

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202258Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202-258

SUPPL # N/A

HFD # 530

Trade Name Victrelis

Generic Name Boceprevir

Applicant Name Schering, Inc

Approval Date, If Known May 13, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505 (b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

5 years

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 #2 YES NO

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

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: Sherly Abraham, R.Ph

Title: Regulatory Project Manager

Date: April 13, 2011

Name of Office/Division Director signing form: Jeffrey Murray, MD

Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

SHERLY ABRAHAM
04/13/2011

JEFFREY S MURRAY
04/19/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202-258 BLA #	NDA Supplement # N/A BLA STN #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Victrelis Established/Proper Name: Boceprevir Dosage Form: 200 mg Capsules		Applicant: Schering, Inc Agent for Applicant (if applicable):
RPM: Sherly Abraham, R.Ph.		Division: Division of Antiviral Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>May 13, 2011</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
<ul style="list-style-type: 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

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

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ 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
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval. May 13, 2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. • Original applicant-proposed labeling • Example of class labeling, if applicable 	<p>May 12, 2011</p> <p>November 15, 2010</p>

³ Fill in blanks with dates of reviews, letters, etc.

❖ 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 checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	May 12, 2011
<ul style="list-style-type: none"> Original applicant-proposed labeling 	November 15, 2010
<ul style="list-style-type: none"> Example of class labeling, if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	May 11, 2011
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	Acceptability Letter February 15, 2011 February 15, 2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM May 13, 2011 <input checked="" type="checkbox"/> DMEPA April 13, 2011 <input checked="" type="checkbox"/> DRISK May 2, 2011 <input checked="" type="checkbox"/> DDMAC April 28, 2011 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	December 15, 2010
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>February 9, 2011</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	5/13/11, 5/11/11, 5/10/11, 5/6/11, 5/5/11, 5/4/11, 5/3/11, 5/2/11, 4/29/11, 4/25/11, 4/22/11, 4/20/11, 4/19/11, 4/18/11, 4/15/11, 4/13/11, 4/5/11, 4/4/11, 3/28/11, 3/25/11, 3/22/11, 3/17/11, 3/15/11, 3/14/11, 3/10/11, 3/2/11, 3/1/11, 2/15/11, 2/14/11, 2/11/11, 2/10/11, 2/8/11, 2/4/11, 1/31/11, 1/26/11, 1/24/11, 1/20/11, 1/14/11, 1/13/11, 12/28/10, 12/22/10, 12/15/10, 12/13/10, 12/8/10, 12/3/10, 12/2/10, 11/30/10, 11/18/10, 10/12/10
❖ Internal memoranda, telecons, etc.	March 23, 2011, December 20, 2010
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg September 29, 2010
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	October 7, 2009 CMC End of Phase 2
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	April 27, 2011
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	May 5, 2011
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 15, 2011
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 13, 2011 May 5, 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 21, 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 17
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	April 15, 2011
• Clinical review(s) (<i>indicate date for each review</i>)	April 15, 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input 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 reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None DRUP Review March 22, 2011

⁵ Filing reviews should be filed with the discipline reviews.

	Thorough QT Study Review March 15, 2011
	Hematology Consult Review March 7, 2011
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested April 15, 2011
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 15, 2011
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None May 12, 2011 April 15, 2011
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 14, 2011
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 14, 2011
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 21, 2011
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 15, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 11, 2011
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 14, 2011
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None April 14, 2011
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None November 30, 2010 Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	April 18, 2011
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	Quality-April 13, 2011 Biopharm- April 8, 2011
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None	Quality-April 12, 2011 Biopharm-April 8, 2011
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None	
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	April 13, 2011	
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: March 16, 2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable	
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation	
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)	

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

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

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

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

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

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

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

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

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

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/s/

SHERLY ABRAHAM
05/17/2011



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 13, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 13, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. Please find the complete list of all the final PMRs and PMCs. Please confirm that you agree with the revised wording and timeframes ASAP.

1. Conduct a single-dose pharmacokinetics study of boceprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine weight-based dosing for children that will result in exposures similar to those observed in adults.

Final Protocol Submission: July, 2011
Trial Completion: February, 2013
Final Report Submission: May, 2013

2. Conduct a trial to evaluate safety and treatment response of boceprevir in combination with pegylated interferon and ribavirin as measured by sustained virologic response (SVR) in pediatric subjects 3 through 17 years of age, including previously untreated subjects and those who have failed a prior course of pegylated interferon and ribavirin therapy. This trial should include at least 5 years follow-up of pediatric subjects to characterize long-term safety of boceprevir, including growth assessment and sexual maturation in pediatric subjects, to determine the durability of response and to characterize boceprevir resistance-associated substitutions.

Final Protocol Submission: February, 2012
Trial Completion: July, 2015

Final Report Submission: October, 2015
Long-term Final Report Submission: November, 2020

POSTMARKETING REQUIREMENTS

Virology

3. Conduct a study to assess the impact of boceprevir treatment-emergent NS3 amino acid substitutions (those that have been observed but not characterized phenotypically) on the anti-HCV activity of boceprevir in the HCV replicon system. Potentially novel resistance-associated substitutions should also be evaluated. The HCV replicon genotype/subtype background used should be consistent with the background in which the specific substitutions have been observed in treated patients. Evaluations should include HCV replicons with previously characterized resistance-associated substitutions spanning the range of susceptibilities as reference standards. Specific examples of substitutions to be assessed include the following:

- a. D168N, with and without linked R155T, genotype 1a replicon
- b. V107I, with and without linked V36M+R155K, genotype 1a replicon
- c. P146S, with and without linked V36M+R155K, genotype 1a replicon
- d. I170V, genotype 1a replicon
- e. V36M, R155K and V36M+R155K, genotype 1a replicon

Final Protocol Submission: June, 2011
Study Completion: June, 2012
Final Report Submission: July, 2012

4. Conduct pooled analyses to characterize the impact of detectable baseline boceprevir resistance-associated polymorphisms on the efficacy of boceprevir + Peg-IFN α /RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg-IFN α /RBV 4-week lead-in (e.g., $<1 \log_{10}$ IU/mL decline, $\geq 1 \log_{10}$ IU/mL to $<2 \log_{10}$ IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype (if data are available). These pooled analyses should be conducted using data from the following completed and currently ongoing boceprevir clinical trials: P03523, P05216, P05101, P05411, P05685, and P06086. These analyses should be completed, and a study report submitted, within 9 months of collection of SVR outcome data from these clinical trials.

Final Protocol Submission: August, 2011
Final Report Submission: April, 2013

5. Conduct a study to analyze NS3/4A protease cleavage sites for the presence of boceprevir treatment-emergent substitutions for a selected subset of subjects (n~10) representative of the virologic failure responses and NS3 protease resistance patterns

observed in Phase 3 trials. An additional subset of subjects (n~10) who experienced virologic failure, but for whom no clear resistance-associated substitutions in NS3/4A were detected, should also be analyzed for the presence of boceprevir treatment-emergent substitutions in NS3/4A protease cleavage sites.

Final Protocol Submission: June, 2011
Study Completion: March, 2012
Final Report Submission: July, 2012

6. Report results from ongoing clinical trial P05063 regarding the long-term persistence of amino acid substitutions that emerged in boceprevir-treated subjects from the following Phase 2 and Phase 3 trials conducted to date: P03523, P03659, P05216 and P05101. For long-term, follow-up analyses of subjects from the Phase 3 trials (P05216 and P05101), if available, the same assay/vendor used initially to identify the treatment-emergent substitutions should continue to be used to monitor the persistence of the substitutions in the follow-up period. The persistence of detectable amino acid substitutions should be assessed for a treatment-free follow up period of approximately 2 years.

Final Protocol Submission: July, 2011
Trial Completion: December, 2011
Final Report Submission: July, 2012

Clinical Pharmacology

7. Conduct an *in vivo* drug-drug interaction trial between boceprevir and an oral contraceptive containing a progesterone component other than drospirenone.

Final Protocol Submission: July, 2011
Trial Completion: February, 2012
Final Report Submission: (b) (4)

8. Conduct an *in vivo* drug-drug interaction trial between boceprevir and methadone.

Final Protocol Submission: May, 2011
Trial Completion: September, 2011
Final Report Submission: March, 2012

9. Conduct an *in vivo* drug-drug interaction trial between boceprevir and a sensitive substrate of p-glycoprotein (*e.g.* digoxin).

Final Protocol Submission: July, 2011
Trial Completion: December, 2011
Final Report Submission: April, 2012

10. Conduct an *in vivo* drug-drug interaction trial between boceprevir and a selective serotonin reuptake inhibitor (SSRI) (*e.g.* escitalopram).

Final Protocol Submission: June, 2011
Trial Completion: December, 2011
Final Report Submission: July, 2012

POSTMARKETING COMMITMENTS

Clinical Pharmacology

11. Conduct an *in-vivo* drug-drug interaction trial between boceprevir and tacrolimus.

Final Protocol Submission: May, 2011
Trial Completion: August, 2011
Final Report Submission: January, 2012

12. Conduct an *in-vivo* drug-drug interaction trial between boceprevir and cyclosporine.

Final Protocol Submission: May, 2011
Trial Completion: September, 2011
Final Report Submission: February, 2012

13. Conduct an *in vivo* drug-drug interaction trial between boceprevir and prednisone.

Final Protocol Submission: December, 2011
Trial Completion: March, 2012
Final Report Submission: August, 2012

Clinical

14. Conduct a trial evaluating shorter treatment durations of pegylated interferon and ribavirin (PR) with and without boceprevir in treatment-naïve patients with the IL28B rs12979860 C/C genotype.

Final Protocol Submission: November, 2011
Trial Completion: April, 2014
Final Report Submission: October, 2014

15. Submit the final report and datasets for Study P05514 (PROVIDE), an open label ongoing efficacy trial in which boceprevir treatment in combination with peginterferon alfa and ribavirin is provided to subjects with chronic hepatitis C genotype 1 who did not respond to the peginterferon alfa and ribavirin control in previous boceprevir trials.

Trial Completion: June, 2013
Final Report Submission: December, 2013

Virology

16. Conduct a study to assess phenotypic susceptibility of baseline and treatment failure isolates from boceprevir-treated subjects (n~10) using the HCV replicon system. These analyses could focus on a subset of subjects whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials. Baseline isolates from a few boceprevir treated subjects (n~5) who achieved SVR should be included in these assessments for comparison. Entire NS3 protease or NS3/4A cassettes should be amplified from patient isolates and cloned into an appropriate HCV replicon vector for phenotypic characterization related to boceprevir susceptibility.

Final Protocol Submission: June, 2011
Study Completion: June, 2012
Final Report Submission: July, 2012

17. Conduct analyses to identify potential mechanisms of persistence of viral populations harboring boceprevir treatment-emergent, resistance-associated substitutions, based on observations in clinical trial P05063. The potential role of compensatory amino acid substitutions or virologic failure category (e.g., breakthrough, non-response, relapse) on the long-term persistence of boceprevir resistance-associated substitutions should be investigated. Also, a subset of subjects (n ~20) whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials should have long-term, follow-up samples characterized genotypically using a sensitive and quantitative nucleotide sequencing assay to characterize the dynamics of the complex viral populations over 1 to 2 years of treatment-free follow-up.

Final Protocol Submission: June, 2011
Study Completion: June, 2012
Final Report Submission: September, 2012

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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/s/

SHERLY ABRAHAM
05/13/2011

From: Chambers, Thomas [thomas_chambers2@merck.com]
Sent: Friday, May 13, 2011 1:48 PM
To: Abraham, Sherly
Subject: RE: Boceprevir-MedGuide
Dear Sherly,

We agree with your proposal below to remove the following statement from the Med Guide:

(b) (4)

We will send our version of the revised MG shortly.

Sincerely,

Tom

From: Abraham, Sherly [mailto:Sherly.Abraham@fda.hhs.gov]
Sent: Friday, May 13, 2011 1:30 PM
To: Chambers, Thomas
Subject: Boceprevir-MedGuide

Hi Tom,

We propose to remove this statement from the Medguide:

(b) (4)

Please let me know if you agree asap.

Thanks,
Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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SHERLY ABRAHAM
05/13/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 11, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: May 11, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Kendall Marcus, M.D., Safety Deputy Director
Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The DAVP is proposing the following postmarketing commitment (PMC). Please provide your responses to this request as soon as possible.

Please provide the DAVP with dates for submission of the following information for the PMC listed below:

- a. final protocol;
- b. study/clinical trial completion; and
- c. final study report.

Submit the final study report and datasets for Study P05514 (PROVIDE). Study P05514 is an open label ongoing trial in which boceprevir treatment in combination with peginterferon alfa and ribavirin is provided to subjects who did not respond to the peginterferon alfa and ribavirin control in previous boceprevir trials.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
05/11/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 10, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: May 10, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Kendall Marcus, M.D., Safety Deputy Director
Poonam Mishra, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The DAVP has revised the following PREA postmarketing Requirements. Please let us know if you agree with these revisions as soon as possible.

1. Conduct a single-dose pharmacokinetics study of boceprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine the weight-based dosing for children that will result in exposures similar to those observed in adults.

Protocol Submission: July, 2011

Study Completion: February, 2013

Final Study Report Submission: May, 2013

2. Conduct a trial to evaluate safety and treatment response of boceprevir in combination with pegylated interferon and ribavirin as measured by sustained virologic response (SVR) in pediatric subjects 3 through 17 years of age, including previously untreated subjects and those who have failed a prior course of pegylated interferon and ribavirin therapy. This trial should include at least 5 years follow-up of pediatric subjects to characterize long term safety of boceprevir, including growth assessment and sexual maturation in pediatric subjects, determination of durability of response, and characterization of boceprevir resistance-associated substitutions.

Protocol Submission: February, 2012
Study Completion: July, 2015
Final Study Report Submission: October, 2015
Long-term follow-up Study Report Submission: November, 2020

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
05/10/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 6, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: May 6, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Kendall Marcus, M.D., Safety Deputy Director
Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The DAVP is proposing the following pediatric studies that are required under PREA as Postmarketing Requirements. Please provide your response and proposed date for submission of the long-term follow-up study report by COB May 6, 2011.

1. Conduct a single-dose pharmacokinetics study of boceprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine whether weight-based dosing for children will result in exposures similar to those observed in adults.

Protocol Submission: July, 2011

Study Completion: February, 2013

Study Submission: May, 2013

2. Conduct a trial to evaluate safety and treatment response of boceprevir in combination with pegylated interferon and ribavirin as measured by sustained virologic response (SVR) in pediatric subjects 3 through 17 years of age, including previously untreated subjects and those who have failed a prior course of pegylated interferon and ribavirin therapy. This trial should include at least 5 years follow-up of pediatric subjects to characterize long term safety of

boceprevir, including growth assessment and sexual maturation in pediatric subjects.

Protocol Submission: February, 2012

Study Completion: July, 2015

Study Submission: October, 2015

Long-term follow-up Study Report Submission:

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
05/06/2011

From: Tyson, Victoria
Sent: Friday, May 06, 2011 8:50 AM
To: 'Chambers, Thomas'
Subject: RE: NDA 202-258-carton and container labels
Good morning Tom,

sorry but I just got a message from our labeling expert and the change in the PI that I sent to you is correct but the only change to the carton and container labels is as follows:

The container label and carton labeling dosage instructions should read:

Four capsules by mouth three times daily (every 7 to 9 hours) with food.

Thanks Vicky

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Thursday, May 05, 2011 3:50 PM
To: Tyson, Victoria
Cc: Abraham, Sherly
Subject: RE: NDA 202-258-carton and container labels

Dear Vicky,

Thank you for your message regarding the further modifications. I have requested the designers to make these changes.

Because I received your message after informing you that the revised artwork would be available for review on May 9, I will have to update you on whether a little extra time will be involved. I will make every effort to deliver the revised material as soon as possible.

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

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Thursday, May 05, 2011 2:23 PM
To: Chambers, Thomas
Cc: Abraham, Sherly
Subject: RE: NDA 202-258-carton and container labels
Importance: High

Hi Tom,

please revise the language in the D&A Section (and other sections of the PI as appropriate) slightly from what was sent to you yesterday to read as:

800 mg (four 200 mg capsules) three times daily (every 7 to 9 hours) with food.

Please incorporate this change in your mock-up of the carton and container labels and let us know when they will be submitted. thanks Vicky

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Monday, May 02, 2011 6:00 PM
To: Tyson, Victoria
Subject: RE: NDA 202-258-carton and container labels

I will notify the team about this request. It is clear. Thank you.

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Monday, May 02, 2011 5:55 PM
To: Chambers, Thomas
Subject: RE: NDA 202-258-carton and container labels

Hi Tom,

sorry if my response was not clear, but yes, if you can submit a mock up of the carton and container with the revisions that we requested prior to the PDUFA date that would be helpful. It would then be attached to the AP letter along with the PI and Med Guide. If that is not possible, we will include language regarding the revised carton and container labels. I am about to leave shortly but can give you a call or you can call me to discuss. thanks Vicky 301-796-0827

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Monday, May 02, 2011 5:49 PM
To: Tyson, Victoria
Subject: RE: NDA 202-258-carton and container labels

Hi Vicky,

To try and be clear on this, were you intending that we submit the revised labelling for the cartons/containers to be used starting mid-late June *before* the PDUFA date of May 15?

Or did you mean that Merck would submit the revised labelling to be used in mid-late June for review by FDA, and that point would be mentioned in the action letter?

