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APPLICATION NUMBER:

202258Orig1s000

OTHER REVIEW(S)

Division of Antiviral Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 202,258

Name of Drug: VICTRELIS (boceprevir) 200 mg Capsules

Applicant: Schering, Inc

Labeling Reviewed

Submission Date: November 10, 2010

Receipt Date: November 15, 2010

Background and Summary Description:

Schering, Inc, subsidiary of Merck and Co submitted a New Molecular Entity (NME) New Drug Application (NDA), boceprevir, VICTRELIS for treatment of chronic hepatitis C virus (HCV) in combination with peginterferon alfa and ribavirin. The Division of Antiviral Products (DAVP) reviewed the Package insert (PI) and Medication Guide and sent the label with our revisions to Schering on April 19, 2011, May 4, 2011, and May 11, 2011. On May 12, 2010, Merck accepted the revisions made to the PI and Medguide and submitted the official version on May 13, 2011. Merck also submitted the carton and container labels on May 11, 2011, and they were found acceptable by DMEPA.

Review

The Package Insert was reviewed and the following changes were made:



(b) (4)

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/s/

SHERLY ABRAHAM
05/13/2011

VICTORIA L TYSON
05/13/2011

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2011</u>
	Study/Trial Completion:	<u>06/30/2012</u>
	Final Report Submission:	<u>07/31/2012</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The information to be gained applies primarily to patients who have failed boceprevir or other agents with overlapping resistance pathways. The information has minimal initial direct impact on patients who have not been previously treated with boceprevir or other agents with overlapping resistance pathways.

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

This study will assess the relationship between genotypic and phenotypic resistance assessment results.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

SHERLY ABRAHAM
05/13/2011

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 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
-

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2011</u>
	Study/Trial Completion:	<u>06/30/2012</u>
	Final Report Submission:	<u>07/31/2012</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Some of the specific treatment-emergent substitutions to be evaluated were identified only after completion of pivotal trials and analysis of treatment failure subjects. The information to be gained applies primarily to patients who have failed boceprevir or other agents with overlapping resistance pathways. The information has minimal initial direct impact on patients who have not been previously treated with boceprevir or other agents with overlapping resistance pathways.

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

This study will provide more complete information regarding the effect of specific boceprevir treatment-emergent amino acid substitutions in the HCV genome on boceprevir anti-HCV activity. The information may be useful to predict virologic responsiveness to treatment with regimens including boceprevir after a patient has failed boceprevir or another agent with overlapping resistance pathways.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

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/s/

SHERLY ABRAHAM
05/13/2011

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 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 log₁₀ IU/mL decline, \geq 1 log₁₀ IU/mL to <2 log₁₀ 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	08/31/2011
	Study/Trial Completion:	(b) (4)
	Final Report Submission:	04/30/2013
	Other:	MM/DD/YYYY

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

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

The information to be gained applies primarily to patients who have failed boceprevir or other agents with overlapping resistance pathways because boceprevir resistance-associated substitutions are relatively rare among patients who have not been previously treated with boceprevir or other agents with overlapping resistance pathways.

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

This study will provide insight regarding the potential effect of boceprevir resistance-associated substitutions on boceprevir-based treatment efficacy. A small proportion of patients never treated with boceprevir or other agents with overlapping resistance pathways carry viral populations with these resistance substitutions detected at a high level as natural polymorphisms. A pooled analysis of such patients enrolled across several large trials is needed for an adequate sample size for the analysis. The information to be gained applies to patients who have failed boceprevir or other agents with overlapping resistance pathways because boceprevir resistance-associated substitutions are relatively rare among patients who have not been previously treated with boceprevir or other agents with overlapping resistance pathways.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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- Are the objectives clear from the description of the PMR/PMC?
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SHERLY ABRAHAM
05/13/2011

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/31/2011</u>
	Study/Trial Completion:	<u>12/31/2011</u>
	Final Report Submission:	<u>07/31/2012</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Two-year follow-up study to assess persistence of detectable boceprevir resistance-associated substitutions following treatment failure. Subject population is from completed Phase 2 and Phase 3 trials.

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

This study will provide insight into the long term persistence of HCV viral populations harboring resistance-associated substitutions that may impact virologic responses to future treatment with boceprevir or other NS3/4A protease inhibitors.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

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

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
This is an ongoing clinical/observational, long-term follow-up study of patients who previously enrolled in boceprevir clinical trials.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
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-

PMR/PMC Development Coordinator:

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

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/s/

SHERLY ABRAHAM
05/13/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: May 2, 2011

To: Debra Birnkrant, MD, Director
Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): Victrelis (boceprevir)

Dosage Form and Route: Capsules

Application Type/Number: NDA: 202-258

Applicant: Schering-Plough Corporation

OSE RCM #: 2010-2504

1 INTRODUCTION

This review is written in response to a request by the Division of Antiviral Products (DAVP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide for Victrelis (boceprevir) Capsules. On November 10, 2010 Schering-Plough Corporation submitted a New Drug Application (NDA) 202-258 for Victrelis (boceprevir) Capsules indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy.

2 MATERIAL REVIEWED

- Draft Victrelis (boceprevir) Capsules Medication Guide (MG) submitted on November 10, 2010, and revised by the review division throughout the review cycle, and provided to DRISK on April 13, 2011.
- Draft Victrelis (boceprevir) Capsules prescribing information (PI) submitted on November 10, 2010, and revised by the review division throughout the review cycle and, provided to DRISK on April 13, 2011.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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/s/

STEVE L MORIN
05/02/2011

LASHAWN M GRIFFITHS
05/02/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: April 28, 2011

To: Sherly Abraham, DAVP

From: Lynn Panholzer, PharmD, DDMAC
Michelle Safarik, PA-C, DDMAC

Re: NDA# 202-258
Boceprevir Capsules

As requested in your consult dated November 24, 2010, DDMAC has reviewed the draft labeling (package insert [PI], Medication Guide, carton and container labels) for boceprevir capsules. DDMAC's comments are based on the proposed, marked-up, substantially complete version of the PI and Medication Guide sent to DDMAC via e-mail by DAVP on April 12, 2011, and on the carton and container labels submitted by the applicant on November 10, 2010, available in the EDR at <\\CDSESUB1\EVSPROD\NDA202258\0001>.

DDMAC's comments on the PI and Medication Guide are provided directly in the attached, marked up copy of the labeling. DDMAC has no comments on the carton and container labels.

If you have any questions about DDMAC's comments on the PI, please contact Lynn Panholzer at 6-0616 or at Lynn.Panholzer@fda.hhs.gov. If you have any questions about our comments on the Medication Guide, please contact Michelle Safarik at 6-0620 or at Michelle.Safarik@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
04/28/2011

MICHELLE L SAFARIK
04/28/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: April 14, 2011

TO: Sherly Abraham, R.Ph., Regulatory Health Project Manager
Poonam Mishra, M.O., Medical Reviewer
Division of Antiviral Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202-258

APPLICANT: Schering-Plough/Merck Corporation

DRUG: Oral Boceprevir

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of chronic hepatitis C in adult patients

CONSULTATION REQUEST DATE: December 17, 2010

DIVISION ACTION GOAL DATE: May 13, 2011

PDUFA DATE: May 15, 2011

I. BACKGROUND:

The sponsor, Schering-Plough/Merck Corporation, has submitted a New Drug Application (NDA) for the use of Boceprevir (SCH503034) for the treatment of chronic hepatitis C infected subjects who failed prior treatment with standard peginterferon/ribavirin or previously untreated. Boceprevir (SCH 503034) is a potent, orally active, novel protease inhibitor, specifically designed to inhibit the hepatitis C virus (HCV) nonstructural protein 3 (NS3) protease, thereby inhibiting viral replication in HCV-infected host cells. The mechanism of inhibition involves formation of a reversible, covalent bond between the ketoamide of boceprevir and the NS3 protease active site serine.

According to the Applicant, the use of Boceprevir constitutes a new and effective method for the treatment of HCV when added to the standard combination therapy with peginterferon and ribavirin for the treatment of chronic hepatitis C. The addition of a third active anti-HCV drug may lead to more rapid viral response and may allow increased rates of sustained virologic response (SVR) and shorter treatment. Chronic hepatitis C subjects who failed previous therapy with standard peginterferon/ribavirin are the population with the greatest unmet medical need.

The Applicant has provided data from two studies, Study P05101 and Study P05216, in support of the approval of the new protease inhibitor. These studies are summarized in the following sections.

Protocol P05101, entitled: “A Phase 3 Safety and Efficacy Study of Boceprevir in Subjects with Chronic Hepatitis C Genotype 1 Who Failed Prior Treatment With Peginterferon/Ribavirin”.

Study P05101 assessed the safety and efficacy of boceprevir in subjects with chronic hepatitis C with a Lead-in 4-week period of PEG+RBV alone prior to addition of boceprevir or placebo. Subjects on the placebo arm (Arm 1) or boceprevir Arm 3 then received 44 weeks of therapy, followed by 24 weeks of post-treatment follow-up. Further treatment course for subjects on boceprevir Arm 2 was determined by their response at treatment week (TW) 8.

The primary objective of this study was to compare the efficacy of two therapeutic regimens of boceprevir 800 mg dosed TID orally (PO) in combination with peginterferon 1.5 ug QW subcutaneously (sc) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400mg/day) PO to therapy with PEG+RBV (WBD) alone in adult subjects with chronic hepatitis C genotype 1 with demonstrated interferon responsiveness who failed prior treatment with peginterferon/ribavirin.

The primary efficacy endpoint of this study was the achievement of sustained virologic response (SVR), defined as undetectable plasma HCV-RNA at follow-up week (FW) 24. If a subject is missing FW24 data and has undetectable HCV-RNA level at week 12, the subject would be considered an SVR. Subjects will be declared treatment failures if, in any treatment arm they have detectable HCV-RNC at either FW24 or TW12.

Protocol P05216, entitled: “A Phase 3 Safety and Efficacy Study of Boceprevir in Previously Untreated Subjects with Chronic Hepatitis C Genotype 1.”

Study P05216 assessed the safety and efficacy of boceprevir in previously untreated subjects with chronic hepatitis C.

This was a randomized multi-center study double-blinded for boceprevir or placebo in combination with open label PEG+RBV (WBO) in previously untreated subjects with chronic hepatitis C genotype 1. The study compared standard-of-care PR (PEG2b 1.5 µg/kg QW plus RBV 600 to 1400 mg/day [WBD]) for 48 weeks to two treatment paradigms containing boceprevir 800 mg TID plus PR for a total duration of 28 or 48 weeks, including a 4-week lead-in with PR. In study P05216, male and female subjects, over 18 years of age, were randomized to one of the three arms in a 1:1:1 allocation ratio.

The primary objective of this study was to demonstrate the efficacy of two therapeutic regimens of boceprevir 800 mg dosed TID orally (PO) in combination with peginteron 1.5 ug QW subcutaneously (sc) plus weight-based dosing (WBD) of ribavirin (600 mg/day to 1400 mg/day) PO to therapy with PEG+RBV (WBD) alone in previously untreated adult subjects with chronic hepatitis C genotype 1.

The primary efficacy endpoint of this study was the achievement of sustained virologic response (SVR), defined as undetectable plasma HCV-RNA at follow-up week (FW) 24. If a subject is missing FW24 data and has an undetectable HCV-RNA level at week 12, the subject would be considered an SVR. Subjects will be declared treatment failures if, in any treatment arm, they have a detectable HCV-RNC at either FW24 or TW 12.

The review division requested inspection of four clinical investigators for the two study protocols (4 sites; 2 foreign sites and 2 domestic sites to cover Study P05101 and 2 domestic sites to cover Study P05216)) as data from the two protocols are considered essential to the approval process. Two foreign clinical investigators and two domestic investigators were chosen for inspection of the two protocols. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, 2) site specific protocol violations, and 3) limited experience with this drug is derived from foreign sites. Schering-Plough/Merck Corporation is the Sponsor of this application.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Stuart Gordon, M.D. Henry Ford Health System 2799W.Grand Blvd. Detroit, MI 48202 Site# 26	Protocol P05101 Number of subjects listed 19	1/12-20/11	NAI
Marc Bourliere, M.D. Hospital Saint Joseph 26 boulevard de Louvain Service Marseille Cedex 08 13285 France Site# FRA-007	Protocol P05101 Number of subjects listed 14	3/30-4/1/11	Pending Preliminary: VAI
Jonathan, McCone M.D. Mount Vernon Endoscopy Center 8109 Hinson Farm Rd.#515 Alexandria, VA 22306 Site# 36	Protocol P05216 Number of subjects listed 36	1/19-24/11	NAI
Bruno, Savino, M.D. Ospedale Fatebenefratelli Oftaimico Unita Comptessa di Epatologia Corso di Porta Nuova,23 Milano, Italy 20121 Site# EU-117	Protocol P05216 Number of subjects listed 23	4/4-8/11	Pending Preliminary: NAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Note: Observations noted below for 2 sites are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol Study P05101

1. **Stuart Gordon, M.D.**
Detroit, MI 48202-2608

a. What Was Inspected: At this site, a total of 24 subjects were screened, five subjects were reported as screen failures. Nineteen (19) subjects were randomized and all subjects completed the study. There were no deaths and no under-reporting of adverse events. Review of Informed Consent Documents for all subject records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 14 random subjects were reviewed, including drug accountability records, vital signs, laboratory test results, IRB records, inclusion/exclusion criteria; source documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

b. General observations/commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Gordon. The medical records reviewed revealed no deficiencies or violations from Federal regulations. There were no known limitations to the inspection.

c. Assessment of Data Integrity: The data, in support of clinical efficacy and safety at Dr. Gordon's site are considered reliable and appear acceptable in support of the pending application.

2. **Marc Bourliere, M.D.**
Marseille Cedex 08, France

a. What Was Inspected: At this site, a total of 20 subjects were screened, six subjects were reported as screen failures. Fourteen (14) subjects were randomized and 8 subjects completed the study. There were no deaths and no under-reporting of adverse events. Review of the Informed Consent Documents, for all subject reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 11 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, inclusion/exclusion criteria, and source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, a 1 item Form FDA 483 was issued to Dr. Bourliere. Our investigation found protocol violations in that the clinical investigator did not document that telephone contact was made for Week 5 visits for 4 subjects. The purpose of the telephone contact was to confirm that subjects

were able to comply with taking the study drug as directed and to remind the subjects of the importance of making their scheduled follow-up visits on time.

c. Assessment of Data Integrity

Although minor regulatory violations were noted, the findings are not likely to affect data integrity. The study appears to have been conducted adequately and the submitted data by the sponsor may be used in support of the pending application.

Protocol study P05216

**3. Jonathan McCone, M.D.
Alexandria, VA 22306**

a. What Was Inspected: At this site, a total of 42 subjects were screened, 6 subjects were reported as screen failures. Thirty six (36) subjects were randomized into the study. Four subjects were terminated early due to identification of detectable HCV-RNA at Week 24 in three subjects and development of suspected drug related rash in one subject. Three additional subjects did not complete the study, two due to loss to follow-up and one due suicide. Review of the Informed Consent Documents, for all subject records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 14 subjects were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria use of concomitant medications; source documents for subjects were compared to case report forms (e-CRFs) and data listings, to include primary efficacy endpoints and adverse events reporting and no discrepancies were noted.

b. General Observations/Commentary: The study appears to have been conducted adequately at this site. The inspection revealed no violations of Federal regulations and no Form FDA 483 was issued to the clinical investigator.

c. Assessment of Data Integrity: The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and the data verifiable. The data generated from Dr. McCone's site are considered reliable and appear acceptable in support of the application.

**4. Bruno Savino, M.D.
Milano, Italy**

a. What was Inspected: At this site, a total of 29 subjects were screened, six subjects were reported as screen failures, 23 subjects were randomized and 20 subjects completed the study. Three subjects were discontinued from the study and the reasons were documented. Review of Informed Consent Documents, for all subject records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for 16 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, diary cards, IRB files, prior and

current medications, inclusion/exclusion criteria, the use of concomitant medications; source documents were compared to case report forms and to data listings for primary efficacy endpoint and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Savino. The medical records reviewed disclosed no adverse finding that would negatively on the reliability of the data. There were no known limitations to this inspection.

c. Assessment of Data Integrity: The data from Dr. Savino’s site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigator sites, two domestic and two foreign sites were inspected in support of this application. The inspections of Drs. Gordon, Bourliere, McCone, and Savino revealed no significant problems that would adversely impact data acceptability. Overall, the data collected in support of this application are considered reliable and acceptable.

Note: Observations noted above for at least 2 inspections are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
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CONCURRENCE:

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/s/

ANTOINE N EL HAGE
04/15/2011

TEJASHRI S PUROHIT-SHETH
04/15/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Label and Labeling Review

Date: April 13, 2011

Reviewer(s): Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh, Acting Deputy Director
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name(s): Victrelis (Boceprevir) Capsules, 200 mg

Application Type/Number: NDA 202258

Applicant/sponsor: Schering Corporation

OSE RCM #: 2010-2482

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

1 INTRODUCTION

This review evaluates the proposed label and labeling for Victrelis (NDA 202258) for areas of vulnerability that can lead to medication errors. The Schering Corporation submitted the container label and carton and insert labeling on November 10, 2010.

1.1 PRODUCT INFORMATION

Victrelis is the proposed proprietary name for Boceprevir Capsules. Boceprevir is an inhibitor of the hepatitis C virus non-structural protein 3 serine protease with a proposed indication for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy. The recommend dose in adults is 800 mg (4 capsules) orally three times daily with food. Dose reduction of Victrelis is not recommended.

Boceprevir capsules will be packaged in a carton with 28 bottles, each containing 12 capsules. The bottles are 30 mL size, clear high-density polyethylene bottles. Victrelis should be refrigerated at 2°C - 8°C (36°F - 46°F) until dispensed. For patient use, refrigerated capsules of Victrelis can remain stable until the expiration date printed on the label. Victrelis can also be stored at room temperature up to 25°C (77°F) for 3 months.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted November 10, 2010
- Carton Labeling submitted November 10, 2010
- Insert Labeling submitted November 10, 2010

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

The following sections discuss deficiencies related to the product design and labeling.

3.1 PRODUCT DESIGN

The product packaging is designed for patient to remove a bottle consisting of the daily dose of Victrelis. This design may improve convenience; however, patients are at risk of ingesting the total daily dose (12 capsules) at one time.

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

3.2 CONTAINER LABEL

This product provides for 28 days supply of Victrelis. Within each carton are individual bottles that contain a total daily dose. However, the container does not contain dosage instructions. This is particularly important because Victrelis must be taken three times daily with food. Without full instructions for use, dosing errors may occur, such as wrong frequency of administration or ingestion without food.

3.3 CARTON LABELING (28 BOTTLES X 12 CAPSULES EACH)

The dosage instructions on the rear panel refer patients to read the package insert. However, the package insert is designed for health care practitioners, not patients. Therefore, it is important to place the dosing instructions on the bottle for the patients. Since the dose instructions for Victrelis do not change or require modification, the dosage can be revised to include the actual dose instructions, 800 mg orally three times daily with food. Additionally, this information should be relocated to the principal display panel, rather than the rear panel so that patients can find the information easily.

