015

TODD D BRIDGES
10/03/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: Labeling Comprehension Study IR
Date: Wednesday, September 30, 2015 1:45:59 PM

Dear Nina,

This is to acknowledge receipt of your request concerning the patient labelling comprehension study.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Wednesday, September 30, 2015 11:31 AM
To: Chambers, Thomas
Subject: NDA 208261: Labeling Comprehension Study IR

Hi Tom:

Kindly acknowledge receipt of the following information request from the Division of Medical Error Prevention and Analysis:

To expedite our review of your labeling comprehension study, we request that you provide information regarding the errors or difficulties with comprehension seen in your labeling comprehension study, any follow up questions that were asked of study participants and their responses, your root cause analyses, discussion of effectiveness of existing mitigation, and your rationale for why additional mitigations are not necessary. Please submit your response by **Friday, October 9, 2015**.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
09/30/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: USPI Comments
Date: Tuesday, September 29, 2015 12:09:03 PM

Thank you Nina,

This is to acknowledge receipt of the commentary on the draft USPI.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Tuesday, September 29, 2015 10:51 AM
To: Chambers, Thomas
Subject: NDA 208261: USPI Comments

Hi Tom:

Kindly acknowledge receipt of the attached USPI (Word and PDF) with Division comments.
Apologies for the slight delay in getting this to you.

Please submit your response by **Tuesday, October 13, 2015**.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
09/29/2015



NDA 208261

MID-CYCLE COMMUNICATION

Merck Sharp & Dohme Corp.
Attention: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for elbasvir and grazoprevir tablet, 50 mg/100 mg.

We also refer to the teleconference between representatives of your firm and the FDA on September 10, 2015. 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 Nina Mani, Regulatory Project Manager at ((240) 402-0333.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
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: September 10, 2015, 10:30 am – 12:00 pm
Application Number: NDA 208261
Product Name: elbasvir and grazoprevir (ELB/GZR)
Indication: Treatment of hepatitis C virus (HCV) genotypes 1, 4 and 6 infection
Applicant Name: Merck Sharp & Dohme Corp.
Meeting Chair: Adam Sherwat, Medical Team Leader, Division of Antiviral Products (DAVP)
Meeting Recorder: Nina Mani, Regulatory Project Manager, Division of Antiviral Products (DAVP)

FDA ATTENDEES

Edward Cox, MD, Director, Office of Antiviral Products (OAP)
John Farley, MD, MPH, Deputy Director, OAP
Debra Birnkrant, MD, Director, DAVP
Jeff Murray, MD, MPH, Deputy Director, DAVP
Poonam Mishra, MD, MPH, Deputy Director Safety, DAVP
Adam Sherwat, MD, Cross Discipline Team Lead, DAVP
Sarita Boyd, PharmD, Clinical Reviewer, DAVP
Prabha Viswanathan, MD, Clinical Reviewer, DAVP
Su-Young Choi, Pharm D, PhD, Clinical Pharm Reviewer
Luning Zhuang, PhD, Pharmacometrics Reviewer
Shirley Seo, PhD, Clinical Pharm Team Lead
Takashi Komatsu, PhD, RAC, Clinical Virology Reviewer, DAVP
Patrick Harrington, PhD, Clinical Virology Reviewer, DAVP
Jules O'Rear, PhD, Clinical Virology Team Lead, DAVP
LaRee Tracy, MA, PhD, Biometrics Reviewer
Greg Soon, PhD, Biometrics Team Lead
Christopher Ellis, PhD, Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Lead, DAVP
Jasminder Kumar, PharmD, RPh, Division of Risk Management, Division of Medical Error Prevention (DMEPA)
Monica Calderon, PharmD, BCPS, Safety Evaluator, DMEPA
Christian Yoder, BSN, MPH, Regulatory Project Manager, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Nina Mani, PhD, MPH, Regulatory Project Manager, DAVP

APPLICANT ATTENDEES

Thomas Chambers, MD, Regulatory Affairs

Laurie MacDonald, MD, Regulatory Affairs
Eliav Barr, MD, Clinical Research
Janice Wahl, MD, Clinical Research
Bach-Yen Nguyen, MD, Clinical Research
Michael Robertson, MD, Clinical Research
Barbara Haber, MD, Clinical Research
Yoshihiko Murata, MD, Clinical Research
Jacqueline Gress, Clinical Research
Chris Gilbert, Clinical Research
Ronald Leong, MD, Clinical Safety and Risk Management
Peggy Hwang, PhD, Clinical Biostatistics
Stephanie Klopfer, PhD, Biostatistics
Todd Black, PhD, Biology-Discovery
Ernest Asante-Appiah, PhD, Biology-Discovery
Christine Fandozzi, PhD, Preclinical Pharmacokinetics and Drug Metabolism
Luzelena Caro, PhD, Quantitative Sciences
Ed Feng, PhD, Quantitative Sciences
Larissa Wenning, PhD, Quantitative Sciences
Wendy Yeh, MD, Clinical Pharmacology
Marian Iwamoto, MD, PhD, Clinical Pharmacology
Sandrine Ferry-Martin, PhD, Toxicology

PDUFA V INDEPENDENT ASSESSOR

Marc Goldstein, Eastern Research Group

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. 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

The following three issues were conveyed to the sponsor. The discussion during the t-con is in *italics*.

Clinical Safety

While we agree with the sponsor's inclusion of a Warning and Precaution for Increased Risk of ALT Elevations, we are strongly considering the inclusion of additional language in the Warnings and Precautions noting the subpopulations with higher rates of these

events, such as females, Asians, and subjects greater than 65 years of age. In addition, we agree with the Hepatic Safety Committee's recommendation to include more specific guidelines for hepatic monitoring. Specifically, we favor hepatic laboratory testing every 4 weeks on treatment and additional testing as clinically indicated.

(b) (4)
(u) (u). We are carefully assessing the one death in a Child-Pugh B subject in ongoing Protocol 059. Until additional data in Child-Pugh B subjects are available and evaluated, and given that the proposed dosage form of this product contains 100 mg of GZR, we remain concerned about the potential risk associated with ELB/GZR in Child-Pugh B subjects.

***Discussion:** The sponsor inquired as to whether they need to provide any further information about the death that occurred in Protocol 059. The Division noted the sponsor already indicated they do not have an autopsy report for this patient. Since the sponsor also stated they have no additional information about this case, there is nothing more the division is requesting at this time.*

Clinical Pharmacology

We are strongly considering limiting the upper bound of acceptability for GZR AUC to either 2-fold or 3-fold (b) (4) for drug interactions. We do not think that the predicted hepatic adverse event rate at the upper bound should be higher than (b) (4) (b) (4) increase in GZR exposure is predicted to have a hepatic adverse event rate of (b) (4).

We are particularly concerned about specific populations whose hepatic adverse event rates were already significantly higher following 100 mg GZR administration. As mentioned in the clinical comment section, the hepatic adverse event rates were higher in elderly, female, and Asian patients. There is the potential for an additive effect on these rates when multiple intrinsic and extrinsic factors are combined, therefore, a more conservative upper bound for GZR AUC for drug interactions would help to limit the high event rates as a result of this potential additive effect.

Pending completion of the NDA review and further internal discussion, changes in the upper acceptability bound may necessitate changes in clinical recommendations for intrinsic and extrinsic factors, including co-administration of ketoconazole. We are also considering contraindications for concomitant drugs which either have been demonstrated to significantly (> 10-fold) increase GZR exposure or have the potential to significantly increase GZR exposure. Since the magnitude of the increase in GZR exposure observed following co-administration of cyclosporine, lopinavir/ritonavir, and atazanavir/ritonavir is unacceptably high, the use of these drugs in combination with GZR cannot be justified under any circumstances.

Clinical Virology/Clinical Efficacy

- i. HCV Gt1 and NS5A polymorphisms: Our analysis shows that both treatment naïve and PR-treatment experienced patients who were infected with HCV genotype 1a virus with one or more polymorphisms at amino acid positions associated with resistance to NS5A inhibitors were significantly less likely to benefit from a 12 week course of ELB/GZR than subjects infected with HCV genotype 1a virus without key NS5A polymorphisms. A similar pattern with respect to impact of NS5A polymorphisms was noted for PR-treatment experienced patients infected with HCV genotype 1b virus. We define key NS5A polymorphisms as polymorphisms occurring at positions 28, 30, 31, 58, and 93.

The prevalence of key NS5A polymorphisms in the U.S. is clinically meaningful, since by pooling all NS5A polymorphisms from all studies we have been able to document these polymorphisms in up to 12% of patients infected with genotype 1a viruses, and up to 15% of patients infected with genotype 1b viruses. The prevalence of the polymorphisms appears similar regardless of the gender, race, or ethnicity of infected patients.

***Discussion:** The sponsor requested clarification on how the data for the prevalence of NS5A polymorphisms were derived. The Division responded that they were derived by pooling the data from all of the sponsor's key studies. The Division counted all of the NS5A resistance-associated polymorphisms at positions 28, 30, 31, 58, and 93, regardless of their cell culture phenotype.*

There are clinically significant consequences of virologic failure for patients with NS5A polymorphisms in genotype 1a. Amongst patients with genotype 1a virus with NS5A polymorphisms who failed treatment, 96% of subjects gained an NS3/4A resistance substitution or additional NS5A substitution(s), approximately 75% of subjects gained an additional NS5A resistance substitution(s), and approximately 60% of subjects gained an additional NS3/4A AND NS5A resistance substitution(s). Similar impacts were noted for genotype 1b infected patients. Treatment failure will therefore substantially impact retreatment options for these patients, potentially generating the equivalent of HCV salvage patients.

Given these concerns, we are strongly considering a recommendation to screen all genotype 1a patients and all treatment experienced genotype 1b patients for NS5A polymorphisms prior to initiation of ELB/GZR using a commercially available assay. The Division is considering the following algorithmic approach to treatment:

1. All genotype 1a patients and all treatment experienced genotype 1b patients are screened for NS5A polymorphisms prior to initiation of therapy using commercially available assays.
2. Patients without key NS5A polymorphisms will receive ELB/GZR for 12 weeks. [Exception: Patients who have failed prior treatment with PR + simeprevir, PR + boceprevir, or PR + telaprevir will receive ELB/GZR + RBV for 12 weeks]
3. Patients with key NS5A polymorphisms will have one of two options:

- a. Receive ELB/GZR + RBV for 16 weeks (as the impact of NS5A polymorphisms appears to be overcome by the addition of RBV plus a longer treatment duration) [Exception: Patients with CKD will receive ELB/GZR without RBV for 16 weeks (as the benefits of RBV may not outweigh the risks in this population)] **OR**
- b. Consider alternative treatment options

Given the demonstrated toxicity of ribavirin and the potential toxicity of an additional four weeks of ELB/GZR, the Division does not believe that recommending a regimen of ELB/GZR + RBV for 16 weeks to all genotype 1a patients and all treatment experienced genotype 1b patients is an acceptable option, as this would expose upwards of 90% of patients to unnecessary toxicity.

***Discussion:** The sponsor inquired about the cut-offs that will be recommended for the screening tests, since commercially available tests using next generation sequencing (NGS) have different cut-offs for reporting resistance associated variants (RAVs). The sponsor was concerned about the sensitivity of commercially available assays.*

The Division clarified that a polymorphism is the predominant sequence in one or more infected individuals that is not the most common predominant sequence found in other infected individuals. These are different from resistance-associated variants which occur naturally at low frequency within the viral population of an infected individual as a result of error prone synthesis. The sponsor's data demonstrated that individuals whose virus expresses a resistance-associated polymorphism had significantly reduced efficacy. The Division agrees with the sponsor that RAVs are less likely to impact efficacy, except possibly when enriched in an individual failing therapy. Both Sanger nucleotide sequence analysis and NGS analysis can identify resistance-associated polymorphisms, though NGS analysis may also identify RAVs occurring at a high frequency. Results from NGS analysis can be reported so as to distinguish between resistance-associated polymorphisms and RAVs. The sponsor noted that the presence of two polymorphisms is linked with a significant decrease in efficacy. The sponsor was advised to contact the assay providers to ascertain how results from their tests will be reported and to submit an update in writing to the Agency.

- ii. With respect to patients who have failed prior treatment with PR + simeprevir, boceprevir, or telaprevir, the Division has a number of concerns specific to this population. Notably, there are very limited data from PN048 on treatment outcomes for GT1b subjects who have NS3 resistance substitutions at key amino acid positions including A156 and D168. Based on cell culture data and the documentation of A156 and D168 as the predominant amino acid positions associated with PI-related treatment-emergent substitutions in ELB/GZR failures, it is anticipated that substitutions at A156 and D168 may substantially impact GZR efficacy. Therefore, in addition to instituting NS5A screening and management as outlined above, we believe it is imperative that the label prominently display the number of subjects with

each of the key NS3 positions (i.e., R155K, A156, and D168) and the treatment outcome for each of these populations of subjects in PN048.

- iii. With respect to your proposal for an (b) (4) (b) (4) the Division believes the (b) (4) (b) (4) is insufficient to determine its adequacy.

- iv. With respect to HCV GT6 patients, the Division is concerned that there are (b) (4) (b) (4) (b) (4) (b) (4)

The sponsor was asked to provide any additional information that they believe will be helpful in addressing the review issues that were conveyed during the meeting. However, they were reminded that the review team is not required to provide a formal response to any additional information provided.

3.0 INFORMATION REQUESTS

There are no outstanding information requests at this time.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Since no major safety concerns have been identified at this time, there is currently no need for REMS.

5.0 ADVISORY COMMITTEE MEETING

Currently there are no plans for an AC meeting.

6.0 LATE-CYCLE MEETING (LCM)/OTHER PROJECTED MILESTONES

The purpose of the LCM is to discuss the status of the review late in the review cycle. The LCM with the sponsor is scheduled for November 19, 2015. We will send you the LCM background package by November 6, 2015 via secure e-mail as a courtesy, and mail a copy as well.

We will send you our proposed labeling changes and post-marketing commitments/requirements by October 30, 2015.

The PDUFA date for this application is January 28, 2016.

7.0 OTHER

- i. Sponsor will contact commercial vendors who conduct resistance tests regarding how results from the test are reported and submit an update in writing.
- ii. Sponsor will submit the NGS data for RAVs, including the assay cut-offs that they propose.
- iii. In a post-Midcycle e-mail communication, the sponsor inquired about the status of the genotype 4 regimens in their application. They were told that these regimens are currently under review.

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/s/

ADAM I SHERWAT
09/23/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261 - Mid Cycle Meeting - Post-Meeting Clarification
Date: Thursday, September 10, 2015 11:19:18 PM

Thank you Nina,
Tom

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Thursday, September 10, 2015 5:55 PM
To: Chambers, Thomas
Subject: RE: NDA 208261 - Mid Cycle Meeting - Post-Meeting Clarification

Hi Tom:

At the current time we have no comments regarding GT4 regimens and their review is ongoing.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Thursday, September 10, 2015 2:20 PM
To: Mani, Nina
Subject: RE: NDA 208261 - Mid Cycle Meeting - Post-Meeting Clarification

Dear Nina,

Thank you and your review team for holding the Mid-Cycle meeting and providing us with your preliminary comments and recommendations.

We realized afterwards that there were no specific comments on the draft labelling for GT4. Can we assume that there are currently no issues with the proposed GT4 regimens or will this be addressed in the ongoing review?

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Tuesday, September 08, 2015 2:53 PM
To: Chambers, Thomas
Subject: RE: NDA 208261 - Mid Cycle Meeting - September 10 - Agenda and attendees

Hi Tom:

Thank you for providing the call-in information.
Please find attached the agenda for the Sep 10 meeting.

Our tentative list of attendees is as follows:

Ed Cox, Director, Office of Antiviral Products (OAP)
John Farley, Deputy Director, OAP
Katherine Schumann, Associate Director for Regulatory Affairs (Acting)
Debra Birnkrant, Director, DAVP
Jeff Murray, Deputy Director, DAVP
Adam Sherwat, Cross Discipline Team Lead, DAVP
Sarita Boyd, Clinical Reviewer, DAVP
Prabha Viswanathan, Clinical Reviewer, DAVP
Su-Young Choi, Clinical Pharm Reviewer, DAVP
Shirley Seo, Clinical Pharm Team Lead, DAVP
Takashi Komatsu, Clinical Virology Reviewer, DAVP
Patrick Harrington, Clinical Virology Reviewer, DAVP
LaRee Tracy, Biometrics Reviewer
Greg Soon, Biometrics Team Lead
Christopher Ellis, Pharmacology/Toxicology Reviewer, DAVP
Hanan Ghantous, Pharmacology/Toxicology Team Lead, DAVP
Jules O'Rear, Clinical Virology Team Lead, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Nina Mani, Regulatory Project Manager, DAVP
PDUFA V Independent Assessor, Eastern Research Group

Following the meeting I will send you the complete list.
Please provide a list of your attendees.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Thursday, September 03, 2015 12:51 PM
To: Mani, Nina
Subject: RE: NDA 208261 - Mid Cycle Meeting - September 10 - teleconference details

Hello Nina,

The teleconference details are as below for Thursday, September 10 from 10:30 AM – 12:00 PM, EST.

[REDACTED] (b) (4)

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Friday, August 28, 2015 12:05 PM
To: Chambers, Thomas
Subject: RE: NDA 208261 - Mid Cycle Meeting - September 10

Hi Tom:

I will send you the meeting agenda a couple of days prior to the t-con.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, August 28, 2015 11:14 AM
To: Mani, Nina
Subject: NDA 208261 - Mid Cycle Meeting - September 10

Dear Nina,

I am just checking in in regard to the scheduled Post-Mid Cycle meeting scheduled for September 10. I expect to be sending you teleconference information during the week next week. Can you comment on whether advice will be sent to us in advance of the meeting, and the expected time frame for that?

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

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/s/

NINA MANI
09/11/2015



**REQUEST FOR METHODS
VALIDATION MATERIALS**

August 24, 2015

NDA 208261

Merck Sharp & Dohme Corp
Attention: Thomas J. Chambers, MD
351 N. Sunneystown Pike
P. O. Box 1000
North Wales, PA 19454-2505

Dear Thomas J. Chambers, MD:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Grazoprevir/Elbasvir Tablets (100/50 mg).

We will be performing methods validation studies on Grazoprevir/Elbasvir Tablets (100/50 mg), as described in NDA 208261.

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

Method, current version

3.2.S.4.2.1: Assay and Impurities (8742-Elbasvir)

3.2.S.4.2.1: Assay and Impurities (5172-Grazoprevir)

Ref 3.3.3: (b) (4)

3.2.P.5.2.2: Assay, Degradates, Identity for Grazoprevir

3.2.P.5.2.3: Assay, Degradates, Identity for Elbasvir

3.2.P.5.2.5: Dose Uniformity

Samples and Reference Standards

2 x 1 g	Elbasvir reference standard
2 x 1 g	Elbasvir drug substance
2 x 1 g	Grazoprevir reference standard
2 x 1 g	Grazoprevir drug substance
1 x 500 mg	Grazoprevir (b) (4)
1 x 500 mg	Sodium Lauryl Sulfate
2 x 200	Grazoprevir/Elbasvir Tablets (100/50 mg)

Equipment

1	(b) (4)	HPLC column; 150 mm x
1		HPLC column; 100 mm x
1	(b) (4)	HPLC Column; 150 mm x 4.6 mm, (b) (4)
1	(b) (4)	HPLC column; 100 mm x

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

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

LAURA POGUE
08/24/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:thomas_chambers2@merck.com)
Subject: NDA 208261: Clinical Virology- NS5A Request
Date: Friday, August 21, 2015 5:02:00 PM

Hi Tom;

Kindly acknowledge receipt of the following Clinical Virology request, and submit your response by **August 31, 2015**.