Sincerely,

Tom

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Monday, May 02, 2011 5:20 PM
To: Chambers, Thomas
Subject: RE: NDA 202-258-carton and container labels

Hi Tom,

yes, please, so that we can refer to it in our Action letter. thanks Vicky

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Monday, May 02, 2011 4:24 PM
To: Tyson, Victoria
Subject: RE: NDA 202-258-carton and container labels

Dear Vicki,

Thank you for the accelerated review of the carton and container labelling and helping us to meet urgent timelines.

If I understand correctly, the new FDA recommendations are to be implemented on the revised labelling to be implemented for the mid-June schedule. Do you want us to submit the revised labelling for your review in advance of implementing the changes?

Sincerely,

Tom

From: Tyson, Victoria [mailto:Victoria.Tyson@fda.hhs.gov]
Sent: Tuesday, April 26, 2011 5:03 PM
To: Chambers, Thomas
Subject: NDA 202-258-carton and container labels
Importance: High

Hi Tom,

in response to the April 25, 2011, submission and electronic submission, regarding the carton and container labeling, you may temporarily proceed with the carton and container labeling originally proposed in the NDA. As described in the submission, packaging operations would start using the revised container and carton labels in mid to late June 2011, after the initial distribution and include the revisions outlined below:.

The carton and container should include the same storage directions:

- Storage: Victrelis Capsules should be refrigerated at 2-8C (36-46F) until dispensed. Refrigerated capsules of Victrelis are stable until the expiration date printed on the label. Victrelis can be stored at room temperature up to 25C (77F) for 3 months.

Also, include the following on the carton and container:

- Four capsules by mouth three times daily (every 7-9 hours) with food.

Thanks Vicky

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/s/

VICTORIA L TYSON
05/06/2011

From: Abraham, Sherly
Sent: Thursday, May 05, 2011 11:51 AM
To: 'Chambers, Thomas'
Subject: Boceprevir - Follow-up to Revised Responses to Microbiology PMRs and PMCsI
[Hi Tom,](#)

Please note that the text in blue and the paragraph at the end should help clarify the request:

2. Report results from ongoing clinical trial P05063 regarding the long term persistence of amino acid substitutions that emerged in boceprevir-treated subjects from the following Phase 2 and Phase 3 trials conducted to date: P03523, P03659, P05216 and P05101. For long-term follow-up analyses of subjects from the Phase 3 trials (P05216 and P05101), if available, the same assay/vendor used initially to identify the treatment-emergent substitutions should continue to be used to monitor the persistence of the substitutions in the follow-up period. [The persistence of detectable amino acid substitutions should be assessed for a treatment-free follow up period of approximately 2 years.](#)

Sponsor Response:

The Sponsor will continue to report analyses from PN05063 for patients that enrolled in PN03523, PN03659, PN05216, and PN05101. A formal protocol for the study is not planned. All ongoing resistance analysis studies will be performed at (b) (4) because the assays employed for all the prior studies are no longer available.

DAVP Response

Please provide a summary of a study plan prior to conducting the study. Since the P05063 protocol has been previously submitted to the IND, you could simply reference this study protocol and summarize the sequence analysis methodology being used.

Please provide the following information:

- Date for submission of the study plan
- Date for study completion
- Date for submission of study report (report of ~2 year follow-up data from all 4 trials; later follow-up data can be included if available)

Sponsor Revised Response:

The Sponsor will continue to report analyses from PN05063 for patients that enrolled in PN03523, PN03659, PN05216, and PN05101 according to the protocol outlined in PN05063. In this study, resistance variants will be followed by population sequencing. For patients enrolled in the long-term follow-up study (PN05063) from Phase 3 studies, resistance analysis will be performed by the same vendor that initially identified the variants. A study plan will be submitted by the end of July 2011. As PN05063 is still currently enrolling patients, a definitive end-date can not be provided at this time. The study report will be submitted within 6 months of the last patient completing the 2-year follow-up time point. However, interim reports will be provided in April of each year until the completion of the study.

DAVP Clarification 5/5/2011

Results from subjects through 2 years of treatment-free follow-up would satisfy the PMR. Therefore, it should be possible to estimate dates of study completion and report submission for these results since all subjects involved have already completed their boceprevir therapy in the indicated Phase 2 and Phase 3 trials (i.e., timing of last date of dosing for last PN05216 or PN05101 subject who failed treatment + 2 years + time for analysis and assembly of report). Please estimate dates of study completion and submission for such a report. To be clear, this report does not have to be in the form of a final study report for PN05063. Of course, we would still be interested in reviewing any longer term follow-up data you have collected in PN05063, but data only through Follow-up Year 2 would be necessary for the purpose of satisfying the PMR. One of our primary interests in this study is to assess the difference, if any, in the persistence of resistance-associated substitutions following the Phase 2 trials versus the Phase 3 trials due to different treatment and study subject management strategies.

Thanks,
Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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/s/

SHERLY ABRAHAM
05/05/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 4, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: May 4, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Kendall Marcus, M.D., Safety Deputy Director
Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer
Michael Pacanowski, Pharm.D., Genomics Team Leader
Shashi Amur, Ph.D., Genomics Reviewer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The DAVP is proposing the following postmarketing commitments (PMCs) and requirements (PMRs). Please provide your responses to these requests by COB May 4, 2011.

Please provide the DAVP with dates for submission of the following information for the PMRs/PMCs listed below:

- a. final protocol;
- b. study/clinical trial completion; and
- c. final study report.

Clinical and Clinical Pharmacology Post-marketing Commitments:

1. Conduct a trial evaluating shorter treatment durations of pegylated interferon and ribavirin (PR) with and without boceprevir in patients with the IL28B rs12979860 C/C genotype. The purpose of this trial is to determine the value of adding boceprevir to PR over PR alone, and to determine whether a shorter duration of PR alone or of boceprevir in combination with PR, based on response-guided therapy, is appropriate in certain subjects. Adequate numbers of black subjects should be included to assess SVR by genotype in that subgroup.

(b) (4)

6. Conduct a drug interaction trial with tacrolimus.
7. Conduct a drug interaction trial with cyclosporine.
8. Conduct a drug interaction trial with prednisone.

Please note that in all future randomized trials subjects should be stratified by IL28B genotype and cirrhosis.

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CORRESPONDENCE. Please feel free to contact me at 301-796-3198 if you have any questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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/s/

SHERLY ABRAHAM
05/04/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: May 3, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: May 3, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH: Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Pat Harrington, Ph.D., Clinical Virology Reviewer

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. Please refer to Merck's responses to FDA request of April 25, 2011, on the Virology post-marketing requirements and commitments. Please provide your responses to these requests by COB May 4, 2011.

Virology PMRs:

1. Conduct a study to assess the impact of boceprevir treatment-emergent NS3 amino acid substitutions (those that have been observed but not characterized phenotypically) on the anti-HCV activity of boceprevir in the HCV replicon system. Potentially novel resistance-associated substitutions should also be evaluated. The HCV replicon genotype/subtype background used should be consistent with the background in which the specific substitutions have been observed in treated patients. Evaluations should include HCV replicons with previously characterized resistance-associated substitutions spanning the range of susceptibilities as reference standards.

Specific examples of substitutions to be assessed include the following:

- a. D168N, with and without linked R155T, genotype 1a replicon
- b. V107I, with and without linked V36M+R155K, genotype 1a replicon

- c. P146S, with and without linked V36M+R155K, genotype 1a replicon
- d. I170V, genotype 1a replicon
- e. V36M, R155K and V36M+R155K, genotype 1a replicon

Merck Response:

The Sponsor agrees to perform this study. A formal protocol for the study is not planned. The analyses will begin in 2010 and the expected completion time is end of June, 2012. The report will be issued shortly thereafter.

DAVP Response

In the absence of a formal protocol, please provide at least a summary of a study plan prior to conducting the study. Please provide the following information:

- Date for submission of the study plan
- Date for submission of the final study report (by end of July 2012 is reasonable from our perspective)

2. Report results from ongoing clinical trial P05063 regarding the long term persistence of amino acid substitutions that emerged in boceprevir-treated subjects from the following Phase 2 and Phase 3 trials conducted to date: P03523, P03659, P05216 and P05101. For long-term follow-up analyses of subjects from the Phase 3 trials (P05216 and P05101), if available, the same assay/vendor used initially to identify the treatment-emergent substitutions should continue to be used to monitor the persistence of the substitutions in the follow-up period. The persistence of detectable amino acid substitutions should be assessed for a treatment-free follow up period of approximately 2 years.

Merck Response:

The Sponsor will continue to report analyses from PN05063 for patients that enrolled in PN03523, PN03659, PN05216, and PN05101. A formal protocol for the study is not planned. All ongoing resistance analysis studies will be performed at (b) (4) because the assays employed for all the prior studies are no longer available.

DAVP Response

Please provide a summary of a study plan prior to conducting the study. Since the P05063 protocol has been previously submitted to the IND, you could simply reference this study protocol and summarize the sequence analysis methodology being used. Please provide the following information:

- Date for submission of the study plan
- Date for study completion
- Date for submission of study report (report of ~2 year follow-up data from all 4 trials; later follow-up data can be included if available)

3. Conduct pooled analyses to characterize the impact of detectable baseline boceprevir resistance-associated polymorphisms on the efficacy of boceprevir + Peg-IFN α /RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg- IFN α /RBV 4-week lead-in (e.g., $<1 \log_{10}$ IU/mL decline, $\geq 1 \log_{10}$ IU/mL to $<2 \log_{10}$ IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype (if data are available). These pooled analyses should be conducted using data from the following completed and currently ongoing boceprevir clinical trials: P03523, P05216, P05101, P05411, P05685, and P06086. These analyses should be completed, and a study report submitted, within 9 months of collection of SVR outcome data from these clinical trials.

Merck Response:

The Sponsor agrees to do this study. A formal protocol for the study is not planned. The analyses will begin in 2011. The results will be presented within 9 months of collection of SVR outcome data from the last clinical trial PN05411. PN05411 will be unblinded in July 2012, and the data available for analysis in August, 2012. The expected date for delivery of the final report is April, 2013.

DAVP Response

In the absence of a formal protocol, please provide at least a summary of a study plan prior to conducting the study. Please provide the following information:

- Date for submission of the study plan

4. Conduct a study to analyze NS3/4A protease cleavage sites for the presence of boceprevir treatment-emergent substitutions for a selected subset of subjects (n~10) representative of the virologic failure responses and NS3 protease resistance patterns observed in Phase 3 trials. An additional subset of subjects (n~10) who experienced virologic failure, but for whom no clear resistance-associated substitutions in NS3/4A were detected, should also be analyzed for the presence of boceprevir treatment-emergent substitutions in NS3/4A protease cleavage sites.

Merck Response:

The Sponsor agrees to perform these analyses. A formal protocol for the study is not planned. The studies will begin in 2011. The expected time of completion of the study will be by end of March, 2012, and the report will be issued shortly afterward.

DAVP Response

In the absence of a formal protocol, please provide at least a summary of a study plan prior to conducting the study. Please provide the following information:

- Date for submission of the study plan
- Date for submission of the final study report (by end of July 2012 is reasonable from our perspective)

Virology PMCs:

1. Conduct a study to assess phenotypic susceptibility of baseline and treatment-failure isolates from boceprevir-treated subjects (n~10) using the HCV replicon system. These analyses could focus on a subset of subjects whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials. Baseline isolates from a few boceprevir-treated subjects (n~5) who achieved SVR should be included in these assessments for comparison. Entire NS3 protease or NS3/4A cassettes should be amplified from patient isolates and cloned into an appropriate HCV replicon vector for phenotypic characterization related to boceprevir susceptibility.

Merck Response:

The sponsor agrees to perform this study. A formal protocol for the study is not planned. The study will begin in 2011. The expected time for completion of the study is end of June, 2012. The report will be issued shortly afterward.

DAVP Response

In the absence of a formal protocol, please provide at least a summary of a study plan prior to conducting the study. Please provide the following information:

- **Date for submission of the study plan**
- **Date for submission of the final study report (by end of July 2012 is reasonable from our perspective)**

2. Conduct analyses to identify potential mechanisms of persistence of viral populations harboring boceprevir treatment-emergent, resistance-associated substitutions, based on observations in clinical trial P05063. The potential role of compensatory amino acid substitutions or virologic failure category (e.g., breakthrough, non-response, relapse) on the long term persistence of boceprevir resistance-associated substitutions should be investigated. Also, a subset of subjects (n ~20) whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials should have long term follow-up samples characterized genotypically using a sensitive and quantitative nucleotide sequencing assay to characterize the dynamics of the complex viral populations over 1 to 2 years of treatment-free follow-up.

Merck Response:

The Sponsor agrees to perform this study. A formal protocol for the study is not planned. The study will begin in 2011. The expected time for completion is end of June, 2012. The report will be issued shortly afterwards.

DAVP Response

In the absence of a formal protocol, please provide at least a summary of a study plan prior to conducting the study. Please provide the following information:

- Date for submission of the study plan
- Date for submission of the final study report (by end of September 2012 is reasonable from our perspective)

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
05/03/2011

From: Abraham, Sherly
Sent: Monday, May 02, 2011 3:36 PM
To: 'Chambers, Thomas'
Subject: ClinPharm PMRs
Hi Tom,

Please find the following comments regarding Clinpharm PMRs that you sent me last week.
Please respond to this asap:

1. For all proposed DDI trials, please clarify if 7 months is necessary for submission of the final study report following completion of the trial. We would prefer to receive the reports sooner, if feasible.
2. We agree with the protocol submission and final trial completion dates for the combined oral contraceptive (COC) trial. However, is 4 months sufficient time to enroll and complete a trial which may require a run-in month of COC use followed by two additional months for evaluation of the DDI (COC alone vs. COC + boceprevir)?
3. Please move-up all dates for the digoxin DDI trial. We prefer the protocol be ready by July 2011 and the study completed by December 2011.

Thanks,

Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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SHERLY ABRAHAM
05/02/2011

From: Abraham, Sherly
Sent: Friday, April 29, 2011 12:37 PM
To: 'Chambers, Thomas'
Subject: RE: Boceprevir - Micro section of the label

Follow Up Flag: Follow up
Flag Status: Red
Dear Tom,

Please refer to the 12.4 of your label submitted on April 28, 2011. Please respond to us asap. We have a labeling meeting planned for Monday.

1. In "...Activity in Cell Culture," you summarized data for a (b) (4). Have these data been submitted to the NDA? If so, please provide the location. If not, please submit a brief report by COB May 2.

2. In "Resistance, In cell culture," you summarized data for (b) (4). Did this change result in *increased* sensitivity to boceprevir? Also, do you have data on the effect of Q80K, Q80R or Q80L substitutions on boceprevir activity in cell culture or biochemical assays? Please submit a brief report of available data by COB May 2.

3. In "Effect of baseline HCV polymorphisms on treatment response," please provide your rationale for (b) (4). Please respond by COB May 2.

Thanks,

Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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SHERLY ABRAHAM
04/29/2011

From: Tyson, Victoria
Sent: Tuesday, April 26, 2011 5:03 PM
To: 'Chambers, Thomas'
Subject: NDA 202-258-carton and container labels

Importance: High

Follow Up Flag: Follow up

Flag Status: Red

Hi Tom,

in response to the April 25, 2011, submission and electronic submission, regarding the carton and container labeling, you may temporarily proceed with the carton and container labeling originally proposed in the NDA. As described in the submission, packaging operations would start using the revised container and carton labels in mid to late June 2011, after the initial distribution and include the revisions outlined below:.

The carton and container should include the same storage directions:

- Storage: Victrelis Capsules should be refrigerated at 2-8C (36-46F) until dispensed. Refrigerated capsules of Victrelis are stable until the expiration date printed on the label. Victrelis can be stored at room temperature up to 25C (77F) for 3 months.

Also, include the following on the carton and container:

- Four capsules by mouth three times daily (every 7-9 hours) with food.

Thanks Vicky

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/s/

SHERLY ABRAHAM
04/29/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: April 25, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: April 25, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Kendall Marcus, M.D., Safety Deputy Director
Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Pat Harrington, Ph.D., Clinical Virology Reviewer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The DAVP is proposing the following Virology-related postmarketing commitments (PMCs) and requirements (PMRs). Please note that additional PMCs and/or PMRs may be proposed after the April 27, 2011 Advisory Committee meeting. Please provide your responses to these requests by April 28, 2011.

Please provide the DAVP with dates for submission of the following information for the PMRs/PMCs listed below:

- a. final protocol;
- b. study/clinical trial completion; and
- c. final study report.

