

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201917Orig1s000**

**OTHER REVIEW(S)**

## Division of Antiviral Products

### REGULATORY PROJECT MANAGER LABELING REVIEW

**Application:** NDA 201-917/Original Submission

**Name of Drug:** INCIVEK™ (Telaprevir) (Film-Coated Tablets, 375 mg)

**Applicant:** Vertex Pharmaceuticals, Inc.

#### **Labeling Reviewed**

- Original PI from Vertex Pharmaceuticals submitted November 22, 2010
- Vertex Pharmaceutical's final draft PI submitted May 20, 2011

#### **Background and Summary Description:**

Vertex Pharmaceuticals, Inc. submitted a New Molecular Entity (NME) New Drug Application (NDA), telaprevir, INCIVEK in combination with Peg-IFN (Pegasys® or PegIntron®) and RBV (Copegus® or Rebetol®), for the treatment of genotype 1 chronic hepatitis C virus infection in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have previously been treated with interferon-alfa (pegylated or non-pegylated) alone or in combination with RBV, including prior relapsers, partial responders, and null responders. Telaprevir is a member of a new class of novel direct-acting antiviral drug, the HCV NS3•4A protease inhibitors, represents one of the first of a new class of small molecule drugs for the treatment of chronic hepatitis C virus (HCV) infection in combination with pegylated interferon-alfa (Peg-IFN) and ribavirin (RBV). Telaprevir has additive antiviral activity when combined with Peg-IFN/RBV in subjects with genotype 1 chronic hepatitis C virus (HCV).

Telaprevir was granted fast-track status and the NDA was submitted as a rolling submission. The first portion (Pre-clinical) was submitted June 24, 2010, second portion (CMC) submitted July 14, 2010 and the final clinical portion was submitted on November 22, 2010 and received on November 23, 2010. This NDA received a priority 6-month review. As this was an NME, this application was presented before the Antiviral Products Advisory Committee on April 28, 2011.

DAVP reviewed PI and MG submitted by Vertex and sent the label with revisions to Vertex on March 2, 2011, May 6, 2011, May 13, 2011, May 18, 2011, May 19, 2011, and May 20, 2011. On May 20, 2011, Vertex accepted the revisions made to the PI and MG and submitted the final official copy. Vertex also submitted the revised carton and container labels on May 20, 2011, and they were acceptable by DMEPA.

## Review

- All symbols, for <, >, ≤, and ≥ were spelled out throughout the text of the label.
- Extensive changes in format and content of the proposed label.
- The term “patients’ were used to refer to individuals who may receive telaprevir in clinical practice and “subjects’ were used to refer to individuals who are enrolled in a clinical trial.
- The figures for duration of treatment (Full Prescribing Information: section 2.1) were replaced with a table incorporating the stopping rules.
- Incorporated information related to the ribavirin pregnancy warning in several sections.
- Some proposed Warnings and Precautions were not considered necessary and were deleted.
- Included limited IL28B substudy information in a specific Pharmacogenomics subsection (section 12.5).
- The Clinical Studies section has been significantly shortened.
- Added several subsections to Section 17 - Patient Counseling Information as this information may be included in the Medication Guide. Some is not included elsewhere in the label.
- Deleted tables and added tables. Due to deletion and addition of tables, the table #s have been re-numbered.
- The proposed trade name (b) (4) was changed to “INCIVEK.”

**The following changes (tracked) to the package insert and Medication Guide were made:**

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MYUNG JOO P HONG  
05/20/2011

VICTORIA L TYSON  
05/23/2011

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

Date: May 20, 2011

To: Debra Birnkrant, MD, Director  
Division of Antiviral Products

Application Type/Number: NDA 201917

Through: Carlos Mena-Grillasca, RPh, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Walter Fava, RPh, MSED., Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Incivek (Telaprevir) Tablets, 375 mg

Applicant/sponsor: Vertex Pharmaceuticals

OSE RCM #: 2010-2557-1

## **1. INTRODUCTION**

This review responds to a request from the Division of Antiviral Products for a review of the revised Incivek (Telaprevir) labels and labeling submitted in response to the Division of Medication Error Prevention and Analysis (DMEPA) previous comments to the Applicant.

## **2. METHODS AND MATERIALS REVIEWED**

We evaluated the revised labeling submitted on May 20, 2011 (see Appendices A through E) and the OSE review 2010-2557 dated May 3, 2011, to assess whether the revision adequately addresses our concerns from a medication error perspective..