Please determine the percentage of NS5A polymorphisms at resistance-associated positions (28, 30, 31, 58, and 93) in each GT4 subtype using available sequence databases.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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NINA MANI
08/21/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers_Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261 - Clinical IR
Date: Wednesday, August 19, 2015 4:37:00 PM

Hi Tom:

Kindly acknowledge receipt of the following request for information, and provide your response by **Thursday, August 27, 2015**.

Please submit all available autopsy reports for deaths that occurred in the GZR/EBR clinical development program.

Regards,
Nina

Nina Mani, PhD, MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

NOTICE:

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/s/

NINA MANI
08/19/2015



ELECTRONIC MAIL CORRESPONDENCE- sNDA INFORMATION REQUEST

Date: August 18, 2015

To: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
Merck Sharp & Dohme Corp.

From: Nina Mani, Regulatory Project Manager, Division of Antiviral Products (DAVP)

NDA/Drug: NDA 208261/ elbasvir/grazoprevir

Subject: **Naming Convention for Products in Labels and Labeling**

Please refer to your New Drug Application (NDA) dated and received May 28, 2015. We have the following recommendations regarding the naming convention for the product container labels and labeling.

DAVP's general recommendation for naming of antiviral products with multiple active ingredients is to list by alphabetical order. One exception is when one active ingredient is a PK booster (e.g., ritonavir, cobicistat); in this case, the PK booster will be listed directly after the drug that is being boosted. Active ingredient names typically are separated by commas plus "and" (e.g., "active1 and active2" or "active1, active2, and active3"). Strengths are typically separated with slashes on container labels.

For this product we recommend the name appear in these formats:

Product Title in Highlights: TRADEMARK™ (elbasvir and grazoprevir) tablets, for oral use

Dosage Forms and Strengths (Highlights): "Tablets: 50 mg elbasvir and 100 mg grazoprevir (3)"

Dosage Forms and Strengths (Section 3): "Tablets: 50 mg of elbasvir and 100 mg of grazoprevir [include identifying characteristics as per 21 CFR 201.57(c)(4)]."

Description (Section 11): "...Each tablet contains 50 mg elbasvir and 100 mg grazoprevir."

Carton, Dosepack, and Blisters:

Trademark™ (elbasvir and grazoprevir) tablets 50mg/100mg

or

Trademark™

(elbasvir and grazoprevir) tablets

50mg/100mg

Please submit revised container labels and labeling by **September 8, 2015**. Additional recommendations will be communicated separately.

PLEASE REPLY BY EMAIL (nina.mani@fda.hhs.gov) to confirm receipt. If you have any questions regarding the contents of this correspondence, please contact me by email or phone (240) 402-0333 or the Division's main number at (301) 796-1500.

{See appended electronic signature page}

Nina Mani, PhD, MPH
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
08/18/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261: Sulfonamide IR
Date: Thursday, August 06, 2015 9:48:00 AM

Hi Tom:

Kindly acknowledge receipt of the Information Request below regarding sulfonamide allergy, and submit your response by **August 20, 2015**.

The structure of MK-5172 includes a sulfonamide moiety. Assuming that drug allergy history was formally collected as part of the medical history in the clinical trials including MK-5172 as a component of treatment, please assess whether patients with a documented sulfa allergy had a greater incidence and/or severity of rash and other adverse events associated with allergic reactions. Please note that the Division generally requests the addition of a Warning in the label for drugs with sulfonamide moieties.

Regards,
Nina

Nina Mani, PhD, MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
08/06/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:thomas_chambers2@merck.com)
Subject: NDA 208261- IR P068
Date: Friday, July 31, 2015 12:16:00 PM

Hi Tom:

Our Clinical Reviewer is asking for the following clarification:

Please explain why Subject 141200008 (AN681642) is excluded from the list of subjects who experienced a hepatic ECI in the P068 CSR (pages 317-318, including Table 12-18). This subject experienced an ALT >3x baseline and >100 IU/L at TW8 and was not associated with virologic failure. The ISS dataset includes this subject in the hepatic ECI population.

Kindly acknowledge receipt of this communication and submit your response by **Monday, August 3, 2015**.

Regards,
Nina

Nina Mani
Regulatory Project Manager
FDA/CDER/OAP/DAVP
Bldg 22, Room 6317
240-402-0333

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/s/

NINA MANI
08/03/2015



NDA 208261

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Merck Sharp & Dohme Corp.
Attention: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) dated and received May 28, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for grazoprevir/elbasvir tablet, 100 mg/50 mg.

We also refer to your amendments dated:

June 3, 2015	June 9, 2015	June 10, 2015
June 18, 2015	June 24, 2015	June 25, 2015
July 1, 2015	July 2, 2015	July 6, 2015
July 8, 2015	July 13, 2015	July 16, 2015
July 17, 2015	July 20, 2015	

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is January 28, 2016. 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>.

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 commitment requests by October 30, 2015.

In addition, the planned date for our internal mid-cycle review meeting is August 19, 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

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

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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

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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

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

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult Division of Antiviral Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

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

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.

If you have any questions, call Nina Mani, Regulatory Project Manager, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
07/27/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Cc: [Winestock, Karen](#)
Subject: RE: NDA 208261: ISS Dataset IR/Advice - Follow-up
Date: Monday, July 13, 2015 12:26:19 PM
Attachments: [image001.png](#)
[image002.png](#)

Dear Nina,

Thank you for your message regarding the ISS data sets, and your additional comment regarding the laboratory data .

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Monday, July 13, 2015 9:22 AM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: RE: NDA 208261: ISS Dataset IR/Advice - Follow-up

Hi Tom:

Please note that we need a treatment emergent flag for both AEs and laboratory data.

Kindly acknowledge receipt.

Thanks,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, July 10, 2015 3:30 PM
To: Mani, Nina
Cc: Winestock, Karen
Subject: RE: NDA 208261: ISS Dataset IR/Advice - Follow-up

Dear Nina,

As discussed on the telephone today, I am writing to confirm the agreement regarding your request of yesterday concerning revision of the ISS data set. As proposed, Merck will provide the revised ISS data set containing PN052 data, with the data including flags for treatment-emergent adverse events. We expect to provide this revised data set by Monday July 20.

Our understanding is that the flagging of treatment-emergent events relates only safety AEs and not laboratory data.

Please let us know if there are additional questions or comments.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Thursday, July 09, 2015 5:12 PM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: NDA 208261: ISS Dataset IR/Advice

Hi Tom:

The review team appreciates your prompt response submitted on July 8, 2015 to our clinical queries made on July 2, 2015. In regard to your response to Clinical Query #1, we would like to remind the Sponsor of their response submitted on 20 February, 2015 to the FDA's pre-NDA meeting package responses:

FDA's Response:

Integrated Safety Population Pool: Datasets

- For the integrated safety dataset, please pool as many of the Phase 2, 2/3, and 3 trials as possible, including those pooled for the written safety summary (as indicated in the first bullet point under Integrated Safety Population Pool) and PN052. Pooling as many trials as possible into the integrated dataset is preferable because it is easier for us to select out trials than it is to combine trials.

Merck's Response:

- For the integrated safety dataset, Merck plans to pool the following Phase 2, 2/3, and 3 trials – PN003, 035, 038, 039, 047, 048, 052, 058, 059, 060, 061, 068, 074 (8- and 12-week arms). Since the request was to pool as many trials as possible, PN074 will be included in this integrated safety dataset.

Given Merck's agreement to include PN052 in the ISS, we respectfully request that the ISS be updated to include both the ITG and the concurrent placebo (DTG) subjects from Study 052 in order to facilitate our safety review. The ISS dataset includes a number of additional variables and flags that are not available in the individual datasets for 052. Please note we do not expect the Sponsor to provide revised analyses based on the updated ISS. We only request the ISS update in order to expedite our internal safety review.

Kindly acknowledge receipt of this communication, and please submit the revised ISS dataset by **Thursday, July 16, 2015**.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
07/13/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Cc: [Winestock, Karen](#)
Subject: RE: NDA 208261: ECG Warehouse information Request
Date: Monday, July 13, 2015 11:26:59 AM

Dear Nina,

Thank you for your message.

This is to acknowledge receipt of your request regarding the PN015 TQT study.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Monday, July 13, 2015 11:11 AM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: RE: NDA 208261: ECG Warehouse information Request

Hi Tom:

Kindly acknowledge receipt of the following request from our TQT-IRT group:

Please submit a subject map file between demographic dataset (DM) and those in the ECG warehouse for Study MK-8742- P015.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Tuesday, June 30, 2015 3:59 PM
To: Mani, Nina
Cc: Winestock, Karen
Subject: RE: NDA 208261: ECG Warehouse information Request

Hi Nina,

Thank you for your message. This is to acknowledge receipt of the requests regarding the QTc studies.

Sincerely,

Tom

Thomas Chambers

Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Tuesday, June 30, 2015 3:42 PM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: NDA 208261: ECG Warehouse information Request

Hi Tom:

Our QT-IRT Team has the following clarifications and requests:

1. MK-8742-P015 trial:

- i. dataset eg.xpt, only has the safety ECGs from standard 12-lead ECGs, where are the PD ECGs from Holter?
- ii. dataset pc.xpt, PK standard unit is 'ng', is that correct?
- iii. ECG waveform files in the ECGWarehouse (under IND114298), no annotations were found, please resubmit those with annotations. We could not assess the analysis quality of the study.

2. MK-5172-049 trial:

- i. QTcP is used, but not in the eg.xpt dataset, is the correction factor (slope) 0.37?

Kindly acknowledge receipt of this communication and submit the requested information by **July 2, 2015**.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
07/13/2015

From: Mani, Nina
To: [Chambers_Thomas\(thomas_chambers2@merck.com\)](mailto:Chambers_Thomas(thomas_chambers2@merck.com))
Cc: Winstock_Karen
Subject: NDA 208261: ISS Dataset IR/Advice
Date: Thursday, July 09, 2015 5:11 00 PM
Attachments: [image001.png](#)
[image002.png](#)

Hi Tom:

The review team appreciates your prompt response submitted on July 8, 2015 to our clinical queries made on July 2, 2015. In regard to your response to Clinical Query #1, we would like to remind the Sponsor of their response submitted on 20 February, 2015 to the FDA's pre-NDA meeting package responses:

FDA's Response:

Integrated Safety Population Pool: Datasets

- For the integrated safety dataset, please pool as many of the Phase 2, 2/3, and 3 trials as possible, including those pooled for the written safety summary (as indicated in the first bullet point under Integrated Safety Population Pool) and PN052. Pooling as many trials as possible into the integrated dataset is preferable because it is easier for us to select out trials than it is to combine trials.

Merck's Response:

- For the integrated safety dataset, Merck plans to pool the following Phase 2, 2/3, and 3 trials – PN003, 035, 038, 039, 047, 048, 052, 058, 059, 060, 061, 068, 074 (8- and 12-week arms). Since the request was to pool as many trials as possible, PN074 will be included in this integrated safety dataset.

Given Merck's agreement to include PN052 in the ISS, we respectfully request that the ISS be updated to include both the ITG and the concurrent placebo (DTG) subjects from Study 052 in order to facilitate our safety review. The ISS dataset includes a number of additional variables and flags that are not available in the individual datasets for 052. Please note we do not expect the Sponsor to provide revised analyses based on the updated ISS. We only request the ISS update in order to expedite our internal safety review.

Kindly acknowledge receipt of this communication, and please submit the revised ISS dataset by **Thursday, July 16, 2015**.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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NINA MANI
07/09/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Subject: RE: NDA 208261: Datasets
Date: Thursday, July 02, 2015 11:22:53 AM

Hello Nina,

Thank you for your message and this is to acknowledge receipt of your information request.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Thursday, July 02, 2015 10:33 AM
To: Chambers, Thomas
Subject: NDA 208261: Datasets

Hi Tom:

Our Clinical Team is requesting clarification on the following issues noted with datasets submitted to the NDA.

1. Data from subjects randomized to the deferred treatment group of Study 052 appear to be missing from the ISS datasets. These comparative data are essential for conducting a thorough safety review for the CKD population.
 - a. If the subjects were included in the ISS datasets, please specify which variables should be used to locate these subjects.
 - b. If the subjects were excluded (intentionally or accidentally), please submit revised ISS datasets which include these 133 subjects.
 - c. If the latter is true and revisions are required, please also include a "treatment emergent" flag(s) in the revised ISS datasets. It is currently very difficult to select this population for analysis.
2. In the laboratory domains of the tabulation datasets (all studies), the Lab Reference Range Indicator variable (LBNRIND) takes on the values "AB", "ABNORMAL", "H", "HN", "HP", "L", "LN", "LP", "N", "NORMAL". The derivation of this variable is not defined in metadata or the Study Data Reviewer's Guide. Please provide definitions for all possible values of LBNRIND.
3. Potential duplicate records were discovered in the laboratory domains in studies 052, 060, 061, 068. These are records where a subject received the same test on the same date/time. In some instances, these records are contradictory.

For example, see the LB domain for study 060, USUBJID “5172-060_010100001”, LBSEQs “2.80E+12” and “4.38E+14”. Both tests are Albumin tests that occurred on 11/13/2014 with different fasting statuses and different results. Please explain how to interpret these records and other potential duplicate records in the four studies listed above.

4. Contradictory dates regarding death were discovered in studies 052, 060, and 068. Please explain how we should interpret the conflicting dates listed below:

Study 052

Subject 5172-052_048200002 has a disposition event of “DEATH” with a start date of [REDACTED] (b) (6) and no end date. This subject has a fatal adverse event (where AETERM, or the reported term, is “unknown case of death”) with a start date of [REDACTED] (b) (6). Why is the disposition event date of death after the fatal adverse event start date?

Subject 5172-052_058700002 has a disposition event of “DEATH” with a start date of [REDACTED] (b) (6). This subject has a fatal adverse event (where AETERM is “Thoracic Aortic Aneurysm”) with an end date of [REDACTED] (b) (6). How did this adverse event end after the subject was reported to have died?

Study 060

Subject 5172-060_010100009 has a disposition event of “DEATH” with a start date of [REDACTED] (b) (6) and no end date. This subject has a fatal adverse event (where AETERM is “Malignant ventricular arrhythmia”) with a start date of [REDACTED] (b) (6). Why is the disposition event date of death after the fatal adverse event start date?

Subject 5172-060_039000019 has a disposition event of “DEATH” with a start date of [REDACTED] (b) (6) and no end date. This subject has a fatal adverse event (where AETERM is “complications of gastroesophageal strangulation due to a hiatal hernia”) with a start date of [REDACTED] (b) (6). Why is the disposition event date of death after the fatal adverse event start date?

Study 068

Subject 5172-068_159300002 has a disposition event of “DEATH” with a start date of [REDACTED] (b) (6). This subject has a fatal adverse event (where AETERM is “septic shock”) with a start date of [REDACTED] (b) (6) and duration of 12 hours. How did this adverse event end after the subject was reported to have died?

Kindly acknowledge receipt of this communication and provide your response by

Wednesday, July 8, 2015.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
07/06/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Cc: [Winestock, Karen](mailto:Winestock.Karen)
Subject: NDA 208261: AE IR
Date: Tuesday, June 30, 2015 8:11:00 PM

Hi Tom:

Our Clinical team requests the following information:

Please specify which grading scale was used to assess severity of AEs as mild, moderate, or severe in Phase 2 and Phase 3 clinical trials. Please clarify how life-threatening events are captured using this classification.

Kindly acknowledge receipt of this communication and submit the requested information by COB, Wednesday, July 1, 2015 (Eastern).

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
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/s/

NINA MANI
07/01/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Cc: [Winestock, Karen](#)
Subject: RE: NDA 208261: ECG Warehouse information Request
Date: Tuesday, June 30, 2015 3:58:50 PM

Hi Nina,

Thank you for your message. This is to acknowledge receipt of the requests regarding the QTc studies.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Tuesday, June 30, 2015 3:42 PM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: NDA 208261: ECG Warehouse information Request

Hi Tom:

Our QT-IRT Team has the following clarifications and requests:

1. MK-8742-P015 trial:

- i. dataset eg.xpt, only has the safety ECGs from standard 12-lead ECGs, where are the PD ECGs from Holter?
- ii. dataset pc.xpt, PK standard unit is 'ng', is that correct?
- iii. ECG waveform files in the ECGWarehouse (under IND114298), no annotations were found, please resubmit those with annotations. We could not assess the analysis quality of the study.

2. MK-5172-049 trial:

- i. QTcP is used, but not in the eg.xpt dataset, is the correction factor (slope) 0.37?

Kindly acknowledge receipt of this communication and submit the requested information by **July 2, 2015**.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP

Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
06/30/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Cc: [Winestock, Karen](#)
Subject: NDA 208261: Clinical Virology IR 6/25/2015
Date: Thursday, June 25, 2015 1:12:00 PM

Hi Tom:

Kindly acknowledge the following request from our Clinical Virology Team:

Please clarify what variable was used to flag samples where genotyping failed (due to poor sequence or technical reasons) as well as a flag to identify all isolates where successful resistance analysis data are reported (please see pg. 13 of "Guidance for Submitting HCV Resistance Data" ([link](#))).

Please submit the requested information by **July 2 , 2015**.

Regards,
Nina

Nina Mani, PhD, MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
06/25/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Cc: [Winestock, Karen](#)
Subject: RE: NDA 208261: Milestone Meetings
Date: Wednesday, June 24, 2015 9:39:54 AM

Noted, thanks.

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, June 24, 2015 9:38 AM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: RE: NDA 208261: Milestone Meetings

Great, Tom!

You'll receive the Late Cycle Briefing Package on November 12, 2015.

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Wednesday, June 24, 2015 9:35 AM
To: Mani, Nina
Cc: Winestock, Karen
Subject: RE: NDA 208261: Milestone Meetings

Thank you Nina. I will place these dates on our calendar.

Sincerely,
Tom

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Wednesday, June 24, 2015 9:31 AM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: RE: NDA 208261: Milestone Meetings

Hi Tom:

I confirm the Late Cycle Meeting for Thursday, November 19, 2015 from 2:30 pm -4:00 pm (Eastern),

And the Post-Midcycle Communication (T-con): Thursday, September 10, 2015, 10:30 am – noon (Eastern).

Regards,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Wednesday, June 24, 2015 9:01 AM
To: Mani, Nina
Cc: Winestock, Karen
Subject: RE: NDA 208261: Milestone Meetings

Hi Nina,

Thursday, November 19 is a preferred date for us.

The September 10 date is also okay.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 306-6722

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Tuesday, June 23, 2015 3:36 PM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: RE: NDA 208261: Milestone Meetings

Hi Tom:

We could do Thursday, November 19, 2015 from 2:30 pm -4:00 pm (Eastern). This of course is right after AASLD.

Let me know.

Thanks,
Nina

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Tuesday, June 23, 2015 2:44 PM
To: Mani, Nina
Cc: Winestock, Karen
Subject: RE: NDA 208261: Milestone Meetings

Nina, is there any flexibility around the November 12 meeting date, even if only one day in advance? This is immediately prior to the AASLD meeting and some of team had planned to be in San Francisco by that day.

Sincerely,
Tom

From: Mani, Nina [<mailto:Nina.Mani@fda.hhs.gov>]
Sent: Tuesday, June 23, 2015 10:25 AM

To: Chambers, Thomas
Cc: Winestock, Karen
Subject: NDA 208261: Milestone Meetings

Hi Tom:

Please let me know regarding your team's availability for two PDUFA V milestone meetings.