4 CONCLUSIONS AND RECOMMENDATIONS

The proposed product packaging increases the risk of medication errors such as wrong frequency of administration and wrong dose errors. The risk of medication errors is further enhanced because there are no clear dose instructions on the container label. Additionally, we identified other areas requiring modification to increase prominence and readability of certain label and labeling statements. We recommend the following:

- A. Product Design
 - Consider developing a different package configuration that minimizes the risk of incorrect dose errors.
- B. Container Label
 - 1. 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 the Victrelis because there are no dosage instructions on the bottle.
 - 2. 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).
 - 3. Revise the strength expression to read *200 mg per capsule*.
- C. Carton Labeling (28 bottles x 12 capsules)
 - 1. 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. Revise the strength expression to read *200 mg per capsule*.

3. Add dosage instructions to the principal display panel.
4. Revise the Medication Guide statement to read as follows:

Dispense the enclosed Medication Guide to each patient
5. Delete the statement, [REDACTED] (b) (4)

If you have further questions or need clarifications, please contact Brantley Dorch, project manager, at 301-796-0150.

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/s/

JIBRIL ABDUS-SAMAD
04/13/2011

CAROL A HOLQUIST
04/13/2011

CDER/DRUP Consultation Response (Tracking No. 226)

Division Consult #	226
To	Sherly Abraham, RPh Office of Antimicrobial Products Division of Antiviral Products
From	Gerald Willett MD, Medical Officer, Division of Reproductive and Urologic Products (DRUP) through Lisa Soule, MD, Medical Team Leader and Scott Monroe MD, Division Director Chongwoo Yu, PhD, Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP) through Myong Jin Kim, PharmD, Team Leader and Edward D. Bashaw, PharmD, Director, Division of Clinical Pharmacology 3, OCP
Names of drug products	Boceprevir (IND 69027; NDA 202-258) Telaprevir (IND 71832; NDA 201-917)
Class of drugs	Protease inhibitors
Sponsors	Merck (previously Schering-Plough) for Boceprevir Vertex for Telaprevir
Re:	Drug interactions with Oral Contraceptives
Date of consult request	February 7, 2011
Desired completion date	March 4, 2011

Background

The Division of Antiviral Products (DAVP) is currently reviewing two protease inhibitors, boceprevir and telaprevir. Each of these drugs will be indicated for the treatment of chronic hepatitis C in combination with currently approved ribavirin and peg-interferon alpha. Telaprevir therapy will be initiated with combination therapy (i.e., consisting of peg-interferon alpha and ribavirin) and will be administered for 12 weeks. Boceprevir will be added to the combination therapy (i.e., consisting of peg-interferon alpha and ribavirin) on Treatment Week 5 for up to 48 weeks, depending on treatment history and response to the therapy. DAVP has questions relating to a) drug-drug interaction (DDI) studies already performed for boceprevir and telaprevir against combination oral contraceptives b) general and specific labeling questions based on the results of these DDI studies and c) possible recommendations concerning additional DDI studies.

Consultation Questions:

Question 1. Drosiprenone exposure (C_{max} and AUC) increased by 2-fold in the presence of boceprevir relative to oral contraceptive alone. Is this magnitude of increase in drosiprenone exposure considered a safety concern? If so, do similar safety concerns apply to other progestational compounds (e.g. norgestimate, norethindrone)?

Consult response:

Although DRUP does not have safety data indicating that a two-fold increase in the C_{max} and AUC of drospirenone (DRSP) increases the risk of adverse events, the Division does have concerns about this magnitude of increase. The principal potential safety concerns for DRSP are thromboembolism and hyperkalemia. As indicated in the labeling for all DRSP-containing products, they should not be used in patients with conditions that predispose to hyperkalemia (i.e., renal or adrenal insufficiency or hepatic dysfunction). The increased exposure to DRSP is of particular concern in regard to the risk of hyperkalemia.

If boceprevir were to cause increases in the C_{max} and AUC of other progestins used in combined hormonal contraceptives (e.g., norgestimate, norethindrone, dienogest, levonorgestrel), hyperkalemia would not be a concern because DRSP is currently the only progestin with antimineralocorticoid activity. Effects of boceprevir-related increases in C_{max} and AUC for all other progestins would most likely result in more irregular bleeding and could potentially increase thromboembolic risk.

While we have potential safety concerns about the increased exposure to DRSP when co-administered with boceprevir, we are also concerned that the drug-drug interaction (DDI) has not been sufficiently characterized. In the drug interaction study conducted with boceprevir and Yaz, the AUC for DRSP was measured only up to 24 hours, while DRSP has a terminal half-life of approximately 30 hours. It may be that the increase in DRSP exposure is even greater than two-fold. In addition, we note that the PK measurements of the Yaz-only treatment were taken on Day 7, which is before both DRSP and ethinyl estradiol have reached their respective steady-states.

Another concern is that while all boceprevir treatments were administered following a meal or a snack, it is unclear whether Yaz was given with or without meals in the Yaz-only treatment period for the first 7 days. Yaz itself exhibits a food effect. While the AUC_{0-24hr} remains unchanged for DRSP administered under fed or fasting conditions, it decreases 20% for ethinyl estradiol under fed conditions. C_{max} of both DRSP and ethinyl estradiol are reduced 40% under fed conditions. If Yaz was given in this study without regard to food or under fed conditions, the maximum drug interaction potential may not have been adequately characterized, given that Yaz was given under varying conditions (i.e., fed vs. fasting) which would result in failure to maintain a true “steady-state” condition.

Question 2. What would be appropriate language for the boceprevir label regarding use of hormonal contraceptives? Should all systemically available hormonal contraceptives be avoided with boceprevir due to safety concerns associated with a doubling of progestational compound exposure?

Consult response:

The larger issue in regard to labeling for both boceprevir and telaprevir is the fact that class labeling for oral contraceptives contraindicates their use in patients with liver disease. There have been recent medical eligibility criteria published by both the World Health Organization and the Centers for Disease Control and Prevention indicating that

oral contraceptives may be used in patients with chronic viral hepatitis. DRUP is presently in the process of revising the labeling guidance for oral contraceptives and is considering these new recommendations and the publications offered in support. However, at present, contraceptive labels include this contraindication. Even if the contraindications are relaxed, the safety of oral contraceptive use in the patients with chronic hepatitis who use both one of these protease inhibitors and an oral contraceptive cannot be determined until a study that directly assesses safety is performed.

DRUP recommends that the boceprevir label clearly state the two-fold increase in DRSP concentrations and the decrease in ethinyl estradiol exposure that were identified in the DDI study. The label should recommend specifically that DRSP-containing oral contraceptive **not be used** with boceprevir and state that it is unknown whether there is a similar interaction with other hormonal contraceptives. We recommend that the use of oral contraceptives containing DRSP be contraindicated in women who are taking boceprevir.

While the extent and impact of drug interactions between boceprevir and hormonal contraceptives containing other progestins are unknown, use of alternative contraceptive methods should be recommended. For women of reproductive age, a reasonable contraceptive option might be the intrauterine device, either Paragard, which contains no hormones, or Mirena, which contains levonorgestrel. Mirena is believed to have local, rather than systemic, activity, and the hepatic contraindication is limited to acute liver disease or liver tumor.

Question 3. Ethinyl estradiol exposure (AUC) decreased by ~25% in the presence of both boceprevir and telaprevir relative to the oral contraceptive alone. Is this decrease in the EE component an efficacy concern, if there is no change (or a relative increase) in the progesterone component? If so, can the concern for contraceptive efficacy or breakthrough bleeding be ameliorated by recommending that only COCs with a minimum EE dose (e.g. 35 or 50 mcg) be used?

Consult response:

DRUP does not have any efficacy data (pregnancy data) from subjects taking both oral contraceptives and protease inhibitors. Generally, contraceptive efficacy is more closely related to progestin dose than to estrogen dose. Although there could theoretically be a decrease in efficacy, it is difficult to speculate based on clinical pharmacology results alone because efficacy is affected by the relative proportions of the estrogen and progestin components and their effects on cervical mucus, ovulation and endometrial lining changes. It is unknown whether recommending a minimum ethinyl estradiol dose may ameliorate the concern and we do not favor making such a recommendation. Unless there are clinical data, it is best to state that the effect of decreased EE exposure on oral contraceptive efficacy is unknown.

Question 4. Given the findings from the telaprevir DDI study, can hormonal contraceptives be reliably used in women while on telaprevir therapy?

Consult response:

Please refer to the response to Question 3 regarding oral contraceptive efficacy. The effect of this protease inhibitor on other estrogens and progestins used in oral contraceptives is not known. We recommend that alternative methods (e.g., IUDs or double barrier methods of contraception) should be used when patients are taking telaprevir.

Question 5. Due to the weaknesses of the DDI study conducted with boceprevir, DAVP is considering asking the Sponsor to conduct another study, which would: (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), and (3) assess a COC with a different progestational compound (e.g. norethindrone). Do the current findings support our request for another trial? If so, are there other study design features that should be recommended, aside from those outlined above?

Clinical Pharmacology Response:

Overall, we do not believe that additional studies are necessary. Boceprevir and telaprevir will be given with ribavirin, which has teratogenic effects and is therefore already contraindicated in women who are pregnant. In addition, the ribavirin label recommends that “extreme care must be taken to avoid pregnancy...” and that patients should use at least two forms of effective contraception and undergo monthly pregnancy testing. In light of the great need to prevent pregnancy in these women, we recommend that alternative non-hormonal (such as double barrier methods of contraception) or intrauterine contraceptive methods should be used when patients take these protease inhibitors with ribavirin.

However, if the Sponsor has already agreed to do additional DDI studies, a study in younger women of child-bearing potential would be preferable to another study in postmenopausal women. Pharmacokinetic characterization of the oral contraceptive to be used in these studies should be carefully considered in designing these studies (e.g., time to reach steady-state, half-life, food effect, etc.) and the study designed to appropriately control for these factors. We also recommend that an oral contraceptive that contains a progestin other than DRSP be studied because of our recommendation that the use of oral contraceptives containing DRSP be contraindicated in women who are taking boceprevir.

More importantly, both drug interaction studies with boceprevir or telaprevir were conducted in healthy subjects, while the target population of these drugs would be patients with liver disease. It is unknown how study results from healthy subjects can be extrapolated to subjects with liver disease.

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/s/

GERALD D WILLETT
03/21/2011

LISA M SOULE
03/21/2011

I concur with the conclusions and recommendations of Drs. Willett and Yu.

SCOTT E MONROE
03/22/2011

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

IND or NDA	202258
Brand Name	Boceprevir
Generic Name	SCH 503034
Sponsor	Schering-Plough Research Institute
Indication	Treatment of chronic Hepatitis C
Dosage Form	Capsule
Drug Class	HCV protease inhibitor
Therapeutic Dosing Regimen	800 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1200 mg
Submission Number and Date	SDN 003/26 Nov, 2010
Review Division	DAVP / HFD 530

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of Boceprevir (800 mg and 1200 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference post-dose between Boceprevir (800 mg and 1200 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. After five days of administration of moxifloxacin, the largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ for moxifloxacin was 11.5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3. However, it is not proper to dose subjects with this antibiotic for 5 consecutive days in a typical TQT study, as indicated in our previous comments to the sponsor's submitted protocol IND 69027 for this study dated on October 31 2006. For determination of assay sensitivity, a single dose of 400 mg of moxifloxacin is sufficient. Since the moxifloxacin reaches steady state by Day 5 and its exposure accumulates about 33%, the predicted largest lower bound after a single dose of moxifloxacin for this study should be around $10.5/1.33=7.97$ ms, which indicates that at least 5 ms moxifloxacin-induced QTc effect after a single dose administration could be detected in this study. We believe assay sensitivity was established.

In this randomized, evaluator blinded, four-period crossover study, 36 healthy subjects received Boceprevir 800 mg, Boceprevir 1200 mg, placebo, and moxifloxacin 400 mg. The overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Boceprevir (800 mg and 1200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
Boceprevir 800 mg	4	1.9	(-0.9, 4.6)
Boceprevir 1200 mg	4	4.4	(1.8, 7.1)
Moxifloxacin 400 mg*	2	13.9	(11.5, 16.3)

- Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 10.6 ms after 5 days of moxifloxacin administration. The predicted largest lower bound after a single dose is 7.97 ms.

The dose of 1200 mg was used as a suprathreshold dose, although we expressed the concern that the dose of 1200 mg might not cover the expected increase in exposure with a high-fat meal or metabolic inhibition by ketoconazole in the previous review for the protocol (IND 69,027). The dose of 1200 mg yields about 15% increase in the maximum exposure, which is insufficient to cover the exposure increase due to coadministration of a strong CYP3A4 inhibitor (42%). The marginal difference in exposure (from 15% to 40% increase) does not appear to lead to concerns of the QT effect, because no apparent concentration-QT relationship was identified in the current study. Another possible high exposure scenario is in patients with hepatic impairment. It does not appear to be a concern because Boceprevir will be contraindicated in patients with severe hepatic impairment.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor has proposed the following language in the current label.

12.2 Pharmacodynamics

Evaluation of Effect of TRADENAME on QTc Interval

(b) (4)

2.2 THE SPONSOR PROPOSED LABEL

QT-IRT recommends that following language in the label. Our recommendations are suggestions only. We defer final labeling decisions to the review division.

The effect of Boceprevir 800 mg and 1200 mg on QTc interval was evaluated in a randomized, multiple-dose, placebo-, and active-controlled (moxifloxacin 400 mg) 4-way crossover thorough QT study in 36 healthy subjects. In the study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction

method (QTcI) was below 10 ms, the threshold for regulatory concern. The dose of 1200 mg yields about 15% increase in the maximum exposure, which is insufficient to cover the exposure increase due to coadministration of a strong CYP3A4 inhibitor (42%). The marginal difference in exposure (from 15% to 40% increase) does not appear to lead to concerns of the QT effect under high exposure scenario, because no apparent concentration-QT relationship was identified.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Boceprevir (BOC, SCH 503034) is a potent, orally administered, novel serine protease inhibitor that specifically inhibits the hepatitis C virus (HCV) non-structural protein 3/4A protease and, thereby, inhibits viral replication in infected host cells.

Boceprevir is indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (18 years and older) with compensated liver disease who are previously untreated or who have failed previous therapy.

3.2 MARKET APPROVAL STATUS

Boceprevir is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From 2.4.22

“No clinically relevant effects were observed in a series of ancillary and safety pharmacology investigations of boceprevir designed to evaluate the cardiovascular (up to 50 mg/kg), respiratory (up to 200 mg/kg), central nervous (up to 200 mg/kg), gastrointestinal (up to 100 mg/kg) and /or renal (up to 100 mg/kg) systems at the highest doses tested in either dog or rats. In addition, no clinically relevant effects were observed in vitro in isolated dog cardiac Purkinje fibers at concentrations up to 0.813 μ M or in the hERG assay up to 1 μ M. In additional cardiovascular studies in monkeys, heart rate increases 16-22% at 4-5 hrs post dose were observed at 200 mg/kg.”

3.4 PREVIOUS CLINICAL EXPERIENCE

Module 5. 3.5.3 (Integrated Summary of Safety, page 343)

“In approximately 2,000 subjects treated with boceprevir plus PR, the overall tolerability was good, with a safety profile largely reflecting the known AEs associated with PR therapy.

“The incidence of treatment-related, treatment-emergent cardiac/vascular AEs is summarized for the ongoing Phase 3 studies in Table 88, ISS. The overall frequency and types of cardiac/vascular events were similar in these ongoing studies to those in the key studies. There were no unanticipated or unique events reported.

“Thirteen subjects in Study P05685, one subject in Study P05514, and three subjects in Study P06086 reported treatment-related, treatment-emergent cardiac/vascular AEs (Table 88, ISS). All of the treatment-related, treatment-emergent cardiac/vascular events

were mild or moderate in severity (Section 14.3.1.1.13 and Section 14.3.1.2.5 of the P05685 Safety Report; Section 14.3.1.1.14 of the P05514 Safety Report; Section 14.3.1.1.12 of the P06086 Safety Report). There was one report of cardiac failure in Study P05685 which was life-threatening and resulted in study drug discontinuation and death (the subject was reported to have died during a sexual act due to heart failure secondary to several tablets of sildenafil). The event was considered unlikely related to study drugs by the investigator. Full summaries are provided in Section 14.3.3 of the P05685 Safety Report. Details about cardiac/vascular-related AEs in P05685, P05514, and P06086 are presented in Section 2.1.3.1.5.2, ISS.”

Table 2: Treatment-Related, Treatment-Emergent Cardiac/Vascular Adverse Events in the Ongoing Phase 3 Studies (Protocol Nos. P05685, P05514, and P06086)

System Organ Class Preferred Term	Number (%) of Subjects		
	P05685 ^a PEG2a/R Control BOC/PEG2a/R n=201	P05514 ^b BOC/PR n=98	P06086 ^b BOC/PR n=418
Median Treatment Duration (Days)	315	113	17
Subjects Reporting Any Adverse Event	13 (6)	1 (1)	3 (1)
Cardiac Disorders	6 (3)	0	3 (1)
Angina	1 (<1)	0	0
Palpitations	4 (2)	0	2 (<1)
Tachycardia	2 (1)	0	1 (<1)
Investigations	2 (1)	1 (1)	0
Blood Pressure Increased	1 (<1)	0	0
Heart Rate Increased	1 (<1)	1 (1)	0
Vascular Disorders	5 (2)	0	0
Hypertension	2 (1)	0	0
Hypotension	3 (1)	0	0

Note: See [Section 8.3.1.5](#) for a complete list of MedDRA Preferred Terms included under “Cardiovascular Adverse Events”. Subjects may have had more than one adverse event.

BOC=boceprevir 800 mg PO TID; MedDRA=Medical Dictionary for Regulatory Activities; PEG2a=peginterferon alfa-2a; P=peginterferon alfa-2b; PO=orally; PR=peginterferon alfa-2b+ribavirin; R=ribavirin; TID=three times daily.

a: BOC/PEG2a/R arm and standard-of-care PEG2a/R control arm combined. Subjects were to be randomized in a ratio of 1:2 (PEG2a/R control to BOC/PEG2a/R treatment).

b: All subjects were to receive BOC/PR; no control arm was included.

Source Data: [Section 8.1.1.4.2.1](#); [Section 8.3.3.15](#)

Source: Table 88, ISS

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of Boceprevir’s clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 69027. The sponsor submitted the study report P04489 for SCH 503034, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

SCH 503034: A Through QT/QTc Study to Evaluate Cardiac Safety for the HCV Protease Inhibitor SCH 503034 in Healthy Volunteers

4.2.2 Protocol Number

P04489

4.2.3 Study Dates

15 Aug 2006 – 26 Oct 2006

4.2.4 Objectives

Primary Endpoint: The effect of both a therapeutic (800 mg TID) and a suprathreshold (1200 mg TID) dose of SCH 503034 (Boceprevir) at steady state on the QT interval, corrected with Fridericia's method (QTcF), as measured by the largest upper bound of the 95% one-sided confidence interval for mean change from time-matched baseline ECG recordings, compared with placebo.