## **3. CONCLUSION AND RECOMMENDATIONS**

The revised labels and labeling submitted by the Applicant addresses the immediate concerns but the Applicant should consider individual blisters for each tablet for future revisions.

If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Brantley Dorch at 301-796-0150.

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WALTER L FAVA  
05/20/2011

CARLOS M MENA-GRILLASCA  
05/20/2011

CAROL A HOLQUIST  
05/20/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** May 19, 2011

**To:** Myung-Joo P. Hong, Project Manager, DAVP

**From:** Jessica Fox, PharmD, Regulatory Review Officer, DDMAC  
Michelle Safarik, PA-C, Regulatory Review Officer, DDMAC  
Sheila Ryan, PharmD, Group Leader, DDMAC

**Subject:** NDA: 201917  
INCIVEK (telaprevir) Tablets

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DDMAC has reviewed the proposed product labeling (package insert [PI] and patient package insert [PPI]) for INCIVEK (telaprevir) tablets. DDMAC provided comments the proposed PI and PPI on April 29, 2011, and at labeling meetings on May 3, 5, 12, and 17, 2011, which have been addressed by DAVP. DDMAC offers the additional following comments:

**PACKAGE INSERT**

**FULL PRESCRIBING INFORMATION**

Clinical Trials Section

We acknowledge small group data and analyses are included in the clinical trials. These data can be used promotionally. For example, the data for African Americans could be used promotionally to promote the product for being more effective in this population than other available treatment options. If these data are not supported by substantial evidence or the clinical significance of these data is unknown, DDMAC recommends deleting these data or including information about the limitations of these data (i.e., the clinical significance of these data are unknown or similar).

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/s/  
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JESSICA M FOX  
05/20/2011

MICHELLE L SAFARIK  
05/20/2011

## 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.

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PMR/PMC Description: Conduct a pharmacokinetics trial (or subtrial) of telaprevir in treatment-naïve pediatric subjects 3 through 17 years of age to determine appropriate dosing for children that will result in exposures similar to those found to be safe and effective in adults.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2011</u>
	Study/Trial Completion:	<u>06/30/2014</u>
	Final Report Submission:	<u>10/31/2014</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
- X Other

Adult trials are completed and ready for approval

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.”

The goal of the study is to evaluate telaprevir exposure in pediatric patients and select the appropriate dose for a longer safety and treatment study. The PK study (or substudy) will evaluate exposure in three age cohorts of pediatric patients. Dose selection for further study will be based on achieving exposure similar to that shown to be safe and effective in the adult clinical trials.

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.

The clinical pharmacology study (or substudy) is intended to evaluate telaprevir exposure in pediatric patients and select the appropriate dose for longer safety and treatment study. The PK study (or substudy) will evaluate exposure in three age cohorts of pediatric patients. Dose selection for further study will be based on achieving exposure similar to that shown to be safe and effective in the adult clinical trials.

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)
  - X 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?

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

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**PMR/PMC Development Coordinator:**

- X *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/  
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MYUNG JOO P HONG  
05/18/2011

KENDALL A MARCUS  
05/18/2011

## 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.

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PMR/PMC Description: Genome-wide association study (GWAS) to identify factor(s) associated with severe rash and severe cutaneous adverse reactions following telaprevir/poegintergeron/ribavirin treatment using cases from existing DNA substudies and appropriately selected controls

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/30/2011</u>
	Study/Trial Completion:	<u>08/30/2012</u>
	Final Report Submission:	<u>03/31/2013</u>
	Other:	_____

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 benefit of telaprevir outweighs risk in the overall population, therefore this information does not preclude approvability. Conducting genomic studies using existing DNA samples in clinical trials enables exploratory studies that will potentially 1) identify genetic risk factors for severe telaprevir-associated rash 2) characterize the mechanism of severe telaprevir-induced rash.

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.”

Telaprevir was associated with severe rash in approximately 5% of subjects, as well as severe cutaneous adverse reactions including one definite case of Stevens-Johnson Syndrome and one definite case of DRESS (drug rash and eosinophilia and systemic symptoms). A retrospective, case-control genetic study was conducted to determine whether HLA alleles are associated with rash that occurs in the course of triple anti-HCV therapy with telaprevir. The results of this study did not produce any statistically convincing results, but had methodological limitations. The proposed study will examine the association between genetic variations and severe rash using an exploratory, non-hypothesis driven, genome-wide association approach.

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.