1. Post-Midcycle Communication (T-con): Thursday, September 10, 2015, 10:30 am – noon (Eastern).
2. Late Cycle Meeting (Face- Face, which at your discretion can be converted to a T-con): Thursday, November 12, 2015, 2:30 pm – 4:00 pm (Eastern).

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
06/24/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Cc: [Winestock, Karen](#)
Subject: RE: NDA 208261- Information Request- 6/23/2015
Date: Tuesday, June 23, 2015 2:20:27 PM

Dear Nina,
Thank you for your message below regarding the ISS.
This is to acknowledge receipt of your request.

Sincerely,
Tom
Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Tuesday, June 23, 2015 1:36 PM
To: Chambers, Thomas
Cc: Winestock, Karen
Subject: NDA 208261- Information Request- 6/23/2015

Hi Tom:

The review team has the following request.

1. Please specify which variable represents the treatment emergent flag in the ISS and individual (052, 060, 061, 068) datasets.
2. Please define the following variables in the ISS dataset:
 - a. Trial Epoch (Treatment, Treatment 1, Treatment 2, Screening, Pretreatment, Post-Study, Follow-up)
 - b. Treatment population flag (as opposed to the safety population flag)
 - c. Trial segment (A, B, C, D)
 - d. Hepatic Fibrosis Stage. Please also comment on how the results from the different fibrosis screening modalities employed in the clinical trials were used in classifying patients into the categories of Metavir F0 to F2, Metavir F3, and Metavir F4. For example, was FibroScan used for binary assessment only (i.e., cirrhosis or no cirrhosis) or was an attempt made to subcategorize patients into different Metavir strata based on FibroScan scoring?
 - e. Pooled Hepatic Fibrosis Stage 1. Please also comment on how the results from the different fibrosis screening modalities employed in the clinical trials were used in classifying patients into the categories of "cirrhotic" versus "non-cirrhotic", and what constitutes "unknown" status.

Kindly acknowledge receipt of this communication, and we request that you submit your response by **Thursday, June 25, 2015**.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
06/23/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261 Carton and Container
Date: Tuesday, June 16, 2015 8:08:00 PM

Hi Tom:

Our review team would greatly appreciate if you could send four samples of the carton and containers by **COB Tuesday June 23, 2015**.

Kindly acknowledge receipt of this request, and please send them to my address below.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
06/16/2015

From: [Chambers, Thomas](#)
To: [Mani, Nina](#)
Cc: [Winestock, Karen](#); [Yoder, Christian](#)
Subject: RE: TQTc Clinical Pharmacology Summary Information
Date: Friday, June 12, 2015 9:19:08 AM

Dear Nina,
Thank you for your message and request regarding the Clin Pharm Summary document.

This is to acknowledge receipt.

Sincerely,

Tom

Thomas Chambers
Merck and Co., Inc.
TEL: (267) 305-6722

From: Mani, Nina [mailto:Nina.Mani@fda.hhs.gov]
Sent: Friday, June 12, 2015 8:50 AM
To: Chambers, Thomas
Cc: Winestock, Karen; Yoder, Christian
Subject: RE: TQTc Clinical Pharmacology Summary Information

Hi Tom:

Please ask your team to fill out this summary document, one of each of the TQTc studies for which ECGs have been uploaded to the ECG Warehouse.
Kindly acknowledge receipt of this request, and submit these to the NDA by **Wednesday, June 17, 2015**.

Regards,
Nina

Nina Mani, PhD, MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in Cmax and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
-------------------	--

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NINA MANI
06/12/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261: Virology IR
Date: Tuesday, June 09, 2015 9:44:00 AM

Hi Tom:

Kindly confirm receipt of the following Virology request for information:

1. Please confirm the genotypic data from the 'hcvrv' datasets for subjects 5172-074_000100092 and 5172-035_041300001. The reference strain that was used for the Baseline sequence (Con1) is different from the strain used for all other timepoints (JFH-1), resulting in many treatment-emergent substitutions for these 2 subjects.
2. Please resubmit all of your genotypic datasets adding rows for each reference sequence used as well as percent conservation and common variants for GT 1a and 1b. Please see pg. 12 of "Guidance for Submitting HCV Resistance Data" ([link](#)).

Please provide the requested information by **June 24, 2015**.

Regards,
Nina

Nina Mani, PhD, MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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NINA MANI
06/10/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261: Coding Dictionary and Foreign Data
Date: Thursday, June 04, 2015 10:42:00 AM
Importance: High

Hi Tom:

Our Clinical Team requests the following information:

1. 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).
2. Please provide a rationale for assuming the applicability of foreign data to the U.S. population, or if already provided, indicate its location in the submission.

Kindly acknowledge receipt and provide the information ASAP.

Thanks,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261: Site IDs
Date: Thursday, June 04, 2015 3:41:00 PM

Hi Tom:

Please explain why the SITEIDs differ between the legacy analyses data sets and the CLINSITE data set.

Kindly acknowledge receipt of this information request and provide your response ASAP.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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NINA MANI
06/04/2015

From: Mani, Nina
To: [Chambers, Thomas \(thomas_chambers2@merck.com\)](mailto:Chambers.Thomas(thomas_chambers2@merck.com))
Subject: NDA 208261: Financial Disclosure information
Date: Wednesday, June 03, 2015 3:03:00 PM

Hi Tom:

We recognize you have provided a financial disclosure document that provides the financial disclosure information; however, due to the table format, it is difficult to review and confirm the specific numbers of investigators overall and some other specific criteria listed below.

Please provide the following information related to financial disclosures:

1. Total number of investigators (primary and sub-investigators) for PN052, PN060, PN061, and PN068
2. For the investigators with disclosable financial interests/arrangements, identify the **number of investigators** with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
 - a. Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:
 - b. Significant payments of other sorts:
 - c. Proprietary interest in the product tested held by investigator:
 - d. Significant equity interest held by investigator in sponsor of covered study:
3. If applicable, please provide a description of the steps taken to minimize potential bias.

Kindly acknowledge receipt of this communication and submit the requested information by Wednesday, June 10, 2015.

Regards,
Nina

Nina Mani, Ph.D., MPH
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Avenue, Building 22
Room 6317
Silver Spring, MD 20993-0002
Phone: 240-402-0333
Fax: 301-796-9883
e-mail: Nina.Mani@fda.hhs.gov

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/s/

NINA MANI
06/03/2015



NDA 208261

NDA ACKNOWLEDGMENT

Merck Sharp & Dohme Corp.
Attention: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

We have received your New Drug Application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: grazoprevir/elbasvir tablet; 100 mg/50 mg

Date of Application: May 28, 2015

Date of Receipt: May 28, 2015

Our Reference Number: NDA 208261

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 July 27, 2015 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

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If you have any questions, call me at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Nina Mani, PhD, MPH
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

NINA MANI
06/02/2015



IND 110261

**RESCIND –
BREAKTHROUGH THERAPY DESIGNATION**

Merck, Sharp & Dohme Corp.
Attention: Thomas Chambers, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454

Dear Dr. Chambers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-5172/MK-8742.

We also refer to our October 18, 2013, letter granting Breakthrough Therapy designation to MK-5172/MK-8742 for treatment of chronic hepatitis C virus infection, and to our February 28, 2014, correspondence amending the October 18, 2013, letter to add the specific HCV genotype (i.e. genotype 1) for which breakthrough designation was granted. Also refer to our January 30, 2015, Intent to Rescind Breakthrough Therapy designation letter. We are rescinding this Breakthrough Therapy designation and any associated Rolling Review agreements. (b) (4)

(b) (4)

For further information regarding Breakthrough Therapy designation, refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>)

If you have any questions, contact Christian P. Yoder, Regulatory Project Manager, at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

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

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/s/

DEBRA B BIRNKRANT
04/14/2015



IND 110261

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Merck, Sharp & Dohme Corp.
Attention: Thomas Chambers, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454

Dear Dr. Chambers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-5172/MK-8742.

We also refer to your February 9, 2015, request for Breakthrough Therapy designation for MK-5172/MK-8742 for the treatment of patients with chronic hepatitis C virus, genotype 1, 4, (b) (4) infection in patients (b) (4)

However, we are granting Breakthrough Therapy designation for the treatment of chronic hepatitis C virus, genotype 1 infection in patients with end stage renal disease on hemodialysis. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of MK-5172/MK8742 for treatment of patients with chronic hepatitis C, genotype 1 infection in patients with end stage renal disease on hemodialysis, to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

discussion at this initial breakthrough therapy meeting².

We note your recent Type B pre-NDA meeting held on February 20, 2015 to discuss the filing strategy for MK-5172/MK-8742. At this point in your drug development program, holding an initial breakthrough therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for MK-5172/MK-8742 for the treatment of patients with chronic hepatitis C, genotype 1 infection in patients with end stage renal disease on hemodialysis is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Christian Yoder, Regulatory Project Manager, at (240) 402-9990.

Sincerely,

{See appended electronic signature page}

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

²<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>

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/s/

DEBRA B BIRNKRANT
04/01/2015



IND 110261

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Merck, Sharp & Dohme Corp.
Attention: Thomas Chambers, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454

Dear Dr. Chambers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-5172/MK-8742.

We also refer to your February 9, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that MK-5172/MK-8742 for the treatment of patients with chronic hepatitis C, genotype 4 virus infection meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of MK-5172/MK8742 for treatment of patients with chronic hepatitis C, genotype 4 virus infection to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.¹

When breakthrough therapy designation is granted, sponsors are asked to submit a Type B meeting request for a multidisciplinary comprehensive discussion of the drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - *Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics*, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting².

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We note your recent Type B pre-NDA meeting held on February 20, 2015 to discuss the filing strategy for MK-5172/MK-8742. At this point in your drug development program, holding an initial breakthrough therapy meeting is not necessary. However, please contact the Regulatory Project Manager noted below to determine if any information is required at this time to expedite the review of your breakthrough designated product.

If the breakthrough therapy designation for MK-5172/MK-8742 for the treatment of patients with chronic hepatitis C, genotype 4 virus infection is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Christian Yoder, Regulatory Project Manager, at (240) 402-9990.

Sincerely,

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

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/s/

DEBRA B BIRNKRANT
04/01/2015

**CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Antiviral Products
27 February 2015**

Summary Box

1. IND: 110261
2. Company: Merck
3. Products: Grazoprevir (MK-5172)/Elbasvir (MK-8742) fixed-dose combination
4. BT Designation Requested for the Following Indication: Treatment of chronic hepatitis C virus (HCV) genotype 4 infection in patients with or without cirrhosis, including those with chronic kidney disease, and those with HCV/HIV-1 co-infection.
5. These drugs are intended to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence indicates that this drug combination may demonstrate substantial improvement over existing therapies on a clinically significant endpoint (safety).

1. Brief description of the drug

Grazoprevir (MK-5172) is a selective inhibitor of hepatitis C virus (HCV) NS3/NS4A protease, and elbasvir (MK-8742) is an HCV NS5A replication complex inhibitor.

2. Brief description of the disease, intended population, and currently available therapies

Approximately 3.2 million people in the United States have chronic HCV infection, which can lead to cirrhosis and hepatocellular carcinoma. Chronic HCV is currently the most common reason for liver transplantation in the United States. A recent CDC analysis of death certificate data found that HCV-attributable deaths increased significantly between 1999 and 2007. CDC estimates there were 15,106 deaths caused by HCV in 2007. The Division considers chronic HCV infection a serious and life-threatening condition.

At least six different HCV genotypes have been identified, numbered 1 to 6, with further breakdown into subtypes for several of the known genotypes (e.g., genotype 1 subtypes 1a and 1b). In the United States, genotype 1 is the most common (70-80%; mostly subtype 1a), followed by genotypes 2 and 3. The remaining genotypes (4, 5, and 6) occur uncommonly in the United States, but may predominate in other parts of the world; genotype 4 predominately occurs in the Middle East and Egypt.

The primary objective of anti-HCV treatment is the achievement of a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the cessation of treatment (i.e., "SVR12"). SVR12 is generally considered a "virologic cure."

Until recently, treatment of HCV genotype 4 infection has consisted of subcutaneous peginterferon (pegIFN) and oral ribavirin (RBV) for up to 48 weeks. In late 2013, sofosbuvir, an NS5B nucleoside inhibitor, was approved for treatment of genotype 4 infection in combination with pegIFN and RBV based on data in 28 subjects. Despite a high response rate (27/28, 96%), the sofosbuvir combination regimen requires the co-administration of pegIFN.

PegIFN is administered as a weekly injection and is poorly tolerated in many patients. It is associated with numerous serious and life-threatening toxicities including neuropsychiatric, autoimmune, ischemic and infectious disorders, and bone marrow suppression. Importantly, a significant proportion of HCV-infected patients are intolerant to IFN or ineligible (based on co-morbidities or age) to use IFN-based therapies, and these patients currently lack antiviral treatment options.

Because of the limitations of IFN-based therapies, there has been great interest in recent years in developing all oral, IFN-free regimens consisting of combinations of multiple classes of HCV oral agents with improved tolerance, shortened duration of treatment, and broader patient populations eligible for treatment.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

The Sponsor is relying on sustained virologic response or SVR12 (described in #2 above) as the efficacy endpoint to support their request for a breakthrough therapy designation. SVR12 is accepted by the Division as a clinically significant endpoint for chronic HCV treatment trials. This surrogate endpoint is known to predict clinical benefit, as achievement of SVR has been associated with reduced all-cause mortality and liver-related morbidity and mortality.

4. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

Breakthrough therapy designations for chronic HCV genotype 4 infection has been granted for the following all oral, IFN-free regimens:

- Paritaprevir, ombitasvir, and ritonavir, which is a combination of an NS3/4A protease inhibitor and an NS5A inhibitor, and is currently approved in combination with dasabuvir only for treatment of HCV genotype 1 infection; and
- GS-5816 and sofosbuvir; GS-5816 is an NS5A inhibitor under development.

These treatments are not currently approved for treatment of HCV genotype 4 infection.

5. Description of preliminary clinical evidence

Safety and efficacy of the combination of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with HCV genotype 4 infection.

Preliminary data with MK-5172/MK-8742 fixed-dose combination from three Phase 3 trials, PN060, PN061, and PN068, support a breakthrough designation for HCV genotype 4. PN060 is a randomized, blinded, placebo-controlled, parallel-group trial evaluating the safety and efficacy of MK-5172/MK-8742 for 12 weeks in 421 treatment-naïve patients with HCV genotype 1, 4, or 6 infection, with or without cirrhosis. PN061 is a single-arm, open-label trial evaluating the safety and efficacy of MK-5172/MK-8742 for 12 weeks in 218 HIV/HCV co-infected treatment-naïve patients with genotype 1, 4, or 6 infection, with or without cirrhosis. PN068 is a randomized, blinded, parallel-group trial evaluating the safety and efficacy of MK-5172/MK-8742 ± twice-daily RBV for 12 or 16 weeks in 420 patients with genotype 1, 4, or 6 infection, with or without cirrhosis, who have failed prior PR therapy.

A total of 103 genotype 4-infected patients have been enrolled and treated with MK-5172/MK-8742 in Phase 2 trials and the Phase 3 trials described above. Preliminary efficacy results show high SVR4 (97%, 63/65) and SVR12 (93%, 56/60) rates in patients with available data who received 12 weeks of MK-5172/MK-8742 treatment without RBV. The addition of RBV resulted in slightly increased SVR4 and SVR12 rates: 100% (25/25) and 96% (22/23), respectively. A longer duration of therapy (16 weeks) does not appear to increase SVR rates.

Preliminary safety results from PN060, PN061, and PN068 are also favorable for genotypes 1, 4, and 6, with comparable rates of death, SAEs, discontinuations due to AEs, and drug-related AEs with MK-5172/MK-8742 (n=316) compared to placebo (n=105). Grade 3 or greater laboratory abnormalities were also comparable between the two groups. Overall, treatment with MK-5172/MK-8742 appears very promising in patients HCV genotype 4 infection as demonstrated by a high SVR rate and favorable safety profile.

6. Division's recommendation and rationale

The breakthrough therapy designation for grazoprevir (MK-5172)/elbasvir (MK-8742) for HCV genotype 4 infection is supported by the following:

1. The Phase 2 and Phase 3 SVR4 and preliminary SVR12 data provide evidence of comparable efficacy to the currently available standard of care but without the need for IFN.
2. The safety profile of the regimen is promising. The regimen is IFN free, resulting in fewer cytopenias, less depression, no flu-like prodrome, and no requirements for injections.
3. Absence of IFN from the regimen will allow many patients with contraindications to IFN to receive an effective regimen.

Based on the data presented, DAVP believes that grazoprevir (MK-5172)/elbasvir (MK-8742) meets the definition of a breakthrough therapy for the treatment of HCV genotype 4, as outlined in Section 903 of the Food and Drug Administration Safety and innovation Act and recommends granting breakthrough therapy designation.

7. Division's next steps and sponsor's plan for future development

The Sponsor plans to submit an NDA for grazoprevir (MK-5172)/elbasvir (MK-8742) with final SVR12 results from PN060, PN061, and PN068 to support an indication for treatment of HCV genotype 4 infection in April 2015.

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/s/

SARITA D BOYD
03/16/2015

ADAM I SHERWAT
03/16/2015

**CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Antiviral Products
27 February 2015**

Summary Box

1. IND: 110261
2. Company: Merck
3. Products: Grazoprevir (MK-5172)/Elbasvir (MK-8742) fixed-dose combination
4. BT Designation Requested for the Following Indication: Treatment of chronic hepatitis C virus (HCV) genotype 1, 4, or 6 infection in patients with chronic kidney disease, including severe renal impairment or end stage renal disease/hemodialysis.
5. These drugs are intended to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence indicates that this drug combination may meet an unmet need for a patient population with a serious condition with no or limited treatments.

1. Brief description of the drug

Grazoprevir (MK-5172) is a selective inhibitor of hepatitis C virus (HCV) NS3/NS4A protease, and elbasvir (MK-8742) is an HCV NS5A replication complex inhibitor.

2. Brief description of the disease, intended population, and currently available therapies

Approximately 3.2 million people in the United States have chronic HCV infection, which can lead to cirrhosis and hepatocellular carcinoma. Chronic HCV is currently the most common reason for liver transplantation in the United States. A recent CDC analysis of death certificate data found that HCV-attributable deaths increased significantly between 1999 and 2007. CDC estimates there were 15,106 deaths caused by HCV in 2007.

At least six different HCV genotypes have been identified, numbered 1 to 6, with further breakdown into subtypes for several of the known genotypes (e.g., genotype 1 subtypes 1a and 1b). In the United States, genotype 1 is the most common (70 to 80 percent; mostly subtype 1a), followed by genotypes 2 and 3. The remaining genotypes occur uncommonly in the United States but may predominate in other parts of the world.

The prevalence rate of HCV among patients undergoing hemodialysis within a U.S. hemodialysis network was reported as 7.8% (range: 5.5 – 9.8%), and it is estimated that over 60,000 HCV-infected patients will require hemodialysis by 2020. A significant relationship has been observed between HCV infection and increased mortality among patients on long-term dialysis. Compared to non-HCV-infected CKD Stage

4/5 patients, HCV-infected CKD Stage 4/5 patients have poor graft survival and higher overall mortality outcomes following renal transplantation. Treatment of HCV infection prior to transplantation, compared to untreated HCV controls, has been shown to decrease the risk of *de novo* glomerulonephritis, post-transplant diabetes mellitus, and chronic allograft nephropathy. The Division considers chronic HCV infection in CKD patients, especially those receiving hemodialysis, a serious and life-threatening condition.