Secondary Endpoints:

- The effect of both a therapeutic (800 mg TID) and a suprathreshold (1200 mg TID) dose of SCH 503034 at steady state on QT intervals without correction, with individual correction (QTcI), and with Bazett's correction method (QTcB), as measured by the largest upper bound of the 95% one-sided confidence interval for mean change from time-matched baseline ECG recordings, compared with placebo.
- The effect of SCH 503034 on QT, QTcI, QTcF, and QTcB, at both a therapeutic (800 mg TID) and a suprathreshold (1200 mg TID) dose at steady state, as measured by categorical change from time-matched baseline ECG recordings, compared with placebo.
- The effect of both a therapeutic (800 mg TID) and a suprathreshold (1200 mg TID) dose of SCH 503034 at steady state on PR, QRS, and RR intervals and heart rate (HR), as measured by the largest upper bound of the 95% one-sided confidence interval for mean change from time-matched baseline ECG recordings, compared with placebo.

4.2.5 Study Description

4.2.5.1 Design

This study was a multi-period, multiple-dose, placebo and active control study conducted in a randomized, evaluator blind, 4-way crossover manner. Each dosing occasion was followed by a 7-day washout period.

4.2.5.2 Controls

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

4.2.5.3 Blinding

All treatment arms except the positive control were evaluated blinded. The positive control was open-labeled.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

- Treatment A: Boceprevir 800 mg (4 x 200 mg) orally t.i.d. with two placebo capsules (placebo to make total pill count match 1200 mg dose of SCH 503034 t.i.d.) for 4 days then as a single AM dose on Day 5
- Treatment B: Boceprevir 1200 mg (6 x 200 mg) orally t.i.d. for 4 days then as a single AM dose on Day 5
- Treatment C: Moxifloxacin 400 mg orally as a single AM dose from Days 1 to 5
- Treatment D: Placebo (Boceprevir 1200 mg-matched) orally t.i.d. for 4 days then as a single AM dose on Day 5

4.2.6.2 Sponsor's Justification for Doses

“SCH 503034 was found to be safe and well tolerated at multiple doses up to 1200 mg TID for 5 days. Two doses of SCH 503034 were to be evaluated in this study: 800 mg TID (projected therapeutic dose) and 1200 mg TID supra therapeutic dose) at steady state. The duration of SCH 503034 dosing (5 days) was chosen so that the maximum effect could be evaluated when steady-state C_{max} had been achieved. Additionally, the study drug (as well as control treatments) was to be dosed with food to achieve optimal exposure for SCH 503034. The bioavailability of Avelox® does not change when administered with food, although a delay in T_{max} has been observed (change from approximately 1 to 2.75 hours).”

Reviewer's Comment:

- *The dose of 1200 mg yields about 15% increase in the maximum exposure, which is insufficient to cover the exposure increase due to coadministration of a strong CYP3A4 inhibitor (42%).*
- *SCH 503034 will be contraindicated in patients with severe hepatic impairment, in which the maximum exposure increases about 61%.*

4.2.6.3 Instructions with Regard to Meals

“The study drug (as well as control treatments) was to be dosed with food to achieve optimal exposure for SCH 503034. The bioavailability of Avelox® does not change when administered with food, although a delay in T_{max} has been observed (change from approximately 1 to 2.75 hours).”

Source: the sponsor’s report, p32.

Reviewer’s Comment: It is acceptable as the food effect showed that food enhanced the exposure of Boceprevir by up to 60% at the 800 mg TID. The bioavailability of Boceprevir was similar regardless of mean type (high fat vs. low fat) or timing of the meal.

4.2.6.4 ECG and PK Assessments

“Digital ECGs using a continuous 12-Lead Holter recorder were to be obtained 9 times/day at baseline (Day -1, 0 hour [predose] to 23-hours) and at steady state (Day 5, 0 hour [predose] to 23-hours). Time-matched ECGs were to be evaluated at each time point in triplicate by a third party reviewer who was blinded to study treatment. These time points were to cover the T_{max} for both Avelox® and SCH 503034 under fed conditions (~4 hours postdose). In addition to digital ECGs, regular ECGs were to be obtained at selected time points so the investigator could monitor the cardiac safety in real time.”

“The Day -1 (baseline) ECGs were to be recorded at corresponding time points as the Day 5 ECGs. The Day -1 ECG at 23 hours was to be recorded prior to Day 1 dosing and also was to serve as the predose (0-hour) ECG for Day 5. Day 5 ECGs were to be recorded at 0-hour (predose), 1, 2, 3, 4, 6, 8, 12, and 23 hours postdose”

“Pharmacokinetic samples for the determination of SCH 534128, SCH 534129, and SCH 629144 plasma concentrations were to be collected on Days 1, 2, 3, and 4 predose (0 hour), and 4 hours postdose. On Day 5 of each period, PK samples were to be collected predose (0 hour), 1, 2, 3, 4, 6, 8, 12, and 24-hours postdose.”

Reviewer’s Comment: The sampling times are acceptable. PK and ECG measurements were collected to cover mean T_{max}.

4.2.6.5 Baseline

The sponsor used time-matched QTc values collected on Day -1 as baseline values.

4.2.7 ECG Collection

During Days -1 and 5 of each confinement period, 12-lead digital Holter recorders were to be used to record continuous, high resolution (1000 Hz) 12-lead ECG data on Compact Flash memory cards capable of storing at least 24 hours of 12-lead digital data. ECGs

recorded on Compact Flash memory cards were to be mailed to a central lab for processing and evaluation by a blinded third party.

For each subject, 9 discrete 12-lead ECG digital files per study day (see below) were to be derived from the Holter recordings using the H-Scribe analysis system (Mortara Instrument, Inc., Milwaukee, Wisconsin) for the measurement RR, PR, QRS and QT intervals, derivation of heart rate and QTc (Fridericia, Bazett and individual correction) and evaluation of the potential for QT prolongation as well as clinical interpretation (abnormal/normal). The average of the triplicate ECG parameters was to be used for evaluation of the potential QT prolongation as well as clinical interpretation.

A standard 12-lead ECG was to be recorded at Screening for protocol eligibility purposes, and also at 4 hours post-dose on Days 1 to 5 and Day 6 (Period 4).

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Thirty-six subjects who met entry criteria were to receive one of the four study treatments for Days 1 to 5 of each treatment period. Five subjects discontinued treatment, three because of non-compliance with protocol and two because of AEs (pregnancy and axillary dermatitis).

Table 3: Demographic Data

	A/C/D/B n=10	B/D/C/A n=9	C/B/A/D n=8	D/A/B/C n=9	Total n=36
Sex (n,%)					
Female	4 (40)	4 (44)	3 (38)	4 (44)	15 (42)
Male	6 (60)	5 (56)	5 (63)	5 (56)	21 (58)
Race (n,%)					
White	8 (80)	7 (78)	5 (63)	7 (78)	27 (75)
Non-White	2 (20)	2 (22)	3 (38)	2 (22)	9 (25)
Black or African American	1 (10)	1 (11)	2 (25)	2 (22)	6 (17)
Multiracial	1 (10)	1 (11)	1 (13)	0	3 (8)
Ethnicity (n,%)					
Hispanic or Latino	2 (20)	2 (22)	4 (50)	2 (22)	10 (28)
Not Hispanic or Latino	8 (80)	7 (78)	4 (50)	7 (78)	26 (72)
Age (yrs)					
Mean (SD)	34.2 (12.4)	27.2 (3.3)	28.5 (8.4)	28.3 (8.3)	29.7 (8.9)
Median	31.5	28.0	25.0	26.0	27.0
Range	20 - 50	22 - 33	20 - 40	19 - 43	19 - 50
Age (n,%)					
19 - <65	10 (100)	9 (100)	8 (100)	9 (100)	36 (100)
Weight (kg)					
Mean (SD)	79.99 (12.71)	77.31 (9.82)	72.43 (15.86)	76.37 (11.76)	76.73 (12.36)
Median	79.05	77.70	71.75	79.60	78.30
Range	59.3 - 98.1	57.4 - 90.5	45.5 - 94.2	54.3 - 96.3	45.5 - 98.1
Height (cm)					
Mean (SD)	172.91 (11.06)	170.04 (7.11)	168.00 (12.14)	167.96 (9.69)	169.86 (9.92)
Median	172.40	168.00	172.80	166.10	169.35
Range	156.0 - 191.0	161.3 - 182.5	147.4 - 181.1	154.9 - 180.0	147.4 - 191.0
BMI					
Mean (SD)	26.67 (2.82)	26.73 (3.05)	25.48 (3.96)	27.01 (3.25)	26.51 (3.17)
Median	26.30	27.50	25.55	27.80	26.70
Range	22.3 - 30.5	21.7 - 29.8	19.5 - 30.8	22.6 - 30.9	19.5 - 30.9

Source: CRF, page 92

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the change from the baseline-adjusted mean difference between Boceprevir 800 mg, Boceprevir 1200 mg, and placebo in QTcF. The sponsor used a mixed effects model. Sponsor’s results are in Table 4. The sponsor found that the therapeutic and suprathapeutic dosages of Boceprevir did not result in elongated QT intervals.

Table 4: Sponsor’s Result of Δ QTcF and $\Delta\Delta$ QTcF for Boceprevir 800 mg, Boceprevir 1200 mg, and Moxifloxacin 400 mg

Hour	N	Δ QTcF: Mean (SD)				$\Delta\Delta$ QTcF: Moxi		$\Delta\Delta$ QTcF: HD		$\Delta\Delta$ QTcF: LD	
		Moxi PBO HD LD	Moxi	PBO	HD	LD	Mean	95% CI	Mean	95% CI	Mean
0	33 34 34 30	0.1 (10.0)	-7.3 (11.5)	2.2 (11.5)	-5.4 (11.2)	8.5	~11.6	7.8	~11.0	2.2	~5.4
1	33 33 34 31	-0.8 (10.6)	-6.5 (8.4)	-5.4 (8.8)	-6.0 (9.8)	6.2	~10.1	1.5	~5.3	0.5	~4.4
2	33 34 33 31	6.1 (11.2)	-7.0 (11.5)	-2.2 (6.6)	-5.7 (9.4)	13.7	~16.4	4.5	~7.3	0.3	~3.1
3	32 34 32 30	7.9 (9.9)	-3.4 (8.8)	-2.3 (9.1)	-3.1 (7.2)	12.4	~15.3	1.5	~4.4	0.8	~3.8
4	32 34 32 31	5.8 (9.1)	-7.6 (9.6)	-1.4 (7.2)	-4.8 (8.4)	13.6	~16.5	5.8	~8.7	2.9	~5.7
6	33 34 33 31	5.9 (11.4)	-0.6 (10.9)	-0.5 (8.7)	-0.8 (8.5)	7	~9.9	0.8	~3.7	-0.2	~2.7
8	33 34 33 31	6.2 (10.2)	-1.6 (10.6)	-0.8 (7.5)	-1.9 (9.8)	8.2	~11.7	0.7	~4.2	0	~3.6
12	30 32 31 31	2.2 (9.6)	-1.6 (8.9)	-3.4 (8.7)	-0.8 (7.4)	4	~7.5	-2.1	~1.4	0.6	~4.2
23	33 33 34 31	2.4 (10.4)	-2.3 (8.8)	-4.8 (8.3)	-5.8 (7.9)	4.7	~8.2	-2	~1.4	-3.4	~0.1

HD (high dose): Boceprevir 1200 mg, LD (low dose): Boceprevir 800 mg, Moxi (moxifloxacin), PBO (placebo)

In Table 4, the sponsor reported the upper 95% confidence bound for Δ QTcF and $\Delta\Delta$ QTcF. It is unclear what the meaning of “~” is. Our independent results agree with the sponsor’s results that Boceprevir does not cause large QT prolongation (see Section 5.2).

4.2.8.2.2 Assay Sensitivity

It is unknown what the sponsor’s result was for the maximum lower limit of the 95% CIs for $\Delta\Delta$ QTcF moxifloxacin. The sponsor claims that the lower limits of the 95% CIs surpassed 10 ms for multiple time points. Our independent analysis agrees with the final conclusions reported by the sponsor (see Section 5.2).

4.2.8.3 Safety Analysis

Randomized subjects receiving at least one dose of study treatment were included in the safety analysis.

Subject 101, randomized to receive treatment sequence B/D/C/A discontinued treatment after the final dose of moxifloxacin on Day 5 of treatment C due to pregnancy.

Subject 105, randomized to receive treatment sequence C/B/A/D, discontinued treatment on Day 2 of treatment B due to the inability to swallow subsequent capsules.

Subject 109, randomized to receive treatment sequence B/D/C/A discontinued treatment following the final placebo dose of treatment D due to noncompliance with protocol.

Subject 160, randomized to receive treatment sequence B/D/C/A discontinued treatment on Day 2 of treatment A due to an adverse event (axillary dermatitis).

Subject 166, randomized to receive treatment sequence C/B/A/D, discontinued treatment due to non-compliance with protocol after receiving the final 1200-mg dose of SCH 503034 of treatment B.

Of the 36 subjects who participated in the study, a total of 29 subjects (81%) reported at least one AE during the study.

AEs were reported by a total of 20 (63%) subjects during the 5 days of treatment with 800 mg SCH 503034, and 19 (53%) subjects during the 5 days of treatment with 1200 mg SCH 503034. The most common AE overall was dysgeusia reported by 14 (44%) of the subjects that received 800 mg SCH 503034, 16 (44%) of the subjects that received 1200 mg SCH 503034, and 1 (3%) of subjects that received placebo. The second most frequent AE was headache reported by 4 (13%) of subjects that received 800 mg SCH 503034, 7 (19%) subjects that received 1200 mg SCH 503034, 4 (11%) of subjects that received moxifloxacin, and 6 (18%) of subjects that received placebo. Nausea was also a frequent AE reported by 6 (19%) of subjects that received 800 mg SCH 503034, 6 (17%) subjects that received 1200 mg SCH 503034, 5 (14%) of subjects that received moxifloxacin, and 1 (3%) of subjects that received placebo. All of the above AEs were considered to be mild in nature (except for one report of headache in the moxifloxacin group which was considered moderate), and were considered by the investigator as unlikely related to treatment and did not require concomitant therapy.

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

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 5 and Table 6 and mean plasma concentration-time profile is displayed in Figure 1. C_{max} and AUC values in the thorough QT study were increased following administration of 1200 mg (Supra therapeutic dose) compared with 800 mg (therapeutic dose) in a less than dose proportional manner. Also mean concentration-time profiles between two doses are substantially overlapped.

Table 5: Summary Statistics for SCH 503034 Pharmacokinetics Parameter Estimates after Multiple Oral Doses of SCH503034 on Day 5.

Parameters	Mean (CV,%)	
	SCH 503034 800 mg (n=31) ^{b,c}	SCH 503034 1200 mg (n=35) ^c
Tmax ^a (hr)	2.00 (1.00-4.00)	2.00 (1.00-4.00)
Cmax (ng/mL)	1690 (19)	1940 (24)
Cmin (ng/mL)	61.9 (41)	79.9 (46)
AUC(τ) (ng.hr/mL)	5320 (23)	6500 (22)
t _{1/2} (hr)	2.31 (68)	3.01 (73)
CL/F (L/hr)	158 (22)	196 (31)
Vd/F (L)	530 (84)	879 (85)

a: Median (range)

b: The four Subjects (101, 109, 160, and 166) were excluded from analysis of the SCH 503034 800 mg dose group as treatment at this dose was not completed

c: Subject 105 was excluded from the analysis of both SCH 503034 treatment groups due to early withdrawal

AUC(τ) = area under the concentration-time curve during the dosing interval, Cmax = maximum observed plasma concentration, Cmin = minimum observed plasma concentration, CL/F = apparent total body clearance, t_{1/2} = terminal phase half-life, Tmax = time of observed maximum concentration, Vd/F = apparent volume of distribution

The values for SCH 503034 represent the calculated value from the sum of SCH 534128 and SCH 534129

Source: the sponsor's report, p76.

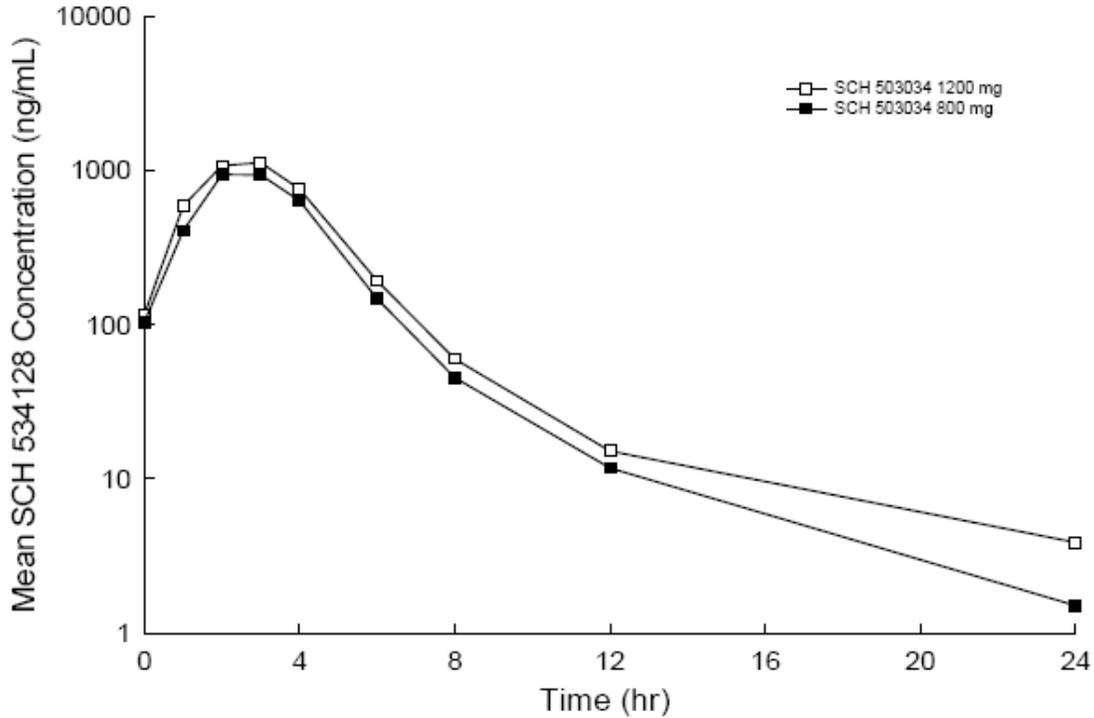
Table 6: Summary Statistics of Mean Plasma Concentrations of SCH 503034, SCH 534128, SCH 534129, and SCH 629144 after Dosing With SCH 503034

P04489 -- Summary Statistics								
Analyte	Treatment	n	Cmax		AUC(τ)		Cmin	
			Mean	CV	Mean	CV	Mean	CV
SCH503034	SCH503034 1200mg	35	1940	24%	6497	22%	80	46%
	SCH503034 800mg	31	1693	19%	5315	23%	62	41%
SCH534128	SCH503034 1200mg	35	1290	23%	4418	23%	59	47%
	SCH503034 800mg	31	1128	22%	3629	25%	45	42%
SCH534129	SCH503034 1200mg	35	669	29%	2079	24%	21	43%
	SCH503034 800mg	31	571	18%	1686	23%	17	42%
SCH629144	SCH503034 1200mg	35	7376	26%	34420	33%	1380	46%
	SCH503034 800mg	31	5156	30%	23170	37%	891	49%

Source: the sponsor's report, p120.