Virology PMRs:

1. Conduct a study to assess the impact of boceprevir treatment-emergent NS3 amino acid substitutions (those that have been observed but not characterized phenotypically) on the anti-HCV activity of boceprevir in the HCV replicon system. Potentially novel resistance-associated substitutions should also be evaluated. The

HCV replicon genotype/subtype background used should be consistent with the background in which the specific substitutions have been observed in treated patients. Evaluations should include HCV replicons with previously characterized resistance-associated substitutions spanning the range of susceptibilities as reference standards. Specific examples of substitutions to be assessed include the following:

- a. D168N, with and without linked R155T, genotype 1a replicon
 - b. V107I, with and without linked V36M+R155K, genotype 1a replicon
 - c. P146S, with and without linked V36M+R155K, genotype 1a replicon
 - d. I170V, genotype 1a replicon
 - e. V36M, R155K and V36M+R155K, genotype 1a replicon
2. Report results from ongoing clinical trial P05063 regarding the long term persistence of amino acid substitutions that emerged in boceprevir-treated subjects from the following Phase 2 and Phase 3 trials conducted to date: P03523, P03659, P05216 and P05101. For long-term follow-up analyses of subjects from the Phase 3 trials (P05216 and P05101), if available, the same assay/vendor used initially to identify the treatment-emergent substitutions should continue to be used to monitor the persistence of the substitutions in the follow-up period. The persistence of detectable amino acid substitutions should be assessed for a treatment-free follow-up period of approximately 2 years.
 3. Conduct pooled analyses to characterize the impact of detectable baseline boceprevir resistance-associated polymorphisms on the efficacy of boceprevir + Peg-IFN α /RBV treatment regimens among subjects who (1) respond relatively poorly to the Peg-IFN α /RBV 4-week lead-in (e.g., $<1 \log_{10}$ IU/mL decline, $\geq 1 \log_{10}$ IU/mL to $<2 \log_{10}$ IU/mL decline, etc.), or (2) have an unfavorable IL28B genotype (if data are available). These pooled analyses should be conducted using data from the following completed and currently ongoing boceprevir clinical trials: P03523, P05216, P05101, P05411, P05685, and P06086. These analyses should be completed, and a study report submitted, within 9 months of collection of SVR outcome data from these clinical trials.
 4. Conduct a study to analyze NS3/4A protease cleavage sites for the presence of boceprevir treatment-emergent substitutions for a selected subset of subjects (n~10) representative of the virologic failure responses and NS3 protease resistance patterns observed in Phase 3 trials. An additional subset of subjects (n~10) who experienced virologic failure, but for whom no clear resistance-associated substitutions in NS3/4A were detected, should also be analyzed for the presence of boceprevir treatment-emergent substitutions in NS3/4A protease cleavage sites.

Virology PMCs

1. Conduct a study to assess phenotypic susceptibility of baseline and treatment-failure isolates from boceprevir-treated subjects (n~10) using the HCV replicon system. These analyses could focus on a subset of subjects whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in

the Phase 3 boceprevir trials. Baseline isolates from a few boceprevir-treated subjects (n~5) who achieved SVR should be included in these assessments for comparison. Entire NS3 protease or NS3/4A cassettes should be amplified from patient isolates and cloned into an appropriate HCV replicon vector for phenotypic characterization related to boceprevir susceptibility.

2. Conduct analyses to identify potential mechanisms of persistence of viral populations harboring boceprevir treatment-emergent, resistance-associated substitutions, based on observations in clinical trial P05063. The potential role of compensatory amino acid substitutions or virologic failure category (e.g., breakthrough, non-response, relapse) on the long term persistence of boceprevir resistance-associated substitutions should be investigated. Also, a subset of subjects (n ~20) whose virologic responses and genotypic resistance patterns are representative of the subject populations studied in the Phase 3 boceprevir trials should have long term follow-up samples characterized genotypically using a sensitive and quantitative nucleotide sequencing assay to characterize the dynamics of the complex viral populations over 1 to 2 years of treatment-free follow-up.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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/s/

SHERLY ABRAHAM
04/25/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: April 22, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: April 22, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Kendall Marcus, M.D., Safety Deputy Director
Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The DAVP is proposing the following postmarketing commitments (PMCs) and requirements (PMRs). Please note that additional PMCs and/or PMRs may be proposed after the April 27, 2011 Advisory Committee meeting. Please provide your responses to these requests by April 26, 2011.

Please provide the DAVP with dates for submission of the following information for the PMRs/PMCs listed below:

- a. final protocol;
- b. study/clinical trial completion; and
- c. final study report.

Clinical Pharmacology PMRs:

1. Conduct an *in vivo* drug-drug interaction trial between boceprevir and an oral contraceptive containing a progesterone component other than drospirenone.
2. Conduct an *in vivo* drug-drug interaction trial between boceprevir and methadone.
3. Conduct an *in vivo* drug-drug interaction trial between boceprevir and a sensitive substrate of p-glycoprotein (e.g. digoxin).
4. Conduct an *in vivo* drug-drug interaction trial between boceprevir and a selective serotonin reuptake inhibitor (SSRI) (e.g. escitalopram).

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
04/22/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: April 19, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: April 19, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Stephen Miller, Ph.D., Quality Team Leader
Mark Seggel, Ph.D., Quality Reviewer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer
Todd Bridges, Pharm.D., DMEPA Team Leader**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. Please find the following carton and container label recommendations on behalf of the review team:

A. Container Label

1. Please add dose instructions to the container label to reduce the likelihood of incorrect dose errors. The container contains the total daily dose in a single bottle. There is potential for incorrect dosing of Victrelis™ because there are no dosage instructions on the bottle.
2. Please ensure the established name is at least ½ size of proprietary name and has a commensurate prominence with proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Please see 21 CFR 201.10(g)(2).
3. Please revise the strength expression to read *200 mg per capsule*.

B. Carton Labeling (28 bottles x 12 capsules)

1. Please ensure the established name is at least ½ size of proprietary name and has a commensurate prominence with proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See 21 CFR 201.10(g)(2).
2. Please revise the strength expression to read *200 mg per capsule*.
3. Please add dosage instructions to the principal display panel.
4. Please revise the Medication Guide statement to read as follows:
Dispense the enclosed Medication Guide to each patient
5. Please delete the statement, (b) (4)

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Sherly Abraham, R.Ph.
Regulatory Project Manager

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/s/

SHERLY ABRAHAM
04/19/2011

From: Abraham, Sherly
Sent: Monday, April 18, 2011 10:45 AM
To: 'Chambers, Thomas'
Subject: RE: Boceprevir - FDA Briefing Document: Request for Clarification
[Dear Tom,](#)

[Please see our clarification to your query below:](#)

During the FDA AC meeting presentation we will be using the analysis based on MedDRA preferred terms only without any grouping of terms. In our analysis, we have included all-causality adverse events reported during the lead-in and treatment phase.

Our analysis of the pooled data (P03523, P05216, and P05101) using the MedDRA preferred terms only shows:

Adverse events of anxiety was reported in 13% of boceprevir-treated subjects compared to 12% in controls (PR alone); depression in 20% of boceprevir-treated subjects compared to 21% in controls (PR alone), and insomnia was reported in similar frequency in both boceprevir treated subjects and controls (33%).

[Thanks,](#)
[Sherly](#)

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Thursday, April 14, 2011 11:02 PM
To: Abraham, Sherly
Subject: RE: Boceprevir - FDA Briefing Document: Request for Clarification

Dear Sherly,

In reviewing the FDA briefing document which we received on April 8, we have a question regarding the FDA analysis of events related to anxiety, depression and insomnia (Section IV.d: Neuropsychiatric Events, page 25).

Since the proportions of patients reporting events of anxiety, depression and insomnia that you have specified for these events differ from those in our own analysis, we assume that you have grouped terms when classifying these events in your analysis.

We therefore request clarification on the rules that were used by the review team to derive the proportions of patients reporting events of anxiety, depression and insomnia.

Sincerely,
Tom
Thomas Chambers

Merck Global Regulatory Affairs
TEL: (267) 305-6722

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SHERLY ABRAHAM
04/18/2011

From: Abraham, Sherly
Sent: Friday, April 15, 2011 10:03 AM
To: 'Chambers, Thomas'
Subject: Clinical Information Request of April 15
Dear Tom,

Please respond to this asap by early afternoon.

Please provide the number and percentage of subjects who actually received 24 weeks of boceprevir 800 mg TID and percentage of subjects who actually received 32 weeks of boceprevir 800 mg TID in combination with PEG2b and ribavirin in the studies P03523, P05216, and P05101. The percentage is in regard to the percentage of all subjects in the respective studies who received boceprevir.

Thanks,
Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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SHERLY ABRAHAM
04/15/2011

From: Abraham, Sherly
Sent: Wednesday, April 13, 2011 3:59 PM
To: 'Chambers, Thomas'
Subject: Information Request
[Dear Tom,](#)

[Please respond to this information request by COB tomorrow, Thursday, April 14, 2011:](#)

[Please provide the number and percentage of subjects who received boceprevir 800 mg TID for 44 weeks in combination with PEG2b and ribavirin in the studies P03523, P05216, and P05101.](#)

[Please confirm receipt of this email.](#)

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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SHERLY ABRAHAM
04/13/2011

From: Abraham, Sherly
Sent: Tuesday, April 05, 2011 10:46 AM
To: 'Chambers, Thomas'
Subject: RE: Boceprevir - ACM Question
Dear Tom,

Please our response to your query below:

We basically used the first approach, with the differences shown in red below:

For early responder comparison:

In RGT arm,
SVR in patients who completed 28 weeks of therapy (SPRINT-2) and were HCV RNA neg at TW8 through TW24
SVR in patients who completed 36 weeks of therapy (RESPOND-2) and were HCV RNA neg at TW8 and neg at TW12.

In BOC48 arm,
SVR in patients who completed more than 31 weeks of therapy (SPRINT-2) and were HCV RNA neg at TW8 through TW24
SVR in patients who completed more than 39 weeks of therapy (RESPOND-2) and were HCV RNA neg at TW8 and neg at TW12.

In the 48 week arm, we used the upper bound of the visit window (for weeks therapy completed) to select subjects.

Thanks,
Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Monday, April 04, 2011 9:34 AM
To: Abraham, Sherly
Subject: RE: Boceprevir - ACM Question

Dear Sherly,

Can we please get comment on the following question?

Can you tell us what analysis or analyses of RGT vs 48 weeks is included in your AdCom Briefing Book ? If more than one analysis is included, is one considered to be primary?

There are several approaches that can be used to compare the efficacy of RGT and 48 week 3-drug therapy. In our Briefing Book we described results from 2 analyses for both SPRINT-2 and RESPOND-2. We are still discussing which analysis to show as part of our core presentation to AdCom.

The first approach used these definitions of early responders:

SVR in patients who completed 28 weeks of therapy (SPRINT-2) and were HCV RNA neg at TW8 through TW24

SVR in patients who completed 36 weeks of therapy (RESPOND-2) and were HCV RNA neg at TW 8.

The second approach used this definition:

SVR in patients who were HCV RNA neg at TW 8 (same criteria for SPRINT-2 and RESPOND-2). This is more like a conditional ITT analysis.

Sincerely,

Tom

Thomas Chambers

Merck Global Regulatory Affairs

TEL: (267) 305-6722

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SHERLY ABRAHAM
04/05/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

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DATE: April 1, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: April 1, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Jeff Florian, Ph.D., Pharmacogenomics Reviewer

Please refer to your submission dated November 10, 2010, a new NDA for Boceprevir for treatment of chronic hepatitis C.

This submission consists of updated questions for the Advisory Committee and slides, preliminary analysis, for discussion at the teleconference scheduled for April 21, 2011, that will be sent in a separate electronic message.

Questions to the Advisory Committee

1. Please comment on the safety of boceprevir in patients with chronic hepatitis C genotype 1, focusing mainly on the hematological effects of boceprevir in combination with pegylated interferon and ribavirin (PR).
2. Considering the overall potential risk and benefits of boceprevir, do the available data support approval of boceprevir for treatment of patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin?

VOTE: Yes/No/Abstain

- a. If no, what additional studies are recommended?
- b. If yes, proceed with the remaining questions.

3. Please comment on the strength of the evidence for use of boceprevir in combination with pegylated interferon/ribavirin in prior null responders (defined as less than 2 log₁₀ decrease in HCV RNA at 12 weeks during previous course of PR therapy), who were not included in the Phase 3 trial, P5101 in subjects who had previously failed PR therapy.
4. Please comment on the strength of the evidence to support response-guided therapy (RGT) with boceprevir in combination with pegylated interferon and ribavirin. Should certain groups of patients receive longer durations of boceprevir plus PR therapy than that evaluated in RGT arms?
 - a. Treatment-naïve patients with detectable HCV RNA at Week 8 and undetectable at Week 24 (late responders)
 - b. Patients such as blacks or those with advanced fibrosis or cirrhosis
 - c. Null responders (if recommended for inclusion in the indication)
 - d. Other groups, such as patients with poor interferon responsiveness (i.e. < 1 log₁₀ HCV RNA decline after the 4 week lead-in therapy with PR)
5. In addition to pediatric studies, are there any other postmarketing studies you would recommend to further define risks or optimal use of boceprevir in clinical practice?

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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VICTORIA L TYSON
04/20/2011



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DATE: April 1, 2011

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Company: Schering Corp	Division of Antiviral Products
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ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: April 1, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer

Please refer to your submission dated November 10, 2010, a new NDA for Boceprevir for treatment of chronic hepatitis C. The following request is being conveyed to you on behalf of the review team. Please respond to this request by COB, Wednesday, April 6, 2011:

Please provide datasets and analysis for all blood chemistry values evaluated during the trials P03523, P05216 and P05101; including but not limited to amylase, lipase, cholesterol, triglycerides, glucose, creatinine, uric acid and electrolytes. Also, please include your summary results and conclusions.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products



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SHERLY ABRAHAM
04/04/2011

MEMORANDUM OF TELECON

DATE: March 23, 2011

APPLICATION NUMBER: NDA 202,258

BETWEEN:

Name: Schering, Inc

Thomas Chambers, Global Regulatory Affairs
Scott Korn-Regulatory
Ann Howell- Regulatory
Laurie MacDonald- Regulatory

AND

Name:

Division of Antivirals (DAVP), Office of Antimicrobials
CDER
FDA

Debra Birnkrant, M.D., Division Director
Jeffrey Murray, M.D, MPH, Deputy Director
Kendall Marcus, M.D., Deputy Director for Safety
Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Reviewer
Sarah Connelly, M.D., Medical Reviewer
Pat Harrington, Ph.D., Clinical Virology Reviewer
Wen Zeng, Ph.D., Statistics Reviewer
Greg Soon, Ph.D., Statistics Team Leader
Sarah Robertson, Ph.D., Clinical Pharmacology Team Leader
Ruben Ayala, Ph.D., Clinical Pharmacology Reviewer
Michael Pacanowski, Pharm.D., Pharmacogenomics Team Leader
Pravin Jadhav, Ph.D., Pharmacometrics Team Leader
Jeffry Florian, Ph.D., Pharmacometrics Reviewer
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Leader
Christopher Ellis, Ph.D., Pharmacology/Toxicology Reviewer
Sherly Abraham, R.Ph., Regulatory Health Project Manager
Victoria Tyson, Chief, Project Management Staff

SUBJECT: DAVP's Preliminary Advisory Committee (AC) Questions

BACKGROUND:

Schering submitted a new molecular entity NDA for boceprevir on November 10, 2010, for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (≥ 18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy. On March 22, 2011, DAVP sent preliminary Advisory Committee (AC) meeting questions to Schering and a document explaining the rationale for considering longer treatment duration in treatment-naïve subjects who are late-responders. This meeting was scheduled to discuss these documents further and clarify any pending questions. Discussion primarily focused on the preliminary AC questions 1, 3, 4 and 5:

DISCUSSION:

Dr. Murray started the discussion by stating that the recommendations/questions that are in the documents are not the final but we will be asking the AC for their feedback on the issues outlined. We are relaying this information to be more transparent and let them know what will be included in the Division's background package in order to avoid discussing time consuming, unresolved issues during the AC meeting.

(b) (4)

ACTION POINTS:

Schering will perform their analysis regarding 14 subjects who received the “wrong” duration of therapy due to false positive HCV RNA results between RGT arm and 48 week triple therapy arm.

Schering will provide us with the articles on the Phase 3 studies that they will be publishing in the New England Journal of Medicine.

Schering will provide us the 80 day assessment on the boceprevir marketing application from EMA.

Sherly Abraham, R.Ph.
Regulatory Health Project Manager

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SHERLY ABRAHAM
04/14/2011



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DATE: March 22, 2011

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Company: Schering Corp	Division of Antiviral Products
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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: March 22, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Jadhav Pravin, Ph.D., Pharmacometrics Team Leader
Jeffry Florian, Ph.D., Pharmacometrics Reviewer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Pat Harrington, Ph.D., Clinical Virology Reviewer
Greg Soon, Ph.D., Statistics Team Leader
Wen Zeng, Ph.D., Statistics Reviewer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team:

Please see the attached draft questions we plan to discuss with the Advisory Committee. In our background document in addition to summarizing our analyses of efficacy and safety data from the key phase 2 and 3 boceprevir clinical trials, including our findings with regard to anemia, rationale for response-guided therapy, rationale for longer (36 weeks) duration of triple therapy in treatment-naïve patients, black patients, and those with cirrhosis or advanced fibrosis, and a discussion of the lead-in response as a surrogate for null-response. We also plan to include summary IL28B response data in our backgrounder, but do not plan to discuss patient management based on IL28B genotype at this time.

Please also see attached document outlining our rationale for longer treatment duration in treatment-naïve subjects who are late-responders.

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questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager

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/s/

SHERLY ABRAHAM
03/22/2011



NDA 202-258

INFORMATION REQUEST

Schering-Plough Corporation
Attention: Thomas Chamber, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-1099

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 Boceprevir, 200 mg Capsules.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We kindly request your response by Tuesday, March 29, 2011.