The primary objective of anti-HCV treatment is the achievement of a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the cessation of treatment (i.e., “SVR12”). SVR12 is generally considered a “virologic cure.” Currently approved treatments for chronic HCV genotype 1 infection consist of interferon (IFN)-sparing all oral direct-acting antivirals, which require no dosage adjustments in patients with creatinine clearance > 30 mL/min. These options include ledipasvir and sofosbuvir (Harvoni); paritaprevir, ombitasvir, ritonavir, and dasabuvir (Viekira Pak); and simeprevir and sofosbuvir, all of which result in high SVR12 rates (93-99%) with favorable safety profiles. However, for sofosbuvir-containing regimens no dosage recommendation can be given for patients with severe renal impairment (eGFR < 30 mL/min) or ESRD due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite. Although Viekira Pak does not require a dosage adjustment in patients with severe renal impairment, no studies in patients with ESRD receiving hemodialysis have been completed and the appropriate dosage for this patient population is unknown; ribavirin is also required as part of the regimen in patients with genotype 1a and with genotype 1b with cirrhosis, and ribavirin may exacerbate CKD-related anemia.

Pegylated IFN with or without ribavirin has been evaluated in advanced CKD patients, and dosing recommendations are available for patients receiving dialysis. However, SVR rates are poor (56%), and tolerability is low. IFN-containing regimens are no longer recommended for treatment of HCV genotype 1 infection. Currently, there is no IFN-free treatment option for HCV genotype 1 infection in patients with end-stage renal disease (ESRD) receiving hemodialysis.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

The Sponsor is relying on sustained virologic response or SVR12 (described in #2 above) as the efficacy endpoint to support their request for a breakthrough therapy designation. SVR12 is accepted by the Division as a clinically significant endpoint for chronic HCV treatment trials. This surrogate endpoint is known to predict clinical benefit, as achievement of SVR has been associated with reduced all-cause mortality and liver-related morbidity and mortality.

4. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

Breakthrough therapy designations for chronic HCV genotype 1 infection were granted for ledipasvir and sofosbuvir (Harvoni) and for paritaprevir, ombitasvir, ritonavir and dasabuvir (Viekira Pak), which are now approved IFN-sparing all oral treatment regimens for HCV genotype 1 infection. However, as stated above, dosing recommendations with either regimen are not available for ESRD patients receiving hemodialysis.

5. Description of preliminary clinical evidence

Safety and efficacy of the combination of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with chronic kidney disease, including severe renal impairment and ESRD/dialysis.

Preliminary data from the Phase 2/3 trial PN052 support a breakthrough designation for treatment of chronic HCV genotype 1 infection in patients with ESRD receiving dialysis. PN052 is an ongoing randomized, parallel-group, placebo-controlled trial evaluating MK-5172 + MK-8742 (immediate treatment group [ITG]) compared to placebo (delayed treatment group [DTG]) for 12 weeks in HCV genotype 1-infected patients with CKD Stage 4 or 5 with or without cirrhosis. A total of 235 patients were randomized (1:1), and 76% are on dialysis. Preliminary efficacy results show high SVR4 (97%, 118/122) and SVR12 (94%, 100/106) rates in patients with available data who received 12 weeks of MK-5172/MK-8742 treatment to date. In the subset of patients receiving dialysis, preliminary SVR4 and SVR12 rates are similar at 96% (88/92) and 93% (78/84), respectively. Importantly, only one subject to date has reportedly experienced virologic failure, which was due to relapse.

Preliminary safety results from PN052 are also favorable with comparable rates of death, SAEs, discontinuations due to AEs, and drug-related AEs with MK-5172/MK-8742 compared to placebo. The most common drug-related AEs that occurred at a higher rate compared to placebo were headache and nausea. Grade 3 or greater laboratory abnormalities were also comparable between the two groups, but decreases in hemoglobin (8.5 to <10 g/dL) occurred more with MK-5172/MK-8742 (24%) compared to placebo (17%). More severe hemoglobin abnormalities (< 8.5 g/dL) occurred at the same rate in both arms (4%). Overall, treatment with MK-5172/MK-8742 appears very promising in patients with ESRD receiving dialysis, as demonstrated by a high SVR rate and favorable safety profile.

The Sponsor is requesting breakthrough designation for treatment of chronic HCV genotype 1, 4, (b) (4) infection in patients with (b) (4) ESRD on hemodialysis. However, PN052 included only genotype 1-infected patients. (b) (4)

Division's recommendation and rationale

The breakthrough therapy designation for grazoprevir (MK-5172)/elbasvir (MK-8742) for HCV genotype 1 infection in patients with ESRD receiving hemodialysis is supported by the following:

1. The Phase 2/3 SVR4 and SVR12 data from PN052 provide preliminary evidence of efficacy for HCV genotype 1-infected patients with ESRD receiving dialysis. This patient population

currently lacks an IFN-free treatment option; currently available IFN-free therapies for HCV genotype 1 either cannot be recommended in patients with severe renal impairment or lack dosing recommendations in patients on dialysis.

2. The safety profile of MK-5172/MK-8742 in patients with advanced CKD, which represents a medically complicated patient population, appears promising. The regimen avoids the use of IFN and ribavirin, which are associated with significant toxicities that may be further exacerbated in patients with ESRD receiving dialysis.
3. Absence of IFN from the regimen will allow patients with contraindications to IFN to receive an effective regimen.

Based on the data presented, DAVP believes that grazoprevir (MK-5172)/elbasvir (MK-8742) meets the definition of a breakthrough therapy for the treatment of HCV genotype 1 infection in patients with ESRD receiving hemodialysis, as outlined in Section 903 of the Food and Drug Administration Safety and Innovation Act and recommends granting breakthrough therapy designation.

In the absence of direct data, the Division cannot support breakthrough designation for (b) (4)

(b) (4)

(b) (4)

7. Division's next steps and sponsor's plan for future development

The Sponsor's trial (PN052) in advanced stage CKD patients with HCV genotype 1 infection is ongoing. The Sponsor plans to submit an NDA for grazoprevir (MK-5172)/elbasvir (MK-8742) with final SVR12 results from PN052 in April 2015.

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/s/

SARITA D BOYD
03/16/2015

ADAM I SHERWAT
03/16/2015



IND 110261

MEETING MINUTES

Merck Sharp and Dohme Corporation
Attention: Thomas Chambers, M.D.
Director, World Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-5172/MK-8742.

We also refer to the telecon between representatives of your firm and the FDA on February 20, 2015. The purpose of the meeting was to meeting to obtain feedback from the FDA regarding the acceptability of the proposed content and filing strategy for MK-5172/MK-8742 for the treatment of chronic HCV infection.

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

If you have any questions, call Sammie Beam, Regulatory Project Manager at (301) 796-0080.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
Merck Responses in Handout



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 20, 2015 3:00pm-4:30pm (ET)
Meeting Location: Teleconference

Application Number: 110261
Product Name: MK-5172/MK-8742
Indication: Treatment of chronic HCV infection
Sponsor/Applicant Name: Merck Sharp and Dohme Corporation (Merck)

Meeting Chair: Debra Birnkrant, MD
Meeting Recorder: Sammie Beam, RPh

FDA ATTENDEES

OND/OAP/DAVP

Debra Birnkrant, MD, Director, Division of Antiviral Products
Jeffrey Murray, MD, MPH Deputy Director
Poonam Mishra, MD, Deputy Director of Safety (Acting)
Mary Singer, MD, PhD, Medical Officer Team Leader
Adam Sherwat, Medical Officer
Sarita Boyd, PharmD, Medical Reviewer
Prabha Viswanathan, MD, Medical Officer
Julian O'Rear, PhD, Virology Team Leader
Takashi Komatsu, PhD, RAC, Virology Reviewer
Christopher Ellis, PhD, Pharmacology/Toxicology Reviewer
Karen Winestock, Chief, Project Management Staff
Elizabeth Thompson, MS, Chief, Project Management Staff
Sammie Beam, RPh, Regulatory Project Manager
Christian Yoder, Regulatory Project Manager
Suzanne Strayhorn, Regulatory Project Manager

OTS/OCP/DCP4

Shirley Seo, PhD, Clinical Pharmacology Team Leader
Su-Young Choi, Pharm.D., PhD, Clinical Pharmacology Reviewer

ONDQA

Stephen Miller, PhD, CMC-Lead

OTS/OB/DBIV

Greg Soon, PhD, Statistical Team Leader

Laree Tracy, PhD, Statistician

OSE

Felicia Duffy, RN, BSN, MEd, Risk Management Analyst

OSI

Anthoine El Hage, PhD

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

Marc Goldstein, Independent Assessor

SPONSOR ATTENDEES

Janice Wahl, MD, Distinguished Scientist, Clinical Research

Michael Robertson, MD, Distinguished Scientist, Clinical Research

Bach-Yen Nguyen, MD, Distinguished Scientist, Clinical Research

Ken Koury, PhD, Executive Director, Biostatistics

Peggy Hwang, PhD, Principal Scientist, Clinical Biostatistics

Stephanine Klopfer, PhD, Senior Principal Scientist, Biostatistics

Edgar Charles, MD, Principal Scientist, Clinical Research

Eliav Barr, MD, Vice President, Clinical Research

Anita Howe, PhD, Senior Principal Scientist, Biology-Discovery

Ercem Atillasoy, MD, Vice President, Regulatory Affairs

Thomas Chambers, MD, Senior Principal Scientist, Regulatory Affairs

Laurie MacDonald, MD, Executive Director, Regulatory Affairs

1.0 BACKGROUND

MK-5172 is a NS3/4A protease inhibitor and MK-8742 is a NS5A inhibitor proposed for the treatment of chronic hepatitis C virus infection. This combination was granted Breakthrough Therapy Designation (BTD) on October 18, 2013, and an Intent To Rescind BTD letter was sent on January 30, 2015. Merck submitted two new requests for Breakthrough Therapy Designation on February 9, 2015.

The purpose of the meeting was to obtain feedback from the FDA regarding the acceptability of the proposed content and filing strategy for MK-5172/MK-8742 for the treatment of chronic HCV infection.

2.0 DISCUSSION

2.1 Clinical

Question 1

Does the Agency agree that the efficacy and safety data from three Phase 3 clinical trials (PN060, PN061, and PN068), together with the Phase 2 and Phase 2/3 data (PN035, PN047, PN048, PN052 and PN074) are adequate to support licensure for the proposed indication, regimens, and treatment durations?

FDA Response to Question 1:

In general, the efficacy and safety data from the trials referenced in Question 1 adequately support an NDA submission for treatment of chronic HCV. Whether the data are adequate to support licensure for the proposed indication, regimens, and treatment durations is a review issue.

(b) (4)

No Meeting Discussion

2.2. Priority Review

Question 2

Does the Agency agree that the MK-5172/MK-8742 NDA will meet the criteria for a priority review based on the demonstration of safety and efficacy in HCV-infected patients with chronic kidney disease?

FDA Response to Question 2:

Conducting a study in patients with chronic kidney disease, including those receiving hemodialysis, is notable. However, we will determine standard or priority review designation during the filing review of the submitted application.

No Meeting Discussion

2.3. Submission Contents

Question 3

Does the Agency agree with the proposed content and format of the New Drug Application as described in the Table of Contents, including the plans for integrated analysis of data from the clinical trials supporting efficacy and safety?

FDA Response to Question 3:

Clinical Comments:

Summary of Clinical Safety (Module 2.7.4)

- Please include a summary of all discontinuations due to any AE, rather than solely discontinuations due to drug-related AEs.
- For all trials for which all patients completed treatment as of 28-Feb-2015, please also present a summary of ECIs as defined in each protocol and late ALT or AST elevations.
- Table 6 in the Background Package indicates that individual descriptions of PN061 and 068 will not be included in the written summary. Please describe these trials individually in the written summary (consistent with the other protocols described in Section 2.7.4.2.1.3) as they are critical for our review of the NDA. For PN061 and 068, please also provide laboratory evaluations as per Section 2.7.4.3.3.
- For all individual trials, please provide summary tables for all laboratory indices that were collected in each trial.

Meeting Discussion:

(Refer to Merck's responses in the attached handout)

Merck agreed to add amylase to the laboratory indices specified in their responses and to use PDLOC (predefined limit of change) to provide summaries. The FDA agreed with Merck's response in regard to the remainder of the comments in this section.

Integrated Safety Population Pool (Module 2.7.4.3.4)

- For the written safety summary, please pool trials PN035 (A-D), 047 (MK-5172/-8742-containing arms), 048, 058, 059 (non-cirrhotic patients), 060 (ITG and DTG), 061, and 068 (12- and 16-week arms). Exclusion of arms that used doses of MK-5172/-8742 other than 100 mg/50 mg and durations less than 8 weeks is acceptable. Please include a safety summary (including all laboratory indices collected [not only those proposed under 2.7.4.3.4] as well as analyses of common AEs, SAEs, discontinuations due to AEs, and ECIs) for each of the following subgroups for the pooled trials: (a) ribavirin-containing vs. ribavirin-free arms, (b) treatment duration of 8 weeks, 12 weeks, 16 weeks, 18 weeks, and 24 weeks, (c) subjects with and without cirrhosis, (d) HCV mono-infected vs. HIV/HCV co-infected subjects, and (e) ITG vs. DTG.

- PN074 should not be included in the pooled trials for the written safety summary because this trial studied a different treatment regimen (i.e., included sofosbuvir). Based on Table 6 of the Background Package, the proposed individual display of safety summary from this trial is acceptable.
- We agree with excluding PN052 from the pooled trials in the written safety summary. Based on Table 6 of the Background Package, the proposed individual display of safety summary from this trial is acceptable.
- In addition to the pooled trials as described above, please pool and display a 12-week safety summary from Phase 3 trials PN060, 061, and 068. Include a safety summary (including all laboratory indices collected [not only those proposed under 2.7.4.3.4] as well as analyses of common AEs, SAEs, discontinuations due to AEs, and ECIs) for each of the following subgroups: (a) ribavirin-containing vs. ribavirin-free arms, (b) subjects with and without cirrhosis, (c) HCV mono-infected vs. HIV/HCV co-infected subjects, and (d) ITG vs. DTG. For PN068, please also compare safety based on 12-week vs. 16-week duration.
- Table 6 in the Background Package indicates that the placebo DTG in PN060 will not be included in the integrated safety population pool. A safety comparison between the ITG and the DTG placebo groups is important for our review of the NDA and should be included in both pooled groups above.
- The pooled studies for the written safety summary (as above) differ from the requested pooling of studies for the datasets (see below).

Meeting Discussion:

(Refer to Merck's responses in the attached handout)

For PN60 the FDA requested a comparison between patients on active drug in the ITG and patients on placebo in the DTG. The FDA also requested that amylase be included with the lab indices. Merck agreed.

FDA agreed with Merck's response in regard to the remainder of the comments in this section.

Integrated Safety Population Pool: Datasets

- For the integrated safety dataset, please pool as many of the Phase 2, 2/3, and 3 trials as possible, including those pooled for the written safety summary (as indicated in the first bullet point under Integrated Safety Population Pool) and PN052. Pooling as many trials as possible into the integrated dataset is preferable because it is easier for us to select out trials than it is to combine trials.
- Please include the following flags in the integrated safety dataset:
 - Individual flags for each clinical trial
 - Ribavirin-containing vs. ribavirin-free arm
 - Individual flags for each treatment duration studied (e.g., 8 weeks, 12 weeks, 16 weeks, 18 weeks, and 24 weeks)
 - Cirrhosis vs. no cirrhosis
 - HCV mono-infection vs. HIV/HCV co-infection
 - ITG vs. DTG
 - Highest toxicity grade ALT reported following nadir AST levels
 - Highest toxicity grade AST reported following nadir ALT levels

- In the ADSL and DM datasets, please have only one entry per subject for all subjects enrolled in the study.
- Please exclude columns in a dataset that have no values.
- Per Appendix 4 the datasets do not include all laboratory indices. Please include all laboratory indices collected in each trial.

Meeting Discussion:

(Refer to Merck's responses in the attached handout)

The FDA agreed with Merck's response but wants the lab subsets put into categories, such as ADLB-chemistry and ADLB-hematology.

Individual Datasets for the Phase 2 and Phase 3 Clinical Trials

- Please use standardized terms in all of the clinical trials (i.e., the same variable names in all studies).

Pool of Clinical Trials to Evaluate MK-5172-Associated Liver Findings

Your proposal is acceptable. However, please separately display in your written summary the patients who were treated with doses higher than MK-5172 100 mg once daily and those who received concomitant treatment with PR.

Safety Narratives:

- Please provide narratives for all discontinuations due to any AE, rather than solely discontinuations due to drug-related AEs.
- Please provide narratives for all Events of Clinical Interest (ECIs) as defined in the protocols for each clinical trial.

Clinical Virology Comments:

We agree with the proposed locations of the nonclinical and clinical virology study reports. With respect to your resistance analyses:

- You state that HCV NS3/4A and NS5A were amplified but data sets containing full-length NS3 and NS5A sequence information for each patient will be submitted in SAS transport format. Please clarify that the sequence data for the HCV NS4A for each patient will also be included.
- Please clarify that all the sequence data, including baseline data, will be submitted following the draft guidance.

In addition, the following virology studies should be included with the NDA package to support labeling, irrespective of whether they have previously been submitted to the INDs:

- Include phylogenetic analyses of the baseline samples from all non-GT1 subjects to confirm the GT and identify the subtype.
- Include data on cross-resistance to other approved drugs for HCV.
- Include data on the combination antiviral activity relationships with 2 members of each class of HIV drugs.
- Include available data on the persistence of resistance substitutions.

- Include an analysis of impact of baseline polymorphisms.

Meeting Discussion:

(Refer to Merck's responses in the attached handout)

The FDA reminded Merck that cross resistance data need to go both ways. The antiviral activity of MK-5172 and of MK-8742 needs to be evaluated against the most common resistance pathways for all approved HCV drugs as well as the activity of approved HCV drugs against the resistance pathways for MK-5172 and MK-8742. The FDA stated that these data will need to be submitted at the time of NDA submission. Merck stated that for some compounds, they may only be able to provide one-way data since drug structures have not been made publically available until recently so they were not able to synthesize these drugs. The FDA requested Merck provide a summary of what data will be submitted to the NDA as well as the timeline of when the remaining data will be available as soon as possible.

The Division agreed with the list of HIV-1 drugs that Merck has chosen. The Division clarified that the primary objective of these studies is to determine whether the combination results in antagonism and that "additive/synergy" are no longer stated in the drug labels. The Division also emphasized that combination studies need to be evaluated both ways and that the active drug should be evaluated at its EC₅₀ value. With respect to choosing the concentrations of the HIV-1 drugs, the FDA recommended that Merck look at the PK profiles of the drugs. Merck responded that they will be using the C_{max} values of the HIV-1 drugs and will include boceprevir as control as they have previous experience with this drug. Finally, the FDA stated that the combination data with the HIV-1 protease inhibitors will need to be included with the NDA submission but agreed that the data for the other classes of HIV-1 drugs may be submitted within 60 days of application receipt. Merck stated that the combination anti-HIV activity data and the combination anti-HCV data for the HIV-1 protease inhibitors and MK-5172 would be included in the NDA submission.