Figure 1: Mean Plasma Concentration-Time Profile of SCH 503034

Log: Linear



Source: the sponsor's report, p122.

4.2.8.4.2 Exposure-Response Analysis

“There was no apparent dose effect of SCH 503034 on the pharmacodynamic parameters evaluated.”

Reviewer's Analysis: The sponsor did not evaluate the concentration and $\Delta\Delta QTc$ relationship. The reviewer's independent analysis is presented in Figure 4.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

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

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI),

and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 7, it appears that QTcI had smaller absolute slopes than QTcF. Therefore, QTcI is a better correction method for the study data.

Table 7: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF	Slope of QTcI	P value
Boceprevir 1200 mg	-0.0158	-0.0135	0.6684
Boceprevir 800 mg	-0.0238	-0.0050	0.0047
Moxifloxacin 400 mg	-0.0098	-0.0005	0.0747
Placebo	-0.0306	-0.0200	0.1298
All	-0.0155	-0.0121	0.1844

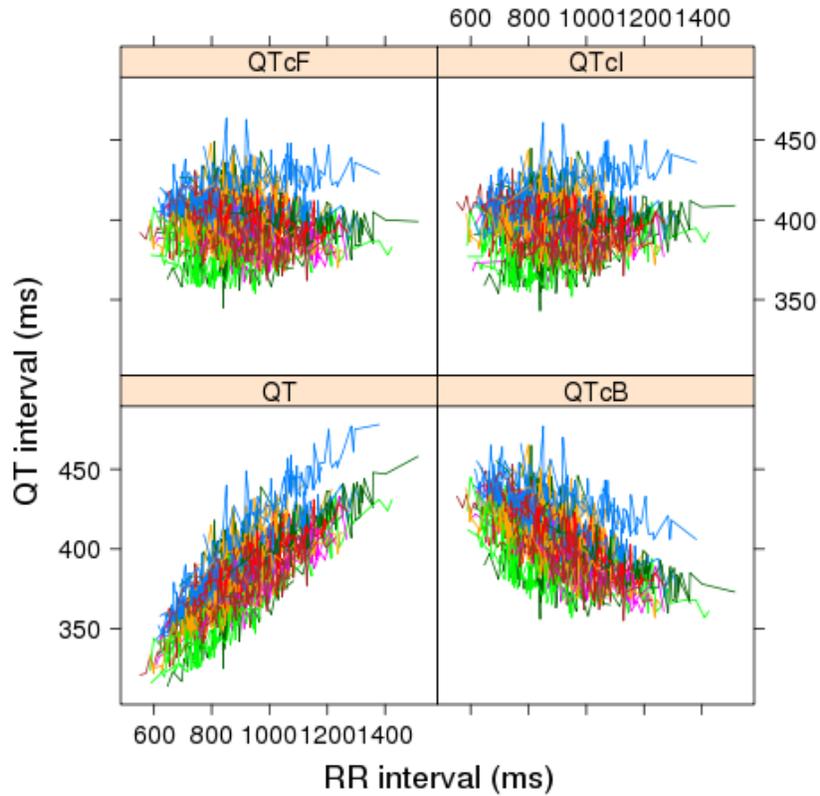
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 8, it also appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. While this is not consistent with the sponsor's use of QTcF for their primary analysis, our evaluation of QTcF produced similar results to QTcI.

Table 8: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
Boceprevir 1200 mg	35	0.0018	35	0.0012
Boceprevir 800 mg	31	0.0023	31	0.0014
Moxifloxacin 400 mg	35	0.0017	35	0.0011
Placebo	34	0.0021	34	0.0012
All	36	0.0015	36	0.0006

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Boceprevir

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment, period, and sequence as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 9: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group A:
Boceprevir 800 mg x 5 days**

Time/(hr)	Δ QTcI: Boceprevir			Δ QTcI: placebo			$\Delta\Delta$ QTc			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0	30	-7.4	2.5	35	-9.2	2.4		1.8	1.9	(-1.3, 4.9)
1	31	-7.3	1.8	35	-7.8	1.7		0.5	2.3	(-3.4, 4.3)
2	31	-8.2	2.7	35	-8.3	2.7		0.1	1.5	(-2.4, 2.6)
3	31	-4.4	1.7	34	-5.0	1.6		0.6	1.8	(-2.4, 3.6)
4	31	-6.5	1.8	35	-8.3	1.7		1.9	1.6	(-0.9, 4.6)
6	31	-2.8	2.0	35	-1.9	1.9		-0.9	1.9	(-4.1, 2.3)
8	31	-2.7	1.8	35	-2.1	1.8		-0.5	2.1	(-3.9, 2.9)
12	31	-2.3	1.8	33	-2.6	1.7		0.3	2.2	(-3.3, 3.9)
23	31	-6.8	1.5	35	-3.4	1.5		-3.5	2.0	(-6.8, -0.1)

**Table 10: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Treatment Group B:
Boceprevir 1200 mg x 5 days**

Time/(hr)	Δ QTcI: Boceprevir			Δ QTcI: placebo			$\Delta\Delta$ QTc			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0	35	-2.7	2.4	35	-9.2	2.4		6.5	1.8	(3.5, 9.5)
1	35	-6.8	1.7	35	-7.8	1.7		0.9	2.2	(-2.8, 4.7)
2	34	-4.3	2.7	35	-8.3	2.7		4.1	1.5	(1.6, 6.5)
3	33	-3.5	1.6	34	-5.0	1.6		1.5	1.8	(-1.4, 4.5)
4	33	-3.9	1.7	35	-8.3	1.7		4.4	1.6	(1.8, 7.1)
6	34	-1.6	1.9	35	-1.9	1.9		0.3	1.9	(-2.9, 3.4)
8	34	-2.0	1.7	35	-2.1	1.8		0.1	2.0	(-3.2, 3.4)
12	33	-5.1	1.7	33	-2.6	1.7		-2.5	2.1	(-6.0, 1.1)
23	34	-5.8	1.5	35	-3.4	1.5		-2.4	2.0	(-5.7, 0.9)

The largest upper bounds of the 2-sided 90% CI for the mean difference (post-dose) between Boceprevir 800 mg and placebo, and between Boceprevir 1200 mg and placebo, were 4.6 ms and 7.1 ms, respectively.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 11. The largest unadjusted 90% lower confidence interval is 11.5 ms. Using a Bonferroni multiple endpoint adjustment for 4 time points, the largest lower confidence interval is 10.6 ms, which indicates that an effect of at least 5 ms QTcI due to moxifloxacin can be detected from the study.

Table 11: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Moxifloxacin

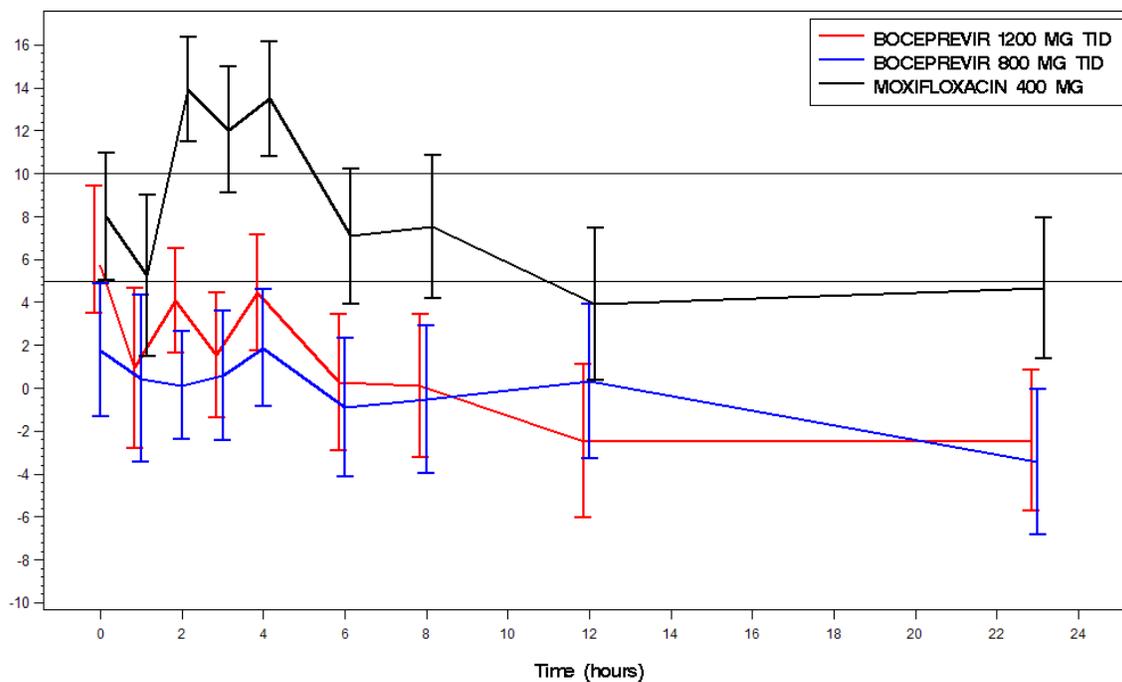
Time/(hr)	Δ QTcI: moxifloxacin			Δ QTcI: placebo			$\Delta\Delta$ QTc				
	N	Mean	SD	N	Mean	SD	N	Mean	SD	Unadjusted 90% CI	Adjusted* 90% CI
0	34.0	-1.2	2.4	35.0	-9.2	2.4		8.0	1.8	(5.0, 11.0)	(3.9, 12.1)
1	34.0	-2.5	1.7	35.0	-7.8	1.7		5.3	2.3	(1.5, 9.0)	(0.1, 10.4)
2	34.0	5.6	2.6	35.0	-8.3	2.7		13.9	1.5	(11.5, 16.3)	(10.6, 17.3)
3	34.0	7.0	1.6	34.0	-5.0	1.6		12.0	1.8	(9.1, 15.0)	(8.0, 16.1)
4	34.0	5.1	1.7	35.0	-8.3	1.7		13.5	1.6	(10.8, 16.2)	(9.8, 17.2)
6	34.0	5.2	1.9	35.0	-1.9	1.9		7.1	1.9	(3.9, 10.2)	(2.8, 11.4)
8	34.0	5.4	1.7	35.0	-2.1	1.8		7.5	2.0	(4.2, 10.9)	(3.0, 12.1)
12	34.0	1.3	1.7	33.0	-2.6	1.7		3.9	2.1	(0.3, 7.5)	(-1.0, 8.8)
23	34.0	1.2	1.4	35.0	-3.4	1.5		4.6	2.0	(1.4, 7.9)	(0.1, 9.2)

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

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

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

Figure 3: Mean and 90% CI* Δ QTcI Timecourse



*All CIs are unadjusted, including moxifloxacin.

5.2.1.4 Categorical Analysis

Table 12 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 12: Categorical Analysis for QTcI

Treatment	N	Value ≤ 450 ms	450 ms $<$ Value ≤ 480 ms
Boceprevir 1200 mg	35	35 (100%)	0 (0.0%)
Boceprevir 800 mg	31	31 (100%)	0 (0.0%)
Moxifloxacin 400 mg	35	33 (94.3%)	2 (5.7%)
Placebo	34	34 (100%)	0 (0.0%)
Baseline	36	36 (100%)	0 (0.0%)

Table 13 lists the categorical analysis results for Δ QTcI. No subject's change from baseline was above 60 ms.

Table 13: Categorical Analysis of Δ QTcI

Treatment Group	N	Value \leq 30 ms	30 ms<Value \leq 60 ms
Boceprevir 1200 mg	35	35 (100%)	0 (0.0%)
Boceprevir 800 mg	31	31 (100%)	0 (0.0%)
Moxifloxacin 400 mg	35	34 (97.1%)	1 (2.9%)
Placebo	34	34 (100%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14 and Table 15. The largest upper limits of 90% CI for the PR mean differences (post-dose) between Boceprevir 800 mg and placebo, and Boceprevir 1200 mg and placebo, are 7.1 ms and 7.0 ms, respectively.

There were no subjects who experienced PR interval greater than 200 ms in both the Boceprevir 800-mg and Boceprevir 1200-mg groups.

Table 14: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group A: Boceprevir 800 mg x 5 days

Time/(hr)	Δ PR: Boceprevir			Δ PR:Placebo			$\Delta\Delta$ PR			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0	30	2.8	1.8	34	-3.1	1.7		5.9	2.1	(2.4, 9.4)
1	31	0.0	2.1	33	-0.6	2.1		0.6	1.4	(-1.7, 3.0)
2	31	2.3	2.1	34	-0.3	2.0		2.6	1.5	(0.0, 5.2)
3	30	4.7	1.7	34	0.7	1.7		4.0	1.9	(0.9, 7.1)
4	31	2.3	1.7	34	0.8	1.6		1.5	1.5	(-1.1, 4.0)
6	31	0.9	2.3	34	2.4	2.2		-1.5	1.4	(-3.8, 0.8)
8	31	2.1	1.7	34	2.0	1.6		0.2	1.8	(-2.8, 3.1)
12	31	0.3	2.5	32	3.1	2.5		-2.8	1.3	(-4.9, -0.7)
23	31	0.9	1.4	33	-2.6	1.4		3.5	1.6	(0.8, 6.3)

Table 15: Analysis Results of Δ PR and $\Delta\Delta$ PR for Treatment Group B: Boceprevir 1200 mg x 5 days

Time/(hr)	Δ PR: Boceprevir			Δ PR: Placebo			$\Delta\Delta$ PR			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0	35	1.2	1.7	34	-3.1	1.7		4.3	2.0	(1.0, 7.7)
1	35	0.8	2.1	33	-0.6	2.1		1.4	1.3	(-0.8, 3.7)
2	34	3.3	2.0	34	-0.3	2.0		3.6	1.5	(1.1, 6.1)
3	33	3.7	1.7	34	0.7	1.7		3.0	1.8	(0.0, 6.0)
4	33	2.7	1.6	34	0.8	1.6		1.9	1.5	(-0.6, 4.4)
6	34	3.5	2.2	34	2.4	2.2		1.1	1.3	(-1.1, 3.4)
8	34	2.4	1.6	34	2.0	1.6		0.4	1.7	(-2.5, 3.3)
12	32	1.8	2.5	32	3.1	2.5		-1.3	1.3	(-3.4, 0.8)
23	34	1.7	1.4	33	-2.6	1.4		4.3	1.6	(1.7, 7.0)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16 and Table 17. The largest upper limits of 90% CI for the QRS mean differences (post-dose) between Boceprevir 800 mg and placebo, and Boceprevir 1200 mg and placebo, are 2.1 ms and 2.0 ms, respectively. There were no subjects who experienced QRS interval greater than 110 ms in both Boceprevir 800 mg and Boceprevir 1200 mg.

There were no subjects who experienced QRS interval greater than 110 ms in both the Boceprevir 800-mg and Boceprevir 1200-mg groups.

**Table 16: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group A:
Boceprevir 800 mg x 5 days**

Time/(hr)	Δ QRS: Boceprevir			Δ QRS: Placebo			$\Delta\Delta$ QRS			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0	30	-1.4	0.7	34	-1.7	0.6		0.3	0.8	(-1.0, 1.6)
1	31	-0.5	0.5	33	-0.9	0.5		0.4	0.6	(-0.7, 1.4)
2	31	-0.4	0.5	34	-1.1	0.5		0.7	0.7	(-0.4, 1.8)
3	30	-0.5	0.5	34	-0.9	0.5		0.3	0.7	(-0.8, 1.4)
4	31	0.0	0.5	34	-0.7	0.5		0.8	0.7	(-0.3, 1.9)
6	31	0.6	0.5	34	-0.5	0.4		1.0	0.6	(0.0, 2.1)
8	31	-0.7	0.4	34	-0.5	0.4		-0.2	0.5	(-1.1, 0.6)
12	31	0.0	0.5	32	-0.1	0.5		0.1	0.7	(-1.0, 1.2)
23	31	-0.4	0.5	33	-0.4	0.5		-0.0	0.7	(-1.2, 1.1)

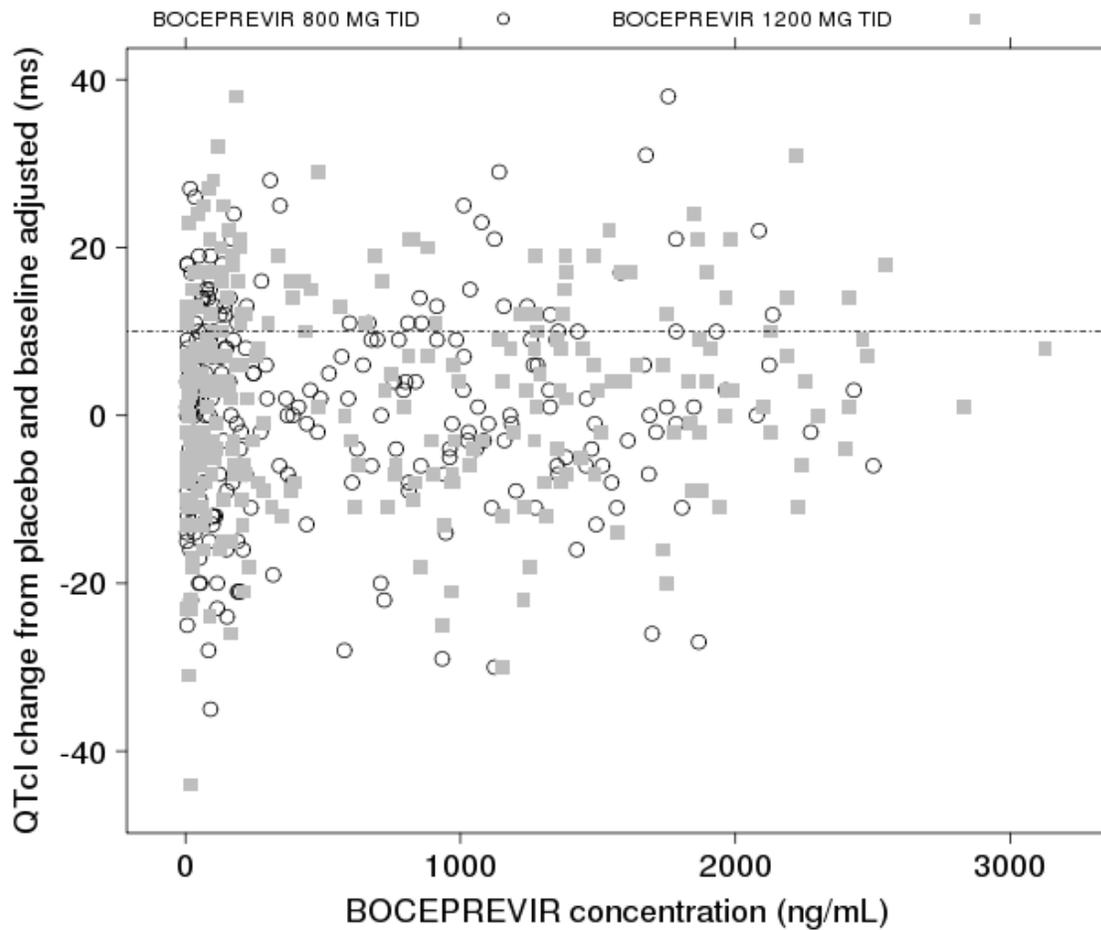
**Table 17: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Treatment Group B:
Boceprevir 1200 mg x 5 days**

Time/(hr)	Δ QRS: Bocprevir			Δ QRS: Placebo			$\Delta\Delta$ QRS			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	90% CI
0	35	-2.2	0.6	34	-1.7	0.6		-0.5	0.7	(-1.7, 0.7)
1	35	-0.5	0.4	33	-0.9	0.5		0.3	0.6	(-0.7, 1.4)
2	34	-0.3	0.5	34	-1.1	0.5		0.9	0.6	(-0.2, 1.9)
3	33	0.1	0.5	34	-0.9	0.5		0.9	0.7	(-0.2, 2.0)
4	33	-0.3	0.5	34	-0.7	0.5		0.4	0.7	(-0.7, 1.5)
6	34	-0.2	0.4	34	-0.5	0.4		0.3	0.6	(-0.7, 1.3)
8	34	-0.1	0.4	34	-0.5	0.4		0.3	0.5	(-0.5, 1.2)
12	32	-1.1	0.5	32	-0.1	0.5		-1.1	0.7	(-2.2, 0.0)
23	34	-0.2	0.5	33	-0.4	0.5		0.1	0.6	(-1.0, 1.2)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcI and Boceprevir concentrations is visualized in Figure 4 with no evident exposure-response relationship (p-value=0.10).