1. The chromatographic columns for assay, related substances, etc., are identified only as, for example, (b) (4), along with dimensions. However, because of the wide variety of columns of each type that are available, more specific details are needed to allow replication of the procedures. Please identify the specific columns that have been validated for each chromatographic procedure.
2. In order to ensure that at least (b) (4) of this immediate release drug product is dissolved within 60 minutes, please revise the dissolution test acceptance criterion from Q (b) (4) at 45 minutes to Q (b) (4) at 60 minutes. Please refer to FDA's Guidance for Industry - Dissolution Testing of Immediate Release Solid Oral Dosage Forms, August 1997.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Sherly Abraham, Regulatory Project Manager the Office of New Drugs (Sherly.Abraham@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Acting Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
03/17/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 15, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: March 15, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Hanan Ghantous, Ph.D., DABT, Nonclinical Team Leader
Christopher Ellis, Ph.D., Nonclinical Reviewer
Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following request is being conveyed to you on behalf of the review team. Please respond to this request by Friday, March 18, 2011:

We have the following nonclinical request concerning section 13.1 "Carcinogenesis, Mutagenesis, Impairment of Fertility" of the draft product label. Please provide justification for the exposure multiple identified in the following sentence:

[REDACTED] (b) (4)

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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/s/

SHERLY ABRAHAM
03/15/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 14, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: March 14, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH: Jules O'Rear, Ph.D., Clinical Virology Team Leader
Pat Harrington, Ph.D., Clinical Virology Reviewer
Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. Please respond to these requests by March 17, 2011:

Two different definitions for "Incomplete Virologic Response" (IVR) were used for the Phase 3 trials P05216 and P05101:

Protocol: $\geq 1 \log_{10}$ IU/mL increase in HCV RNA from nadir with HCV RNA $> 1,000$ IU/mL if both samples being compared were collected the same number of days after the last PEG2b injection. If timing of PEG2b injection differed, a $\geq 2 \log_{10}$ IU/mL increase from nadir was required to meet IVR criteria.

Expert Review: Simply defined as a $\geq 1 \log_{10}$ IU/mL increase from nadir, with no requirement of a $> 1,000$ IU/mL value, and no requirement for a $\geq 2 \log_{10}$ IU/mL increase depending on PEG2b timing.

It is not entirely clear when each definition is used for specific efficacy analysis purposes. Examples of inconsistencies include:

P05216 Clinical Study Report: first paragraph of Section 11.4.1.7 (pg. 194) states that IVR was based on the Protocol definition, but the last sentence of the same paragraph

refers readers to the Expert Review definition. Also, Table 36 (pg. 196) notes the Protocol definition is used to calculate IVR rates, but the source data tables note the Expert Review definition was used.

Summary of Clinical Efficacy: Table 18 (pg. 94) notes that the Protocol definition was used to report IVR rates

Resistance Analysis Update: Table 1 (pg. 13) uses the Expert Review Definition to report IVR rates.

Please clarify exactly when each IVR definition was used for the following purposes related to clinical trials P05216 and P05101:

- Efficacy analysis tables (e.g., reporting IVR rates)
- Resistance reports (e.g., resistance analysis update)
- Resistance datasets

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Sherly Abraham, R.Ph.
Regulatory Project Manager

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/s/

SHERLY ABRAHAM
03/14/2011

From: Abraham, Sherly
Sent: Monday, March 14, 2011 8:57 AM
To: 'Chambers, Thomas'
Subject: Clarification: FDA Clin and Clin Pharm Requests of March 10
[Dear Tom,](#)

[Here are the responses to your questions below and an additional request:](#)

We agree with the proposed summary table for question 1.

With regard to Question 2, we agree with combining grades 1 and 2, but would like to see grades 3 and 4 displayed separately in the table.

Please provide the information for individual studies (P03523, P05216 and P05101) as well as pooled data.

We also have an additional information request:

Please provide the details of the adverse events associated with thrombocytopenia in the three trials P03523, P05216 and P05101.

Thanks,
Sherly

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Friday, March 11, 2011 11:00 AM
To: Abraham, Sherly
Subject: FW: Clarification: FDA Clin and Clin Pharm Requests of March 10

Question 1: We propose the following summary table. Note that dose amounts were not collected on the Case Report Form.

Table 1.

Summary of Concomitant Use of Psychiatric Medications

Appears this way on original

	PR	
Subjects with Psych Meds at Baseline	n(%)	n
Subjects with Psych Med added to Baseline Med after Initiation Of Boceprevir	n(%)	n

Subjects Switching from Baseline Psych Med to Different Psych Med after Initiation of Boceprevir	n(%)
Subjects without Psych Med at Baseline but Started Psych Med after Initiation of Boceprevir	n(%)

Question 2: We propose the following two tables. We interpret the request as reporting permutations of decrease in the three lab tests, by grade categories.

(b) (4)

Table 2.

(b) (4)

Table 3.

(b) (4)



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/s/

SHERLY ABRAHAM
03/14/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 10, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: March 10, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following requests are being conveyed to you on behalf of the review team. Please provide your responses to these requests by March 16, 2011.

1. Please provide the details regarding the concomitant use of antidepressant medications during the trials P03523, P05216 and P05101. Please include the details for individual trials, as well as for pooled data (for P03523 and P05216), for each of the treatment arms. Please report how many subjects were on antidepressants or any other psychiatric medications at the time of initiation of study medications. Also include how many subjects had to be started on these medications after the initiation of boceprevir/placebo for worsening symptoms or had dose adjustments or addition of new drugs to their antidepressant regimen.
2. Please provide the details regarding the number of subjects who had decrease in all three hematopoietic cell lines; hemoglobin, neutrophils count, and platelet count. Include the grades of the laboratory abnormality and also the hemoglobin cut-offs of 8.5 to <10 g/dL and < 8.5 g/dL. Please provide the individual trial data (P03523, P05216 and P05101) as well as pooled analyses (for P03523 and P05216), for each treatment arm.

3. Please provide a line listing of all women who received an oral contraceptive or other systemically available hormonal contraceptive (e.g. contraceptive implants, patches or vaginal rings) concomitantly with boceprevir in the clinical trials P03523, P05216 and P05101. Please report all adverse events for these women. In addition, please provide a line listing of all pregnancies that occurred during these clinical trials and indicate whether a hormonal contraceptive was being used at the time of the pregnancy.
4. Please provide the details of adverse events in subjects with and without Granulocyte colony-stimulating factor (G-CSF) use in the three trials P03523, P05216 and P05101.

We are providing this above information via telephone facsimile for your convenience.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
03/10/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: March 2, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: March 2, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Medical Team Leader
Sarah Connelly, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following request is being conveyed to you on behalf of the review team. Please provide your response to this request by March 9, 2011.

We received your February 23, 2011, response to our request for dataset variables to indicate previous HCV treatment response. The Protocol P03659 clinical study report states "subjects selected for this trial were primarily null responders". Please provide the number and percentage of subjects in Protocol P03659 who were prior null responders, partial responders and relapsers (if applicable). This information should be presented for all subjects and for each treatment arm. In addition, please submit a listing of individual subjects (by USUBJID), treatment arm (by TXGROUP) and prior treatment response (e.g., null responder, partial responder) in an excel spreadsheet.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-3198 if you have any questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager

Division of Antiviral Products

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SHERLY ABRAHAM
03/02/2011

From: Abraham, Sherly
Sent: Tuesday, March 01, 2011 9:08 AM
To: 'Chambers, Thomas'
Subject: Boceprevir ClinPharm Request.March1, 2011
[Dear Tom,](#)

[Please see our request below from our clinpharm team:](#)

In your October 12, 2009, correspondence you stated the following, "We are planning to conduct UGT inhibition and induction studies with boceprevir and will submit this information to the Agency when available." What is the status of these in vitro studies? If the results were submitted with the NDA, please direct us to the location of the study reports.

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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/s/

SHERLY ABRAHAM
03/01/2011

From: Abraham, Sherly
Sent: Tuesday, March 01, 2011 8:47 AM
To: 'Chambers, Thomas'
Subject: RE: Boceprevir Request: Clinical Microbiology Questions
[Dear Tom,](#)

[Please find our request below:](#)

In your response to the Division of Antiviral Products Clinical Question # 3 of February 4, 2011 on the Boceprevir NDA, you reported long-term follow-up data for a single subject who achieved SVR in a Phase 3 boceprevir trial based on an LLOQ cutoff but not based on an LOD cutoff . Please comment if there were any additional subjects from either of the Phase 2 boceprevir trials P03523 or P03659. If so, please summarize any long term follow-up HCV RNA data from these subjects as well.

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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SHERLY ABRAHAM
03/01/2011



NDA 202258

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Schering Corporation
c/o:
Thomas J. Chambers, MD
PO Box 1000
UG2D-68
North Wales, Pennsylvania 19454-1099

ATTENTION: Thomas J. Chambers, MD
Director, Global Regulatory Affairs

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) dated November 10, 2010, received November 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Boceprevir Capsules, 200 mg.

We also refer to your November 18, 2010, correspondence, received November 18, 2010, requesting review of your proposed proprietary name, Victrelis. We have completed our review of the proposed proprietary name, Victrelis and have concluded that it is acceptable.

The proposed proprietary name, Victrelis, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 18, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Brantley Dorch, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0150. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Sherly Abraham at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
02/15/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 15, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: February 15, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer
Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team:

In order to better understand the potential safety implications for boceprevir when administered with strong inhibitors of CYP3A4/5, please provide a comprehensive list of all subjects who received concomitant administration of boceprevir with strong inhibitors of CYP3A4/5 during your Phase 3 trials. The list should contain the following items:

- Subject IDs for all subjects who took CYP3A4/5 inhibitors during treatment with boceprevir.
- Type, dose, frequency, and duration of the CYP3A4/5 inhibitors.
- Adverse events reported by the subjects during co-administration with boceprevir and CYP3A4/5 inhibitors.
- Actual or approximate systemic concentrations of boceprevir during the period of co-administration, if PK samples were collected.

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CORRESPONDENCE. Please feel free to contact me at 301-796-3198 if you have any questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Product

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SHERLY ABRAHAM
02/15/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 14, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: February 14, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Medical Team Leader
Sarah Connelly, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following request is being conveyed to you on behalf of the review team. Please provide your response to this request by February 25, 2011.

Please identify the appropriate P03659 dataset(s) and variable(s) that indicate previous HCV treatment response.

We are providing this above information via telephone facsimile for your convenience.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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/s/

SHERLY ABRAHAM
02/14/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 10, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: February 10, 2011

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mark Seggel, Ph.D., Quality Reviewer
Stephen Miller, Ph.D., Acting Branch Chief, ONDQA
Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader
Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team:

Quality:

In Protocol No. P03659, we note that Batch 81713-132 is identified as both a 100 mg boceprevir product and as a 200 mg placebo (see Table 5, p. 43). Several of the boceprevir 200 mg products listed in Table 5 are described elsewhere as 100 mg products (see Table 20, pp. 31-33, section 3.2.P.2.2). Several of the other batches listed in Table 5 (e.g., K-H07280, K-H07287) are not included in Table 20.

Please provide a comprehensive list of all boceprevir drug product batches (and placebos) used in the Phase I, Phase II and Phase III clinical studies described in the NDA. Please include formulation, strength, batch size, date and site of manufacture, and clinical study protocol number.

In addition, please provide a tabulation of the formulations for all clinical batches (e.g., FM3886-1-1, FM005009-1-1, FM005009-8-4).

Clinical Pharmacology:

The results of the drug-drug interaction (DDI) study conducted with the drospirenone-containing combined oral contraceptive (COC) indicate hormonal contraceptives may not be used safely in combination with boceprevir. However, it is unclear if the doubling of exposure would necessarily occur for other progestational components (e.g. norgestimate or norethindrone). In addition, the design of the completed DDI study makes interpretation of the findings difficult. It may be unrealistic for many women of child-bearing potential to rely on 2 barrier methods while on concomitant treatment with ribavirin. Therefore, we are requesting that you conduct another DDI study evaluating the effect of boceprevir on another COC. The new study should (1) enroll younger women of child-bearing potential, (2) assess the combination after a full cycle of COC (one cycle of COC alone, followed by one cycle with boceprevir), (3) assess a COC with a different progestational compound (e.g. norethindrone) and (4) include assessments of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and progesterone. Please submit a protocol for review prior to proceeding with the study. This study should be initiated as soon as possible.

We are providing this above information via telephone facsimile for your convenience.

THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE. Please feel free to contact me at 301-796-3198 if you have any questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Product

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/s/

SHERLY ABRAHAM
02/11/2011

REQUEST FOR CONSULTATION

TO (Office/Division): **Office of Drug Evaluation III
Division of Reproductive and Urologic Products**

FROM (Name, Office/Division, and Phone Number of Requestor):
**Sherly Abraham, Rph
Office of Antimicrobial Products/Division of Antiviral
Products
301 796 3198**

DATE
February 7, 2011

IND NO.
69,027

NDA NO.
**202-258
201-917**

TYPE OF DOCUMENT
NME NDAs

DATE OF DOCUMENT
**November 10, 2010
November 23, 2010**

NAME OF DRUG
**Boceprevir
Telaprevir**

PRIORITY CONSIDERATION
Priority NDA

CLASSIFICATION OF DRUG
Protease Inhibitor

DESIRED COMPLETION DATE
March 4, 2011

NAME OF FIRM: **Merck (previously Schering Inc.) and Vertex**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: **Please see the attached document for questions, tables and figures**

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SHERLY ABRAHAM
02/07/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: February 4, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

Total no. of pages including cover:

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: February 4, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Pat Harrington, Ph.D., Clinical Virology Reviewer
Greg Soon, Ph.D., Statistics Team Leader
Wen Zeng, Ph.D., Statistics Reviewer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. Please respond to these requests as soon as possible, preferably prior to COB February 11, 2011.

1. In order to align primary efficacy analyses (SVR24) for each of the pending marketing applications, we have decided to use HCV RNA <25 IU/mL rather than limit of detection (LOD <10 IU/mL) as the cutoff for SVR24. This will affect only follow-up off treatment timepoints, and is not to be used as a surrogate for 'undetectable HCV RNA' for on-treatment or end-of-treatment timepoints. Please provide a reanalysis of SVR24 in the pivotal studies using the <25 IU/mL cutoff, and compare to the SVR24 analysis using the LOD (<10 IU/mL) cutoff.

2. We concur with your approach to determine SVR24 by imputing HCV RNA data from later follow-up off treatment timepoints, or follow-up week 12 if no other subsequent timepoints, in cases where the 24 week (or within the specified window) data off-treatment are missing.

3. Because we are changing the viral load cutoff for SVR24, determinations for the primary efficacy analysis, we need to confirm that subjects who had a low detectable, but unquantifiable HCV viral load measurement at follow-up Week 24 based on a sensitive viral load assay continued to remain virologically suppressed over the long term. Using available interim data from long term follow-up trial P05063, please characterize the long term virologic suppression of subjects who did not achieve SVR24 based on an LOD cutoff, but who would have achieved SVR24 if using the lower limit of quantification of the assay used (<25 IU/mL or <30 IU/mL, according to P05063 study report).

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CORRESPONDENCE. Please feel free to contact me at 301-796-3198 if you have any questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager

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/s/

SHERLY ABRAHAM
02/04/2011

From: Abraham, Sherly
Sent: Monday, January 31, 2011 4:39 PM
To: 'Chambers, Thomas'
Subject: RE: Boceprevir ClinPharm Request
[Dear Tom,](#)

Please find the request for clarification below from ClinPharm team. Please provide us this information by Monday, February 7, 2011. Please let me know if you need a teleconference to discuss this further:

As described in your biopharmaceutics summary document (2.7.1), acidification of samples prevents the interconversion of boceprevir diastereomers in plasma. In trials P03533, P03747, and P04486, plasma samples were not acidified before bioanalysis using methods SN04921 or SN03330. Please comment on whether interconversion between SCH534129 and SCH534128 might have occurred in these plasma samples. If so, what effect would interconversion have on the concentrations of SCH534128 reported in these trials? If stabilization was adequately achieved via freezing or placing samples on ice, why were subsequent methods introduced with the addition of acidification?

In the same trials, SCH503034 concentrations were directly measured by analyzing plasma samples using method SN03330. Please comment on the stability of SCH503034 in these plasma samples, given the instability of SCH534129 as described in the validation report for method SN04921. Please explain how the combination of diastereomers could be stable while one of the isomers is not stable, under similar storage conditions.

To help us better understand the issues related to analyte validation and stability of the 3 components (SCH534129, SCH534128 and SCH503034) across the various analytical methods, please expand on the background provided in 2.7.1 by fully describing the progression of your assay development, specifically addressing how interconversion of isomers and the stability of the individual diastereomers were addressed as the assay methods progressed. In addition, indicate how these issues affect the interpretation of PK data across studies.

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

From: Chambers, Thomas [mailto:thomas_chambers2@merck.com]
Sent: Monday, January 31, 2011 3:52 PM
To: Abraham, Sherly
Subject: RE: Boceprevir Pharmacometrics Request

Dear Sherly,

Please confirm with respect to request for Viral Load data for the trials indicated, that data for all subjects is needed, not just those for which PK sampling was also obtained?

If all Viral Load data are requested, is it necessary to create a flag for each sample that had a concomitant PK sample obtained?