The FDA stated that a (b) (4) cutoff is arbitrary and that Merck should focus more on the key resistance pathways identified in the cell culture and clinical studies for their drugs. Merck responded that the (b) (4) cutoff was chosen based on the variability observed with their assays. The FDA stated that the performance characteristics of the assays will need to be included in the NDA submission. The FDA will conduct their own analysis for all genotypes and regardless of any phenotype data. The FDA also stated that the frequency of the relevant polymorphisms in the relevant genotypes will need to be included citing the HCV NS3 Q80K polymorphism as an example where such data were important. Of particular interest are data for resistance pathways that are unique to MK-5172 and MK-8742. Merck agreed to include the frequency data.

Statistical Comment:

The proposed efficacy dataset and analyses as outlined in the table of contents are acceptable. To further facilitate our review, we request additional efficacy data sets as outlined in the attached document, Appendix 2 (HCV Efficacy Data Submission.doc).

Meeting Discussion:

The FDA requested submission of complete data for all Phase 3 trials, and any large Phase 2 trials that will serve as supportive for efficacy, at the time of NDA submission in the format as listed as Appendix 2 (HCV Efficacy Data Submission) along with statistical review aid. These data should be supplied along with the typical efficacy data (and associated programs) as part of the NDA submission. Merck noted that details on previous interferon and ribavirin products were not collected nor were liver biopsies read centrally. The FDA replied that it was acceptable that these data fields are omitted in the requested efficacy dataset. The FDA also agreed that it was acceptable for Merck to code negative SVR4 outcomes as TD unquantifiable or TND.

2.4. Safety Update Report

Question 4

Does the Agency agree with the proposed timetable for submission of the 3-month Safety Update Report, and with the proposed content of the report?

FDA Response to Question 4:

In order to accommodate a possible priority review, please provide the Safety Update Report two months after the NDA submission with an appropriate data cut-date to meet this request. In the report please also include narratives for all discontinuations due to any AE, rather than solely discontinuations due to drug-related AEs. Otherwise, we agree with the proposed content of the report.

Meeting Discussion:

(Refer to Merck's responses in the attached handout)

FDA stated that Merck's responses were acceptable.

2.5. OSI Data

Question 5

Does the Agency agree with Merck's proposed format for submission of summary level clinical site data sets to aid CDER's Office of Scientific Investigations (OSI) data integrity review and inspection planning?

FDA Response to Question 5:

We agree with your proposed format. For protocols 052, 060, 061, and 068, please ensure to include the following information for each site:

1. Ratio of subjects screened : enrolled
2. A description of major protocol deviations

Also, please refer to the “Office of Scientific Investigations (OSI) Requests” section of this document for additional requests.

Exclusion of financial disclosure information from the summary site level dataset is acceptable. However, please submit financial disclosure information consistent with the February 2013 Financial Disclosure Guidance.

Meeting Discussion:

(Refer to Merck’s responses in the attached handout)

OSI and the review team agreed there is no need for Merck to provide data sets from PN035, 047 and 048 at this time. However, if during the review concerns arise, the review team and OSI will notify Merck.

Additional Comments

Clinical

We recommend that you have an independent expert committee perform a formal written assessment of the hepatic safety profile of the MK-5172/MK-8742 combination regimen including an assessment of the adequacy of your proposed labeling to address this issue. This report should be made available for our review along with your currently proposed hepatic safety analyses. In the event that you do not already have an expert committee selected, we recommend that the committee be comprised of DILI experts as well as practicing HCV clinicians to allow for a breadth of opinion.

Meeting Discussion:

(Refer to Merck’s responses in the attached handout)

The FDA agreed the written hepatic safety assessment by the independent expert committee could be submitted within 60 days after NDA submission.

Clinical Pharmacology

Complete method validation reports and bioanalytical reports should be submitted for MK-5172 and MK-8742 as well as for any analytes that were analyzed in drug-drug interaction trials. If these are not provided, the study results may not be used to support labeling decisions (e.g., clinical recommendations in Section 7 or description of pharmacokinetics in Section 12).

The review team requests comprehensive summary tables for each method validation report and bioanalytical report. For each validated method, you should provide clinical studies and bioanalytical reports supported (e.g., PN001, bioanalytical report001), brief method description (e.g., protein precipitation followed by LC/MS) and performance (e.g., validation range, QC levels, precision, accuracy, and stability) in a table.

No meeting discussion

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed and agreement was reached on the following:
 - 1) In the Safety Analysis and Pooling, amylase will be added as laboratory indices and subcategories will be added.
 - 2) For clinical virology additional cross resistance analyses with HIV and polymorphisms with a timeline when other data is available.
 - 3) For OSI, only pivotal trials are required and Phase 2 trials may be submitted later.
 - 4) The “HCV Efficacy Data Submission” will be submitted at time of NDA submission.
 - 5) The hepatic safety review may be submitted within 60 days of submission of NDA.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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

We acknowledge receipt of your Agreed iPSP on January 13, 2015, and our concurrence with your Agreed iPSP on February 10, 2015. Please plan to submit the Agreed iPSP to the NDA along with any corresponding requests for waiver and/or deferral of pediatric studies.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues require further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submission of summary of what cross-resistance data to approved HCV drugs will be submitted to the NDA as well as timeline of when the remaining data will be available.	Merck	TBD

6.0 ATTACHMENTS AND HANDOUTS

Merck provided a handout with responses to the FDA preliminary comments for the Pre-NDA meeting.

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

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

/s/

DEBRA B BIRNKRANT
03/03/2015



IND 110261

MEETING PRELIMINARY COMMENTS

Merck Sharp and Dohme Corporation
Attention: Thomas Chambers, M.D.
Director, World Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-5172/MK-8742.

We also refer to your March 19, 2014, correspondence, received March 19, 2014, requesting a meeting to gain feedback from the FDA regarding the acceptability of the proposed Phase 3 clinical development program for MK-5172 and MK-8742 for the treatment of chronic HCV-infected patients.

Our preliminary responses to your meeting questions are enclosed.

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

If you have any questions, contact me at (301) 796-0080 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Sammie Beam, RPh
CAPT, USPHS
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobials
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: May 22, 2014 11:00am-12:30pm (ET)
Meeting Location: White Oak Building 22, Conference Room: 1421

Application Number: IND 110261
Product Name: MK-5172/MK-8742
Indication: Treatment of chronic Hepatitis C virus infection
Sponsor/Applicant Name: Merck Sharp and Dohme Corp

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 22, 2014, 11:00am-12:30pm (ET) between Merck Sharp & Dohme Corp (Merck) and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of the meeting is to gain feedback from the FDA regarding the acceptability of the proposed Phase 3 clinical development program for MK-5172 and MK-8742 for the treatment of chronic HCV-infected patients.

MK-5172 is a NS3/4A protease inhibitor and MK-8742 is a NS5A inhibitor proposed for the treatment of chronic hepatitis C virus infection. This combination was granted Breakthrough Therapy

Designation on October 18, 2013. As a result of this designation, a meeting was held between Merck and the Division of Antiviral Products on January 31, 2014, to discuss product development.

2.0 DISCUSSION

2.1. Clinical Pharmacology

Question 1:

Does the Agency agree that registration of the single entities (SEs) of MK-5172 and MK-8742 can be supported by the proposed Phase 1 bioequivalence trial using variance scaled no-effect boundaries?

FDA Response to Question 1:

Your proposed plan for the Phase 1 bioequivalence trial using a mixed, variance scaled, no-effect boundary design is reasonable. Please refer to the following publication for additional information on acceptable statistical methods for this design:

Davit, BM et al, 2012. "Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration"

Alternatively, it is possible that you could use the results of PN055 for the approval of MK-5172 and MK-8742 single entities. In this case, you should be aware that this trial would then be considered a pivotal assessment of bioavailability (traditionally referred to as a "pivotal BE trial"). With that designation, the clinical and bioanalytical sites associated with PN055 would be subject to OSI inspections. Additionally, you should ensure retention of the test and reference drug product samples at the trial site.

With the above-mentioned considerations, if you consider using PN055 to support the registration of the single entities, please provide the full study report of PN055 to discuss further regarding the possibility of using PN055 for the registration of single entities. Your full study report should include justification for your statistical comparisons. Also, you should provide justification that the PK parameters that did not meet the BE criteria (i.e., C_{max} of MK-5172 and MK-8742) do not have clinically significant effects on the safety and efficacy of either MK-5172 or MK-8742 using Phase 2 and Phase 3 exposure-response data.

2.2. Clinical Development

Question 2:

Does the Agency agree that the Phase 2 data are sufficient to support initiation of the planned Phase 3 clinical trials?

FDA Response to Question 2:

Yes, the Agency agrees that the Phase 2 data are sufficient to support initiation of the planned Phase 3 clinical trials.

Question 3:

Does the Agency agree with the proposed design of the Phase 3 clinical trial evaluating the FDC of MK-5172/MK-8742 in treatment-naïve subjects with CHC genotypes 1, 4, 5, and 6 infection (PN060)?

- a) Does the Agency agree with the patient population?**
- b) Does the Agency agree with the MK-5172 and MK-8742 dose selection and the 12-week treatment duration?**
- c) Does the Agency agree with immediate vs. deferred treatment trial design?**
- d) Does the Agency agree with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint?**
- e) Does the Agency agree with the statistical analysis approach, the historical sustained virologic response (SVR) reference rate, and the criteria for success on the primary efficacy endpoint?**

FDA Response to Question 3:

FDA provided specific comments and recommendations to the Sponsor on PN060 in a correspondence dated 22 April 2014. Please refer to this correspondence for clinical and virology comments in addition to the responses provided below.

- a) Yes, in general the Agency agrees with the patient population proposed. Please refer to the 22 April 2014 correspondence for additional details.*
- b) Yes, the Agency agrees with the MK-5172 and MK-8742 dose selection and the 12-week treatment duration.*
- c) Yes, the Agency agrees with immediate vs. deferred treatment trial design.*
- d) Yes, the Agency agrees with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint.*
- e) Yes, your statistical methodology and proposed historical SVR reference rate is acceptable.*

Question 4:

Does the Agency agree with the proposed design of the Phase 3 clinical trial evaluating the FDC of MK-5172/MK-8742 in treatment-naïve subjects with CHC genotypes 1, 4, 5, and 6 infection who are co-infected with HIV (PN061)?

- a) Does the Agency agree with the patient population?**
- b) Does the Agency agree with the MK-5172 and MK-8742 dose selection and the 12-week treatment duration?**
- c) Does the Agency agree with single-arm, open-label trial design?**
- d) Does the Agency agree with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint?**
- e) Does the Agency agree with the statistical analysis approach, the historical SVR reference rate, and the criteria for success on the primary efficacy endpoint?**

FDA Response to Question 4:

FDA provided specific comments and recommendations to the Sponsor on PN061 in a correspondence dated 22 April 2014. Please refer to this correspondence for clinical comments in addition to the responses provided below.

- a) Yes, in general the Agency agrees with the patient population proposed. Please refer to the 22 April 2014 correspondence for additional details.*
- b) Yes, the Agency agrees with the MK-5172 and MK-8742 dose selection and the 12-week treatment duration.*
- c) The Sponsor's plan for a single-arm, open-label trial design not employing a deferred group is acceptable. The Sponsor should be aware that the safety profile in HIV/HCV co-infected subjects may not directly mirror that of the HCV monoinfected population, simply by virtue of the study population and events potentially unrelated to study drugs. Therefore, comparing safety in PN061 to that of PN060 (as suggested by the Sponsor) may cast the safety profile in HCV/HIV co-infected subjects in a potentially unfavorable light.*
- d) Yes, the Agency agrees with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint.*
- e) Yes the applicant's statistical proposals are acceptable.*

Question 5:

Does the Agency agree with the proposed design of the Phase 3 clinical trial evaluating the FDC of MK-5172/MK-8742 in treatment-naïve subjects with CHC genotypes 1, 4, 5, and 6 infection who are on opiate substitution therapy (PN062)?

- a) Does the Agency agree with the patient population?**
- b) Does the Agency agree with the MK-5172 and MK-8742 dose selection and the 12-week treatment duration?**
- c) Does the Agency agree with immediate vs. deferred treatment trial design?**
- d) Does the Agency agree with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint?**
- e) Does the Agency agree with the statistical analysis approach, the primary efficacy analysis population, the historical SVR reference rate, and the criteria for success on the primary efficacy endpoint?**

FDA Response to Question 5:

FDA provided specific comments and recommendations to the Sponsor on PN062 in a correspondence dated 22 April 2014. Please refer to this correspondence for clinical and virology comments in addition to the responses provided below. The Division appreciates that the Sponsor has already addressed several of our recommendations in the current submission.

- a) Yes, in general the Agency agrees with the patient population proposed. Please refer to the 22 April 2014 correspondence for additional details.*
- b) Yes, the Agency agrees with the MK-5172 and MK-8742 dose selection and the 12-week treatment duration.*
- c) Yes, the Agency agrees with immediate vs. deferred treatment trial design.*
- d) Yes, the Agency agrees with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint.*
- e) The historical SVR reference rate is acceptable.*

Provided that subjects discontinuing with less than 75% of therapy are not excluded from mFAS, the primary efficacy population is acceptable.

Please describe any stratification factors proposed for this trial.

Question 6:

Does the Agency agree with the proposed design of the Phase 3 clinical trial evaluating the FDC of MK-5172/MK-8742 in subjects who have failed prior treatment with pegylated interferon and ribavirin with CHC genotypes 1, 4, 5, and 6 infection (PN068)?

- a) Does the Agency agree with the patient population?**
- b) Does the Agency agree with the MK-5172 and MK-8742 dose selection, the plan to evaluate treatment arms with and without ribavirin, and plan to evaluate treatment durations of 12- and 16-weeks?**
- c) Does the Agency agree with 4-arm, open-label trial design?**
- d) Does the Agency agree with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint?**
- e) Does the Agency agree with the plan to assess the efficacy of the 12-week treatment arms independent of the 16-week treatment arms, and that results for the 12-week treatment arms alone (if successful) will be sufficient to support the filing?**
- f) Does the Agency agree with the statistical analysis approach, the historical SVR reference rate, and the criteria for success on the primary efficacy endpoint?**

FDA Response to Question 6:

FDA provided specific comments and recommendations to the Sponsor on PN068 in a correspondence dated 22 April 2014. Please refer to this correspondence for clinical and virology comments in addition to the responses provided below.

- a) Yes, in general the Agency agrees with the patient population proposed. Please refer to the 22 April 2014 correspondence for additional details.*
- b) Yes, the Agency agrees with the MK-5172 and MK-8742 dose selection, the plan to evaluate treatment arms with and without ribavirin, and plan to evaluate treatment durations of 12- and 16-weeks.*
- c) The Sponsor's plan for a 4-arm, open-label trial design not employing a deferred group is acceptable.*
- d) Yes, the Agency agrees with definition of the primary efficacy endpoint, and the timepoint for assessment of the primary endpoint.*
- e) Yes, the Agency agrees with the plan to assess the efficacy of the 12-week treatment arms independent of the 16-week treatment arms, and that results for the 12-week treatment arms alone (if successful) may be sufficient to support the filing.*
- f) The applicant's proposal is acceptable.*

Question 7:

Does the Agency agree that data from the Phase 3 trials in subjects with CHC genotypes 1, 4, 5, and 6 infection as outlined below will support the initial registration of MK-5172/MK-8742 in treatment-naïve subjects and in subjects who have failed prior pegylated interferon/ribavirin therapy with HCV genotype 1, 4, 5, (b) (4) infection, both cirrhotic and noncirrhotic, including those with chronic kidney disease and those with HCV/HIV-1 coinfection?

FDA Response to Question 7:

The final determination of the adequacy of data to support a treatment indication in a specific population will be a review issue. The Agency agrees that the data from the proposed Phase 3 trials may support registration of MK-5172/MK-8742 in the populations outlined by the Sponsor in Question 7 assuming adequate safety and efficacy results in the trials enrolling these populations.

(b) (4)

2.3. Nonclinical safety assessment

Question 9:

Does the Agency agree that the completed and planned safety pharmacology, genotoxicity, repeat-dose toxicity, and developmental and reproductive toxicity studies are sufficient to support the proposed Phase 3 program as well as filing and registration of the FDC of MK-5172/MK-8742 and of MK-5172 and MK-8742 as single entities, and that carcinogenicity studies are not warranted based on the clinical use which is intended to be less than 6 months in duration?

FDA Response to Question 9:

Pending Agency review of all studies, we agree that the completed and planned nonclinical safety studies for both MK-5172 and MK-8742 appear sufficient to support the proposed Phase 3 program as well as filing and registration of the FDC of MK- 5172/MK-8742 and of MK-5172 and MK-8742 as single entities. Given the proposed treatment duration to be studied in your phase 3 program, we also agree that carcinogenicity studies would not be required for filing or registration. However, if the intended duration of clinical use changes, the necessity of carcinogenicity study data to support your program may need to be reevaluated.

Additional FDA Comments

The Division of Medication Error Prevention and Analysis (DMEPA) would like to inquire when you intend to submit a Request for Proprietary Name Review. We encourage you to submit your request as soon as possible in order to allow ample time to work with you in finding an acceptable name for your proposed product, preferably prior to your NDA submission.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#).

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
05/20/2014



IND 110261

**GRANT –
BREAKTHROUGH THERAPY DESIGNATION**

Merck Sharp and Dohme Corporation
Attention: Thomas Chambers, M.D.
Director, World Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-5172/MK-8742.

We also refer to your August 26, 2013 request for Breakthrough Therapy designation. We have reviewed your request and have determined that MK-5172/MK-8742 for treatment of chronic hepatitis C virus infection meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of MK-5172/MK-8742 for the treatment of chronic hepatitis C virus infection, including providing advice on generating evidence needed to support approval of the drug in an efficient manner. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the draft *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>)

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to the *Guidance for Industry: Formal Meetings between FDA or Sponsors and Applicants*¹ for procedures on requesting a meeting.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

If you have any questions, contact Sammie Beam, RPh, Regulatory Project Manager, at (301) 796-0080 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

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/s/

DEBRA B BIRNKRANT
10/18/2013

**CDER Medical Policy Council Brief
Breakthrough Therapy Designation
Division of Antiviral Products
18 October 2013**

Summary Box

1. IND: 110261
2. Company: Merck
3. Products: MK-5172 & MK-8742
4. Indication: Treatment of Chronic Hepatitis C Infection
5. These drugs are intended to treat a serious or life-threatening disease or condition.
6. The preliminary clinical evidence indicates that this drug combination may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints (efficacy and safety).

1. Brief description of the drug

MK-5172 is a selective inhibitor of hepatitis C virus (HCV) NS3/NS4A protease and MK-8742 is an HCV NS5A replication complex inhibitor.

2. Brief description of the disease, intended population, and currently available therapies

Approximately 3.2 million people in the United States have chronic HCV infection, which can lead to cirrhosis and hepatocellular carcinoma. Chronic hepatitis C is currently the most common reason for liver transplantation in the United States. A recent CDC analysis of death certificate data found that HCV-attributable deaths increased significantly between 1999 and 2007. CDC estimates that there were 15,106 deaths caused by HCV in 2007. The Division considers chronic HCV infection a serious and life-threatening condition.

At least six different HCV genotypes have been identified, numbered 1 to 6, with further breakdown into subtypes for several of the known genotypes (e.g., genotype 1 subtypes 1a and 1b). In the United States, genotype 1 is the most common (70 to 80 percent; mostly subtype 1a), followed by genotypes 2 and 3. The remaining genotypes occur uncommonly in the United States, but may predominate in other parts of the world.