Figure 4: $\Delta\Delta$ QTcI vs. Boceprevir Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

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

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 94% of the ECGs were annotated in the primary lead II, with less than 0.07 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Boceprevir does not affect PR and QRS duration.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

o Table 1: Highlights of Clinical Pharmacology		
Therapeutic dose	800 mg TID	
Maximum tolerated dose	NA	
Principal adverse events	No specific AE discernible when administered as monotherapy; anemia and dysgeusia when in combination with Standard of Care (P/r)	
Maximum dose tested	Single Dose	800 mg
	Multiple Dose	1200 mg TID
Exposures Achieved at Maximum Tested Dose	Single Dose (fed)	Mean (%CV) Cmax 1710 ng/mL (18) Mean (%CV) AUC 6350 ng.hr/mL (14)
	Multiple Dose (fed)	Mean (%CV) Cmax 1964 ng/mL (23) Mean (%CV) AUC 6614 ng.hr/mL (23)
Range of linear PK	100 to 800 mg TID	
Accumulation at steady state	Minimal, mean R values range: 0.773-1.45 200-800 mg TID	
Metabolites	Major metabolite SCH 629144, inactive	
Absorption	Absolute/Relative Bioavailability	Absolute BA unknown
	Tmax	<ul style="list-style-type: none"> • Median (1-4) for parent 2 hrs • Median (2-4) for metabolites 3 hrs
Distribution	Vd/F or Vd	Mean (%CV) Vd/F ~ 772 (99) L
	% bound	Mean (%CV) 73.6 (3)

Elimination	Route	<ul style="list-style-type: none"> Primary route hepatic; percent dose eliminated 79% 																																																
	Terminal t _{1/2}	<ul style="list-style-type: none"> Mean (%CV) for parent ~3.4 (90) Mean (%CV) for metabolites 2.78 (13) 																																																
	Effective t _{1/2}	<ul style="list-style-type: none"> Mean (%CV) 5.98 (14) for parent Mean (%CV) for metabolites not determined 																																																
	CL/F or CL	Mean (%CV) 161 (36) L/hr																																																
Intrinsic Factors	Age	No effect																																																
	Gender	Clearance was estimated to be 19% lower in females (155 L/h) than males (191 L/h)																																																
	Race	No effect																																																
	Hepatic Impairment	<p>Specify mean changes in C_{max} and AUC</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Group</th> <th>LS Mean^a</th> <th>Treatment Comparison</th> <th>Ratio Estimate %</th> <th>90% CI</th> </tr> </thead> <tbody> <tr> <td rowspan="4">AUC(tf) (ng-hr/mL)</td> <td>1 (Mild)</td> <td>1587</td> <td>Mild vs Healthy</td> <td>91</td> <td>83-131</td> </tr> <tr> <td>2 (Moderate)</td> <td>1981</td> <td>Moderate vs Healthy</td> <td>114</td> <td>79-163</td> </tr> <tr> <td>3 (Severe)</td> <td>2591</td> <td>Severe vs Healthy</td> <td>149</td> <td>104-213</td> </tr> <tr> <td>4 (Healthy)</td> <td>1743</td> <td></td> <td>-</td> <td>-</td> </tr> <tr> <td rowspan="4">C_{max} (ng/mL)</td> <td>1 (Mild)</td> <td>509</td> <td>Mild vs Healthy</td> <td>100</td> <td>82-161</td> </tr> <tr> <td>2 (Moderate)</td> <td>544</td> <td>Moderate vs Healthy</td> <td>107</td> <td>88-172</td> </tr> <tr> <td>3 (Severe)</td> <td>822</td> <td>Severe vs Healthy</td> <td>161</td> <td>100-260</td> </tr> <tr> <td>4 (Healthy)</td> <td>510</td> <td></td> <td>-</td> <td>-</td> </tr> </tbody> </table>	Parameter	Group	LS Mean ^a	Treatment Comparison	Ratio Estimate %	90% CI	AUC(tf) (ng-hr/mL)	1 (Mild)	1587	Mild vs Healthy	91	83-131	2 (Moderate)	1981	Moderate vs Healthy	114	79-163	3 (Severe)	2591	Severe vs Healthy	149	104-213	4 (Healthy)	1743		-	-	C _{max} (ng/mL)	1 (Mild)	509	Mild vs Healthy	100	82-161	2 (Moderate)	544	Moderate vs Healthy	107	88-172	3 (Severe)	822	Severe vs Healthy	161	100-260	4 (Healthy)	510		-	-
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Renal Impairment	Mean changes in C _{max} (GMR 81%) and AUC (GMR 90%) ESRD subjects																																																	

	PG Factors in PK, PD or Safety	Known or suspected PG factors - IL28b																											
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC																											
		<table border="1"> <thead> <tr> <th rowspan="2">Co-administered Drug (Study)</th> <th colspan="2">Ratio estimate^a of Boceprevir PK Parameters (in combination vs alone) (90% CI of the ratio estimate)</th> </tr> <tr> <th>Change in mean Cmax</th> <th>Change in mean AUC(τ)</th> </tr> </thead> <tbody> <tr> <td>Ketoconazole</td> <td>1.41 ↑ (1.00-1.97)</td> <td>2.31 ↑ (2.00-2.67)</td> </tr> <tr> <td>Ibuprofen</td> <td>0.94 — (0.67-1.32)</td> <td>1.04 — (0.90-1.20)</td> </tr> <tr> <td>Diflunisal</td> <td>0.86 — (0.66-1.32)</td> <td>0.96 — (0.79-1.17)^c</td> </tr> <tr> <td>Ritonavir</td> <td>0.73 ↓ (0.57-0.93)</td> <td>0.81 ↔ (0.73-0.91)</td> </tr> <tr> <td>Clarithromycin (in combination with Diflunisal)</td> <td>1.36 ↑ (1.04-1.78)</td> <td>1.21 ↔ (1.06-1.38)</td> </tr> <tr> <td>Efavirenz</td> <td>0.92 ↔ (0.78-1.08)</td> <td>0.81^d ↔ (0.75 – 0.89)</td> </tr> <tr> <td>Tenofovir</td> <td>1.05 — (0.98-1.12)</td> <td>1.08^d — (1.02-1.14)</td> </tr> <tr> <td>Peginterferon alfa-2b</td> <td>0.88 — (0.66-1.18)</td> <td>1.00^d — (0.89-1.13)</td> </tr> </tbody> </table>	Co-administered Drug (Study)	Ratio estimate ^a of Boceprevir PK Parameters (in combination vs alone) (90% CI of the ratio estimate)		Change in mean Cmax	Change in mean AUC(τ)	Ketoconazole	1.41 ↑ (1.00-1.97)	2.31 ↑ (2.00-2.67)	Ibuprofen	0.94 — (0.67-1.32)	1.04 — (0.90-1.20)	Diflunisal	0.86 — (0.66-1.32)	0.96 — (0.79-1.17) ^c	Ritonavir	0.73 ↓ (0.57-0.93)	0.81 ↔ (0.73-0.91)	Clarithromycin (in combination with Diflunisal)	1.36 ↑ (1.04-1.78)	1.21 ↔ (1.06-1.38)	Efavirenz	0.92 ↔ (0.78-1.08)	0.81 ^d ↔ (0.75 – 0.89)	Tenofovir	1.05 — (0.98-1.12)	1.08 ^d — (1.02-1.14)	Peginterferon alfa-2b
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Peginterferon alfa-2b	0.88 — (0.66-1.18)	1.00 ^d — (0.89-1.13)																											
		<table border="1"> <thead> <tr> <th rowspan="2">Co-administered Drug (Study)</th> <th colspan="2">Ratio estimate^a of Co-administered Drug PK Parameters (in combination vs alone) (90% CI of the ratio estimate)</th> </tr> <tr> <th>Change in mean Cmax</th> <th>Change in mean AUC(τ)</th> </tr> </thead> <tbody> <tr> <td>Midazolam</td> <td>2.77 ↑ (2.36-3.25)</td> <td>5.30 ↑ (4.66-6.03)</td> </tr> <tr> <td>Efavirenz</td> <td>1.11 ↔ (1.02-1.20)</td> <td>1.20 ↔ (1.15-1.26)</td> </tr> <tr> <td>Drospirenone/ Ethinyl estradiol</td> <td>Drospirenone: 1.57 ↑ (1.46-1.70) Ethinyl estradiol: 1.00 - (0.91-1.10)</td> <td>Drospirenone: 1.99 ↑ (1.87-2.11) Ethinyl estradiol: 0.76 ↓ (0.73-0.79)</td> </tr> <tr> <td>Tenofovir</td> <td>1.32 ↑ (1.19-1.45)</td> <td>1.05 — (1.01-1.09)</td> </tr> <tr> <td>Peginterferon alfa-2b</td> <td>NA</td> <td>0.99^{b,c} — (0.83-1.17)</td> </tr> </tbody> </table>	Co-administered Drug (Study)	Ratio estimate ^a of Co-administered Drug PK Parameters (in combination vs alone) (90% CI of the ratio estimate)		Change in mean Cmax	Change in mean AUC(τ)	Midazolam	2.77 ↑ (2.36-3.25)	5.30 ↑ (4.66-6.03)	Efavirenz	1.11 ↔ (1.02-1.20)	1.20 ↔ (1.15-1.26)	Drospirenone/ Ethinyl estradiol	Drospirenone: 1.57 ↑ (1.46-1.70) Ethinyl estradiol: 1.00 - (0.91-1.10)	Drospirenone: 1.99 ↑ (1.87-2.11) Ethinyl estradiol: 0.76 ↓ (0.73-0.79)	Tenofovir	1.32 ↑ (1.19-1.45)	1.05 — (1.01-1.09)	Peginterferon alfa-2b	NA	0.99 ^{b,c} — (0.83-1.17)							
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	Food Effects	Administration with food increased the oral bioavailability of boceprevir relative to the fasted state, by 40% to 60% based on AUC, and tended to slightly delay median Tmax from ~ 1 hour to ~ 2 hours. Meal type (eg, high vs low fat), and timing of meal administration (5 minutes prior, during, or immediately after breakfast), did not notably affect the increase in exposure. Therefore, boceprevir should be administered with food in order to maximize exposure.
Expected High Clinical Exposure Scenario	~2x	

6.2 (CLIN) TABLE OF STUDY ASSESSMENTS

Copy from protocol/study report

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

/s/

JOANNE ZHANG
03/14/2011

JANICE BRODSKY
03/14/2011

JOO YEON LEE
03/14/2011

HAO ZHU
03/15/2011

MONICA L FISZMAN
03/15/2011

NORMAN L STOCKBRIDGE
03/15/2011

M E M O R A N D U M

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

Date: March 7, 2011

From: Andrew Dmytrijuk M.D.
Medical Officer
Division of Hematology Products

Through: Kathy Robie-Suh M.D., Ph.D.
Medical Team Leader
Division of Hematology Products

Subject: Consult Request regarding Boceprevir
NDA 202258

To: Sherly Abraham
Division of Antiviral Products

Request:

Consultation is requested to obtain assessment of anemia as a treatment emergent adverse event for Boceprevir (BOC, B), a drug under review for treatment of chronic hepatitis C virus (HCV) infections when administered in combination with pegylated interferon (P) and ribavirin (RBV, R). The Division of Antiviral Products (DAVP) is also seeking consultation regarding the sponsor's proposed guidelines for the use of erythropoietin (EPO) for patients who develop anemia. The NDA was submitted as a rolling review. The NDA was first submitted on September 30, 2010 and the rest of the NDA (including clinical components was submitted on November 10, 2010. The PDUFA goal date for the NDA is May 13, 2011.

Materials reviewed:

- DAVP consult request and questions (see appendix 1 of this review).
- NDA 202258 (letter date November 10, 2010) submission including but not limited to modules 2.5 and 2.7 and module 5 of submission 0001; and available patient narratives. The key studies for the integrated safety assessment include P03523, P05216, and P05101. Subjects in P03523 (treatment naïve), P05216 (treatment naïve), and P05101 (previous treatment failures) received P plus R in the PR control arms, and B and P plus R in the B/PR arms. Studies P05216 and P05101 had a 4-week lead-in with PR, followed by 44 weeks of placebo/PR or B/PR. Study P03523 compared PR for 48 weeks to five treatment paradigms containing B. The protocol-specified total treatment durations in the key studies ranged from 28 to 48 weeks.

- Medical officer email regarding anemia as a treatment emergent adverse event (personal communications, e-mail sent February 24, 2011 (see appendix 2 of this review).
- Beutler, E. et al. William's Hematology sixth edition. 2001.
- Literature:
 - Kwo, P.Y. et al.: Efficacy of boceprevir, an NS3 Protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized multicenter phase 2 trial. 2010. *Lancet*. 376(9742):705-716.
 - McHutchinson, J.G. et al.: Strategies for managing anemia in hepatitis C patients undergoing antiviral therapy. 2007. *Am J. Gastroenterol*. 102(4):880-889.
 - Willett, A.B. et al.: Determination of hemolytic anemia through the study of 51Cr Red Cell Survival and Splenic Sequestration. 2008. *J. Nuc. Med. Tech*. 36(2):95-98.
- Epoetin alfa (Procrit and Epogen), Ferrlecit (sodium ferric gluconate), Venofer (iron sucrose) and Retrovir (zidovudine) labels.

Summary of relevant materials:

Boceprevir (BOC, B) is a specific inhibitor of the HCV NS 3/4A protease. It inhibits viral replication in infected host cells. B is a new molecular entity, and the first of the direct acting antiviral agents to be submitted as an NDA for treatment of HCV in combination with pegylated interferon (P) and ribavirin (R). The proposed indication is for the treatment of chronic HCV genotype 1 infection in combination with P and R, in adult patients (≥ 18 years) with compensated liver disease who are previously untreated or who have failed previous therapy. The proposed dosing regimen is P+R x 4 weeks then add B 800 mg orally three times a day at week 5. Depending on the results of HCV testing at week eight and week 12 or week 24 therapy the duration of treatment with B and P+R may change. The proposed duration of treatment with B, P and R is shown in the table below.

Proposed Duration of Treatment



(b) (4)

3 drugs = B+P+R

The efficacy of B as a treatment for chronic hepatitis C (genotype 1) infection was assessed in approximately 1500 adult subjects who were previously untreated or who had failed previous therapy in Phase III clinical studies. The sponsor includes two key clinical studies which support the labeling for B. Study P05216 (SPRINT-2) entitled, "A Phase 3, Safety and Efficacy Study of B in Previously Untreated Subjects with Chronic Hepatitis C Genotype 1". This study was a randomized (1:1:1), double-blind, placebo-controlled study. Patients were stratified according to viral load ($\leq 400,000$ IU/ml and $> 400,000$ IU/ml). P was given at dose of 1.5 mcg/kg/week subcutaneously and R was given at a dose of 600-400 mg orally once daily and B was administered at 800 mg orally three times daily. Patients were randomized to one of three treatment arms as follows:

- P+ R x 48 weeks. N= 363 patients.
- P+R x 4 weeks then B+P+R from week 5–24. N= 368 patients.
- P+R x 4 weeks then B+P+R from week 5-44. N = 366 patients.

Based on the sponsor's analyses the addition of B to P and R significantly increased the SVR rates compared to P and R alone in the combined cohort (63% to 66% B containing arms vs. 38% P+R control) for randomized subjects who received at least one dose of any study medication in patients who were previously untreated for HCV.

The second study P05101 (RESPOND-2) entitled, "A Phase 3 Safety and Efficacy Study of B in Subjects with Chronic Hepatitis C Genotype One Who Failed Prior Treatment with P+R", was a randomized (1:2:2), double-blind, parallel group study. Patients were stratified according to their response to previous HCV therapy as either those who relapsed or those who previously responded. In this study the dosing of P, R and B was similar to the SPRINT-2 trial. Patients were randomized to one of three treatment arms as follows:

- P+R x 48 weeks. N= 80 patients.
- P+R x 4 weeks then B+P+R from week 5-32. N = 162 patients.
- P+R x 4 weeks then B+P+R from week 5-44. N = 161 patients.

Based on the sponsor's analyses in patients who previously failed P+R therapy the addition of B to P and R therapy significantly increased the SVR rates compared to P+R alone (59% to 66% B-containing arms vs. 21% P+R control) for randomized subjects who received at least one dose of any study medication.