This study will evaluate the relationship between 500,000 to 1 million markers across the genome and rash and other severe cutaneous adverse reactions. Cases will be sampled from previous conducted or ongoing clinical trials where DNA has been collected and stored. Cases will be sampled according to prespecified criteria for rash severity. Controls, matched by age, race, trial, and treatment, will be selected at a ratio of at least 4 controls per case.

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  
Exploratory pharmacogenomic study to identify genetic risk factors for telaprevir-induced rash.

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?

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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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05/18/2011

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05/18/2011

## 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.

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PMR/PMC Description: Conduct a trial (VX11-950-115) to evaluate treatment responses and safety among treatment naïve and experienced HIV/HCV co-infected subjects.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/31/2012</u>
	Study/Trial Completion:	<u>06/30/2014</u>
	Final Report Submission:	<u>12/31/2014</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

Up to 30% of patients with HIV infection are also infected with HCV and liver disease in these co-infected patients may progress more rapidly than in patients with HCV only. Patients with HIV/HCV co-infection have also historically been more difficult to treat; response to treatment has been poor with standard interferon-based regimens. HIV/HCV co-infected patients were excluded from the Phase 3 clinical trials of telaprevir and remain an unstudied population with an unmet clinical need for improved treatment.

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.”

To determine the safety and antiviral activity of telaprevir in HIV/HCV co-infected patients.

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.

This study is designed as an open label, single arm, multi-center study. It will combine HCV treatment-naïve and treatment-experienced populations however endpoints will be analyzed separately for each population. Because of known drug-drug interactions, only certain specified HIV treatment regimens will be allowed; allowable HAART regimens will include efavirenz, ritonavir-boosted atazanavir or raltegravir based regimens that contain nucleos(t)ide backbones of tenofovir plus lamivudine/emtricitabine or abacavir plus lamivudine/emtricitabine. This study will also evaluate the response-guided therapy approach to HCV treatment with telaprevir given for 12 weeks and peginterferon/ribavirin given for 24 or 48 weeks depending on early treatment response.

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)
- X 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?

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

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**PMR/PMC Development Coordinator:**

- X *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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MYUNG JOO P HONG  
05/18/2011

KENDALL A MARCUS  
05/18/2011

## 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.

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PMR/PMC Description: Conduct a trial to evaluate treatment response and safety among Blacks/African Americans compared to non-Blacks/African Americans.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2011</u>
	Study/Trial Completion:	<u>04/30/2014</u>
	Final Report Submission:	<u>09/31/2014</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

Blacks/African Americans are disproportionately affected by chronic hepatitis C infection and historically have poor response to treatment compared to Caucasians. The clinical trials of telaprevir enrolled a very small number of Blacks/African Americans (5-10% of Phase 3 trial enrollment). Although these subjects appeared to benefit from telaprevir added to peginterferon/ribavirin, they were less likely to have a positive response than Caucasians. Because this population responds less well to standard treatment, there is a clear unmet clinical need for improved treatment options.

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.”

The goal of this trial is to further characterize telaprevir treatment in combination with a response-guided therapy approach to peginterferon/ribavirin in treatment naïve Black/African American patients, including those with cirrhosis.

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.

This is an open label, multi-center trial that will enroll 200 treatment naïve Black/African American patients, including a cohort with cirrhosis, and compare response rates to those in non-Black/African American patients, also including cirrhotic patients. The trial will measure the proportion of subjects achieving Sustained Virologic Response after treatment with 12 weeks of telaprevir in combination with either 24 or 48 weeks of peginterferon/ribavirin using the response-guided therapy approach; patients with undetectable HCV RNA at weeks 4 and 12 of treatment will be eligible to receive the shorter total treatment duration.

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?

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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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MYUNG JOO P HONG  
05/18/2011

KENDALL A MARCUS  
05/18/2011

## 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 trial to evaluate treatment response and safety among treatment naïve and experienced subjects with cirrhosis compared to subjects without cirrhosis.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2011</u>
	Study/Trial Completion:	<u>03/31/2014</u>
	Final Report Submission:	<u>08/31/2014</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

Patients with cirrhosis have historically been less responsive to treatment with peginterferon/ribavirin than non-cirrhotic patients. The Phase 3 clinical trials of telaprevir enrolled relatively few patients with cirrhosis, particularly in the treatment-naïve trials. Because they respond less well to current standard treatment, this population has a clear clinical need for improved treatment options.

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.”