The primary objective of anti-HCV treatment is the achievement of a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the cessation of treatment (i.e., "SVR12"). SVR12 is generally considered a "virologic cure". The current standard-of-care treatment for

HCV genotype 1 infection is a combination of pegylated interferon alpha (Peg-IFN α), RBV, and one of two recently approved HCV NS3 protease inhibitors (boceprevir or telaprevir) administered for 24 to 48 weeks depending on the specific drug regimen and patient population. These regimens are associated with favorable efficacy (65-75% SVR12 rates) in treatment-naïve patients without the severe liver complications of HCV infection, but have lower efficacy in certain difficult-to-treat populations, for example those with cirrhosis or who respond poorly to Peg-IFN α /RBV. The regimens are difficult to administer (Peg-IFN α is given as a weekly injection, boceprevir and telaprevir are given 3 times daily with food restrictions) and are poorly tolerated in many patients, as each drug is associated with numerous serious and life-threatening toxicities including neuropsychiatric, autoimmune, ischemic and infectious disorders (Peg-IFN α), teratogenicity (RBV), anemia (RBV, telaprevir, boceprevir), bone marrow suppression (Peg-IFN α , RBV) and severe rash (telaprevir- boxed warning). Furthermore, like many other HCV direct-acting antivirals (DAAs), boceprevir and telaprevir have relatively narrow genotype-specificity, and therefore are not approved for the treatment of non-genotype 1 HCV. Current standard-of-care for non-genotype 1 HCV infection is a 24- to 48-week duration of Peg-IFN α /RBV, which has limited efficacy in certain populations. Importantly, a significant proportion of HCV-infected patients are believed to be intolerant or ineligible (based on comorbidities or age) to use interferon-based therapies and these patients currently have no viable antiviral treatment options.

Because of the limitations of interferon-based therapies, there has been great interest in recent years in the development of all oral, interferon-free regimens consisting of combinations of multiple classes of HCV DAAs. After several years of development and optimization, several interferon-free, combination HCV DAA regimens being developed by various pharmaceutical sponsors are now being studied in pivotal Phase 3 clinical trials. It is widely anticipated that at least some of these regimens will have substantially improved efficacy over the current standard-of-care, particularly for HCV genotype 1, with treatment duration possibly as short as 12 weeks. Most importantly, because these regimens do not require the use of interferon, they are expected to have a substantially improved safety and tolerability profile compared to the current standard-of-care regimens, and will be available to patients who cannot use interferon-based therapies.

Despite their promise, the use of interferon-free HCV DAA regimens will bring new treatment considerations and challenges. The breadth of HCV genotype coverage varies dramatically for different treatment regimens. For example, some HCV DAA regimens have poor efficacy for HCV genotype 1a relative to genotype 1b. For most HCV DAA-containing regimens, treatment failure is associated with the emergence of HCV resistance to the drug(s) and cross-resistance to other drugs in the same class(es), which can impact future treatment options. Drug-drug interactions will be an important consideration with the use of many regimens, particularly for patients co-infected with HIV who are on antiretroviral therapy. Furthermore, as noted above, certain regimens must still be dosed with RBV which will bring additional safety considerations.

3. Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area

The Sponsor is relying on sustained virologic response or SVR12 (described in #2 above) as the efficacy endpoint to support their request for a breakthrough therapy designation, and this endpoint will also be used in the Sponsor's pivotal trials of this drug combination. SVR12 is accepted by the Division as a clinically significant endpoint for chronic HCV treatment trials. This is a surrogate endpoint known to predict clinical benefit, as achievement of SVR has been associated with reduced all-cause mortality, and liver-related morbidity and mortality.

4. Brief description of any drugs being studied for the same indication that received breakthrough therapy designation

Three breakthrough therapy designations were recently granted for interferon-sparing all oral HCV treatment regimens. The first was for Bristol Myers Squibb's all oral DAA combination of daclatasvir (DCV), asunaprevir (ASV) and BMS-791325 (325) for the treatment of genotype 1 treatment-naïve chronic HCV-infected patients. DCV is an NS5A replication complex inhibitor, ASV is a selective inhibitor of HCV NS3 protease and BMS-791325 is a selective non-nucleoside NS5B polymerase inhibitor of the hepatitis C virus. The second was for AbbVie's all oral DAA combination of ABT-450/r (ritonavir-boosted HCV NS3/4A protease inhibitor), ABT-267 (HCV NS5A inhibitor) and ABT-333 (non-nucleoside HCV NS5B-palm polymerase inhibitor). The third was for Gilead's combination of GS-7977 (nucleotide analog HCV NS5B inhibitor) and GS-5885 (HCV NS5A inhibitor). Merck's data to-date compares favorably with these other programs.

5. Description of preliminary clinical evidence

Safety Background of MK-5172 (in combination with Peg-IFN α and RBV):

MK-5172 was studied in combination with Peg-IFN α and RBV in a Phase 2b trial. Two hepatic findings were observed in this trial: (1) An early onset, dose-dependent increase in predominantly unconjugated bilirubin levels. This was deemed by the Sponsor to be predominately due to the result of an inhibitory effect of MK-5172 on hepatocellular membrane transporters and unlikely to be of clinical concern. (2) A late increase in transaminase levels in a subset of patients. This typically occurred after the initial normalization expected with HCV treatment. The increases in transaminase levels were observed after Treatment Week 4 (TW4). The risk for transaminase increases occurring after TW4 was dose and exposure-dependent, with ALT peak values > 5x ULN occurring almost entirely at daily doses of 400 mg and 800 mg. The elevations in transaminases were considered clinically relevant and led to the product being placed on hold for safety. The study drug was taken off hold after the Division was satisfied of the dose-dependent nature of the adverse events and the safety profile of the subsequently selected dose of 100 mg daily for current and future trials.

Safety Background of MK-8742:

The available safety data for MK-8742 (outside of PN035 which is discussed in detail below) is limited to short dosing durations (5-10 days) of MK-8742 in healthy as well as HCV-infected subjects. No safety signal of concern has been detected in these early phase studies.

Safety and Efficacy of MK-5172 and MK-8742 used in combination:

The primary data to support a breakthrough designation is provided by the interim results of Part A of Merck's Protocol 035 (henceforth referred to as PN035). PN035 Part A is an ongoing, randomized trial comparing 100 mg of MK-5172 in combination with two doses of MK-8742 ± RBV in treatment-naïve, non-cirrhotic subjects with chronic HCV genotype 1 infection. Part A of the trial was designed to randomize 48 subjects in a 1:1 ratio to 2 treatment arms in which open-label MK-5172 at 100 mg once daily (QD) was administered concomitantly with blinded MK-8742 doses of either 20 or 50 mg QD, with twice daily (BID) RBV. Subjects in these two arms were stratified by GT1a vs. GT1b with at least 50% of treatment arms 1 and 2 comprised of GT1a subjects. A third arm of 12 subjects infected with GT1b studied a regimen of MK-5172 at 100 mg QD with MK-8742 at 50 mg, without RBV. The treatment duration was 12 weeks in all arms. The treatment arms are summarized below:

- Arm 1: MK-5172(100 mg)/MK-8742 (20 mg) + RBV (GT1a and GT1b subjects)
- Arm 2: MK-5172(100 mg)/MK-8742 (50 mg) + RBV (GT1a and GT1b subjects)
- Arm 3: MK-5172(100 mg)/MK-8742 (50 mg) (GT1b subjects)

Summary of Efficacy from PN035 (Part A):

Robust efficacy (based on preliminary SVR4 data) was demonstrated in each arm of the study with SVR4 rates ranging from 96-100%. Of the 65 randomized subjects, 62 have completed study therapy. The remaining 3 subjects did not complete therapy; they discontinued therapy for reasons other than virologic failure or treatment-related AEs. All subjects in the per protocol population who reached the treatment week 4 (TW4) visit suppressed HCV RNA to <25 copies/mL, and >70% of the subjects in each group had undetectable (target not detected [TND]) HCV RNA at that visit. All subjects who completed therapy had undetectable HCV RNA (TND) at the end of treatment (TW12), regardless of the treatment regimen or the HCV sub-genotype, and all but one of the subjects who reached the follow-up week 4 visit (FU4) have achieved SVR4; the one exception is an HCV GT1a infected subject in Arm 2 (MK-5172 100 mg + MK-8742 50 mg + R) who relapsed at the FU4 visit. The following table summarizes the efficacy results including the preliminary SVR4 data of greatest interest which is displayed in the far right column:

Efficacy Results of PN035 Part A (Per Protocol Population)

Dose Group	Segment	N	TW4 (%)			N	TW12 (%)			N	SVR4 (%)
			TND	TDu	FAIL		TND	TDu	FAIL		
MK-5172 100 mg + MK-8742 20 mg + R	Overall	23	74%	26%	0%	22*	100%	0%	0%	21	100%
	G1a	18	72%	28%	0%	17	100%	0%	0%	16	100%
	G1b	5	80%	20%	0%	5	100%	0%	0%	5	100%
MK-5172 100 mg + MK-8742 50 mg + R	Overall	24	92%	8%	0%	24	100%	0%	0%	24	96%[†]
	G1a	17	88%	12%	0%	17	100%	0%	0%	17	94%
	G1b	7	100%	0%	0%	7	100%	0%	0%	7	100%
MK-5172 100 mg + MK-8742 50 mg	G1b	12	75%	25%	0%	12	100%	0%	0%	11	100%

Preliminary Data as of 12-Aug-2013. DATA SOURCE: PPD Central Laboratory Database
 For TW4 and 12, the % is calculated as 100%*(n with TND, TDu or TDq at a given timepoint)/(N with a measurement at that timepoint). Subjects who experienced virologic failure prior to the relevant timepoint are counted as FAILs. SVR4 are calculated as 100%*(n achieving TDu or TND at the relevant timepoint)/N with a measurement at that timepoint).
 * One subject withdrew consent at TW5 for personal reasons. This subject's HCV RNA was TND at TW4. This subject is included at TW4 but not at subsequent time points.
 † One subject had confirmed relapse at the FU4 visit. Viral resistance data are pending.

TND = Target Not Detected, HCV RNA not detected

TD (u) = Target Detected, unquantifiable, HCV RNA < LLoQ (25 IU/mL)

TD(q) = Target Detected, quantifiable HCV RNA ≥ LLoQ (25 IU/mL)

Relapse: Relapse is defined as any subject who currently has HCV RNA ≥ 25 IU/mL and was previously target not detected at end of treatment.

Based on the Division's experience with a number of HCV development programs, the Division expects an excellent correlation between SVR4 data and SVR12 data (i.e. the primary efficacy endpoint for this study). Therefore, the Division is comfortable relying on preliminary SVR4 data as the basis of our decision as to whether a breakthrough therapy designation is appropriate.

Summary of Safety from PN035 (Part A):

The safety profile for this drug combination appears acceptable to date. There was 1 SAE reported for an unintentional overdose. The subject in question took 2.5 times the prescribed dose of MK-8742 and reported only mild nausea related to the event. However, the protocol specifies that any AE reported in association with an overdose must be reported as an SAE. The only discontinuation due to an AE in the trial to date was related to ALT elevation at baseline that was reported prior to receiving study drug. The subject was discontinued on Day 3 of the study.

Based on the known safety profile of MK-5172 (see section entitled "Safety Background of MK-5172 (in combination with Peg-IFNα and RBV)," the Division required that the Sponsor closely monitor for hepatic adverse events and designate the following as events of clinical interest (ECIs): 1) first instance of ALT or AST >500 IU/L, 2) first instance of ALT or AST >3x baseline AND >100 IU/L, and 3) first instance of alkaline phosphatase >3x ULN. Two subjects experienced a hepatic ECI. One subject discontinued study drugs due to a baseline ALT abnormality which was described in the preceding paragraph. The second ECI related to an ALT elevation occurring four weeks after study drug discontinuation. The subject had a baseline ALT of 46 IU/L and had normalized his ALT by Day 7. His ALT remained normal during the rest of the study, including at the end of treatment (at Week 12) and at his 2 week post treatment visit. Four weeks after the end of treatment, his ALT was 380 IU/L; his AST was also elevated at 182 IU/L, but his total bilirubin was normal at 0.24 mg/dL. He was asymptomatic but reported an episode of heavy drinking the weekend before the visit. His ALT was 33 IU/L and his AST was 16 IU/L

upon repeat testing a week later. It appears unlikely that this subject's transient elevation in AST and ALT was due to study drug(s) and may instead be related to heavy alcohol use.

In summary, based on limited safety data available to date the safety profile of MK-5172/MK-8742 (with or without RBV) appears favorable in comparison to currently approved Peg-IFN α -based regimens. The potential for hepatic toxicity in this DAA regimen remains an issue, but the currently available safety data from MK-5172/MK-8742 (with or without RBV) and from ongoing and/or completed studies of MK-5172 at a daily dose of 100 mg provides some reassurance with respect to the hepatic safety profile. Preliminary data suggests the MK-5172/MK-8742 (with or without RBV) regimen offers improvements with respect to safety compared to the current standard-of-care regimens. Use of this DAA all oral regimen will likely lead to a substantive decrease in the high incidence of significant cytopenias (and subsequent use of Granulocyte Colony Stimulating Factors and erythropoiesis-Stimulating Agents), the worsening of depression or other mental health conditions, the incidence flu-like symptoms and will eliminate the need for injection therapy.

6. Division's recommendation and rationale

The breakthrough therapy designation for MK-5172/MK-8742 (with or without RBV) is supported by the following:

1. The MK-8742 component of this regimen has a novel mechanism of action that represents a previously untargeted pathway. Currently there are no approved anti-HCV NS5A inhibitors.
2. The Phase 2 SVR4 data provide preliminary evidence of substantial improvement in efficacy compared to the currently available standard of care. Additionally, efficacy was observed in "harder-to-treat" patients who are genotype 1a and those with IL28B non-CC host genotype.
3. The MK-5172/MK-8742 (+/- RBV) all oral regimen for a 12 week duration provided high rates of efficacy (SVR4 96-100%) compared to up to 48 weeks of current boceprevir or telaprevir in combination with Peg-IFN α /RBV (SVR ~ 65-75%).
4. The safety profile of MK-5172/MK-8742 (+/- RBV) appears promising. The regimen is IFN and (potentially) ribavirin-free, potentially resulting in fewer cytopenias, depression or other psychiatric manifestations, a lower incidence of flu-like illness, and no injections.
5. While the initial development program has focused on treatment-naïve genotype 1 subjects, expansion to include prior partial and null responders, cirrhotic subjects, and subjects with HIV/HCV co-infection is ongoing in Part B of PN035. (b) (4)

(b) (4)

Based on the data presented, DAVP believes that MK-5172/MK-8742 (+/- RBV) meets the definition of a breakthrough therapy for the treatment of genotype 1 treatment-naïve chronic hepatitis C patients as outlined in Section 903 of the Food and Drug Administration Safety and Innovation Act and recommends that MK-5172/MK-8742 (+/- RBV) be given a breakthrough therapy designation.

7. Division's next steps and sponsor's plan for future development

The Division plans to work closely with the Sponsor to advance their development program. Specifically, the Division intends to present the Sponsor with possible options to initiate their Phase 3 trials ahead of the completion of their Phase 2 program.

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/s/

ADAM I SHERWAT
10/14/2013

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 208261

LATE-CYCLE MEETING MINUTES

Merck Sharp & Dohme Corp.
Attention: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for elbasvir and grazoprevir tablet, 50 mg/100 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 19, 2015.

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 Nina Mani, Regulatory Project Manager at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Adam Sherwat, MD
Cross-Discipline Team Lead
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:

Late Cycle Meeting Minutes
Appendix 1- FDA Slide Set
Appendix 2- Merck Slide Set



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 19, 2015; 2:30 pm – 4:00 pm
Meeting Location: White Oak, Bldg 22 Room 1415

Application Number: NDA 208261
Product Name: Zepatier (elbasvir/grazoprevir)
Applicant Name: Merck Sharp & Dohme Corp.

Meeting Chair: Adam Sherwat
Meeting Recorder: Nina Mani

FDA ATTENDEES

Edward Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
John Farley, MD, Deputy Director, OAP
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Poonam Mishra, MD, MPH, Deputy Director for Safety, DAVP
Adam Sherwat, MD, Cross Discipline Team Lead, DAVP
Sarita Boyd, PharmD, Medical Officer, DAVP
Prabha Viswanathan, MD, Medical Officer, DAVP
Takashi Komatsu, PhD, RAC, Clinical Virology Reviewer, DAVP
Patrick Harrington, PhD, Clinical Virology Reviewer, DAVP
Lisa Naeger, PhD, Clinical Virology Reviewer, DAVP
Damon Deming, PhD, Clinical Virology Reviewer, DAVP
Jules O'Rear, PhD, Clinical Virology Team Lead, DAVP
Su Young Choi, PharmD, PhD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCPIV) OCP, DCPIV
Luning Zhang, PhD, Pharmometrics Reviewer, OCP, DCPIV
Shirley Seo, PhD, Clinical Pharmacology Team Lead, OCP, DCPIV
Jeff Kraft, PhD, Genomics Reviewer, OCP
LaRee Tracy, PhD, Statistical Reviewer
Thamban Valappil, PhD, Statistical Team Lead (Acting)
Christopher Ellis, PhD, Non-Clinical Reviewer
Hanan Ghantous, PhD, DABT, Non-Clinical Team Lead
Robert Pratt, Pharm D, Division of Risk Management, Office of Surveillance and Epidemiology, Regulatory Project Manager (RPM)
Sarah Connelly, MD, Clinical Reviewer, DAVP
Kimberly Struble, PharmD, Clinical Team Lead, DAVP

Tanvir Bell, MD, Clinical Reviewer, DAVP
Russ Fleischer, PA-C, MPH, Senior Clinical Analyst and Acting Team Lead, DAVP
Christian Yoder, BSN, MPH, RPM, DAVP
Suzanne Strayhorn, MSc, RPM, DAVP
Karen Winestock, Chief, Project Management Staff, DAVP
Nina Mani, PhD, MPH, RPM, DAVP

EASTERN RESEARCH GROUP ATTENDEES

Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES

Sandra Milligan M.D., J.D., Senior Vice President, Global Regulatory Affairs and Clinical Safety
Eliav Barr, MD, Vice President, Global Clinical Development, Infectious Diseases
Ercem Atillasoy, MD, Vice President, Global Regulatory Affairs and Clinical Safety
Daria Hazuda, PhD, Vice President, Research Science, Infectious Disease and Vaccines
Laurie MacDonald, MD, Executive Director, Global Regulatory Affairs and Clinical Safety
Bach-Yen Nguyen, MD, Executive Director, Clinical Research
Janice Wahl, MD, Executive Director, Clinical Research
Michael Robertson, MD, Executive Director, Clinical Research
Todd Black, PhD, Executive Director, Biology/Discovery
Ron Leong, MD, Distinguished Scientist, Clinical Safety and Risk Management
Thomas Chambers, MD, Director, Global Regulatory Affairs and Clinical Safety
Wendy Yeh, MD, Senior Principal Scientist, Clinical Pharmacology
Peggy Hwang, PhD, Senior Principal Scientist, Clinical Biostatistics
Ernest Asante-Appiah, PhD, Director, Biology/Discovery
Nicole Mahoney, PhD, Director, Global Regulatory Policy
Kimberly Doyle, MS, RPh, Associate Director, Office of Promotion and Advertising Review

1.0 BACKGROUND

NDA 208261 was submitted on May 28, 2015 for Zepatier (elbasvir/grazoprevir; EBR/GZR).

Proposed indication(s): Treatment of hepatitis C virus (HCV) genotypes 1, 4 and 6 infections

PDUFA goal date: January 28, 2016

FDA issued a Background Package in preparation for this meeting on November 6, 2015.