The Warnings and Precautions section of the proposed B product label contains anemia as a potential adverse reaction. The product label states that,

"Anemia has been reported with peginterferon alpha and ribavirin therapy. The addition of TRADENAME (*Boceprevir*) to peginterferon alpha and ribavirin is associated with an additional decrease in serum hemoglobin concentrations. Complete blood count should be obtained pretreatment, treatment week four, treatment at week eight (b) (4)

The sponsor analyzed 3 key studies to support the safety of B in which 547 patients were treated with P+R and 1548 patients were treated with B+P+R. Protocols P05101 and 05216 were described in this review previously. The third study was protocol P03523 entitled, "A Safety and Efficacy Study of SCH 503034 (B) in Previously Untreated Subjects with Chronic Hepatitis C Infected with Genotype 1". There were 36 patients who crossed over from P+R to B+P+R due to treatment failure in study P03523 and are not included in the total 1548 patients that were treated with B+P+R. This was an open label, randomized (1:1:1:1:1), multicenter, phase 2 study. The dosing of P, R and B was similar to that in the key clinical efficacy studies. The study compared P+R x 48 weeks to five treatment paradigms containing B. The total treatment durations in the key safety studies ranged from 28-48 weeks. The overall median treatment duration was similar between patients treated with P+R and those who received B+P+R (198 compared to 201 days respectively). The protocols for the key studies provided guidelines for the use of EPO and/or R dose reduction to treat anemia. However, the management decisions for individual patients (including the decision whether to use EPO) were at the discretion of the investigator. The use of EPO or R dose reduction was recommended at hemoglobin concentrations < 10 g/dl. R dose reduction was recommended at hemoglobin < 8.5 g/dl and treatment interruptions were not to exceed 2 consecutive weeks. The sponsor states that anemia was observed in 49% (758/1548) of subjects treated with the combination of B with P+R compared with 29% (158/547) of subjects treated with P+R alone. The nadir hemoglobin in the range of 9.5 to < 11g/dl was observed in 45% (690/1548) in B+P+R treated patients compared to 38% (203/547) of P+R treated patients. B was associated with an additional decrease of approximately 1 g/dL in hemoglobin concentration. The mean decreases in hemoglobin values from baseline were larger in previously treated patients compared to patients who had never received prior therapy.

Anemia was managed similarly in those treated with B+P+R or P+R. Patients either had a reduction in R dose, the addition of EPO and/or red blood cell transfusions. The frequency of study drug discontinuation to manage anemia was <1% in both arms. Dose modifications due to anemia/hemolytic anemia occurred in 26% of patients treated with B+P+R compared to 13% of patients treated with P+R. The proportion of subjects who received a transfusion for the management of anemia was 3% of subjects in the B containing arms compared to <1% in P+R alone arms. Overall, there were 43% (667/1548) patients treated with B+R+P who received EPO and 24% (131/547) of patients treated with P+R who received EPO. Despite recommendations regarding the use of EPO in the key safety trials, i.e., to initiate EPO therapy for hemoglobin < 10 g/dl, overall 3 patients treated with B+P+R and 3 patients treated with P+R initiated treatment with EPO whose hemoglobin levels were >12 g/dl. In these studies 4% (26/667) of patients treated with B+P+R compared to 9% (12/131) patients treated with P+R initiated treatment with EPO whose hemoglobin was > 11 g/dl; 26% (173/667) of patients treated with B+P+R compared to 34% (45/131) treated with P+R initiated treatment with EPO

whose hemoglobin was >10 g/dl. The response to EPO therapy in terms of anemia correction can be seen in the sponsor's figure below. Mean hemoglobin concentrations were below 12 g/dl over the course of the studies.

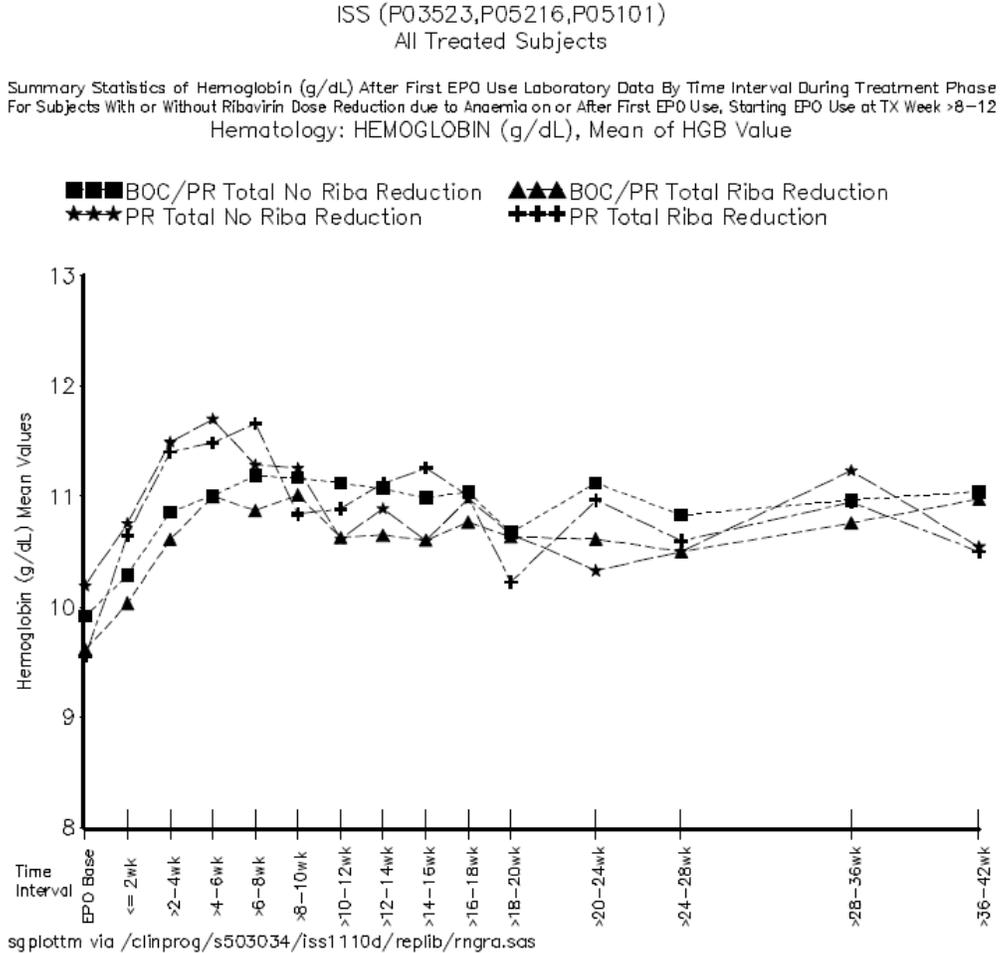


Figure 10 Mean Hemoglobin Concentration in Subjects Starting Erythropoietin After TW 8 up to TW 12, With and Without Ribavirin Dose Reduction

Protocol Nos. [P03523](#), [P05216](#), and [P05101](#) (Source Data: [Section 8.4.1.25. ISS](#))

(TW=treatment week).

There were 51% (340/667) of patients treated with B+P+R and 56% (74/131) of patients treated with P+R who received EPO and had a hemoglobin level >12 g/dl response at any time during the study. There were 6% (40/667) of patients treated with B+P+R and 11% (15/131) of patients treated with P+R who received EPO and had a hemoglobin >14 g/dl response at any time during the study. There were a total of 10% (82/798) patients treated with B+P+R or P+R who had at least 2 hemoglobin values \geq 13 g/dl after treatment with EPO during the studies.

Anemia is a common side effect that begins soon after the initiation of P+R in the treatment of HCV infection. It can cause symptoms that negatively impact quality of life (QOL) and is the most common reason for reducing the dose and temporarily or permanently discontinuing ribavirin and may impact the response to anti-viral therapy. Administering EPO can improve anemia caused by peginterferon and ribavirin therapy and is more effective than dose reduction at improving QOL during treatment. However, EPO, which is not approved by the U.S. Food and Drug Administration (FDA) for use in patients with HCV infection, adds another parenteral drug to the patient's treatment regimen, and is associated with additional costs, inconvenience, and potential side effects. (McHutchinson 2007).

In the current submission the sponsor states that the possible mechanism for the anemia observed in the clinical trials of B appears to be non-hemolytic in nature. Drugs may cause immune hemolytic injury of red blood cells by three mechanisms. These types of red blood cell injuries are classified by the end effector mechanisms of the hemolysis, since the induction mechanisms of antibody formation are generally poorly understood.¹ The hapten/drug adsorption mechanism involves covalent binding of drug to red blood cell membranes and attachment of antidrug antibody to the membrane bound drug which opsonizes the cells for destruction by splenic macrophages. The ternary complex mechanism is characterized by formation of a trimolecular immune complex consisting of drug, red blood cell membrane bound antigen and an antibody that recognizes that compound neoantigen formed by drug and membrane antigen. Red blood cell destruction occurs intravascularly by activation of the whole complement sequence. The antibodies involved in the hapten/drug adsorption and ternary complex mediated hemolysis are drug dependent since the drug must be present with the red blood cell and antibody *in vivo* or *in vitro* for the antibody to cause red blood cell hemolysis. In sharp contrast to these mechanisms, some drugs induce formation of true autoantibodies indistinguishable from the autoantibodies seen in autoimmune hemolytic anemia. T-lymphocyte immunomodulation may play a role in this mechanism of drug-induced hemolysis. However in this autoimmune hemolytic anemia mechanism the drug is not necessary for red blood cell hemolysis to occur.

The hemolysis with drug-related immune mechanisms is generally mild but severe and sometimes fatal hemolysis can be seen in cases mediated by the ternary complex mechanism and in patients with chronic lymphocytic leukemia with autoantibodies induced by purine analogues. Specifically, patients with the hapten/drug adsorption hemolytic mechanism, e.g., penicillin and autoimmune mechanism, e.g., alpha-methyl dopa exhibit mild to moderate red blood cell destruction with insidious onset of symptoms developing over a period of days to weeks. In contrast, patients with hemolysis mediated by the ternary complex mechanism, e.g., cephalosporins or quinidine may have sudden onset of severe hemolysis with hemoglobinuria. In patients with the ternary complex mechanism hemolysis can occur after only one dose of the drug if the patient has been previously exposed to the drug. Acute renal failure may accompany severe hemolysis by the ternary complex mechanism. Cephalosporins are drugs that can cause severe, even fatal, hemolysis by the ternary complex mechanism. Withdrawal of the offending drug is usually the only treatment required. However, for patients with

severe hemolytic anemia prednisone therapy may be necessary. Furthermore, in patients with G6PD (glucose-6-phosphate-dehydrogenase) deficiency hemolytic anemia may be caused by an oxidative process due to the lack of the important hexose monophosphate shunt enzyme G6PD. In addition, patients with G6PD deficiency may have infection induced hemolysis again due to an oxidative process related to the infection. In fewer than 5% of patients who receive cephalosporin antibiotics positive antiglobulin reactions due to nonspecific adsorption of plasma proteins to red blood cell membranes may occur. This may occur within a day or two after the drug has been administered. Multiple plasma proteins including immunoglobulins, complement, albumin, fibrinogen and other proteins may be detected on red cell membranes in such cases. Hemolytic anemia due to this mechanism has not been reported. The clinical importance of this phenomenon is its potential to complicate crossmatch procedures unless the drug history is taken into account. As noted above cephalosporin antibiotics also may induce red cell injury by the hapten/drug mechanism or the ternary complex mechanism. These later reactions are more serious but apparently occur less frequently than the nonimmunologic reaction. (Beutler 2001).

Reviewer comment: The decision to add EPO to the treatment regimens of B+P+R or P+R in order to manage anemia was at the discretion of the investigator. Despite recommendations regarding the use of EPO, i.e., to initiate treatment at hemoglobin < 10 g/dl in the key safety trials, overall 27% (218/798) of patients treated with B+P+R or P+R initiated treatment with EPO whose hemoglobin was >10 g/dl. There were overall, 7% (55/798) of patients treated with B+P+R or P+R who had a hemoglobin > 14g/dl response after treatment with EPO at any time during the studies. There were a total of 10% (82/798) patients treated with B+P+R or P+R who had at least 2 hemoglobin values \geq 13 g/dl after treatment with EPO during the studies. These results suggest that despite proposed labeling recommendations, clinicians may feel that treatment with EPO is necessary, which may increase the chances to improve the SVR but may also increase the patient's exposure to risks associated with EPO.

Discussion:

Question 1: The sponsor has stated that the mechanism of anemia associated with B use appeared to be non-hemolytic in nature. Please provide some insight into the possible mechanism of the anemia associated with the secretary use?

Response to Question 1

The sponsor states that the mechanism of anemia associated with B appears to be non-hemolytic in nature. Decreases in hemoglobin concentration and concomitant anemia are well recognized side effects of P+R combination therapy. Interferon causes bone marrow suppression and results in a low level of anemia (approximate 0.5 g/dL decrease in Hgb) when used as monotherapy. However, R causes a dose-dependent hemolysis which, when combined with the marrow inhibition of interferon and its blunting of an appropriate reticulocytosis, results in an approximate 2 g/dL to 3 g/dL decrease in Hgb during interferon/RBV combination therapy. Also, the sponsor reports that Boceprevir as a single agent did not cause anemia in animal studies or in Phase 1 monotherapy clinical

studies. However, in the key trials the overall proportion of subjects reporting anemia/hemolytic anemia was higher in the B treatment arms (49%) compared with the control arms (29%). Dose modifications due to anemia/hemolytic anemia occurred twice as often in the BOC/PR arms (26%) compared with PR control arms (13%). The degree of anemia was also greater in the B arms compared to control in the key studies as shown in the sponsor's figure below.

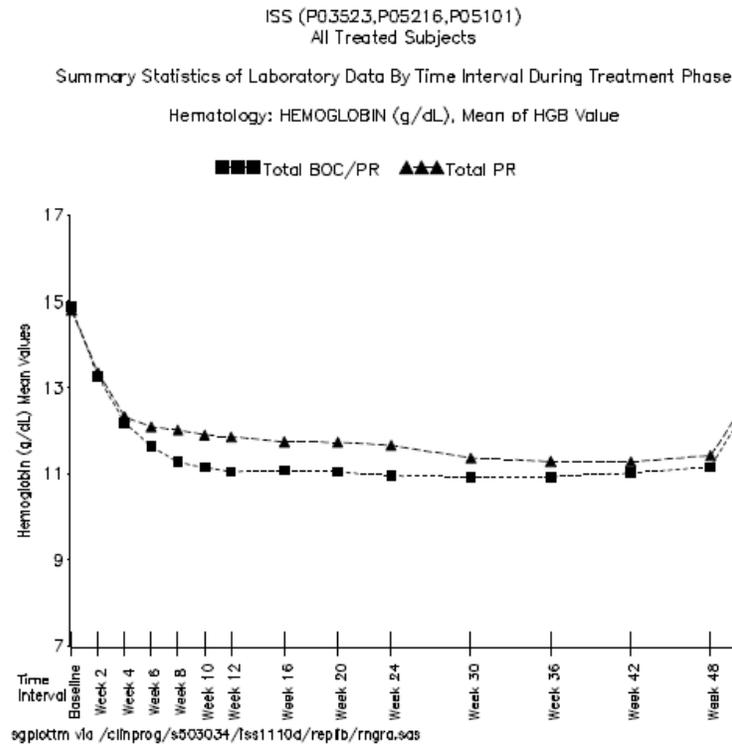


Figure 2 Mean Hemoglobin Concentration Over Time by Treatment Arm in the Key Studies

Protocol Nos. [P03523](#), [P05216](#), and [P05101](#) (Source Data: [Section 8.4.1.8](#), ISS).

The sponsor tried to determine the effect of B on red blood cell (RBC) survival in a study entitled, “Assessment of the Effects of Boceprevir (SCH 503034) on Red Blood Cells in Healthy Male Volunteers (Protocol No. P05351).” This was a randomized, placebo-controlled, third-party/evaluator blind study of B in healthy male volunteers.

Approximately 16 healthy adult male subjects were to be enrolled (Cohort 1); eight were to receive B and eight were to receive placebo. The primary endpoint for the study was RBC survival half-life (days). The average RBC survival half-life is approximately 26 days and the standard deviation is about 3.8 days. The study with eight subjects in each group could have been able to detect a difference of 4.2 days in mean RBC survival half-life between B and placebo with 80% power and $\alpha = 0.1$ one sided. A second cohort of 16 subjects (eight in each group) may have been enrolled if the results from Cohort 1 were inconclusive. A difference of 2.9 days could have been detected with 16 subjects in

each group pooled from both cohorts, and with 80% power and $\alpha = 0.1$ one sided. The dose of B was 800 mg (4 x 200-mg capsule) three times daily. The primary endpoint was the mean RBC survival half-life in all treated subjects. The secondary Endpoints were as follows:

- Mean RBC volume in all treated subjects.
- Relative extent of RBC sequestration throughout the body using gamma-camera imaging in all treated subjects.
- Mean RBC fragility ex vivo (LC50 [lytic concentration 50%]) or ectocytometer analysis (membrane deformability) in all treated subjects.
- In addition, the following pharmacodynamic (PD) parameters were assessed: flow cytometry (cluster of differentiation [CD]34, CD34/CD45, CD47, CD55, CD59), cytokine analyses (serum tumor necrosis factor [TNF]- α , interleukin [IL]-6, or IL-1), and anemia panel.

All 16 subjects were Caucasian males with a mean age of 38.1 years (range, 21-55 years) and a mean body mass index of 24.34 kg/m² (range, 20-27.5 kg/m²). Red Blood Cell Survival and Volume: RBC survival and volume were similar in B - and placebo subjects. RBC survival and volume were similar in B and placebo subjects. The labeled 51Cr RBC evaluation of survival showed a mean of 28.9 days for the placebo group and a mean value of 27.0 days for the B group. The difference of -1.9 days with the associated upper limit of the 90% one-sided confidence interval of 2.0 days suggests that administration of B versus placebo did not adversely affect RBC survival or suggest a hemolytic anemia in healthy subjects. No evidence of a different sequestration pattern was noted on scintigraphy between treatment groups. Furthermore, flow cytometry results showed that none of the five CD markers (CD34, CD34/CD45, CD47, CD55, CD59) showed any remarkable changes from baseline through the 56-day period of either study drug or placebo administration. These results suggest that B did not interfere with either the differentiation or proliferation of RBCs, and that B did not accelerate the clearance of RBCs from the systemic circulation. This is also supported by the hemoglobin concentrations, which did not show either a discernible pattern over time or any notable difference between B or placebo treatment. The CD59 marker declined in several subjects to about 65% of baseline values at single timepoints in both the B - and placebo-treated groups without any discernable pattern. The CD59 values rebounded to baseline levels while therapy was continuing and were not specifically associated with changes in hemoglobin values in those subjects. Markers of anemia associated with iron transport and hemolysis (serum ferritin, haptoglobin, hepcidin, transferrin) had no notable changes over time either within subject or across treatment groups (B versus placebo). Serum erythropoietin concentrations did not show any discernible change over time in either the B or placebo-treated groups, and concentrations were within the normal expected range. There were no notable changes of concentrations of serum TNF- α , IL-6, or IL-1 over time during either placebo or B administration compared at baseline or during therapy. The reticulocyte count observed in both the placebo and B treated groups was stable. No clinically significant changes in blood chemistry or hematological parameters, vital signs, or electrocardiography occurred in any treatment group.

Reviewer comment: The data suggest that anemia related to B is not due to a hemolytic process but may be related to bone marrow suppression. A bone marrow biopsy would be required to determine the extent of marrow involvement if any. It would be expected that if hemolysis would occur there would be a greater difference in RBC survival in the two treatment group and that there would be some differential sequestration of 51Cr. Willett et al. conclude that testing 51Cr labeled RBC is one of the few definitive tests for hemolytic anemia. 51Cr Labeled RBC studies may be considered by physicians who suspect autoimmune or acquired hemolytic disorders, especially when blood and serum tests fail to provide a definitive diagnosis.