The goal of this trial is to further characterize telaprevir treatment in combination with a response-guided therapy approach to peginterferon/ribavirin in treatment naïve cirrhotic patients. The trial may be incorporated into the trial to evaluate Black/African American patients.

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.

This is an open label, multi-center trial that will enroll patients with compensated cirrhosis. The trial will measure the proportion of subjects achieving Sustained Virologic Response after treatment with 12 weeks of telaprevir in combination with either 24 or 48 weeks of peginterferon/ribavirin using the response-guided therapy approach; patients with undetectable HCV RNA at weeks 4 and 12 of treatment will be eligible to receive the shorter total treatment duration.

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)

X 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?

X Does the study/clinical trial meet criteria for PMRs or PMCs?

X Are the objectives clear from the description of the PMR/PMC?

X Has the applicant adequately justified the choice of schedule milestone dates?

X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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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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MYUNG JOO P HONG  
05/18/2011

KENDALL A MARCUS  
05/18/2011

## 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 the following telaprevir treatment emergent amino acid substitutions on phenotypic susceptibility of telaprevir in the HCV replicon system.

- I132V (genotype 1a and 1b replicon)
- K244R (genotype 1a and 1b replicon)
- K360R (genotype 1a and 1b replicon)
- R155K ± NS4A\_A36V (genotype 1a)
- NS4A\_E53K (genotype 1a and 1b replicon)

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>07/30/2011</u>
	Study/Trial Completion:	<u>10/30/2011</u>
	Final Report Submission:	<u>11/30/2011</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
- X Other - resistance

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 telaprevir or other agents with overlapping resistance pathways. The information has minimal initial direct impact on patients who have not been previously treated with telaprevir 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 telaprevir treatment-emergent amino acid substitutions in the HCV genome on telaprevir anti-HCV activity. The information may be useful to predict virologic responsiveness to treatment with regimens including telaprevir after a patient has failed telaprevir 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?

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**PMR/PMC Development Coordinator:**

*X 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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MYUNG JOO P HONG  
05/17/2011

KENDALL A MARCUS  
05/17/2011

## 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 PK study in subjects with end-stage renal disease (ESRD) on intermittent hemodialysis (HD) to determine the effect of HD on telaprevir exposure, in order to provide dosing recommendations for HCV patients on HD.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>April, 2012</u>
	Study/Trial Completion:	<u>July, 2013</u>
	Final Report Submission:	<u>December, 2013</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 renal impairment study conducted during pre-NDA development evaluated single-dose telaprevir PK in subjects with severe renal impairment. The data from this study is sufficient to determine the appropriateness of telaprevir dosing in patients with mild, moderate and severe renal impairment. However, the effect of hemodialysis (HD) on telaprevir pharmacokinetics (PK) has not been determined. There is insufficient information in the NDA to support dosing recommendations for patients on intermittent HD.

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.”

There is insufficient information to be able to determine the effect of HD on telaprevir PK. Based on its properties (molecular weight, protein binding, etc), telaprevir may be appreciably removed HD. An in vivo trial in subjects with end-stage renal disease (ESRD) maintained on HD is necessary to determine the extent to which telaprevir PK is affected by intermittent HD in order to provide appropriate dosing in this setting.

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.

The clinical trial may be either a single-dose or multiple-dose PK study conducted in subjects with ESRD maintained on intermittent HD. The primary objective of the study will be to determine the effect of HD on telaprevir PK and the extent to which telaprevir is removed by HD, in order to provide dosing recommendations for this population.

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?

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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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MYUNG JOO P HONG  
05/17/2011

KENDALL A MARCUS  
05/17/2011

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

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/30/2011</u>
	Study/Trial Completion:	<u>09/30/2014</u>
	Final Report Submission:	<u>02/28/2015</u>
	Other: <u>Long-term safety follow-up report</u>	<u>02/28/2019</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

Pediatric patients with chronic hepatitis C infection have limited treatment options – interferon or peginterferon plus ribavirin – and only about half of those with genotype 1 HCV are expected to respond to the standard therapy. The pediatric PMR is appropriate as a post-approval requirement because the pediatric study design is under discussion with multiple stakeholders and the product is ready for approval in adult patients.

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.”

The goal of the pediatric clinical trial is to assess the safety and treatment benefit of telaprevir given in combination with peginterferon/ribavirin in pediatric patients.

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.