2.0 DISCUSSION

The discussion at the meeting is in *italics*.

LCM AGENDA

1. Introductory Comments

Meeting Discussion:

Following Sponsor and FDA introductions it was noted that the meeting's focus will be on the one outstanding substantive review issue, namely Clinical Efficacy/Clinical Virology and the Division's recommendation for baseline HCV NS5A screening for resistance-associated amino acid polymorphisms. The Sponsor agreed with Agency recommendations on the Clinical Safety and Clinical Pharmacology issues sent in the LCM Background package; hence no discussion on these issues occurred at the meeting. The FDA presentation on the NS5A screening issue was followed by the Sponsor's presentation on the issue. Since the Sponsor did not send the Agency their slides in advance of the meeting they were informed that the Agency would be unable to comment or discuss their content.

The FDA's opening statement noted that after careful evaluation of the Sponsor's position regarding NS5A screening, the Division's position is that it is critical to have a recommendation for baseline screening in the label. The Sponsor was informed that this view has been vetted at the highest levels of leadership in the Office of New Drugs.

The Agency concerns are as follows:

- *Baseline NS5A amino acid polymorphisms in question impact a substantial proportion of the GT1a population (~12%), the predominant HCV genotype and subtype in the U.S.*
- *The presence of these polymorphisms leads to a substantial reduction in efficacy; and*
- *Virologic failure is frequently associated with the accumulation of additional NS3 PI and/or NS5A resistance substitutions that may significantly impact future treatment options.*

Further, the Agency did not agree with the Sponsor's assertion that screening for NS5A baseline polymorphisms places an undue burden on HCV treatment providers since the assay is commercially available and readouts include a clear listing of polymorphisms. The Agency noted that a short delay in treatment in order to maximize treatment success and preserve future treatment options is in the best interest of this patient population.

The Sponsor was informed that if an agreement on this issue was not reached in an expeditious manner, it is very likely that an Advisory Committee (AC) meeting will need to be convened. The AC would focus not only on issues of efficacy related to the impact of NS5A polymorphisms, but also issues of clinical safety (including hepatotoxicity), as well as any relevant issues from the other review disciplines.

The time required to organize and convene an AC would risk delaying drug approval and regardless of the AC's consensus opinion on this issue, the Agency is still free to strongly advocate for a screening recommendation in the label based on the strength of the data.

2. Discussion of Substantive Review Issues

Please note that these issues affect labeling. Each issue is introduced by FDA and followed by a discussion.

- a. Clinical Safety: Hepatic Issues- **No discussion at meeting**
 - i. Child-Pugh B
 - ii. Hepatic Monitoring

- b. Clinical Pharmacology:- **No discussion at meeting**
 - i. Co-administration of strong CYP3A4 inhibitors
 - ii. Co-administration of strong CYP3A4 inducers and efavirenz
 - iii. Co-administration with tacrolimus
 - iv. Co-administration of lovastatin, fluvastatin, or simvastatin

- c. Clinical Efficacy/Clinical Virology
 - i. HCV GT1a and NS5A resistance-associated polymorphism screening

Meeting Discussion:

DAVP reiterated their rationale behind labeling recommendations for screening of all GT1a patients for baseline NS5A resistance polymorphisms prior to initiating treatment with EBR/GZR (LCM Background Package, and FDA Slide Deck (Appendix-1)). The FDA discussed the concerns they had with the methodologies Merck used to analyze the NS5A polymorphism data for EBR/GZR and Harvoni (FDA's Slides- Appendix 1). The FDA also noted the challenges associated with cross study comparisons.

The Division made the following points in their slide presentation:

- i. *For the NS5A polymorphism analyses conducted by Dr. Lisa K. Naeger for the HarvoniTM virology review, population sequences or consensus amino acid sequences derived from the next generation sequencing (NGS) data were used. Therefore, Sponsor's original data using population sequencing are more relevant for comparison with Harvoni, and additional analyses using NGS data to include minor variants present at $\geq 1\%$ of the viral population do not change our position on this issue. Inclusion of minority variants detected by NGS dilutes the impact with EBR/GZR.*

- ii. *All 4 of the ledipasvir/sofosbuvir relapsers in the 12 week non-cirrhotic arm (treatment-experienced subjects) had two critical NS5A resistance-associated polymorphisms at baseline (see Dr. Naeger's review pg. 65-67 Subjects 79378, 79303, 79214 and 79179). Sponsor's data indicate that a single NS5A resistance-associated polymorphism can impact efficacy of EBR/GZR (of the 24 VF's with NS5A polymorphisms, 19 subjects had only 1).*

- iii. *Pooling of GT1a and GT1b treatment-experienced subjects dilutes the impact that polymorphisms have on GT1a EBR/GZR virologic failure rates.*

- v. *Patients with NS5A polymorphisms who fail EBR/GZR would likely gain additional NS3/4A and NS5A resistance substitution(s), which may severely limit the efficacy of subsequent re-treatment. This risk of virologic failure and multiple-class DAA resistance with EBR/GZR can be minimized if HCV GT1a patients are screened for the presence of NS5A resistance-associated polymorphisms.*

The Sponsor presented the following points to support their position against recommending baseline screening for GT1a patients (Merck Slide Set- Appendix 2). Counter-points provided by the Division are also noted where applicable.

- vi. *High SVR rates were achieved in GT1a patients (RAP population) who received the proposed EBR/GZR regimens (Merck- Slide 5)*
- vii. *While 2 or more NS5A polymorphisms at baseline have a high impact on treatment efficacy with EBR/GZR, the presence of single NS5A polymorphisms also affects efficacy (Merck- Slide 6)*
- viii. *There is a low overall prevalence of the relevant NS5A polymorphisms in the US population (Merck- Slide 8)*
- ix. *Overall virologic failure rates are low when patients are treated with EBR/GZR (Merck- Slide 8)*
- x. *Only 2% of treatment-naïve or prior P/R relapsers had baseline NS5A polymorphisms and relapsed when treated with EBR/GZR, and some relapses also occurred in patients without NS5A polymorphisms (Merck- Slide 8)*
- xi. *The Sponsor provided an analysis of SVR rates for EBR/GZR and Harvoni based on next generation sequencing with a 1% sensitivity cutoff, and according to lists of NS5A polymorphisms that are specific for each regimen (Merck- Slide 11). The Sponsor argued based on this analysis EBR/GZR and Harvoni are comparable in terms of the prevalence and impact of NS5A polymorphisms in GT1a patients, yet Harvoni's label does not have an NS5A screening recommendation. The Sponsor noted that the screening issue may result in an unfair promotional advantage for their competitors. The Division agreed with the sponsor that certain NS5A polymorphisms or combinations of polymorphisms may impact treatment efficacy with other NS5A inhibitor-containing regimens like Harvoni, but the Division also had significant concerns about the Sponsor's analysis because of the methods used, and directed the sponsor to FDA cross-study analyses presented in FDA slides 4 and 5. The FDA analyses provided a direct comparison between EBR/GZR and Harvoni, considering the same NS5A positions and using the more consistent and clinically relevant polymorphism detection methodology (population sequencing or consensus/high prevalence variants by NGS). These analyses*

showed that NS5A polymorphisms, particularly viruses with single NS5A polymorphisms that are far more common than viruses with multiple resistance polymorphisms, clearly have a much greater impact on the 12-week EBR/GZR regimen compared to Harvoni. The Division further noted that statistical analyses demonstrated the impact of single NS5A resistance polymorphisms significantly reduced EBR/GZR efficacy, but not Harvoni. The Division emphasized the differences in potential resistance consequences with the different regimens and noted that when Harvoni was approved it had been the first NS5A inhibitor-containing regimen, and that the HCV treatment landscape and tools have changed tremendously in the last few years.

- xii. A major concern brought up by the Sponsor is that the readout from commercial resistance tests for the NS5A component do not discriminate or test for all relevant baseline NS5A polymorphisms. The Sponsor also noted that the testing methodology used by commercial vendors is proprietary and that their reporting is not harmonized (Merck- Slide 10). In addition, resistance-associated polymorphisms that have no impact on EBR/GZR response are reported by the commercial vendors. Furthermore, if a baseline NS5A polymorphism is detected it is possible that due to the non-specific nature of the readout (Merck- Slide 13), physicians and patients may erroneously believe that they have no NS5A treatment options. In addition, payers may use these results to deny access to all NS5A containing treatment regimens. The Agency acknowledged this concern and noted that Monogram Biosciences has indicated publicly they will consider changing the reporting once the Merck product gets approved. The Sponsor was requested to continue to reach out to Monogram Biosciences and Quest Diagnostics to work out the above mentioned issues and optimize resistance data reporting to ensure the most clinically meaningful resistance information is communicated to clinicians.*
- xiii. As far as the consequences of failure with EBR/GZR are concerned, the Sponsor presented new data which showed that while in the immediate term patients who fail treatment do accumulate NS3 resistance-associated substitutions, these are often lost by week 24 post treatment; however, NS5A resistance substitutions do persist (Merck- Slide 15). The Sponsor also noted there are good emerging re-treatment options for DAA failures, especially for those with NS5A resistance substitutions, including a regimen that uses EBR/GZR (Merck- Slide 17). The Division commented that these data, particularly from the C-SWIFT relapsers, are not directly relevant to the re-treatment of patients who failed treatment with ≥ 12 weeks of EBR/GZR as shorter treatment durations often do not enrich for drug resistant virus to the same extent.*
- xiv. The Sponsor wanted the Agency to define the terms RAV and polymorphism.*

In further discussion, the Division noted that the two sides are interpreting the data differently, resulting in scientific disagreement on the NS5A screening issue. The Division noted that its recommendation for baseline NS5A screening in the label is based on maximizing SVR, and the Sponsor responded that NS5A resistance testing will not result in 100% SVR, since a number of other factors govern treatment response.

The Sponsor noted that they are not in favor of a product specific AC on the NS5A screening issue, though they would prefer an AC where all companies with NS5A products could present their views on the topic. The Sponsor agreed that the presence of NS5A polymorphisms affects efficacy and they want to describe this finding in the label so physicians will be informed, but they are seeking fairness in their label and commented that no DAA regimens are specifically approved for treatment of patients with NS5A resistance polymorphisms. They noted that the recently approved Harvoni labeling does not include screening recommendations. Again, the Division emphasized that in the most relevant and direct comparisons GT1a NS5A polymorphisms have a greater efficacy impact on the 12-week EBR/GZR regimen compared to recommended Harvoni regimens.

The Sponsor requested that if screening language were to be in the label that it not be placed in Section 2 (DOSAGE & ADMINISTRATION), but rather in Section 12 (CLINICAL PHARMACOLOGY) sub-section 12.4 (Microbiology) and/or Section 14 (CLINICAL STUDIES). They also requested that instead of stating a strong “recommendation” for screening, softer language, such as “(b) (4)” be used. The Division disagreed with this approach and emphasized the need for language in Section 2, and requested the Sponsor submit their proposed language for these sections for the Division’s consideration.

The Division commented that their strong desire is to come to an agreement on the general inclusion of screening language in Section 2 of the label so that subsequent discussions can focus on the specific NS5A polymorphisms to be recommended for screening. The Sponsor raised concerns about the Division’s analyses and recommendations focusing on five key NS5A positions (28, 30, 31, 58 and 93) and requested a meeting/telecon to discuss the NS5A polymorphisms that are relevant to EBR/GZR, their impact on clinical efficacy, and how this information is expressed in the label. The Division agreed to such a discussion, pending agreement on the general screening recommendation. The Division advised the Sponsor that the current efficacy standard in the proposed treatment populations is well in excess of 90% and that this should be taken into consideration in deciding the relevant NS5A polymorphisms.

The Sponsor inquired if the Division would consider additional data from patients treated with the 16-week EBR/GZR+RBV regimen to support including this regimen in labeling for patients with NS5A polymorphisms. The Division responded that a relatively small dataset of patients with NS5A polymorphisms with favorable efficacy may be sufficient to provide a recommendation of 16-weeks EBR/GZR+RBV for patients with baseline NS5A polymorphisms.

The Division summarized that the NS5A screening recommendations will help personalize the use of Zepatier, and emphasized the very strong desire to maximize DAA treatment efficacy, minimize virologic failure and the need for retreatment.

3. Additional Applicant Data

NGS dataset submitted by applicant: **No discussion at meeting**

4. Postmarketing Requirements/Postmarketing Commitments: **No discussion at meeting**

As this NDA triggers PREA, pediatric studies will be required as PREA PMRs. These PMRs will reflect studies outlined in the Agreed iPSP.

5. Review Plans

Begin labeling review and negotiations

Meeting Discussion: *Sponsor was told that after receiving their proposed labeling regarding screening, the Division will make the decision on how to move forward.*

6. Wrap-up and Action Items

- a. *The Sponsor will submit their labeling proposal regard baseline NS5A screening for Sections 2, 12.4 and 14. In an e-mail communication, the Sponsor agreed to submit this information by November 30, 2015 – On November 30, 2015 Sponsor submitted revised labeling, which is being reviewed by the Division.*
- b. *DAVP will consider setting up a meeting, if necessary, to discuss the specific NS5A polymorphisms that affect EBR/GZR and the phrasing for them in the label – Sponsor will be sent revised labeling with detailed comments on NS5A polymorphisms and other issues.*

7. Post Meeting Follow Up

- *Following the LCM, the Division contacted both diagnostic companies and discussed the above-mentioned concerns. The companies in turn have indicated their willingness to consider alternate reporting formats.*

Methodologies Used by Merck in the NS5A Polymorphism Analyses

(Table 2 from “MERCK RESPONSE TO FDA COMMENTS ON BASELINE NS5A RAV TESTING IN GT1 PATIENTS”)

We have identified some concerns with the methodologies that were used:

Parameter	EBR/GZR NDA Submission	EBR/GZR New Analysis	LED/SOF FDA Virology Report [3], USPI†
Studies Included	Phase 2/3 Studies	Phase 2/3 Studies	Phase 2/3 Studies
Regimens Included	12, 16, 18 weeks; ±RBV	12, 16, 18 weeks; ±RBV	8, 12, 24 weeks
Patients Included	TN, TE, ±cirrhosis, ±HIV, ±CKD	TN, TE, ±cirrhosis, ±HIV, ±CKD	TN, TE, ±cirrhosis
Handling of non-virologic failures	RAV analyses considered only virologic failures	RAV analyses considered only relapse rates (matching the FDA review of LED/SOF)	In the FDA review of RAVs, only relapses are considered [3]
Assay Methodology	100 % population sequencing	For GT1a: 99.4% had population sequencing, 69.0% had NGS at 1% ST For GT1b: 99.3% had population sequencing, 22.1% had NGS at 1% ST	For TE: 100% NGS For TN 8 wk data: 100% NGS For TN 12 Wk data: 81% NGS All NGS at 1% ST
RAVs evaluated	RAVs that result in > 5-fold decrease in EBR potency <i>in vitro</i> replicon assays	Any RAV at any of the NS5A positions (24, 28, 30, 31, 32, 38, 58, 92 and 93) associated with resistance to any NS5AI as listed in the LED/SOF NDA virology review	Any RAV at any of the NS5A positions (24, 28, 30, 31, 32, 38, 58, 92 and 93) associated with resistance to any NS5AI as listed in the LED/SOF NDA virology review

Focus should be on recommended regimens

Not a fair comparison:

- All failures w/recommended LDV/SOF regimens were relapsers
- On-treatment virologic failures with EBR/GZR should have been included

Apples vs Oranges:

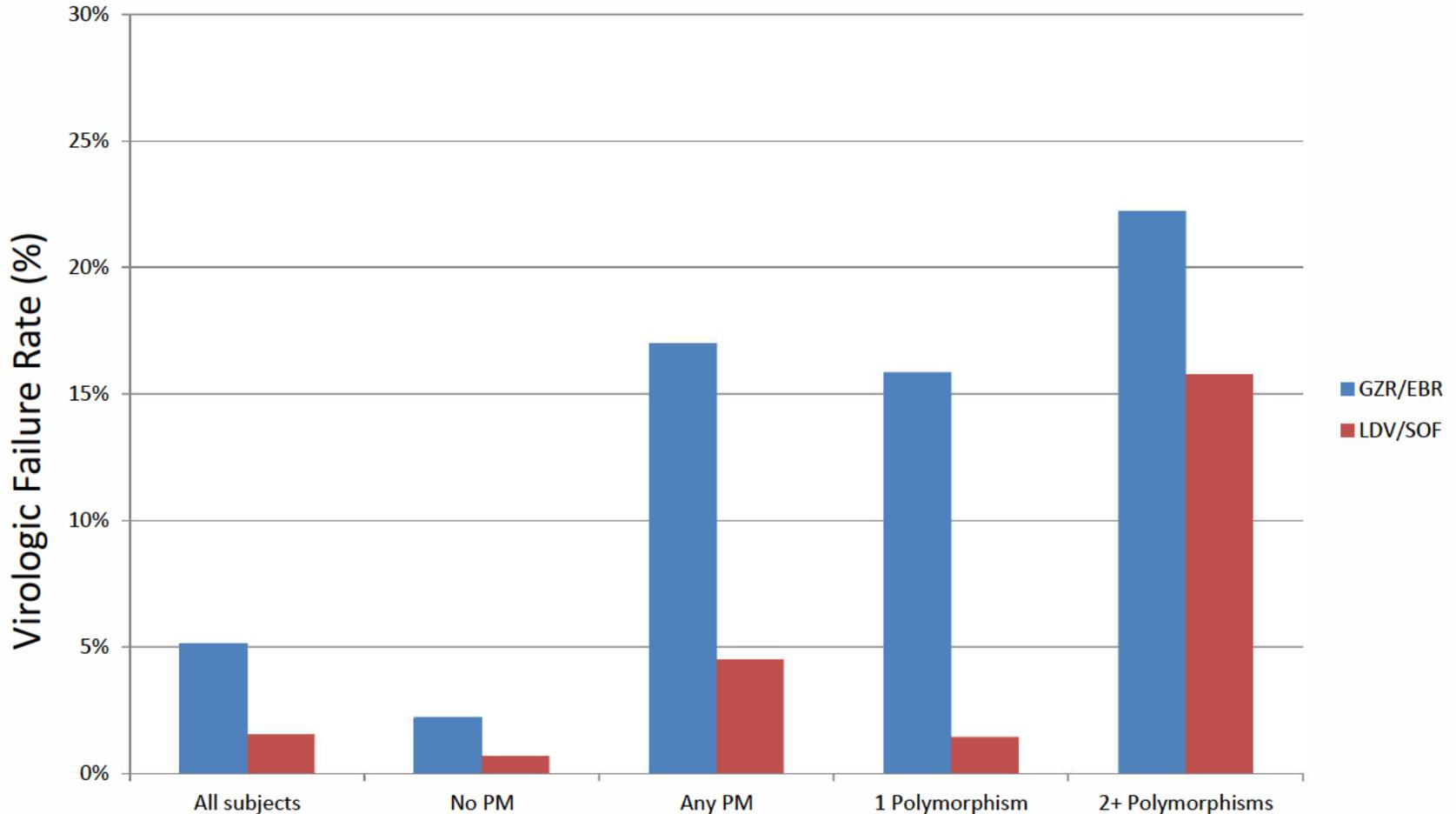
- LDV/SOF Baseline analyses based on population or consensus NGS sequences
- Inclusion of minority variants detected by NGS dilutes impact with EBR/GZR