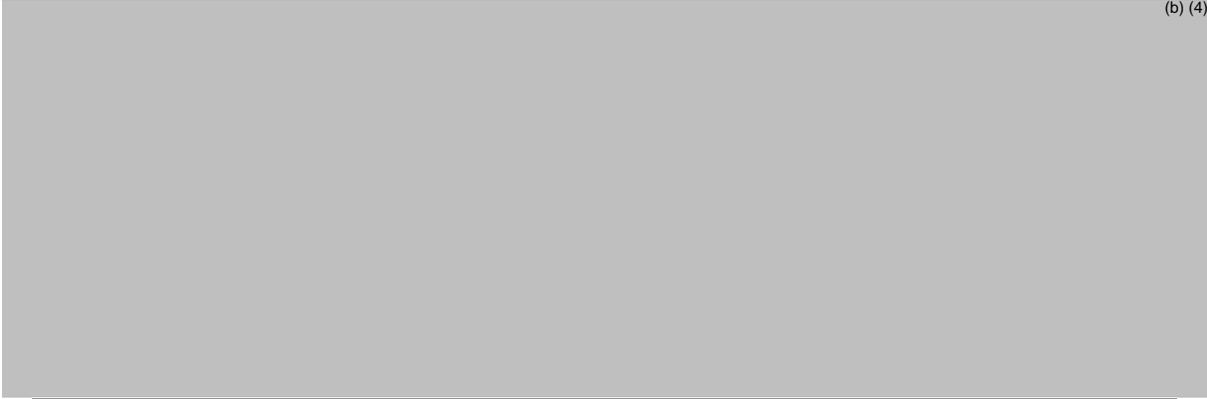
(b) (4)

Response to Question 2.

The sponsor reports that with the addition of B at treatment week 4 the hemoglobin concentrations continued to decline up to treatment week 6 to treatment week 8. In the key studies, the change in hemoglobin over time beyond treatment week 8 was confounded by the use of EPO in approximately 38% of subjects (24% in the PR control arms and 43% in the B/PR arms)

(b) (4)

(b) (4)



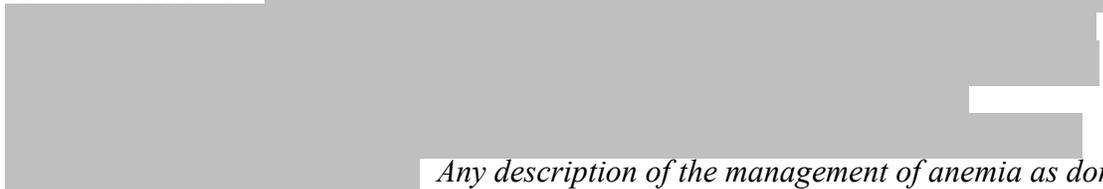
Across all B-containing arms and control arms in both study populations, anemia was consistently associated with higher SVR rates, with the majority of the anemic subjects having received EPO to manage their anemia. SVR rates were between 8% and 32% higher in anemic subjects compared to non-anemic subjects in the B-containing arms of the two studies. SVR was also increased in those subjects receiving erythropoietin compared to those subjects who did not receive erythropoietin.

Epoetin alfa currently is labeled for the following conditions:

- Treatment of anemia in cancer patients on chemotherapy
- Treatment of anemia of chronic renal failure patients who are not on dialysis but are symptomatic.
- Treatment of anemia in zidovudine-treated HIV-infected patients.
- Treatment of anemia in cancer patients on chemotherapy.
- Reduction of allogeneic blood transfusion in surgery patients.

Reviewer comment:

(b) (4)



Any description of the management of anemia as done in the study should be included within section 14 Clinical Studies subsection describing the particular trial (b) (4) The study description should give some information as to how many patients (proportion) received concurrent epoetin alfa therapy. (b) (4)



Also, as was noted previously, some patients did not have their anemia managed per protocol despite recommendations regarding the use of EPO. Overall 27% (218/798) of patients treated with B+P+R or P+R initiated treatment with EPO whose hemoglobin was >10 g/dl. There were 7% (55/798) of patients treated with

B+P+R or P+R who had a hemoglobin > 14g/dl after treatment with EPO at any time during the studies. There were a total of 10% (82/798) patients treated with B+P+R or P+R who had at least 2 hemoglobin values \geq 13 g/dl after treatment with EPO during the studies.

[REDACTED] (b) (4)

Question 3. Do you think the sponsor should await the final results of the ongoing study evaluating the use of erythropoietin in the management of anemia [REDACTED] (b) (4)?

Response to Question 3.

The sponsor has an ongoing phase 3, randomized, multicenter, parallel arm, open label study (protocol P06086) in which the objective is to compare the effect on the efficacy of EPO use versus R dose reduction for the management of anemia in subjects who become anemic with hemoglobin \leq 10g/dl or hemoglobin <11 g/dl if there appears to be a trend in hemoglobin to a level \leq 10g/dl during the treatment of HCV genotype1 infection with B+P+R therapy. The sponsor will test oral B 800 mg three times daily plus EPO 40,000 units subcutaneously once weekly for 48 weeks. The dose of EPO will be adjusted for each subject to achieve and maintain hemoglobin levels between 10-12g/dl. A total of 444 subjects have been enrolled.

Reviewer comment: The final results of the study protocol P06086 may inform the safety and dosing of EPO in the proposed patient population particularly with regard to potential serious adverse events such as arterial thrombosis and pure red cell aplasia. Also, waiting for the final results of the study protocol P06086 may enhance the understanding of the use of EPO when treating anemia associated with the combination B+P+R therapy for the of chronic HCV.

Question 4. Has the division observed or have been notified of any increased risk of arterial/Venus 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?

Response to Question 4.

The sponsor's table below shows that there were 6 patients with the treatment emergent serious adverse event of thrombosis (deep vein thrombosis/pulmonary embolism, cerebral ischemia, arterial thrombosis and myocardial infarction) that appeared to be associated with EPO use in the key studies. One patient (subject # 94/10112) developed a hepatic neoplasm.

Table 50 Treatment-Emergent Serious Adverse Events Potentially Associated With Erythropoietin Use, in Subjects With Erythropoietin Use in the Key Studies

Protocol Nos. P03523, P05216, and P05101

Site/Subject No. Sex/Age/Race	Preferred Term/ Severity/ Relationship to Study Drugs	Timing of Event Begin/End Day ^a	Event Outcome	Additional Information
P03523 Arm 4 BOC/PR (48 wks, no PR lead-in) ^b				
76/000176 F/34/W	Deep vein thrombosis/ Severe/ Unlikely	77 / 264 (186)	Additional Medications, Hospitalization, Study Drug Discontinuation	CV risk factors/Relevant medical history: Obesity, hyperlipidemia, tobacco abuse. Subject had elevated cholesterol on Day 1 (7.01 mmol/L) and elevated triglycerides at TW 4 (4.13 mmol/L). At TW 10, the subject experienced a deep vein thrombosis and pulmonary embolism.
	Pulmonary embolism/ Severe/ Unlikely			
P05216 Arm 2 RGT (28/48 wks, PR lead-in) ^c				
2/000280 M/48/W	Pulmonary embolism/ Severe/ Possible	124/ 129 (5)	Additional Medications, Hospitalization, Study Drug Discontinuation	CV risk factors/Relevant medical history: tobacco abuse. Resolved within 1 week. The Investigator assessed as possibly related to study drugs and considered erythropoietin as a co-suspect medication.
1/000052 M/45/W	Cerebral ischaemia/ Severe/ Probable	175 / 176	Study Drug Discontinuation	CV risk factors/ Relevant medical history: Right bundle branch block. For two days during TW 25, subject experienced severe alteration of visual field. EPO was discontinued. A magnetic resonance imaging revealed posterior occipital ischemia.
P05216 Arm 3 BOC/PR (48 wks, PR lead-in) ^d				
49/007492 F/56/B	Arterial thrombosis/ Life-Threatening/ Unlikely	109 / 142 (21)	Additional Medications, Hospitalization, Study Drug Discontinuation, Disability, Study Drug Reduced	CV risk factors/ Relevant medical history: Obesity, hypertension. During TW 16 study drugs and EPO were discontinued. The following week, subject was diagnosed with mononeuritis multiplex. Later she returned to the same hospital and received a diagnosis of acute arterial insufficiency of the left lower extremity with thrombosis involving the left common and external iliac segments with no flow below the mid popliteal artery. During the following week she had a left amputation performed 10 cm below the knee.

Table 50 Treatment-Emergent Serious Adverse Events Potentially Associated With Erythropoietin Use, in Subjects With Erythropoietin Use in the Key Studies

Protocol Nos. P03523, P05216, and P05101

Site/Subject No. Sex/Age/Race	Preferred Term/ Severity/ Relationship to Study Drugs	Timing of Event Begin/End Day ^a	Event Outcome	Additional Information
P05101 Arm 2 RGT (36/48 wks, PR lead-in) ^d				
19/10062 F/64/B	Myocardial infarction/ Life- Threatening/ Unlikely	148 (1) / 148 (1)	Additional Medications, Hospitalization, Study Drug Discontinuation	CV risk factors/ Relevant medical history: Hypertension. EPO treatment was initiated during study treatment at Day 56 for mild anemia (Hgb = 9.2 g/dL).
P05101 Arm 3 BOC/PR (48 wks, PR lead-in) ^d				
18/10001 M/49/W	Deep vein thrombosis/ Life-Threatening/ Unlikely	185 / 311	Additional Medications, Hospitalization, Study Drug Interrupted	CV risk factors/ Relevant medical history: Obesity, borderline diabetes mellitus, and hypertension. No contributory concomitant medications noted.
94/10112 F/53/W	Hepatic neoplasm malignant/ Moderate/ Unlikely	358 (21) / Ongoing	None	Relevant medical history: cirrhosis.

B = black; W = white (non-black); F = female; M = male; AE = adverse event; BOC = boceprevir 800 mg TID; HCV-RNA = hepatitis C virus-ribonucleic acid; Hgb = hemoglobin; PEG2b, P = peginterferon alfa-2b 1.5 µg/kg; RBV, R = ribavirin 600 to 1400 mg/day [Note P03523: 800 to 1400 mg/day for Arms 1-6 and 400 to 1000 mg/day for Arm 7]; RGT = response-guided therapy; TID = three times daily; TW = Treatment Week.

^a Days since randomization; () = days since last dose of study medication.

^b Arm 4 (48 weeks, no PR lead-in): BOC/PR for 48 weeks.

^c Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 24 weeks (subjects with undetectable HCV-RNA at Treatment Week [TW] 8 and all subsequent assays through TW 24) or BOC/PR for 24 weeks followed by placebo/PR for 20 weeks (subjects with detectable HCV-RNA at TW 8 or any subsequent assay through TW 24). Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

^d Arm 2 (RGT) = PR lead-in for 4 weeks, then BOC/PR for 32 weeks (if undetectable HCV-RNA at TW 8) or BOC/PR for 32 weeks followed by placebo/PR for 12 weeks (if detectable HCV-RNA at TW 8). Arm 3 (BOC/PR48) = PR lead-in for 4 weeks, then BOC/PR for 44 weeks.

Source Data: Section 14.3.3, Section 14.3.2.2.5, CSR P03523; Section 14.3.2.2.16, CSR P5216 CSR; Section 14.3.3 CSR P05101

In addition, there was one case of pure red cell aplasia (PRCA) reported in the follow-up of study P05216. The patient was a 56 year old female (subject # P05216-080-002163) with a history HCV but no other significant past medical history. The patient's baseline hemoglobin was 13.9 g/dl. The patient was randomized to the B/PR48 arm of the study and began treatment with PR. Approximately one month later B was added to the

treatment regimen. Approximately 2 weeks later the patient had a decrease in hemoglobin to 9.0 g/dl and she received EPO 40,000 units three times a week for approximately the next seven weeks. The patient had adjustment in her EPO to twice a week and then once weekly over the next eight weeks. The patient's hemoglobin remained above 14 g/dl and her EPO dose was interrupted. Approximately 4 weeks later the patient had to decrease in hemoglobin down to 9.5 g/dl and she was restarted on EPO 40,000 units three times a week for approximately the next eight weeks. The patient's hemoglobin increased to 12.8 g/dl. The patient's EPO dose was decreased to once weekly for the next four weeks. The patient complained of asthenia and discomfort and saw her primary care physician. The patient had a hemoglobin of 6.0 g/dl. The patient discontinued all study drugs and EPO treatment. She received two transfusions with packed red blood cells and her hemoglobin stabilized for the next few weeks. However, her hemoglobin decreased again to 8.3 g/dl and she was started on darbepoetin alfa. Her hemoglobin continued to decrease to 6.6 g/dl. The patient was admitted to hospital. A bone marrow biopsy at the time was consistent with PRCA. Antibody testing was positive for anti-EPO antibodies. The patient was treated with packed red blood cell transfusions. The sponsor reports that the PRCA is ongoing. The investigator considered the incidence of anemia initially to be related to B and PR therapy and the PRCA event unlikely related to B and PR therapy.

The Epoetin alfa labels contain a black box warning that states there is an increased risk of mortality, serious cardiovascular events, thromboembolic events, stroke and an increased risk of tumor progression or recurrence in patients with chronic renal failure and cancer. In addition, the Warnings section of the product label states that cases of pure red cell aplasia with or without other cytopenias, associated with neutralizing antibodies to EPO have been reported in patients treated with Procrit. The product label states that pure red cell aplasia has predominantly been reported in patients with chronic renal failure receiving ESAs while undergoing treatment for HCV with interferon and R. Any patient who develops a sudden loss of response to Epoetin alfa, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: Lack or Loss of Response). If anti-erythropoietin antibody-associated anemia is suspected, withhold Procrit and other ESAs. The prescriber is instructed to contact CENTOCOR ORTHO BIOTECH at 1 888 2ASK OBI (1-888-227-5624) to perform assays for binding and neutralizing antibodies. Procrit should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other ESAs as antibodies may cross-react. Furthermore, in the Warnings and Precautions section of the Procrit label patients the following is stated:

- If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated:
 1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy.
 2. Underlying infectious, inflammatory, or malignant processes.
 3. Occult blood loss.

4. Underlying hematologic diseases (i.e., thalassemia, refractory anemia, or other myelodysplastic disorders).
5. Vitamin deficiencies: Folic acid or vitamin B12.
6. Hemolysis.
7. Aluminum intoxication.
8. Osteitis fibrosa cystica.
9. Pure Red Cell Aplasia (PRCA) or anti-erythropoietin antibody associated anemia: In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin

Reviewer comment: There may be a risk for red cell aplasia in the population for which B+P+R is indicated. In addition, the use of EPO itself carries with it an increased risk for thromboembolic events and stroke. Patients that are treated with the proposed combination of B+P+R and in whom EPO is also used should be evaluated as per the recommendation and instructions in the EPO labels. The use and safety of EPO in this clinical setting would need to be studied in more depth

EPO dosing recommendations for this population should be evaluated in an appropriately designed study.

Specific

Question 5. Do you suggest any additional risk management activities in addition to Medication Guide to mitigate the risks associated with anemia? In your opinion, how frequently should hematology parameters be monitored in the clinical practice setting, if B received marketing approval?

Response to Question 5.

The proposed medication guide for B states that,

for B states that,

In addition the medication guide

Reviewer comment: Some of the clinical benefit observed in the SVR may be due to patients remaining on anti-viral therapy despite the adverse associated event of anemia was, because the anemia associated with B, P and R was managed with epoetin alfa.

Question 6. Please share the Division's experience with any other products whose package inserts refer to the use of erythropoietin.

Response to Question 6.

The parenteral iron supplements Ferrlecit (sodium ferric gluconate) and Venofer (iron sucrose) have the following indications respectively:

Ferrlecit:

- Ferrlecit (sodium ferric gluconate complex in sucrose injection) is indicated for treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Venofer:

- Venofer® is indicated in the treatment of iron deficiency anemia in the following patients:
 - non-dialysis dependent-chronic kidney disease (NDD-CKD) patients receiving an erythropoietin
 - non-dialysis dependent-chronic kidney disease (NDD-CKD) patients not receiving an erythropoietin
 - hemodialysis dependent-chronic kidney disease (HDD-CKD) patients receiving an erythropoietin
 - peritoneal dialysis dependent-chronic kidney disease (PDD-CKD) patients receiving an erythropoietin.

The nucleoside reverse transcriptase inhibitor has the following indication:

Retrovir:

- Treatment of HIV-1
- Prevention of maternal-fetal HIV-1 transmission

Reviewer comment: In the clinical studies of Ferrlecit and Venofer in patients with chronic renal failure on hemodialysis, ESA was a concurrent treatment. However, the product labels for Ferrlecit and Venofer do not specifically refer to any ESA product or provide directions for managing the dosing of ESAs in these patients. In section 2.3 Dosage and Administration section of the Retrovir label with regard to anemia the label states that, "If marrow recovery occurs following dose interruption, resumption in dose may be appropriate using adjunctive measures such as epoetin alfa at recommended doses, depending on hematologic indices such as serum erythropoietin level and patient

tolerance.” No specific guidelines regarding epoetin alfa are included in the Retrovir label.

Question 7. Do you have any other recommendations to address this safety concern?
Response to Question 7.

There are no further recommendations.

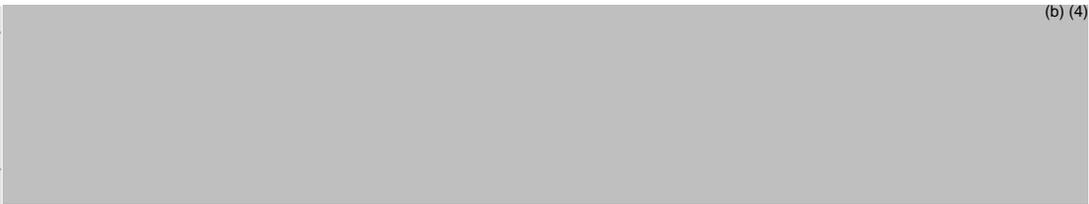
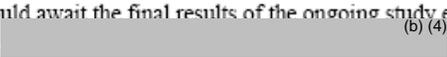
Conclusions and Recommendations:

The Division of Antiviral Products (DAVP) is also seeking consultation regarding the sponsor’s proposed [REDACTED] (b) (4) and the mechanism of anemia in patients with chronic HCV who are being treated with B+P+R for NDA 202258 submitted as a rolling review on September 30, 2010 and November 10, 2010. The PDUFA goal date for the NDA is May 13, 2011. The following recommendations should be forwarded to the review division and sponsor:

- The data suggest that anemia related to boceprevir is not due to a hemolytic process but may be related to bone marrow suppression.
- Patients in the pivotal trials received EPO according to a pre-specified dose adjustment schedule. While some mention of epoetin alfa use in the clinical trials should be included in the clinical studies section, the studies were not designed to provide information for the dosing and safety of EPO in these patients. The use and safety of EPO in this clinical setting would need to be studied in an appropriately designed trial [REDACTED] (b) (4)
- The final results of the study protocol P06086 may be helpful in informing EPO use in these patients and in planning any future studies.
- There may be a risk for red cell aplasia in the population for which B+P+R is indicated. [REDACTED] (b) (4)
- The monitoring plan proposed by the sponsor in the labeling appears to be appropriate.