Sincerely,

Tom
Thomas Chambers
Global Regulatory Affairs
Merck and Co., Inc
TEL: (276) 305-6722
FAX: (267) 305-6407
email: thomas_chambers2@merck.com

From: Abraham, Sherly [mailto:Sherly.Abraham@fda.hhs.gov]
Sent: Monday, January 31, 2011 11:43 AM
To: Chambers, Thomas
Subject: RE: Boceprevir Pharmacometrics Request

Dear Tom,

Please find the requested information below from our Pharmacometrics team. Please submit this info within one week (February 7, 2011):

Please provide us with the viral load versus time measurements for each patient treated in trial P03516 (data used for creating Figure 1 from the Phase 1 / 2 PK-PD report), P04487/P04531 (data used for Figure 6 from the Phase 1 / 2 PK-PD report), P03527, and P03648. Specifically, we request datasets for each trial with the following information:

- a) Study ID
- b) Unique subject ID (USUBJID)
- c) Treatment
- d) Important baseline factors (Body weight, BMI, Sex, Race, Age, Genotype, baseline viral load, liver disease status, prior treatment status etc.)
- e) Sample time relative to start of treatment
- f) Viral load matched to sampling time

Please confirm receipt of this and earlier correspondences.

Thanks,
Sherly

Notice: This e-mail message, together with any attachments, contains information of Merck & Co., Inc. (One Merck Drive, Whitehouse Station, New Jersey, USA 08889), and/or its affiliates Direct contact information

for affiliates is available at
<http://www.merck.com/contact/contacts.html>) that may be confidential,
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SHERLY ABRAHAM
01/31/2011

From: Abraham, Sherly
Sent: Monday, January 31, 2011 10:20 AM
To: 'Chambers, Thomas'
Subject: Boceprevir Virology Request

Dear Tom,

We have the following request for clarification of HCV genotypic resistance dataset formats.

Regarding all of the Phase 3 trial resistance datasets (P05101 and P05216) and the long-term follow-up resistance datasets (P05063) included in the boceprevir NDA, please confirm that our following assumptions are correct :

When amino acid substitutions/variants from reference were detected as mixtures with wild-type/reference amino acid sequences, they were reported in the electronic datasets as the 'variant' sequence. In other words, no mixtures of wild-type/variant sequences are reported as such, rather only the variant sequence is reported.

Even if the 'variant' amino acid sequence was detected as the minority species in a mixture with the wild-type/reference amino acid sequence, the 'variant' sequence was still the one reported in the electronic datasets.

We would appreciate an emailed response to this request as soon as possible, preferably by COB Tuesday, February 1, 2011. The response can then be subsequently submitted to the NDA.

Thanks,

Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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SHERLY ABRAHAM
01/31/2011

From: Abraham, Sherly
Sent: Wednesday, January 26, 2011 8:57 AM
To: 'Chambers, Thomas'
Subject: Boceprevir Pediatric Plan Submission. NDA 202-258
[Dear Tom,](#)

[Please provide me the requested information below by COB today:](#)

Please provide proposed dates for submission of pediatric protocols; and submission of pediatric study reports.

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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/s/

SHERLY ABRAHAM
01/26/2011

From: Abraham, Sherly
Sent: Monday, January 24, 2011 4:25 PM
To: 'Chambers, Thomas'
Subject: Stats Questions Discussed at Jan.24, 2011 T-Con

Attachments: Questions List for NDA202,258 from Stat.doc
[Hi Tom,](#)

[Please find the attached document containing questions from today's t-con. We would appreciate if you can respond to these item asap.](#)

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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/s/

SHERLY ABRAHAM
01/24/2011



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: January 20, 2011

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: January 20, 2011

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam mishra, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. In order to address your request for pediatric waiver and deferral, please submit the following information for our upcoming meeting with the CDER Pediatric Review Committee (PeRC). We request that this information be submitted no later than January 24, 2011:

1. Please submit the Pediatric Development Plan for boceprevir to your NDA.
2. Please submit any amendments/revisions (or requests for such) to the European Medicines Agency (EMA) Pediatric Investigation Plan (PIP), which was submitted previously under the IND 69,027.
3. Please complete the information on the attached form which is required for our upcoming Pediatric Review Committee (PeRC) meeting.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-796-3198 if you have any questions regarding the contents of this transmission .

Sherly Abraham, R.Ph.
Regulatory Project Manager

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/s/

SHERLY ABRAHAM
01/20/2011



NDA 202-258

INFORMATION REQUEST

Schering-Plough Corporation
Attention: Thomas Chamber, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-1099

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 Boceprevir, 200 mg Capsules.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

To facilitate our review of the manufacturing processes, please provide an unexecuted master batch record for the proposed commercial manufacturing processes for drug substance and drug product. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (Jeannie.David@fda.hhs.gov), and Sherly Abraham, Regulatory Project Manager the Office of New Drugs (Sherly.Abraham@fda.hhs.gov).

If you have any questions regarding this letter, call Jeannie David at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Acting Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

STEPHEN P MILLER
01/14/2011

From: Abraham, Sherly
Sent: Thursday, January 13, 2011 10:10 AM
To: 'Chambers, Thomas'
Subject: RE: BOCEPREVIR - Info Request

Attachments: HighlightsofClinicalPharmacology.doc
[Hi Tom,](#)

[Can you please complete this and return it asap. Please also submit this officially.](#)

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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/s/

SHERLY ABRAHAM
01/13/2011



NDA 202,258

FILING COMMUNICATION

Schering-Plough Corporation
Attention: Thomas Chamber, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-1099

Dear Dr. Chambers:

Please refer to your New Drug Application (NDA) dated November 10, 2010, received November 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for boceprevir 200 mg capsules.

We also refer to your submissions dated November 29, 2010, December 2, 2010, December 8, 2010, December 10, 2010 and December 15, 2010.

We remind you of our December 13, 2010, electronic facsimile request for an additional HCV genotype/subtype analysis. Please provide a timeline for completion of one of the suggested analyses and submission of the data to the NDA.

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 May 15, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 17, 2011.

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.

REQUIRED PEDIATRIC ASSESSMENTS

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

We acknowledge receipt of your request for a waiver of pediatric studies in children less than 3 years of age, for this application. Once we have reviewed your request, we will notify you if the waiver request is denied.

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

If you have any questions, call Sherly Abraham, R.Ph., Regulatory Project Manager, at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

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

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/s/

SHERLY ABRAHAM
12/22/2010

JEFFREY S MURRAY
12/28/2010



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: December 22, 2010

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: December 22, 2010

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Charles Cooper, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team:

We noticed the following regarding the vertical lab data set and the use of the min flag to identify the lowest post-baseline hemoglobin measurements for study 5216:

1. Please explain why there are more than one lab min flag for some patients. If there are multiple measures that are identical, please flag the earliest post-baseline measurement.
2. Please explain why 74 patients are missing a flag.
3. Please explain why some of the flagged measurements do not match what is reflected in the HgB min variable in (b) (4)
4. Please inform us if there are similar issues with the other studies.

Please address these concerns as soon as possible.

We are providing this above information via telephone facsimile for your convenience.

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CORRESPONDENCE. Please feel free to contact me at 301-796-3198 if you have any questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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/s/

SHERLY ABRAHAM
12/22/2010

REQUEST FOR CONSULTATION

TO (Office/Division):
**Office of Oncology Products
Division of Hematology Products**

FROM (Name, Office/Division, and Phone Number of Requestor):
**Sherly Abraham, OAP/DAVP
301-796-3198**

DATE December 21, 2010	IND NO. 69,027	NDA NO. 202,258	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT November 10, 2010
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NAME OF DRUG Boceprevir	PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG Protease Inhibitor	DESIRED COMPLETION DATE February 28, 2011
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NAME OF FIRM: **Schering Plough**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Boceprevir is the first direct antiviral agent under evaluation for treatment of chronic hepatitis C in combination with pegylated interferon and ribavirin. Anemia has been identified as a key safety issue with boceprevir use. This NDA was submitted as a rolling review, with the non-clinical and quality sections submitted on 9/30/10; and the rest of the NDA (including clinical components) on 11/10/10. This is an NME with a priority review, an Advisory Committee meeting on April 27, 2011, and a PDUFA goal date of May 13, 2011. Please see attachment.

Division of Antiviral Products (DAVP) would like Division of Hematology Products (DHP) to address the following questions:

- Sponsor has stated that the mechanism of the anemia associated with boceprevir use appeared to be non-hemolytic in nature. Please provide some insight into the possible mechanism of the anemia associated with boceprevir use?

- 3. Do you think Sponsor should await the final results of the ongoing study evaluating the use of erythropoietin in the management of anemia (b) (4)?
- 4. Has the Division observed or have been notified of any increased risk of arterial/venous thrombotic events, pure red cell aplasia events or any other significant adverse events associated with the erythropoietin use during the treatment of chronic hepatitis C?
- 5. Do you suggest any additional risk management activities in addition to Medication Guide to mitigate the risks associated with anemia? In you opinion, how frequently should hematology parameters be monitored in clinical practice setting, if boceprevir receives marketing approval.
- 6. Please share the Division's experience with any other products whose package inserts refer to the use of Erythropoietin.
- 7. Do you have any other recommendations to address this safety concern?

Please find the link to the submission below:
 \\CDSESUB1\EVSPROD\NDA202258\202258.ENX

SIGNATURE OF REQUESTOR Sherly Abraham, Project Manager, DAVP	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SHERLY ABRAHAM
12/21/2010

MEMORANDUM OF TELECON

DATE: December 20, 2010

APPLICATION NUMBER: NDA 202,258

BETWEEN:

Name: Schering, Inc

Representing: Schering, Inc

Thomas Chambers, Global Regulatory Affairs
Seth Thompson, Infectious Diseases Statistics
Patricia Egidio, Global Regulatory Operations
Peter Savino, Clinical Programming
Becky Liou, Clinical Programming
Heather Tang, Project Management
Ann Howelll, Global Regulatory Affairs
Samir Gupta, Drug Metabolism Pharmacokinetics
Margaret Burroughs, Clinical Research
Ruiyun Jiang, Infectious Disease Statistics
Ann O'henny, Global Regulatory Operations
Claudia Kassera, Clinical Pharmacology
Sharon Olmstead, Regulatory Global Affairs US Policy and International
Steven Kopytek, Safety Assessment

AND

Name: Division of Antivirals, Office of Antimicrobials
CDER
FDA

Debra Birnkrant, M.D., Division Director
Jeffrey Murray, M.D, MPH, Division Director
Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Reviewer
Chuck Cooper, M.D., Medical Reviewer
Sarah Connelly, M.D., Medical Reviewer
Jules O'Rear, Ph.D., Clinical Virology Team Leader
Pat Harrington, Ph.D., Clinical Virology Reviewer
Wen Zeng, Ph.D., Stats Reviewer
Ruben Ayala, Ph.D., Clinical Pharmacology

Shashi Amur, Ph.D., Pharmacogenomics Reviewer
Jeffry Florian, Ph.D., Pharmacometrics Reviewer
Sherly Abraham, R.Ph., Regulatory Health Project Manager

SUBJECT: Applicant Orientation Meeting

BACKGROUND: Schering submitted a new molecular entity NDA for boceprevir on November 10, 2010, for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (≥ 18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy. This meeting was scheduled to help the review team better orient to the content and format of the application.

ACTION POINTS:

- Schering will provide the missing PK-PD data.
- Schering will provide an explanation for why some subjects have more than one value in maximum/ minimum group in labchem domain and provide revised datasets.
- DAVP will request clarification on certain AIMS data.
- Schering will provide chemistry and hematology datasets, including subject identifier, upper and lower limits of normal, merged standard demographics and study phase information for Phase I individual studies.
- Schering will let us know which SAS programs were used to create the SAS datasets in the \C (b) (4) t subfolder from the raw CRF datasets in (b) (4) subfolder.

Sherly Abraham, R.Ph.
Regulatory Health Project Manager

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/s/

SHERLY ABRAHAM
12/22/2010



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products**

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: December 15, 2010

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: December 15, 2010

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Sarah Connelly, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team:

Please submit copies of the Protocol 03523, 03659, 05101, and 05216 investigator-signed financial disclosure forms for (a) all investigators reporting "significant payments of other sorts" on Form 3455, and (b) all investigators not reporting payments of other sorts from Schering-Plough, but with evidence to the contrary based on disclosure forms signed by Schering-Plough and submitted with the NDA.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
12/15/2010



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

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DATE: December 13, 2010

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Company: Schering Corp	Division of Antiviral Products
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ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: December 13, 2010

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH: Jules O'Rear, Ph.D., Clinical Virology Team Leader
Patrick Harrington, Ph.D., Clinical Virology Reviewer

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team:

We have concerns about your approach to determining HCV genotype/subtype in P05216 and P05101:

- The TRUGENE™ assay, while commercially available, is not acceptable to compare efficacy for patients infected with HCV subtype 1a versus 1b.
- Your secondary genotype/subtype analysis approach, while potentially an improvement over the TRUGENE™ assay, is unconventional, was not universally applied to all subjects, and is highly unlikely to be used to determine HCV genotype/subtype in clinical practice. Furthermore, we do not agree with your rationale of 'inferring' HCV subtype indirectly based on successful RT-PCR amplification of the NS3/4A gene, and no performance data were provided to support this rationale.

Please conduct at least one of the following analyses for pre-treatment samples from subjects enrolled in P05216 and P05101, and submit the data to the NDA as soon as possible. The same analysis should be conducted universally for all study subjects (note that the five HCV genotype 6 subjects-by NS5B phylogenetic analysis-can be excluded).

- NS5B phylogenetic analysis, for those subjects not already analyzed by this method

- NS3/4A phylogenetic analysis; this can be conducted using available baseline data collected for resistance analysis purposes
- Line-probe assay targeting 5'-NCR + Core (e.g., VERSANT® HCV Genotype 2.0)

The data should be submitted as individual electronic datasets (1 dataset for each trial). Please include the following line item information in each dataset:

- Subject number
- Treatment arm
- SVR24 result: Y or N
- HCV genotype/subtype method #1: TRUGENE
- HCV genotype/subtype method #1 result: 1a, 1b, 1, not available, etc.
- HCV genotype/subtype method #2: NS3-4A/NS5B (i.e., 'secondary' analysis summarized above)
- HCV genotype/subtype method #2 result: 1a, 1b, 1, not available, etc.
- HCV genotype/subtype method #3: (NS5B phylogenetic analysis, NS3/4A phylogenetic analysis, or LiPA 5'-NCR + Core)
- HCV genotype/subtype method #3 result: 1, 1a, 1b, not available, etc.
- Flag to identify subjects with discordant HCV genotype/subtype data generated from methods #2 and #3

Also, this submission should include a report describing the assay methodology used for genotype/subtype method #3, if different from the NS5B phylogenetic assay used by

(b) (4)

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
12/13/2010

DSI CONSULT: Request for Clinical Inspections

Date: December 8, 2010

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Antoine El Hage, Ph.D., Pharmacologist, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Poonam Mishra, M.D., Clinical Reviewer, DAVP
Mary Singer, M.D., Clinical Team Leader, DAVP

From: Sherly Abraham, R.Ph., Regulatory Project Manager, DAVP

Subject: Request for Clinical Site Inspections

I. General Information

Application#: NDA 202,258

Applicant/ Applicant contact information (to include phone/email):

Thomas Chambers, M.D.
Director, Global Regulatory Affairs

Schering Corporation
2000 Galloping Hill Rd

Kenilworth, NJ 07033
thomas_chambers2@merck.com

TEL: (267) 305-6722
FAX: (267) 305-6407

Drug Proprietary Name: Pending

NME or Original BLA (Yes/No): Yes

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of chronic Hepatitis C

PDUFA: May 15, 2011

Action Goal Date: May 13, 2011

Inspection Summary Goal Date:

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Enrolled	Indication
Clinical Site # 36 McCone, Jonathan M.D. Mount Vernon Endoscopy Center 8109 Hinson Farm Road, #515 Alexandria VA, 22306 USA	P05216	36	Treatment of chronic Hepatitis C
Clinical Site # EU - 117 Bruno, Savino M.D. Ospedale Fatebenefratelli Oftalmico Unita Complessa di Epatologia Corso di Porta Nuova, 23 Milano 20121 Italy	P05216	23	Treatment of chronic Hepatitis C
Clinical Site # FRA - 7 Bourliere, Marc M.D. Ben Ali, Souad M.D. (CO-PI) Hopital Saint Joseph 26 Boulevard de Louvain Service d'HepatoGastroEnterologie Marseille Cedex 08, 13285 France	P05101	14	Treatment of chronic Hepatitis C
Clinical Site # 26 Gordon, Stuart M.D. Henry Ford Health System 2799 W. Grand Blvd Detroit MI, 48202 USA	P05101	19	Treatment of chronic Hepatitis C

III. Site Selection/Rationale

Rationale for DSI Audits

This NDA application is for an NME. As such, a DSI audit is warranted.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): The Division would like to have at least 1 domestic site inspected.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify):
 - Enrollment of large numbers of study subjects;As this is a new molecular entity and some of the limited experience with this drug has been from foreign sites; it would be desirable to include foreign sites in the DSI audits to verify the quality of conducted study.

IV. Tables of Specific Data to be Verified (if applicable)

Page 4-Request for Clinical Inspections

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, Sherly Abraham, R.Ph. (RPM) at 301-796-3198 or Poonam Mishra, M.D. (Clinical Reviewer) at 301-796-4274

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for
5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

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SHERLY ABRAHAM
12/08/2010



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: December 8, 2010

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
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ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: December 8, 2010

SPONSOR: Schering Corporation

NDA: 202,258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH: Mary Singer, M.D., Ph.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer
Greg Soon, Ph.D., Statistics Team Leader
Wen Zeng, Ph.D., Statistics Reviewer

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. Please also refer to your electronic facsimile dated December 5, 2010, requesting clarification on applicant orientation meeting. Your questions are in regular font and DAVP responses are in bold:

In regard to review of the NDA components, including the datasets, will it be necessary to view the actual content of the documents and the contents of the datasets, or are views of the contents of the folders sufficient?