Virologic failure rate in Dr. L.Naeger's review of Harvoni

NS5A Polymorphisms		Any	1	2	3
LED/SOF 12 weeks		5.6% (8/144)	1.7% (2/115)	22% (6/27)	0% (0/2)

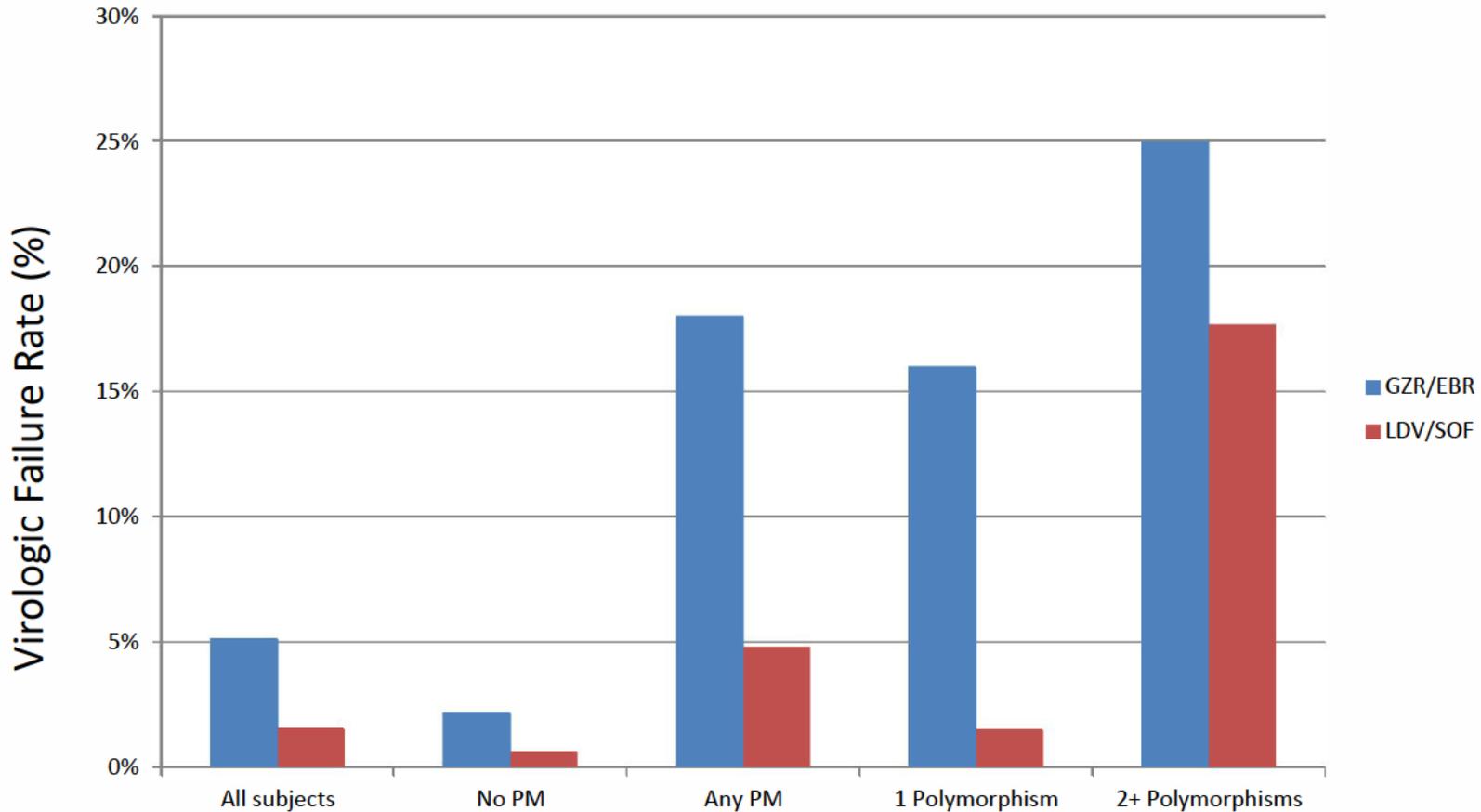
- **Single NS5A polymorphisms (considering positions 24, 28, 30, 31, 32, 58, 92, 93) do not have a significant impact on LDV/SOF 12-week efficacy**
- Pooled GT1a/GT1b

GT1a Virologic Failure Rate for All Subjects (Any NS5A Polymorphisms at Positions 24, 28, 30, 31, 58, 92, or 93)



Regimen	All subjects	No PM	Any PM	1 Polymorphism	2+ Polymorphisms
GZR/EBR	5.1% (26/506)	2.2% (9/406)	17% (17/100)	16% (13/82)	25% (4/18)
LDV/SOF	2% (6/389)	0.7% (2/300)	4% (4/89)	1% (1/70)	16% (3/19)

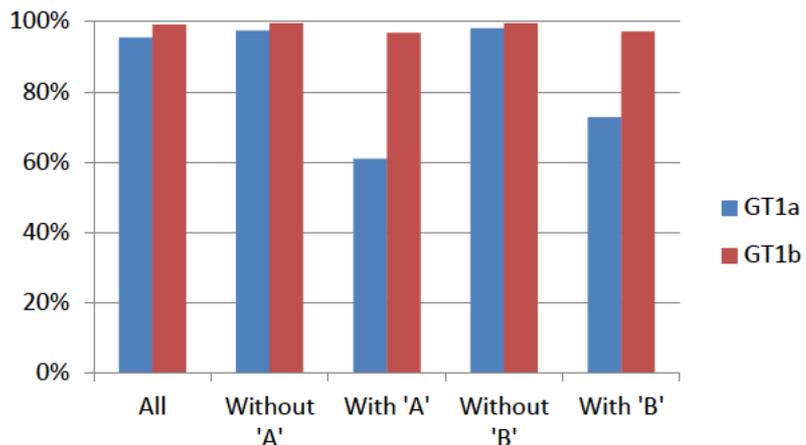
GT1a Virologic Failure Rate for All Subjects (Any NS5A Polymorphisms at Positions 28, 30, 31, 58, or 93)



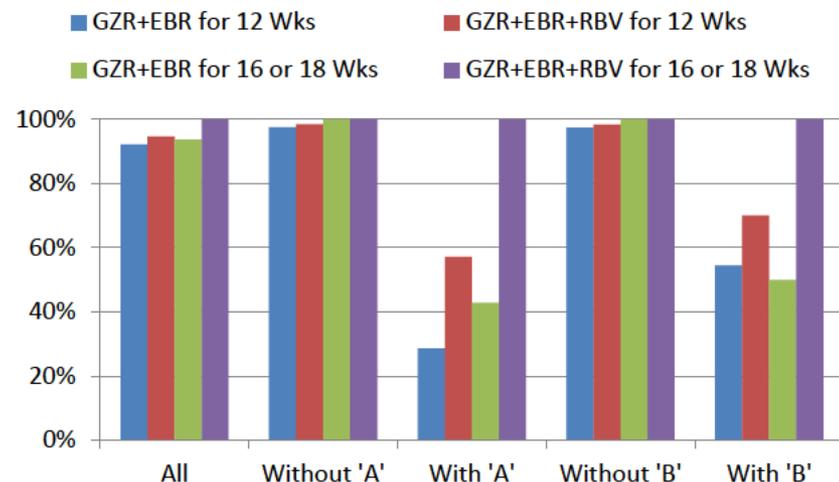
Regimen	All subjects	No PM	Any PM	1 Polymorphism	2+ Polymorphisms
GZR/EBR	5.1% (26/506)	2.2% (9/411)	18% (17/95)	16% (13/79)	25% (4/16)
LDV/SOF	2% (6/389)	0.7% (2/306)	5% (4/83)	2% (1/66)	18% (3/17)

SVR Rates in TN/TE Subjects (NS5A) (GZR/EBR 12W)

TN
(GT1a/1b)



		SVR	95%CI	Plot
Total (TN)	GT1	638/659 (97%)	95, 98	
	GT1a	397/416 (95%)	93, 97	
	Without 'A'	383/393 (97%)	95, 99	
	With 'A'	14/23 (61%)	39, 80	
	Without 'B'	365/372 (98%)	96, 99	
	With 'B'	32/44 (73%)	57, 85	
	GT1b	241/243 (99%)	97, 100	
	Without 'A'	211/212 (100%)	97, 100	
	With 'A'	30/31 (97%)	81, 100	
	Without 'B'	207/208 (100%)	97, 100	
With 'B'	34/35 (97%)	83, 100		



		95%CI	Plot
ALL	12 Wks	74, 90	
	12 Wks+RBV	86, 98	
	16/18 Wks	84, 98	
	16/18 Wks + RBV	94, 100	
Without 'A'	12 Wks	91, 100	
	12 Wks+RBV	89, 100	
	16/18 Wks	92, 100	
	16/18 Wks + RBV	94, 100	
With 'A'	12 Wks	5.1, 70	
	12 Wks+RBV	20, 88	
	16/18 Wks	12, 80	
	16/18 Wks + RBV	40, 100	
Without 'B'	12 Wks	90, 100	
	12 Wks+RBV	91, 100	
	16/18 Wks	92, 100	
	16/18 Wks + RBV	93, 100	
With 'B'	12 Wks	25, 82	
	12 Wks+RBV	35, 92	
	16/18 Wks	17, 83	
	16/18 Wks + RBV	52, 100	

A = Has M/L28A/T, Q/R30H/K/R, L31F/M/V, H58D, Y93C/H/N at Baseline
 B = Has M/L28A/T/V, Q/R30H/K/L/R, L31F/M/V, H58D, Y93C/H/N/S at Baseline

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

/s/

ADAM I SHERWAT
12/14/2015



NDA 208261

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Merck Sharp & Dohme Corp.
Attention: Thomas J. Chambers, MD
Director, Global Regulatory Affairs
351 N. Sumneytown Pike
P. O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for elbasvir and grazoprevir tablet, 50 mg/100 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for November 19, 2015.
Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Nina Mani, Regulatory Project Manager, at (240) 402-0333.

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, MD
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: November 19, 2015 and 2:30 pm - 4:00 pm
Meeting Location: Bldg 22 Rm 1415

Application Number: NDA 208261
Product Name: Zepatier (elbasvir and grazoprevir; EBR/GZR)
Indication: Treatment of chronic hepatitis C genotypes 1 or 4 infection in adults
Sponsor/Applicant Name: Merck Sharp & Dohme Corp.

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 (if scheduled), 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 Safety

The Division strongly recommends a contraindication for EBR/GZR in patients with moderate hepatic impairment (i.e., Child-Pugh B). A Child-Pugh B subject with cirrhosis died in P059, which is of significant concern. It is difficult to determine whether the events leading to death were solely due to the subject's underlying hepatic disease or whether EBR/GZR contributed to the course of events which continued to progress after completion of treatment. While the subject did not experience a late ALT elevation event, the nature of drug-related toxicity may differ in patients with more severe underlying hepatic disease. Furthermore, the dosage of GZR in this fixed-dose combination product is 100 mg, whereas the dosage explored in P059 in Child-Pugh B subjects with cirrhosis was 50 mg. We also note (b) (4)

(b) (4). The Division believes a contraindication in this patient population may be more effective in deterring potential off-label use of EBR/GZR in Child-Pugh B patients and may minimize the risk of hepatic decompensation or hepatic failure, which has been associated with other HCV protease inhibitors.

The Division accepts the Sponsor's alternative monitoring plan for hepatic laboratory testing. The Division maintains that the rates of ALT elevations in subpopulations (e.g., female sex, Asian race, and age >65 years) belong in Section 5.1 of the label. According to the *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*, the description of the warning should include the known risk factors for the adverse reaction such as age, gender, and race; therefore, it is most appropriate to highlight subpopulations that may be at higher risk in this section.

Clinical Efficacy/Clinical Virology

We appreciate the new NGS data that you have submitted and the amount of work put into preparing the submission, and we agree that your analyses indicate that low minority HCV variants with changes at NS5A inhibitor resistance-associated amino acid positions likely have less of an impact on clinical outcome relative to those that predominate in the viral population.

However, to make the comparison with ledipasvir/sofosbuvir, please note that the NS5A polymorphism analyses that were conducted by Dr. Lisa K. Naeger for the Harvoni™ virology review used population sequences or consensus amino acid sequences derived from the NGS data. As described in Dr. Naeger's NDA 205834 review, please see pg. 14: "For baseline samples where population sequencing only or both population and deep sequencing data were available, analyses using the population sequence were reported. For baseline samples that only had deep sequencing data, consensus sequences were generated and used for analysis." Therefore, your original data using population sequencing are the more relevant for comparison, and your additional analyses using

NGS data to include minor variants present at (b) (4) % of the viral population do not change our previous position.

Furthermore, all 4 of the ledipasvir/sofosbuvir relapsers in the 12 week non-cirrhotic arm you have cited in Table 5 (pg. 15) of your document had two critical NS5A resistance-associated polymorphisms at baseline (see Dr. Naeger's review pg. 65-67 Subjects 79378, 79303, 79214 and 79179). Your data indicate that a single NS5A resistance-associated polymorphism can impact efficacy of EBR/GZR (of the 24 VF's with NS5A polymorphisms, 19 subjects had only 1).

We also refer you to our midcycle communication where we have outlined our concerns about the resistance consequences of virologic failure. Patients with NS5A polymorphisms who fail EBR/GZR would likely gain additional NS3/4A and NS5A resistance substitution(s), which may severely limit the efficacy of subsequent re-treatment. This risk of virologic failure and multiple-class DAA resistance with EBR/GZR can be minimized almost entirely if HCV GT1a patients are screened for the presence of NS5A resistance-associated polymorphisms.

Therefore, with respect to labeling, the Division does not agree with placement of information related to the impact of baseline NS5A polymorphisms on treatment response solely in Section 12.4 of the label. We recognize that there may be some situations in which EBR/GZR could be a reasonable treatment option even in patients with NS5A polymorphisms (e.g., patients with end stage renal disease receiving hemodialysis for whom other treatment options are not currently available), (b) (4). Therefore, we are considering (b) (4) the inclusion of a recommendation for testing for baseline NS5A polymorphisms in Section 2 under a subsection entitled "Testing Prior to Initiation of EBR/GZR". The Division is also amenable to stating that the optimal treatment regimen and duration for all GT1a infected patients with baseline NS5A polymorphisms is unknown, rather than the original proposal (b) (4). However, the Division wishes to reiterate that although EBR/GZR with RBV for 16 weeks appears to overcome the effect of baseline NS5A polymorphisms, additional data are necessary to support this preliminary finding.

The Division is also amenable to removing the proposed screening recommendation (b) (4)

The Division does not agree that screening for NS5A baseline polymorphisms places an undue burden on HCV treatment providers. (b) (4)

(b) (4) Additionally, the Division does not agree that employing screening leads to a clinically meaningful delay in treatment. The

For the reasons outlined above, the Division believes strongly that screening recommendations for baseline NS5A polymorphisms for HCV GT1a infected patients should be displayed prominently in the label. Please note that the labelling counter-proposal outlined above, which is currently under consideration by the Agency, represents the Division's threshold for acceptability with respect to this issue. If the Sponsor and the Division are unable to reach agreement on this issue, the Division will need to consider other regulatory steps to address this matter, which may include convening an Advisory Committee.

Clinical Pharmacology

a. Co-administration of strong CYP3A4 inhibitors

The clinical recommendations for the use of strong CYP3A4/P-gp inhibitors will be made on a case-by-case basis. Based on the drug interaction study results with ketoconazole and ritonavir, we agree that most CYP3A4 inhibitors can be co-administered with GZR/EBR. However, we do not recommend the co-administration of ketoconazole or cobicistat-containing regimens for the following reasons.

For ketoconazole, the review team has concluded that a 3-fold or more increase in GZR exposure is clinically relevant. Therefore, we concluded that concomitant use of ketoconazole is not recommended. Additionally, ketoconazole carries a boxed warning for hepatotoxicity. Concomitant use of ketoconazole and GZR/EBR (with the anticipated 3.3-fold increase in GZR levels) may increase the overall risk of hepatotoxicity. As such, we do not recommend the co-administration of ketoconazole.

A cobicistat-containing regimen is not recommended as cobicistat is an OATP1B inhibitor and the effects on GZR and EBR exposures have not been characterized. The effects of cobicistat on GZR or EBR exposures are expected to be determined once study PN081 (drug interactions with Stribild and MK-5172A FDC) is completed. The recommendation can be revised if the study shows no clinically relevant effects of Stribild on GZR and EBR exposures.

b. Co-administration of strong CYP3A4 inducers and efavirenz

We recommend contraindication for the co-administration of strong CYP3A4 inducers and efavirenz. Efavirenz decreased GZR AUC by 83% and strong CYP3A4 inducers will likely decrease GZR AUC to a similar extent or more. GZR exposures when co-administered with strong CYP3A4 inducers and efavirenz are expected to be comparable to those following the administration of GZR 25 mg or less.

Although no dose-ranging study of GZR was conducted with EBR, results of a dose-ranging study with PegIFN/RBV (PN038) indicated that GZR efficacy is likely to be compromised at doses below 50 mg. At 25 mg, the efficacy was clearly lower (54%) as compared to 50 mg or 100 mg of GZR (> 80%). Thus, co-administration is not justified under any circumstances due to the potential for compromising efficacy, which may lead to the development of resistance to the drug or the co-administered antiviral agent (EBR), and limit future treatment options.

Furthermore, we have recommended contraindication of strong CYP3A4 inducers in the past with hepatitis C drugs if the exposure-response relationship for efficacy does not support the use of CYP3A4 inducers. This is in line with recommendations for the use of Viekira Pak and the use of Daklinza with strong CYP3A4 inducers.

c. Co-administration with tacrolimus

In consultation with the Division of Transplant and Ophthalmology Products, we concluded that the magnitude of the increase in tacrolimus exposure by the co-administration of GZR/EBR is clinically relevant. We recommend frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration.

d. Co-administration of lovastatin, fluvastatin, or simvastatin

In consultation with the clinical pharmacology review team for endocrinology and metabolism products, we concluded that a specific dosing recommendation cannot be made in the labeling for these statins based on drug interaction study results with other statins (i.e., atorvastatin or rosuvastatin).

ADVISORY COMMITTEE MEETING

The final determination of the need for an Advisory Committee has not been made.

REMS OR OTHER RISK MANAGEMENT ACTIONS

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

LCM AGENDA

1. Introductory Comments – 5 minutes (Nina Mani, Regulatory Project Manager/Adam Sherwat, Cross-Discipline Team Lead)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 45 minutes

Please note that these issues affect labeling. Each issue will be introduced by FDA and followed by a discussion.

- a. Clinical Safety: Hepatic Issues
 - i. Child-Pugh B
 - ii. Hepatic Monitoring
- b. Clinical Pharmacology:
 - i. Co-administration of strong CYP3A4 inhibitors
 - ii. Co-administration of strong CYP3A4 inducers and efavirenz
 - iii. Co-administration with tacrolimus
 - iv. Co-administration of lovastatin, fluvastatin, or simvastatin
- c. Clinical Efficacy/Clinical Virology
 - i. HCV Gt1a and NS5A resistance associated polymorphism screening

3. Additional Applicant Data – 5 minutes

NGS dataset submitted by applicant

4. Postmarketing Requirements/Postmarketing Commitments – 5 minutes

As this NDA triggers PREA, pediatric studies will be required as PREA PMRs. These PMRs will reflect studies outlined in your Agreed iPSP.

5. Review Plans – 5 minutes

Begin labeling review and negotiations

6. Wrap-up and Action Items – 5 minutes

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

/s/

DEBRA B BIRNKRANT
11/06/2015