Appendix 1: Consult Request Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		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
NAME OF DRUG Boceprevir	PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG Protease Inhibitor	DESIRED COMPLETION DATE February 28, 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 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		
<p>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.</p> <p>Division of Antiviral Products (DAVP) would like Division of Hematology Products (DHP) to address the following questions:</p> <p>1. 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?</p>				

2.  (b) (4)	
a.	
b.	
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 your 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

Appendix 2: Additional Information from the DAVP (Division of Antiviral Products)

NDA 202258 (Boceprevir)

B(SCH 503034) is a specific inhibitor of the HCV NS 3/4A protease, and thereby, inhibits viral replication in infected host cells. Bis a new molecular entity, and the first of the direct acting antiviral agents to be submitted as an NDA for treatment of chronic hepatitis C in combination with pegylated interferon and ribavirin.

Proposed Indication: Treatment of chronic hepatitis C genotype 1 infection in combination with peginterferon alpha and ribavirin, in adult patients with compensated liver disease who are previously untreated or who have failed previous therapy

Proposed Treatment Regimen: B800 mg TID in combination with peginterferon alpha and ribavirin



The Advisory Committee Meeting to discuss this new NME is scheduled on April 27, 2011.

Clinical Studies

(Phase 3 and key Phase 2b Studies pooled for Safety Analyses by the Sponsor)

Study Number	Study Design	Treatment Regimen	No. of Subjects Randomized/ Treated
P03523 (SPRINT-1) Treatment-naive	Phase 2, open-label, two-part study. <u>Part 1</u> included five treatment arms with BOC/PR for 28 or 48 weeks, with and without a 4-week lead-in with PR. <u>Part 2</u> included exploration of BOC/P/low-dose RBV (400 to 1000 mg/day) for 48 weeks. Randomization was stratified by race (black vs. white) and by cirrhosis vs. no cirrhosis (Part 1).	Part 1 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 800 to 1400 mg/day Part 2 BOC 800 mg TID PEG2b 1.5 µg/kg QW RBV 400 to 1000 mg/day	Total: 598/ 595 Part 1: 520 treated Part 2: 75 treated
P05216 (SPRINT-2) Treatment-naive	Phase 3, double-blind, placebo-controlled study comparing two regimens of Bresponse-guided therapy (RGT) treatment paradigm of BOC/PR (28/48 wk) and BOC/PR (48 wk) to PR (48 wk). 2 cohorts: Cohort 1 (white) and	BOC 800 mg TID (or placebo) PEG2b 1.5 µg/kg QW RBV 600 to 1400 mg/day	1099/ 1097 Cohort 1: 938

	<p>Cohort 2 (black) Randomization to 3 treatment arms (1:1:1) in each cohort.</p> <p>Stratified by HCV genotype 1a vs 1b and by viral load ($\leq 400,000$ IU/mL vs $>400,000$ IU/mL) within cohort.</p> <p>28- or 48-wk treatment duration; 4-week lead-in with PR.</p>		<p>nonblack treated subjects</p> <p>Cohort 2: 159 black treated subjects</p>
<p>P05101 (RESPOND-2) Previous PEG/RBV Treatment Failures</p>	<p>Phase 3, double-blind, placebo-controlled study comparing two regimens of Bresponse-guided therapy (RGT) treatment paradigm of BOC/PR (36/48 wk) and BOC/PR (48 wk) to PR (48 wk).</p> <p>Randomization to 3 treatment arms in a 1:2:2 ratio Stratified by previous treatment in qualifying treatment regimen and by HCV genotype 1a vs 1b.</p> <p>36- or 48-wk treatment duration; 4-week lead-in with PR.</p>	<p>BOC 800 mg TID (or placebo) PEG2b 1.5 μg/kg QW RBV 600 to 1400 mg/day</p>	<p>404/403</p>

Dose Finding Study (Not pooled for Safety Analyses by Sponsor)

<p>P03659 (RESPOND-1) Previous PEG/RBV Treatment Failures</p>	<p>Phase 2, double-blind (for RBV), placebo-controlled study to determine the safe and effective dose range of B(100 to 800 mg) and PEG2b with or without RBV.</p> <p>Up to 49-wk treatment duration.</p>	<p>BOC (or placebo) 100, 200, 400, or 800 mg PO TID PEG2b 1.5 μg/kg QW RBV (or placebo) 800 to 1400 mg/day</p>	<p>357/357</p>
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Key Points from Sponsor's Integrated Summary of Safety:

Decreases in hemoglobin concentration and concomitant anemia are well recognized side effects of interferon/ribavirin (RBV) combination therapy. Interferon causes bone marrow suppression and results in a low level of anemia (approximate 0.5 g/dL decrease in hemoglobin) when used as monotherapy. However, ribavirin causes a dose-dependent hemolysis which, when combined with the marrow inhibition of interferon and its blunting of an appropriate reticulocytosis, results in an approximate 2 to 3 g/dL decrease in hemoglobin during interferon/RBV combination therapy.

Bas a single agent did not cause anemia in animal studies or in Phase 1 monotherapy clinical studies.

The protocols for the key studies provided guidelines for the use of erythropoietin and/or RBV dose reduction, but anemia management decisions (including the decision whether to use erythropoietin) were at the discretion of the investigator. The use of erythropoietin and/or RBV dose reduction was recommended if the hemoglobin concentration decreased to <10 g/dL; it was recommended that RBV be interrupted or discontinued if the hemoglobin concentration decreased to <8.5 g/dL. Treatment interruptions were not to exceed 2 consecutive weeks in duration. The proportion of subjects that met dose reduction and dose discontinuation criteria was higher in the boceprevir/pegylated interferon + ribavirin (BOC/PR) arms than in the pegylated interferon + ribavirin (PR) control arms. The applicant states that guidelines for the use of erythropoietin to treat anemia appear to have been followed by most investigators and were effective based on a detailed review of when treatment began (73% had hemoglobin values ≤ 10 g/dL) and the lack of significant overshooting of target hemoglobin levels.

Bwas associated with an additional decrement of about 1 g/dL in hemoglobin concentration during treatment that was reached about 4 weeks after the start of Btreatment (at treatment week [TW 8]). Hemoglobin levels in the pooled boceprevir-containing arms remained fairly constant thereafter. In Btreated subjects, the mean decreases in hemoglobin concentrations from baseline at the hemoglobin nadir were somewhat larger in subjects who were previous treatment failures (-4.47 at TW 36; Hgb=10.67) compared with treatment-naïve subjects (-3.86 at TW 24; Hgb=10.99), resulting in a nadir hemoglobin difference of roughly 0.3 g/dL. In PR-treated control subjects, the nadir hemoglobin was reached somewhat later in both treatment-naïve (-3.46 at TW 42; Hgb=11.21) and treatment-failure subjects (-3.46 at TW 48; Hgb=11.52). Note that, due to the futility rule, only about a third of the control-treated subjects who had been previous treatment failures had hemoglobin laboratory values at TW 20 or later. After the discontinuation of study medication, mean hemoglobin concentrations returned to near baseline by follow-up week (FW) 12 in both populations.

To assess the relative contribution of Bto PR therapy, with respect to the incidence of anemia, the proportion of subjects reporting anemia was compared across treatment arms. Consistent with the described effect on hemoglobin levels, the proportion of subjects reporting anemia was higher in the Barms (49%) compared with the control arms (29%). Dose modifications due to anemia occurred twice as often in the BOC/PR arms (26%) compared with PR control arms (13%). No subject died due to anemia in any arm of the key safety studies. Life-threatening AEs due to anemia occurred in <1% of boceprevir-treated subjects. The frequency of study drug discontinuation due to anemia AEs was 1% in both arms.

In subjects with anemia (hemoglobin <10 g/dL), the anemia was managed by RBV dose reduction alone in 10% and 7% of PR-treated and BOC/PR-treated subjects, respectively; with erythropoietin use alone in 37% and 33% of subjects, respectively, and with both RBV dose reduction and erythropoietin use in 32% and 46% of subjects, respectively. None of these methods was used for the management of hemoglobin <10 g/dL in 21% of PR-treated subjects and 14% of BOC/PR-treated subjects.

Of the 2095 treated subjects in the key studies, 41 (2%) received a transfusion for the management of anemia; 2 (<1%) subjects in the pooled PR control arms and 39 (3%) subjects in the BOC/PR arms

As per applicant, anemia with BOC/PR was successfully managed in the same way as anemia with PR therapy, with RBV dose reduction, erythropoietin use, and/or transfusions. In addition, BOC/PR also had

an effect on the other hematopoietic cell lines beyond that seen with PR, which led to somewhat increased rates of neutropenia and thrombocytopenia compared to PR control. The use of G-CSF in the BOC/PR arms vs. the PR arms was also somewhat higher (9% vs. 6%, respectively).

Additionally, Sponsor is conducting a study, Protocol 06086, an ongoing Phase 3 open-label trial in treatment-naïve HCV subjects, comparing erythropoietin use versus ribavirin dose reduction for the management of anemia. The primary objective is to compare the effect on efficacy, as measured by sustained virologic response, of erythropoietin use versus RBV dose reduction for the management of anemia in subjects who become anemic during HCV treatment with BOC/PR. Eligible subjects will receive treatment with PR for a 4 week lead-in, followed by BOC plus PR for 44 weeks. Subjects will continue in the Pending Randomization Arm if their hemoglobin remains >10 g/dL throughout the 48-week treatment period. Subjects who become anemic within the 48-week treatment period are randomized in a 1:1 ratio (at the time they become anemic) to Arm 1 (RBV dose reduction) or Arm 2 (erythropoietin use) for management of the anemia. The total duration of therapy for all subjects is to be 48 weeks. Subjects who have hemoglobin values ≤ 8.5 g/dL will be declared anemia management strategy failures. These subjects may remain in the trial at the discretion of the investigator, and additional interventions may be initiated, including further RBV dose reduction and the use of erythropoietin for subjects in Arm 1. If the hemoglobin value continues to decrease to ≤ 7.5 g/dL, the subject must be discontinued from the trial. As of April 16, 2010, 418 subjects out of a planned 660 subjects received at least one dose of PR. Of those subjects, 122 (29%) received at least one dose of boceprevir. Mean treatment duration (standard deviation [SD]), including the 4-week PR lead-in, was 23.2 (20.1) days; for the 122 subjects who received at least one dose of boceprevir, the mean duration (SD) of Btreatment was 21 (16.6) days. Maximum treatment duration was approximately 14 weeks.

DAVP Reviewer's Comments:

On preliminary review, there is one reported case of arterial thrombosis in Study P05216 which resulted in below-the-knee amputation and disability and the investigator assessed the event of arterial thrombosis to be possibly related to erythropoietin.

There was one case diagnosed as PRCA reported in the follow-up period of Study P05216. As per sponsor, this single case of PRCA occurred after prolonged exposure to high doses of EPO that exceeded protocol-recommended guidelines.

Cases of Deep Vein Thrombosis and Pulmonary Embolism were also reported in the key safety studies.

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

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

- 2.



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 your opinion, how frequently should hematology parameters be monitored in clinical practice setting, if Brexacas 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?

Appendix 2.

Good afternoon-

I am one of the Division of Antiviral Products clinical reviewers for NDA 202258/Bfor treatment of chronic hepatitis C and I wanted to contact you about our consult to your Division regarding anemia. Internally we have had numerous discussions about boceprevir's hematologic effects pertaining to the possible mechanism, the magnitude, associated risk factors and management (e.g., use of ESA since they were allowed in the Phase 3 trials).

Given the fact this aspect of boceprevir's profile will be a matter of discussion at the upcoming April AC, we thought it may be mutually beneficial to meet and discuss your interpretation of Band allow us to provide you with any additional clarifying information. If you concur, our PM can find an appropriate time.

In addition, I wanted to point out that a non-IND trial was conducted in healthy men for 57 days to explore the potential MOA associated with anemia, Protocol 05351 (you can find the study report and data electronically within GS Review). They selected various markers to follow and I am interested if you agree with their interpretations. An excerpt from my summary review of their study report follows at the end of this email.

Thank you so much for your help in this review-
Sarah

Sarah Connelly, MD
Medical Officer
DAVP
301 796-2085

Labeled 51Chromium RBC was used to determine RBC survival and volume. Mean RBC survival half-life was similar between the two groups: 27 days in the BOC group and 28.9 days in the placebo group with a difference of -1.9 days and an upper limit of the 90% one-sided confidence interval of 2.0 days. These data indicate administration of BOC versus placebo did not adversely affect RBC survival or suggest a hemolytic anemia in healthy subjects. Mean RBV volume was also similar between the two groups. Relative extent of RBC sequestration throughout the body was determined using gamma-camera imaging. No evidence of a different sequestration pattern was noted on scintigraphy between treatment groups. At variable time points, the RBC deformability at a shear stress of 3.87 Pa was somewhat reduced in some subjects; however, this recovered at the following time point. Overall, RBC deformability remained within the physiological range. Markers associated with RBC differentiation and proliferation (Cell surface CD markers: CD34, CD34/CD45, CD47, CD55, CD59; IL-6; IL-1; TNF- α), haptoglobin, ferritin and iron did not support an explanation for BOC-associated anemia. Erythropoietin concentrations remained within normal range.

Median Day 1 hemoglobin was 15.9 g/dL (13.5, 16.4) and 15.1 g/dL (14.2, 16.1) in the BOC and placebo groups, respectively. Median change from Day 1 in the BOC group were -0.4g/dL (Day 14), -0.4 g/dL (Day 28), -1.0 g/dL (Day 42) and -1.0 g/dL (Day 57). Median change in the placebo group were -0.3g/dL (Day 14), -0.3 g/dL (Day 28), -0.6 g/dL (Day 42) and -0.6 g/dL (Day 57).

One Btreated subject, 000108, had hemoglobin Δ Day 1-14 and Δ Day 1-21 of -2.3 g/dL and -2.4 g/dL, respectively. In addition, platelet Δ Day 1-14 and Δ Day 1-28 counts were -67 109/L and -112 109/L, respectively. White blood cell and neutrophil counts were within normal ranges.

Mechanistic results suggest that B did not interfere with either the differentiation or proliferation of RBCs, and that B did not accelerate the clearance of RBCs from the systemic circulation; however, one subject did demonstrate decreased Hgb and platelet counts within 2-4 weeks after starting boceprevir, though all values were <Grade 1. White blood cell and neutrophil counts remained within the normal range. This subject's hematologic parameters returned to baseline following trial completion.

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

/s/

ANDREW DMYTRIJUK
03/07/2011

KATHY M ROBIE SUH
03/07/2011

DSI CONSULT: Request for Clinical Inspections

Date: December 17, 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: Jeffrey Murray, M.D., MPH, Deputy Director, DAVP
Mary Singer, M.D., Clinical Team Leader, DAVP
Poonam Mishra, M.D., Clinical Reviewer, 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

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects Enrolled	Indication
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)

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)

<u> </u>	<u> X </u>	Medical Team Leader
<u> </u>	<u> X </u>	Medical Reviewer
<u> </u>	<u> X </u>	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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/s/

SHERLY ABRAHAM
12/17/2010

RPM FILING REVIEW

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

Application Information		
NDA # 202,258 BLA#	NDA Supplement # N/A BLA STN #	Efficacy Supplement Type SE-N/A
Proprietary Name: Victrelis (proposed) Established/Proper Name: Boceprevir Dosage Form: Capsules Strengths: 200 mg		
Applicant: Schering Corporation Agent for Applicant (if applicable):		
Date of Application: November 10, 2010 Date of Receipt: November 15, 2010 Date clock started after UN:		
PDUFA Goal Date: May 15, 2011		Action Goal Date (if different): May 13, 2011
Filing Date: January 14, 2011		Date of Filing Meeting: December 10, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): 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.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input checked="" type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 69,027				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application: \$1,405,500</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="201 1436 1349 1570"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>			<p>X</p>																	

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i>	X			
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</p> <p>Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</p> <p>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</p>			X	Application is electronic

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p>If yes, date consult sent to the Controlled Substance Staff:</p> <p><u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff :</p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p>If yes, notify PeRC RPM (PeRC meeting is required)²</p> <p>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			

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

<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA (NDAs/NDA efficacy supplements only):</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>		X		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	X			
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i></p>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
<p>Check all types of labeling submitted.</p>	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
<p>Is Electronic Content of Labeling (COL) submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p>	X			
<p>Is the PI submitted in PLR format?⁴</p>	X			

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?			X	
<i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send <i>WORD</i> version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?				
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?				
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?				
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	X			
<i>If yes, specify consult(s) and date(s) sent: QT/IRT-November 22, 2010</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): November 2, 2007	X			
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?				

Date(s): September 29, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): February 28, 2006 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 10, 2010

BLA/NDA/Supp #: 202,258

PROPRIETARY NAME: Victrelis (proposed)

ESTABLISHED/PROPER NAME: Boceprevir

DOSAGE FORM/STRENGTH: Capsules/200 mg

APPLICANT: Schering Corporation

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): 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.

BACKGROUND: The rolling review was granted under IND 69,027, on June 24, 2010. Pre-NDA meeting was held on September 29, 2010. NDA 202,258 Part I with nonclinical section was submitted and received on September 30, 2010. Final piece of the NDA was submitted on November 10, 2010, and received on November 15, 2010.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Sherly Abraham	Y
	CPMS/TL:	Victoria Tyson	Y
Cross-Discipline Team Leader (CDTL)	Mary Singer		Y
Clinical	Reviewer:	Poonam Mishra Sarah Connelly Chuck Cooper	Y Y
	TL:	Mary Singer	Y
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	Pat Harrington	Y
	TL:	Jules O'Rear	Y

Clinical Pharmacology	Reviewer:	Ruben Ayala	Y
	TL:	Sarah Robertson	Y
Biostatistics	Reviewer:	Wen Zeng	Y
	TL:	Greg Soon	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Christopher Ellis	Y
	TL:	Hanan Ghantous	Y
Product Quality (CMC)	Reviewer:	Mark Seggel	Y
	TL:	Stephen Miller	N
Facility Review/Inspection	Reviewer:	Karen Takahashi	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:	Mary Dempsey	N
	TL:		
OC/DCRMS (REMS)	Reviewer:	Steven Morin	Y
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Antoni El-Hage	N
	TL:	Tejashri Purhoit-Sheth	N
Other reviewers:QT Review	Kozeli Devi		N
Other attendees	Neha Gada, Kendall Marcus, Kellie Reynolds		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i> 	<input checked="" type="checkbox"/> YES Date if known: April 27, 2011 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<i>mitigation, treatment or prevention of a disease</i>	
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL PHARMACOLOGY	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIostatistics	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

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

CMC Labeling Review	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ed Cox, MD, MPH	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	<ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

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

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

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

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

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

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

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

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

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

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

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

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
12/15/2010