Please be prepared to navigate any document and to open any dataset, as necessary.

For instance, will you be needing us to display the detailed contents of the SAS transport files and the tables for the AIMS including review of the format and layout of the data included in these files?

It would be very helpful if you could explain the relationship between the three sets of datasets submitted:

- **In the original NDA submission, datasets in the analysis (b) (4) subfolder and datasets in the (b) (4) / subfolder. The datasets in the legacy subfolder seem to be the raw CRF data.**

- **Datasets in the analysis/ subfolder in the original NDA submission and new AIMS submission. We noticed that sizes of files were increased in AIMS datasets. Please let us know which variables were added.**
- **In the new AIMS submission, three vertical displayed datasets were included, [REDACTED] (b) (4). Please give a detailed tour of these three datasets and how to link them back to their horizontal displayed datasets. [REDACTED] (b) (4)**

Additional question that can be discussed at the meeting:

In addition to a general introduction to the data, and navigation of the application and reviewer aids, etc, we would be interested in hearing how the AE coding (syndrome vs. symptom, etc) was done, and whether it was done consistently across the application. We'd also like to hear specifically how deaths are presented in the application. For example, in the ISS dataset, there are 10 deaths reported; but in Table 24 in the ISS (Adverse Events Resulting in Death), only 8 deaths are listed. We may have additional questions regarding the datasets as we review them.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
12/08/2010



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Office of Antimicrobial Products

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: December 8, 2010

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

**THROUGH: Mary Singer, M.D., Medical Team Leader
Poonam Mishra, M.D., Medical Officer**

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team:

Please submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It will be most helpful if this is submitted 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).

Please also submit the "Sponsor UTD Dictionary" which has been referenced in some studies and also provide any other dictionaries that have been used. Please provide an explanation for how the different dictionaries were integrated into the ISS datasets, with a focus on the implications for analyses across studies.

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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SHERLY ABRAHAM
12/08/2010



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Office of Antimicrobial Products

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ELECTRONIC MAIL CORRESPONDENCE

Department of Health and Human Services
Public Health Service
Division of Antiviral Products

DATE: December 8, 2010

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH: Jules O'Rear, Ph.D., Clinical Virology Team Leader
Patrick Harrington, Ph.D., Clinical Virology Reviewer

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team. Please provide responses to these requests by COB Thursday, December 9, 2010.

1. Please confirm our understanding of your HCV genotype/subtype analysis methods used for the Phase 3 boceprevir trials P05101 and P05216:
 - a. TRUGENETM (5'-NCR target) assay was used for screening and stratification.
 - b. Samples identified as subtype 1a by TRUGENETM assay were subjected to the following secondary analysis:
 - Subtype-designed primers for NS3/4A RT-PCR amplification were used for resistance assessments. If RT-PCR amplification using subtype 1a-designed primers was successful, then the sample was considered subtype 1a. For these instances, NS3/4A RT-PCR amplifications using subtype 1b-designed primers were not conducted.
 - If NS3/4A RT-PCR amplification with subtype 1a-designed primers was unsuccessful, then genotype 1b-designed primers were used; if amplification was successful then sample was considered subtype 1b.
 - NS5B RT-PCR, nucleotide sequencing, and phylogenetic analyses were not conducted for subjects identified as subtype 1a by TRUGENETM assay.

- c. Samples identified as subtype 1b (or non-determined subtype) by TRUGENE™ assay were subjected to the following secondary analysis:
- NS5B RT-PCR, nucleotide sequencing, and phylogenetic analysis.
2. For the resistance datasets for P05101 and P05216, there are 11 subjects not included: 1 subject for P05101 and 10 subjects for P05216. It is our understanding that these subjects were either infected with non-genotype 1 HCV or had an undetermined HCV genotype. Please provide a listing of these subjects, the genotype/subtype analysis methods used, and the genotype/subtype results (indicate if analysis failed or genotype undetermined, etc., as appropriate). Also, if NS3 or NS3/4A sequence analyses were conducted for any of these 11 subjects, please submit the available data; a separate resistance dataset for such subjects is acceptable (i.e., data do not need to be merged with other datasets).

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Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products



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SHERLY ABRAHAM
12/08/2010

From: Abraham, Sherly
Sent: Friday, December 03, 2010 11:38 AM
To: 'Chambers, Thomas'
Subject: RE: Applicant Orientation Presentation Meeting
Dear Tom,

Please see our responses in red to your questions below:

As far as the conduct of the meeting, we would also like to know if you want to review all components of the NDA, including Quality and Nonclinical sections, or if this should be more focused on the Clinical documents and the associated data sets?

We'd like them to review all of the components except Quality/CMC, including the datasets.

For instance, do you envision the meeting to proceed with us stepping through the navigation of the entire eCTD, with explanation of the document folders and data folders and links, while answering questions along the way? **Yes.**

Also, are there any specific questions or issues that your review team will be particularly concerned about with respect to the documents and data sets?

Not at this time; but we will forward any specific questions prior to the Orientation Meeting if we have any.

Thanks,
Sherly

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room(6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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/s/

SHERLY ABRAHAM
12/03/2010

From: Abraham, Sherly
Sent: Thursday, December 02, 2010 12:38 PM
To: Chambers, Thomas
Cc: 'Giovinazzo, Lisa A'; MacDonald, Laurie
Subject: RE: BOCEPREVIR NDA AC Meeting
[Dear Tom,](#)

[Please note that Boceprevir AC meeting has been tentatively scheduled for April 27, 2011. Designated Federal Official \(DFO\) Paul Tran will contact with more details.](#)

[Thanks,](#)
[Sherly](#)

Sherly Abraham, RPh
Regulatory Project Manager
10903 New Hampshire Ave., Bldg 22, Room (6369)
Silver Spring, MD 20903
(301) 796-3198
Sherly.Abraham@fda.hhs.gov

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/s/

SHERLY ABRAHAM
12/02/2010



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

RECORD OF ELECTRONIC MAIL CORRESPONDENCE

DATE: November 30, 2010

To: Thomas Chambers	From: Sherly Abraham, R.Ph.
Company: Schering Corp	Division of Antiviral Products
Fax number: (267) 305-6407	Fax number: 301-796- 9883
Phone number: (267) 305-6722	Phone number: 301-796-3198

Total no. of pages including cover:

Comments:

Please acknowledge the receipt of the communication

Document to be mailed: YES NO

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ELECTRONIC MAIL CORRESPONDENCE

**Department of Health and Human Services
Public Health Service
Division of Antiviral Products**

DATE: November 30, 2010

SPONSOR: Schering Corporation

NDA: 202, 258

DRUG: Boceprevir

TO: Thomas Chambers, M.D.

FROM: Sherly Abraham, R.Ph.

THROUGH:

Mary Singer, M.D., Medical Team Leader

Poonam Mishra, M.D., Medical Officer

Sarah Connelly, M.D., Medical Officer

Please refer to your submission dated November 10, 2010, for a new NDA for Boceprevir for treatment of chronic hepatitis C. The following comments are being conveyed to you on behalf of the review team. Please provide us the clarification of this issue by Friday, December 3, 2010.

In the NDA submission module 1, section 1.3.4, it is reported that (b) (6) did not disclose that he, his spouse and dependent children have a financial arrangement with Schering-Plough, whereby the value of compensation could be influenced by the outcome of the study. However, (b) (6) did disclose interest in a sister boceprevir study.

Please clarify the type of financial arrangement that (b) (6) had with Schering-Plough, and specifically how the value of compensation could be influenced by the outcome of the study.

We are providing this above information via telephone facsimile for your convenience.
**THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL
CORRESPONDENCE.** Please feel free to contact me at 301-796-3198 if you have any
questions regarding the contents of this transmission.

Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products

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/s/

SHERLY ABRAHAM
11/30/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **DDMAC**

FROM (Name, Office/Division, and Phone Number of Requestor):
Sherly Abraham, OAP/DAVP, 301-796-3198

DATE
November 24, 2010

IND NO.
69,027

NDA NO.
202,258

TYPE OF DOCUMENT
New NME NDA

DATE OF DOCUMENT
November 10, 2010

NAME OF DRUG
Boceprevir

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG
Protease Inhibitor

DESIRED COMPLETION DATE
March 1, 2011

NAME OF FIRM: **Schering-Plough**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This new NME NDA for Boceprevir was received on November 15, 2010, for treatment of Chronic Hepatitis C. The PDUFA goal date is May 15, 2010.

General review PI, Medguide, carton and container label, and REMS for promotional claims.

Here is the location of the NDA:

The network location is : \\CDSESUB1\EVSPROD\NDA202258\202258.ENX

SIGNATURE OF REQUESTOR
Sherly Abraham,

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Reference ID: 2868794

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/s/

SHERLY ABRAHAM
11/24/2010

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/s/

SHERLY ABRAHAM
11/24/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Devi Kozeli**
Div of Cardiovascular Renal Prod (QT IRT)

FROM (Name, Office/Division, and Phone Number of Requestor):
Sherly Abraham, OAP/DAVP
301-796-3198

DATE
November 22, 2010

IND NO.
69,027

NDA NO.
202,258

TYPE OF DOCUMENT
New NDA

DATE OF DOCUMENT
November 15, 2010

NAME OF DRUG
Boceprevir

PRIORITY CONSIDERATION
ASAP

CLASSIFICATION OF DRUG
Protease Inhibitor

DESIRED COMPLETION DATE
March 17, 2011

NAME OF FIRM: **Schering Plough**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|--|--------------------------------------|
| <input checked="" type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|--|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: On April 1, 2008, DAVP submitted a QT IRT consult to Division of Cardiovascular Products for IND 69,027 for review of the TQTc study (submitted March 25, 2008). The consult was cancelled by IRT and deferred until the time of the NDA submission since the Sponsor was not able to provide the additional requested data.

On November 15, 2010, Schering submitted the NDA for boceprevir. This submission is a priority NDA and the PDUFA goal date for this NDA is May 15, 2011. The Division is requesting IRT review of the thorough QTc study (P04489).

Here is the electronic link to the submission:

Reference ID: A67151
The network location is : \\CDSESUB1\EVSPROD\NDA202258\202258.ENX

SIGNATURE OF REQUESTOR Sherly Abraham, Project Manager, DAVP	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SHERLY ABRAHAM
11/22/2010



NDA 202,258

NDA ACKNOWLEDGMENT

Schering-Plough Corporation
Attention: Thomas Chamber, M.D.
Director, Global Regulatory Affairs
P.O. Box 1000, UG2D-68
North Wales, PA 19454-1099

Dear Dr. Chambers:

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

Name of Drug Product: Boceprevir, 200 mg Capsules

Date of Application: November 10, 2010

Date of Receipt: November 15, 2010

Our Reference Number: NDA 202,258

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 January 14, 2011, 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.

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

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

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

If you have any questions, call me, at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

Sherly Abraham, R.Ph
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SHERLY ABRAHAM
11/18/2010



NDA 202, 258

NDA PRESUBMISSION ACKNOWLEDGEMENT

Schering-Plough Corporation
Attention: Ursula Marek, Pharm.D.
Manager, Global Regulatory Affairs
2000 Galloping Hill Road, K6-1 Mailstop
1350 Kenilworth, NJ 07033-0530

Dear Dr. Marek:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: Boceprevir, 200 mg Capsules

Date of Submission: September 30, 2010

Date of Receipt: September 30, 2010

Our Reference Number: NDA 202,258

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning 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

If you have any questions, call Sherly Abraham, R.Ph., Regulatory Project Manager, at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

Sherly Abraham, R.Ph.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

SHERLY ABRAHAM
10/12/2010



IND 69,027

MEETING MINUTES

Schering-Plough Corporation
Attention: Thomas Chambers
Manager, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Dear Mr.Chambers:

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

We also refer to the meeting between representatives of your firm and the FDA on September 29, 2010. The purpose of the meeting was to discuss the format and content of the planned NDA for boceprevir that is being developed for use in combination with the current standard-of-care for the treatment of chronic hepatitis C (CHC) in treatment-naïve and treatment-experienced adults infected with Genotype 1 virus, without liver decompensation.

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

If you have any questions, call Sherly Abraham, R.Ph., Regulatory Project Manager, at (301) 796-3198.

Sincerely,

{See appended electronic signature page}

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 29, 2010
Meeting Location: White Oak Building 22
Room 1313

Application Number: 69,027
Product Name: Boceprevir
Indication: Treatment of Genotype 1 Hepatitis C viral infection
Sponsor/Applicant Name: Schering-Plough Corporation

Meeting Chair: **Russell Fleischer, PA-C**

Meeting Recorder: **Sherly Abraham, R.Ph.**

FDA ATTENDEES

Debra Birnkrant, M.D., Director, Division of Antiviral Products, DAVP
Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Kendall Marcus, M.D., Safety Deputy Director, DAVP
Linda Lewis, M.D., Medical Team Leader, DAVP
Russell Fleischer, PA-C., Medical Officer, DAVP
Mary Singer, M.D., Medical Team Leader, DAVP
Poonam Mishra, M.D., Medical Officer, DAVP
Hanan Ghantous, Ph.D., DABT, Pharmacology/Toxicology Team Leader, DAVP
Christopher Ellis, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Wen Zeng, Ph.D., Statistics Reviewer, DAVP
Kelly Reynolds, Pharm.D., Clinical Pharmacology Deputy Director, DAVP
Sarah Robertson, Pharm.D., Clinical Pharmacology Team Leader, DAVP
Stanley Au, Pharm. D., Clinical Pharmacology Reviewer, DAVP
Ruben Ayala, Pharm.D., Clinical Pharmacology Reviewer, DAVP
Shashi Amur, Ph.D., Genomics Reviewer, OCP
Jeffrey Florian, Ph.D., Pharmacometrics Reviewer, OCP
Julian O'Rear, Ph.D., Clinical Virology Team Leader, DAVP
Patrick Harrington, Ph.D., Clinical Virology Reviewer, DAVP
Lisa Naeger, Ph.D., Clinical Virology Reviewer, DAVP
Mark Seggel, Ph.D., Quality Reviewer, ONDQA
Dorota Matecka, Ph.D., Quality Team Leader, ONDQA
David Roeder, Associate Director Regulatory Affairs, OAP
Victoria Tyson, Chief, Project Management Staff, DAVP
Sherly Abraham, R.Ph., Regulatory Project Manager, DAVP

Venessa Perry, Regulatory Project Manager, DAVP
Brantley Dorch, Project Manager, OSE
Michael Pacanowski, Genomics Acting Team Leader, OCP
Jiang Liu, Pharmacometrics Reviewer, OCP
Antoine El-Hage, DSI Reviewer, OC

SPONSOR ATTENDEES

Janice Wahl- Clinical Research
Janice Albrecht- Clinical Research
Clifford Brass-Clinical Research
Claudia Kasserra-Clinical Pharmacology
Navdeep Boparai- Statistics
Stephan Kopytek- Drug Safety
Robert Ralston- Discovery
Adrian Dana- Pharmacovigilance
Nancy Ruiz- Project Management
Scott Korn-Regulatory
Thomas Chambers- Regulatory
Ann Howell- Regulatory
Laurie MacDonald- Regulatory
Ekopimo Okon Ibia- Regulatory

BACKGROUND

On June 17, 2010, Schering-Plough Corporation submitted a request for a Type B, pre-NDA face-to-face meeting to IND 69,027, boceprevir capsule, for the treatment of Chronic Hepatitis C virus infection; Genotype 1, treatment-naïve and treatment-experienced adults. Schering is developing boceprevir for use in combination with the standard-of-care. The purpose of this meeting was to discuss the format and content of the upcoming new molecular entity NDA. DAVP sent preliminary responses to the questions posed in the briefing package to Schering-Plough on September 27, 2010. Although all of the questions were discussed during the meeting, it primarily focused on questions one and nine. Schering-Plough's questions are in bold followed by DAVP's responses and discussion in italics.

2. DISCUSSION

A. Clinical Data

Question 1

As previously discussed with the Agency at the boceprevir Clinical Development Meeting on November 7, 2007, two pivotal Phase 3 trials have been conducted to support the registration of boceprevir for the proposed indication; one each in treatment-naïve (n=1097) and treatment failure (n=403) patient populations. In both studies, the addition of boceprevir (800 mg TID) to

treatment with peginterferon alfa-2b (1.5 µg/kg/week) plus ribavirin (600-1,400 mg/day) significantly increased the proportion of patients who achieved a sustained virologic response (undetectable HCV-RNA levels 24 weeks after the end of treatment) compared to control groups that received peginterferon alfa-2b plus ribavirin alone. These results are further supported by two Phase 2 studies; one in treatment-naïve subjects (n=598) and one in null responders (n=357).

The intended indication is as follows:



Does the Agency agree that efficacy and safety data from the two pivotal Phase 3 studies together with the Phase 2 data are adequate to support licensure for the proposed indication?

We acknowledge that the addition of boceprevir to pegylated interferon α -2b and ribavirin combination therapy for 28 or 44 weeks appears to substantially increase SVR rates in both treatment-naïve and certain well-defined treatment-experienced subjects. The final decision on the adequacy of the data to support the proposed indication will be a review issue. Further, the final wording of the indication, including any important usage caveats, will also be a review issue.

The efficacy of a Hepatitis C Virus (HCV) Direct Acting Antiviral (DAA) in combination with Peg-IFN α /RBV is clearly related to previous virologic responses to Peg-IFN α /RBV combination therapy. Therefore, healthcare providers and patients should be fully aware of the specific patient populations in whom boceprevir efficacy has been established. In the phase 3 boceprevir studies, efficacy of boceprevir has not been established in patients who had a "null response" ($< 2 \log_{10}$ IU/mL reduction in HCV RNA at week 12) to previous Peg-IFN α /RBV therapy. It may be appropriate to describe SVR results by virologic responses during the lead-in period, but the response during the lead-in period should not be used as a surrogate to classify someone as a "null responder" because it is a misrepresentation of the term.

We currently recommend using the following definitions for describing virologic responses in subjects who failed previous Peg-IFN α /RBV therapy:

Null Responder: $< 2 \log_{10}$ IU/mL reduction in HCV RNA at week 12 of Peg-IFN α /RBV

Partial Responder: $\geq 2 \log_{10}$ IU/mL reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with Peg-IFN α /RBV

Responder Relapser: HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up.

Schering was asked to provide an analysis of virologic response for each of these treatment-failure subgroups, based on prior response to Peg-IFN/RBV therapy.

Further, Schering was asked to clarify the patient population studied in Phase 2 clinical trial P03659. According to our review records this trial included both previous Peg-IFN α /RBV “partial responders” ($\geq 2 \log_{10}$ IU/mL plasma HCV RNA decline after 12 weeks of treatment, but never achieving undetectable HCV RNA), and previous “null responders” ($< 2 \log_{10}$ IU/mL plasma HCV RNA decline after 12 weeks of treatment).

Discussion:

Schering agreed to use the definitions proposed for null and partial responders. Schering evaluated pegylated interferon/ribavirin responsiveness from the IDEAL trial, and found a high concordance between Week 4 $< 1 \log_{10}$ IU/mL decline and Week 12 $< 2 \log_{10}$ IU/mL decline in predicting failure to achieve SVR. Schering stated the response rates in subjects who received a delayed start were numerically better in the Phase 2 treatment-naïve trial. DAVP expressed general concern with using the term “null responder” in describing patient populations in the two completed Phase 3 trials, as “null responders” to previous treatment were not included in the trials, and noted that it has been used in abstracts public presentations such as at the AASLD meeting. The sponsor replied that guidelines for AASLD are less strict, and agreed to use terms such as “poorly interferon responsive” rather than “null responder” when describing patients’ virologic responses during pegylated interferon/ribavirin lead-in phases.

The results of the SPRINT-2 trial were discussed and Schering stated they were able to increase the SVR rate using Response Guided Therapy (RGT), in subjects who had $< 1 \log_{10}$ drop at Week 4 during the SOC lead-in period, with the addition of boceprevir to SOC. The results from both Phase 3 trials show that treatment-naïve and treatment-experienced subjects benefited by adding boceprevir to background therapy. Schering plans to compare the week 4 virologic responses to prior Peg-IFN/RBV to the week 4 responses observed during retreatment with Peg-IFN/RBV in Respond 2. The DAVP asked Schering to include a breakdown of the response at Week 36 and Week 48 using RGT for the subjects who achieved an SVR and for those who didn’t. The DAVP also requested the sponsor include the mean time since previous SOC therapy for the Phase 3 trial in previous treatment failures. Schering agreed to include these data and stated all SVR data are based on the whole regimen. Schering asked what the caveats for use might be in the Indications and Usage section. At this time the DAVP can not comment on the caveats for use.

B. Priority Review

Question 2

The Sponsor considers that boceprevir offers a significant improvement over the current standard of care for the treatment of CHC and therefore plans to request priority review. Currently, treatment of CHC consists of therapies to stimulate the immune system and interfere in a non-specific manner with HCV replication. There is clear need for new strategies for the treatment of

CHC. Boceprevir is a novel peptidomimetic NS3/4A protease inhibitor that has potent antiviral activity in vitro, and in patients with genotype 1 disease has produced significantly higher rates of SVR than has standard of care.

Does the Agency agree that boceprevir meets the criteria for a priority review?

DAVP agrees that the boceprevir NDA meets the criteria for a priority review.

Discussion:

Schering commented that the last piece of the rolling NDA will be submitted by November 12, 2010. DAVP mentioned that Advisory committee meeting will be held likely in April 2011. A filing letter will be issued by Day 60 since boceprevir NDA will have a priority review.

C. Labeling

Question 3





(b) (4)

Does the Agency agree with the proposed

(b) (4)



(b) (4)

In

order to support labeling for erythropoietin alfa use, data from an adequate and well controlled prospective trial demonstrating benefit of erythropoietin alfa use in increasing SVR rates or demonstration of improvement in anemia are recommended.

Please clarify when the final study results of the ongoing study P06086 will be available.

Discussion:

Study P06086 has 668 patients enrolled and the initial study results of this ongoing study will be available in January 2011. [REDACTED] (b) (4)

[REDACTED]. *The Division raised the issue that EPO use in pivotal trials was up to the individual investigator's discretion and would like to see the data from these studies with a breakdown of the SVR for subjects who were treated with EPO versus subjects who did not receive EPO.* [REDACTED] (b) (4)

[REDACTED] *The inclusion of recommendations for EPO use in the label will be a review issue.*

Question 4

The pivotal Phase 3 boceprevir studies utilized early virologic response data to shorten the length of treatment for 'early responders.' This Response Guided Therapy (RGT) paradigm provides for shorter treatment durations for a significant proportion of the HCV genotype 1 population.

The Sponsor proposes to include RGT guidelines for treatment duration in the Dosage and Administration section of the label. These guidelines will closely follow the guidelines for RGT included in the pivotal boceprevir Phase 3 clinical protocols. A draft of the text to be included in the label is provided below.

[REDACTED] (b) (4)

(b) (4)



Based on the summary data, does the Agency agree it is reasonable to propose RGT guidelines as part of the Dosage and Administration section of the package insert, recognizing that final labeling can only be agreed upon once the review is complete?

The decision regarding a response guided therapy (RGT) approach and any subsequent guidelines in the package insert will be a review issue.

DAVP noted that for both Phase 3 trials there was a small but consistent trend of greater SVR rates in non-RGT arms relative to the RGT arms in many of the various subgroups presented, particularly for subjects who likely had reduced responsiveness to Peg-IFN α -2b/RBV background therapy. Any trend of a minor reduction in SVR rate is important to consider because most subjects who experience virologic failure (relapse, breakthrough, etc.) will likely have an HCV population that is highly enriched with NS3/4A protease inhibitor-resistant variants that can persist for years.

If guidelines for RGT are included in labeling, it is likely that a more simplified approach to such recommendations will be needed.

Discussion:

If the guidelines for RGT are included in the labeling, the Division recommended using a simplified approach.

The DAVP noted the SVR rates appeared lower with RGT compared to non-RGT and asked Schering to provide an explanation for the divergence. Schering responded that the apparent lower responses with RGT were due to differences in baseline prognostic factors.

Schering has IL28B data in about 60% of patients from the two Phase 3 clinical trials and will conduct a retrospective analysis. IL28B data is being collected in all studies now. Schering will not provide specific identifier data associated with the genotype data due to confidentiality concerns.

Question 5

REMS/Medication Guide

According to FDA's Guidance Document: Guidance for Industry Format and Content of Proposed Risk Evaluation Mitigation Strategies (REMS), REMS Assessments, and REMS Modification (Sept 2009) a Medication Guide is required for a product if the FDA determines that one or more of the following circumstances exist:

The drug product is one for which patient labeling could prevent serious adverse effects.

1. The drug product is one that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or to continue to use the product.
2. The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The Sponsor is proposing a Risk Evaluation Mitigation Strategy for boceprevir which will include a Medication Guide. The Medication Guide will include information on the safety profile of boceprevir including information on anemia and drug interactions.

Does the Agency agree with the submission of a Medication Guide only REMS with the boceprevir NDA?

We agree that a Medication Guide will be required for boceprevir based on its safety profile and it seems reasonable to propose a REMS consisting of a Medication Guide. Please submit the proposed REMS and Medication Guide in your application. However, a complete review will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

Discussion:

The Division assured Schering that a REMS review will not impact the timelines for review of the application. Medication Guide and Assessment timelines are expected to be included in the NDA.

D. Submission Contents

Question 6

As part of the NDA, the Sponsor plans to include a Risk Management Plan (RMP) in Module 1. The RMP will be formatted using the EU-RMP template (Appendix 3 of the EMEA Guideline on Risk Management Systems for Medicinal Products for Human Use EMEA/CHMP/96268/2005).

Does the Agency agree that the EU-Risk Management Plan template/format will suffice as the RMP to be included in Module 1 of the NDA?

DAVP agrees with your proposal.

Question 7

The sponsor's NDA will be provided in an electronic format with an XML backbone, following the recommended folder organization and file names per ICH2: Electronic Technical Document Specification and organized according to ICH Guidance: M4 Organization of the CTD. A draft

Table of Contents, including non-clinical and clinical study reports for the eCTD is included in [Appendix 6](#).

Case report forms (CRFs), in addition to safety narratives, will be provided for all deaths, serious adverse events, discontinuations due to adverse events, and medically significant events from all of the completed Phase 1 and 2 studies at the time of NDA filing. For the completed pivotal Phase 3 studies (P05101 and P05216) case report forms will be submitted for all study subjects. For any ongoing studies at the time of NDA filing, only safety narratives will be provided for deaths and for events deemed medically significant (case report forms will not be provided).

Does the Agency agree that the overall content and format of the NDA, as presented in the draft Table of Contents, is acceptable?

The NDA should also include narratives for all deaths, serious adverse events, discontinuations (regardless of relatedness to study drug) in addition to the case report forms from the completed pivotal Phase 3 studies.

Please clarify whether SAS transport files will be provided for ongoing studies P05101, P05216, P03523, and P03659. In section 5.3.7.2 of NDA contents, it states that "SAS transport files will not be provided for ongoing studies (P05101, P05216, P03523, and P03659)."

Please provide SAS programs for generating efficacy datasets, and SAS programs for analyzing the primary efficacy endpoint and key secondary efficacy endpoints.

Discussion:

Schering will provide narratives for all deaths, serious adverse events, discontinuations (regardless of relatedness to study drug) in addition to case report forms from the completed pivotal Phase 3 studies. Schering also stated that they will provide the SAS transport files for P05101 and P05216, but not for studies P03523 and P03659.

Schering agreed to provide SAS programs for generating efficacy datasets and analyzing the primary efficacy endpoint and key secondary efficacy endpoints.

Question 8

As included in correspondence with the Agency, (August 9, 2010; SN 374) IL28B genotype testing was an optional test in the pivotal Phase 3 studies (P05101 and P05216). Samples are only available from a total of approximately 61 subjects from both studies. The exploratory analyses of the IL28B genotype data will not be included in the individual clinical study reports for the P05101 and P05216 studies or in the ISE/ISS for the boceprevir NDA, but will be included as a separate report in Module 5 of the NDA where the data is combined from both studies in order to get higher precision for the estimates.

Does the agency agree with the placement of the IL28B genotype data within the NDA?

Please clarify whether IL28B genotype data is available for 61 patients (as stated in the Pre-NDA briefing document, pages 13-14) or in 61% of the subjects (n=912) from the Phase 3 clinical trials (as stated in the response to FDA electronic mail correspondence dated July 15, 2010). If 61% of subjects had IL28B testing performed, please provide analyses for the two studies separately in addition to the combined analysis. Please also include all available individual subject IL28B genotype data in the electronic HCV resistance datasets.

Discussion:

Schering clarified that IL28B genotype data are available for 62% of the patients in the treatment-naïve study and 66% in the treatment failure study, and will provide both separate and combined analyses. Schering will not provide the genotype data at the time of filing but will submit a separate report in Module 5 of the NDA. The IL28B delinked database only contains demographics and efficacy information in addition to IL28B data. Because the IL28B data will be de-identified, genotypic resistance data will not be linked with the IL28B data.

Question 9

Mutation data will be described in the individual clinical study reports for the pivotal Phase 3 studies (P05101 and P05216), in addendum reports to the Phase 2 clinical study reports (P03659 and P03523), and in the long-term follow-up study report (P05063) submitted with the NDA. In addition, this information will be summarized in Section 5.3.5.3 - Integrated Summary of Efficacy in Module 5 of the boceprevir NDA.

Does the Agency agree with the placement of the mutation data?

- a. *For the pre-NDA meeting, please confirm our understanding of your plans for submitting HCV resistance data to the boceprevir NDA:*
- *Resistance datasets from the two Phase 2 trials (P03659 and P03523) will be included, and assembled according to the June 2006 guidance.*
 - *Resistance datasets from the two Phase 3 trials (P05101 and P05216) will be included, and assembled using the standardized column headings and variables communicated to you on August 10, 2010, and August 27, 2010.*
- b. *We refer to your resistance dataset for P03523 submitted on September 17, 2010. Thank you for providing this dataset in advance of the pre-NDA meeting. It is our understanding that the dataset for P03659 will include the same column headings and variables. For both of these datasets, please include the following data in the form of additional columns/variables:*

Column heading: variable (notes)

SVR12: Y or N (identifies which subjects achieved obtained SVR12)

SVR24: Y or N (identifies which subjects achieved SVR24)

End-of treatment sample: Y or NULL (one 'Y' per subject; identifies the end-of-treatment sample timepoint with sequence data; this sample timepoint can be within ~24 hours of stopping treatment; if no end-of-treatment sample was obtained or analyzed, please indicate the last on-treatment sample analyzed)

Last FU sample: Y or NULL (one 'Y' per subject; identifies the last follow-up sample with sequence data)

Virologic response: BREAKTHROUGH, INCOMPLETE RESPONSE, RELAPSE, SVR, etc. (notes the endpoint protocol-defined virologic response for each subject)

Lead-in Response: \log_{10} IU/mL HCV RNA decline at Week 4 from baseline for subjects in a Peg-IFN α /RBV lead-in arm, or NULL for subjects not in a Peg-IFN α /RBV lead-in arm

*Also, please include additional columns and variables for any protocol-defined interim virologic responses, e.g., Week 8 Undetectable: Y or N

- c. *Your plan to include summaries of resistance data in individual clinical study reports and the Integrated Summary of Efficacy is acceptable. In addition, please provide a Virology Summary in Module 2, Section 2.7 Clinical Summary, subsection 2.7.2.4 Special Studies, which should provide an integrated summary of nonclinical and clinical virology-related studies. Hyperlinks for study reports used to construct the Virology Summary should be included in the document. Also, in this summary document please provide a listing (with hyperlinks to files) of all electronic virology/resistance datasets included in the NDA.*
- d. *Please place all electronic virology/resistance datasets included in the NDA in Section 5.3.5.4, and include hyperlinks to the datasets in the individual clinical study reports.*
- e. *For your Phase 3 clinical trial resistance analyses, please provide a complete listing of all subjects who did not achieve SVR with a boceprevir-containing regimen and who did not have a treatment failure or early follow-up isolate subjected to nucleotide sequence analysis. For each subject, identify the specific reason(s) why nucleotide sequence analysis of a treatment failure or follow-up isolate was not conducted (e.g., no treatment failure or follow-up sample with HCV RNA $\geq 10,000$ IU/mL, etc.).*
- f. *Regarding your criteria summarized on pg. 46 for selecting samples for resistance analyses in your Phase 3 trials, we believe any subjects with detectable HCV RNA at end-of-treatment, or meeting a virologic stopping rule, should also*

have been included in your resistance analyses (i.e., an HCV RNA increase “after nadir” should not be required). In such cases, nucleotide sequence analysis should have been conducted for the last on-treatment sample if HCV RNA levels were amplifiable by RT-PCR (generally $\geq 1,000$ IU/mL); if HCV RNA levels were not adequate for RT-PCR, then the first amplifiable follow-up sample should have been evaluated. Note: “the subject had met the TW12/TW24 futility rule” (pg. 50) is not an acceptable reason for a subject not having a post-baseline treatment failure sample included in your resistance analyses. It is important to understand the reasons and potential resistance-related consequences of boceprevir treatment failure. Please comment.

- g. Please summarize your plans for reporting HCV resistance data from long-term follow-up trial P05063. Will a separate resistance dataset be assembled for this trial, or will the data be compiled with the other Phase 2 or Phase 3 trial datasets? If submitted in a separate dataset, please include the following information: donor boceprevir clinical trial, treatment arm, patient population (e.g., previous partial responders, relapsers, treatment-naïve), total duration of boceprevir exposure, end-of-treatment or last available on-treatment amino acid sequence data, protocol-defined virologic response (e.g., breakthrough, relapse, etc.), lead-in Week 4 virologic response, and HCV RNA concentration for each plasma sample with reported amino acid sequence data.*
- h. We refer to your statement on pg. 18, (b) (4)*
- i Please provide data from any non-clinical studies that evaluated boceprevir antiviral activity against non-genotype 1 HCV.*

Discussion:

Schering agreed to provide all the requested items in comments 9a through 9e in comments section.

For comment 9f, Schering stated they will provide the analyses specified in the protocol. The Division expressed concern that the analyses specified in the protocol were not adequate, noting that there may be many subjects who failed treatment with suspected

boceprevir resistance, but who were not included in the resistance analyses. Schering stated they will perform a gap analysis to summarize subjects who failed treatment but were not included in resistance analyses, but the gap analysis may not be available at the time of filing. Schering will let the Division know by next week. The Division stated that the greatest concern was for the patients who were not included in resistance analyses because they met treatment futility rules, and these subjects are predicted to have viral

populations highly enriched with drug resistant variants.

For comment 9g, Schering is planning to report HCV resistance data in a separate report and dataset. The long term resistance analysis dataset will include resistance data from all available timepoints for each patient. All patients enrolled in boceprevir studies were invited to enroll in the long-term follow-up study. Schering will include blank columns as appropriate for compatibility between different datasets.

For comment 9h, Schering clarified that the statement on page 18 was an error (b) (4)

The Division also clarified that the resistance information should be included in the Microbiology section of the label, and not in the Clinical section.

For comment 9i, Schering will provide data from any non-clinical studies that evaluated boceprevir antiviral activity against non-genotype 1 HCV in the NDA.

E. Rolling NDA

Question 10

The Agency agreed to a rolling review of the boceprevir NDA in a correspondence dated June 24, 2010. The Sponsor's original proposal was for a 2 part rolling submission: Part 1 (non-clinical data) to be submitted in September 2010; Part 2 (remaining NDA CTD sections) to be submitted in December 2010. We have been able to accelerate our filing timelines and would like to propose the submission of Part 2 approximately one month earlier, in November 2010.

Does the Agency agree with the new proposed timelines for the rolling submission of the NDA?

We acknowledge your new proposed timelines for submission.

Discussion:

Schering stated that the first part of the NDA will be released on September 30, 2010.

F. Safety Update

Question 11

For the original NDA submission, there will be five ongoing clinical studies (P05063, P05411, P05514, P05685, and P06086) that have safety cut-off dates spanning 3 months (from March 4, 2010 to June 4, 2010). Safety reports for these ongoing studies will be included in Module 5. These studies will still be ongoing at the time of submission of the Safety Update Report. The safety cut-off dates from these five ongoing studies for the Safety Update Report will span approximately 3 weeks (from Nov 9, 2010 to Nov 29, 2010).

The Sponsor proposes to submit the Safety Update Report in March 2010, which is approximately 4 months after the submission of the last document to the NDA. The safety update report will include all deaths, serious adverse events, discontinuations due to adverse events, and medically significant events. In addition, case report forms will be provided with the Safety Update Report for all deaths and for all subjects who discontinue treatment due to an adverse event.

Does the Agency agree with the content and the proposed timeframe for submission of the safety update report during the review of the NDA for boceprevir?

If boceprevir is reviewed under the Priority Review timelines, we prefer the Safety Update Report be submitted approximately 3 months after the final component of the NDA submission. The safety update should include narratives for all deaths, serious adverse events, discontinuations (regardless of relatedness to study drug) in addition to the corresponding case report forms from the ongoing studies.

Discussion:

Schering will provide the safety update in March on about 1000 patients:

EPO Study: 660 patients

Rollover study of Peg/Riba controls-Boceprevir: 100 patients

Type 2a Study-full dataset: 200 patients

HIV co-infection study: 100 patients

The Safety Update will include narratives for all deaths, serious adverse events, discontinuations (regardless of relatedness to study drug) in addition to the corresponding case report forms from the ongoing studies approximately 3 months after the final component of the NDA submission. This safety update will include the high level summary based on the endpoint for ease of review.

The DAVP asked if antiviral activity data from the Peg-IFN alpha-2a trial will be included in the Safety Update and Schering agreed to submit these data. However, after further consideration the DAVP would prefer to limit the data submitted in the Safety Update since the application will be granted a priority review. Schering stated they will provide summary antiviral activity data from this trial with the Safety Update.

G. Pediatric Deferral

Question 12

 (b) (4)
As discussed and agreed to at the Clinical Development Meeting on June 1, 2006, pediatric studies will not begin until the completion of the adult pivotal Phase 3 studies, therefore a pediatric deferral is requested for the initial NDA application.

Does the Agency agree that a pediatric deferral is acceptable at the time of NDA filing?

(b) (4)
Comments regarding your PPSR were sent recently to you.

A request for a pediatric deferral is appropriate, and should be included with the NDA submission.

Discussion:

Schering will submit a request for a pediatric deferral with the NDA submission. (b) (4)

Additional Comments:

1. Please consider genotyping subjects for ITPA polymorphisms, such that the relationship between inosine triphosphate deficiency and treatment-related anemia can be explored.
2. Please provide analysis of efficacy (SVR) and safety (especially anemia, thrombotic and cardiac events) by erythropoietin alfa use.
3. The population pharmacokinetic analysis plan should evaluate the impact of key intrinsic and extrinsic covariates on drug exposure, including the impact of potential inhibitors and inducers of boceprevir metabolism that may have been used in the Phase 3 trials. Exposure-response analyses should also be performed and submitted with the NDA evaluating key efficacy (e.g., SVR) and safety (e.g., anemia) events based on derived PK parameters (e.g., C_{trough} , $C_{\text{avg,ss}}$, C_{max} , AUC_{ss}) from Phase 3. Finally, please submit the following datasets and codes/scripts for reviewers to recreate modeling and simulations:
 - All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Discussion:

Schering will provide genotyping subjects for ITPA polymorphisms to explore the relationship between inosine triphosphate deficiency and treatment-related in the 3 month safety update. They will also provide analysis of efficacy (SVR) and safety (especially anemia, thrombotic and cardiac events) by erythropoietin alfa use in the NDA. All the requested items in comment 3 will be provided in the NDA.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

4.0 ACTION ITEMS

- Schering will include a breakdown of the response at Week 36 and Week 48 using RGT of the subjects who achieved an SVR and those who didn't and will include the mean time since prior therapy.
- Schering will provide IL28B genotypic data analyses for studies P05101 and P05216 separately in addition to the combined analysis.
- Schering will provide resistance datasets from the two Phase 2 trials P03659 and P03523, and from the two Phase 3 trials (P05101 and P05216) as per previous communications.
- Schering will provide a Virology Summary in Module 2, Section 2.7 Clinical Summary, subsection 2.7.2.4 Special Studies, which should provide an integrated summary of nonclinical and clinical virology-related studies. Hyperlinks for study reports used to construct the Virology Summary will also be included in the document. Also a listing (with hyperlinks to files) of all electronic virology/resistance datasets will be included in the NDA.
- Schering will place all electronic virology/resistance datasets included in the NDA in Section 5.3.5.4, and include hyperlinks to the datasets in the individual clinical study reports.
- Schering will provide a gap analysis and complete listing of all subjects who did not achieve SVR with a boceprevir-containing regimen and who did not have a treatment failure or early follow-up isolate subjected to nucleotide sequence analysis for the Phase 3 clinical trial resistance analyses. Schering will also identify the specific reason(s) why nucleotide sequence analysis of a treatment failure or follow-up isolate was not conducted (e.g., no treatment failure or follow-up sample with HCV RNA $\geq 10,000$ IU/mL, etc.).

- Schering will provide narratives for all deaths, serious adverse events, discontinuations (regardless of relatedness to study drug) in addition to case report forms from the completed pivotal Phase 3 studies.
- Schering will provide data from any non-clinical studies that evaluated boceprevir antiviral activity against non-genotype 1 HCV in the NDA.
- Schering will provide the safety update including narratives for all deaths, serious adverse events, discontinuations (regardless of relatedness to study drug) in addition to the corresponding case report forms from the ongoing studies approximately 3 months after the final component of the NDA submission. Schering will also provide with the safety update a summary of antiviral activity data from clinical trial P05685 evaluating boceprevir in combination with Peg-IFN α -2a/RBV.
- Schering will submit a request for a pediatric deferral with the NDA submission.
- Schering will provide genotyping subjects for ITPA polymorphisms to explore the relationship between inosine triphosphate deficiency and treatment-related in the 3 month safety update.
- Schering will also provide analysis of efficacy (SVR) and safety (especially anemia, thrombotic and cardiac events) by erythropoietin alfa use in the NDA.
- Schering will provide all the requested items in comment 3 in the NDA.

5.0 ATTACHMENTS AND HANDOUTS

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

/s/

SHERLY ABRAHAM
10/21/2010

JEFFREY S MURRAY
10/21/2010



IND 69,027

ADVICE/INFORMATION REQUEST

Schering-Plough Corporation
Attention: Frank Grande
Senior Manager and Liaison, Global Regulatory Affairs-CMC
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Dear Mr. Grande:

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

We also refer to the meeting between representatives of your firm and the FDA on October 7, 2009. The purpose of the meeting was a CMC-specific, End of Phase II discussion of plans to support the marketing application.

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

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

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Pharmaceutical Assessment Lead
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure



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

Sponsor Name:	Schering-Plough Corporation
Application Number:	IND 69,027
Product Name:	SCH 503034 (boceprevir)
Meeting Requestor:	Frank Grande, Sr. Manager and Liaison Global Regulatory Affairs - CMC
Meeting Type:	Type B End-of-Phase 2 Meeting - Teleconference
Meeting Category:	Chemistry, Manufacturing and Controls (CMC)
Meeting Date and Time:	Wednesday, October 7, 2009, 1:00 PM – 2:00 PM EST
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	September 4, 2009
Meeting Chair:	Stephen Miller, Ph.D.
Meeting Recorder:	Jeannie David, M.S.

FDA ATTENDEES:

Center for Drug Evaluation and Research (CDER)

Office of New Drug Quality Assessment (ONDQA)

George Lunn, Ph.D., Chemistry Reviewer
Stephen Miller, Ph.D., Pharmaceutical Assessment Lead
Houda Mahayni, Ph.D., Biopharmaceutics Reviewer
Jeannie David, M.S., Regulatory Project Manager

Division of Anti-Viral Products (DAVP)

Kuei-Meng Wu, Ph.D., Pharmacology/Toxicology Reviewer
Anita Bigger, Ph.D., Pharmacology/Toxicology Reviewer
Hanan Ghantous, Ph.D., Pharmacology/Toxicology Team Leader
Russell Fleischer, M.D., Clinical Reviewer
Linda Lewis, M.D., Clinical Team Leader

EXTERNAL ATTENDEES:Schering-Plough Corporation

Niya Bowers, Ph.D., Director, Oral and Specialty Product Development
Michael Mitchell, Ph.D., Vice President, Oral and Specialty Product Development
George Wong, Ph.D., Sr. Fellow, Chemical and Physical Sciences
David Andrews, Ph.D., Sr. Director, Chemical and Physical Sciences
Elmer Mirro, DVM, Global Scientific Advisor, Drug Safety and Metabolism
Meg Casais, Director, Global Regulatory Affairs-CMC
Frank Grande, Sr. Manager and Liaison, Global Regulatory Affairs-CMC
Sharon Olmstead, Vice President, Regulatory Policy & Intelligence
Diane Zezza, Ph.D., Vice President, Global Regulatory Affairs-CMC
Barry McIntyre, Ph.D., DABT, Sr. Principal Scientist, Drug Safety and Metabolism
Penelope Giles, Ph.D., Sr. Director, Global Regulatory Affairs

BACKGROUND

Schering-Plough Corporation requested a Type B meeting, letter dated August 11, 2009, to discuss plans to support the marketing application pertaining to SCH 503034 (boceprevir), 200 mg capsules, intended for the treatment of chronic hepatitis C. Boceprevir Phase II clinical trials have been completed and Phase III clinical trials are ongoing. Schering-Plough is currently projecting an NDA filing date of 4Q 2010 and is requesting a CMC Guidance Meeting to discuss key points of their development and registration strategy.

Two FDA information request letters were issued pertaining to this meeting, both dated September 11, 2009. Schering-Plough responded to both letters with a single submission dated September 28, 2009.

After reviewing the Preliminary Responses, the sponsor requested by email on October 6, 2009, that this meeting be converted to a teleconference, and to focus the discussion on FDA responses to Questions 3A and 3B.

Sponsor Questions and FDA Response:

- 1. Based on the absence of structural alerts, no evidence of toxicities in similar peptide-like structures and the established qualification level of (b) (4) or higher for Category 1 impurities, does the Agency agree with our proposal to set the qualification limit of the Category 2 impurities at (b) (4) ?**

FDA Response:

Yes. Please include in the NDA the analysis of the compounds in the lots that were used in the toxicological studies which support the proposed qualification levels for the Category 1 related substances.

Meeting Discussion:

The sponsor agreed with the FDA Response provided. No further discussion was necessary.

2. Does the Agency agree with our proposal to set the identification and qualification threshold at (b) (4) for Category 3 impurities?

FDA Response:

Yes.

Meeting Discussion:

The sponsor agreed with the FDA Response provided. No further discussion was necessary.

- 3A. Does the Agency agree that (b) (4) do not pose a mutagenic risk based on these Ames assay findings?

FDA Response:

The data show that (b) (4) is genotoxic and (b) (4) and (b) (4) should be limited at a combined daily exposure of (b) (4) which are equivalent to a combined limit of (b) (4) for clinical trials of greater than 12 months duration, according to the FDA's draft Guidance for Industry entitled "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (December 2008)."

Meeting Discussion:

FDA indicated that while results publicly available on (b) (4) in the literature appear equivocal, the Agency considers (b) (4) genotoxic based on more recent data. (b) (4)

Schering-Plough indicated that they have no other information on (b) (4) from the manufacturer (b) (4) other than what is provided in the MSDS.

When asked, Schering-Plough indicated that their carcinogenic study was performed on material that did not utilize (b) (4) and therefore would not be expected to contain (b) (4).

(b) (4)

3B. Does the Agency agree that given the low levels of (b) (4) and the (b) (4) and high multiples with regard to total daily intake and estimated plasma levels there is no clastogenic/genotoxicity risk to patients?

FDA Response:

*No. It is not appropriate to extrapolate from concentrations in the *in vitro* mammalian cell genotoxicity tests to safety factors for human doses. (b) (4) and (b) (4) should be regulated with a combined daily exposure of (b) (4) as described in the response to Question 3A.*

Meeting Discussion:

FDA emphasized that extrapolations from *in vitro* studies to safety factors would not be considered valid (please refer to FDA Post-Meeting Comment 2, below). We do agree, however, that (b) (4) may have a threshold below which it would not present a danger to humans and it would be extremely helpful to know the results of tests of (b) (4) in *in vivo* genotoxicity assays.

The Agency made further comment that since the toxicity of the (b) (4) of (b) (4) is unknown, this would be useful information to have. It would be also useful to know how readily (if at all) (b) (4) is reconverted to (b) (4). In addition, please see FDA Post-Meeting Comment 3.

Schering-Plough clarified that the data considered here is for the purposes of the NDA, not the current IND. They project to submit the NDA at the end of 2010/early 2011. The Agency commented that this allows time to take a weight of evidence approach in determining the relevance of the genotoxicity of (b) (4) (b) (4) to humans and that further studies on their genotoxicity would be helpful.

4. Does the Agency agree with our assessment that (b) (4) and included in the assay of the total active?

FDA Response:

Yes.

Meeting Discussion:

The sponsor agreed with the FDA Response provided. No further discussion was necessary.

5A. Does the Agency agree with our assessment that the intended commercial image capsules are equivalent to the blue capsules used in Phase II and III clinical studies, and that no further bridging clinical studies are required?

FDA Response:

Yes, based on the information presented, no bridging clinical study is required. Based on the dissolution data of Phase III Clinical batches, as seen in Appendix 1 and 2, it seems that the acceptance criteria need to be revised during the NDA review.

We also request that you submit a dissolution method development report to the IND.

Meeting Discussion:

The sponsor agreed with the FDA Response provided. No further discussion was necessary.

5B. Based on in vitro comparability data establishing equivalency of the blue and yellow / orange capsules, does the Agency agree that the proposed stability package is adequate to support a shelf life projection for the commercial image?**FDA Response:**

The proposed stability package is adequate although the adequacy of the actual data is an NDA review issue.

Meeting Discussion:

The sponsor agreed with the FDA Response provided. No further discussion was necessary.

6. Does the Agency agree that the proposed strategy supports consideration of a label storage statement allowing Patient-in-Use at room temperature for up to 3 months?**FDA Response:**

The adequacy of the data is an NDA review issue. However, the data that you describe are the kind of data that we would like to review before making our decision. We would find it particularly valuable to receive, during the course of the review process, similar stability data for commercial image capsules made with drug substance manufactured using the final commercial process. These capsules should be stored refrigerated for an appropriate time and then at 25°C/60% RH for 3 months.

Meeting Discussion:

The sponsor agreed with the FDA Response provided. No further discussion was necessary.

FDA POST-MEETING COMMENTS:

1. The information was provided electronically to Schering-Plough on October 30, 2009.

2. Short term genotoxicity tests require higher doses than would generally be used clinically in order to compensate for the brevity of the test, and cannot be expected to mimic in vivo physiological conditions exactly (e.g. in vivo metabolism and tissue specific toxicity); therefore, it is appropriate to use them for hazard identification but not for extrapolation to a safe human dose.
3. If (b) (4) is determined to be non-genotoxic and shown not to reconvert to (b) (4) then it would not be necessary to reach a combined (b) (4) and (b) (4) limit of (b) (4)

ACTION ITEMS:

There are no further action items other than those recorded in the meeting discussion sections above.

CONCURRENCE:

{See appended electronic signature page}

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

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-69027	GI-1	SCHERING CORP	SCH 503034 HVC PROTEASE INHIBITOR

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/s/

JEANNIE C DAVID
11/06/2009

STEPHEN P MILLER
11/06/2009
I concur.