The sponsor has agreed to conduct a clinical trial to assess the treatment benefit of telaprevir in combination with peginterferon and ribavirin in pediatric patients 3 through 17 years of age. Using the dose selected in the PK study (or substudy) the trial will evaluate the rate of SVR achieved with 12 weeks of telaprevir added to peginterferon/ribavirin. Both treatment naïve and those who have failed previous treatment will be enrolled. Additionally, the trial will assess safety of the telaprevir combination regimen, specifically issues such as the emergence of resistance substitutions, growth and sexual maturation, and the rates and severity of telaprevir-associated toxicity identified in the adult clinical trials (e.g., rash, pruritus, and anemia).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- X 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)
  - X 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?

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

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**PMR/PMC Development Coordinator:**

*X 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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MYUNG JOO P HONG  
05/17/2011

KENDALL A MARCUS  
05/17/2011

## 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 analyze a representative subset of samples from subjects who experienced virologic failure in the Phase 3 studies, but for whom no clear resistance-associated substitutions in NS3/4A were detected, for the presence of substitutions in NS3/4A protease cleavage sites.

---

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>06/30/2011</u>
	Study/Trial Completion:	<u>07/31/2011</u>
	Final Report Submission:	<u>08/31/2011</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

This concern is theoretical; however, failure to respond to treatment can often be attributed to resistance. All resistance pathways for these drugs may not be fully characterized to date.

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

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/  
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MYUNG JOO P HONG  
05/17/2011

KENDALL A MARCUS  
05/17/2011

**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 18, 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: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): INCIVEK (telaprevir)

Dosage Form and Route: Film Coated Tablets

Application Type/Number: NDA 201-917

Applicant: Vertex Pharmaceuticals Incorporated (Vertex)

OSE RCM #: 2010-2558

## 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 (MG) for INCIVEK (telaprevir) Film Coated Tablets. The purpose of the Applicant's submission is to seek approval of this proposed New Molecular Entity (NME), in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have previously been treated with interferon based treatment, including prior null responders, partial responders, and relapsers.

On April 25, 2011, the DRISK Risk Management Analyst completed a review that recommended the proposed Medication Guide-only REMS for telaprevir no longer be required. The Medication Guide will be approved as part of labeling.

## 2 MATERIAL REVIEWED

- Draft INCIVEK (telaprevir) film coated tablets Medication Guide (MG) received on November 22, 2010, revised by the Review Division throughout the current review cycle and provided to DRISK on April 15, 2011.
- Draft INCIVEK (telaprevir) film coated Tablets prescribing information (PI) received November 22, 2010 revised by the Review Division throughout the current review cycle and received by DRISK on May 9, 2011.

## 3 REVIEW METHODS

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

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SHARON R MILLS  
05/18/2011

LASHAWN M GRIFFITHS  
05/18/2011

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

Date: May 3, 2011

To: Debra Birnkrant, MD, Director  
Division of Antiviral Products

Subject: Label and Labeling Review

Reviewer: Walter Fava, R.Ph., MSED., Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Carlos M Mena-Grillasca, R.Ph., Team Leader  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, R.Ph., Director  
Division of Medication Error Prevention and Analysis

Drug Name/Strength: Incivek (Telaprevir) Tablets, 375 mg

Application Type/Number: NDA 201917

Applicant: Vertex Pharmaceuticals

OSE RCM #: 2010-2557

\*\*\* 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 Incivek (Telaprevir) tablets, for areas of vulnerability that can lead to medication errors. These labels were submitted by the Applicant with the initial NDA.

### **1.1 PRODUCT INFORMATION**

Incivek is the proposed proprietary name for Telaprevir Tablets. Telaprevir is an inhibitor of the hepatitis C virus non-structural protein 3-4A protease inhibitor 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 750 mg (2 tablets) orally three times daily with a meal. Dose reduction of Telaprevir is not recommended.

Telaprevir tablets will be packaged in blister strips, each strip will contain three blisters and each blister will contain two tablets. There are seven strips (42 tablets) in a weekly carton and four weekly cartons (168 tablets) in each monthly carton. Telaprevir will also be packaged in bulk bottles of 168 tablets for institutional pharmacy use.

## **2 METHODS AND MATERIALS REVIEWED**

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container and Blister Labels submitted November 22, 2010
- Carton Labeling submitted November 22, 2010
- Insert Labeling submitted November 22, 2010
- Packaging Research summary submitted April 6, 2011
- Packaging Research raw data submitted April 20, 2011

## **3 RESULTS AND DISCUSSION**

DMEPA acknowledges that the blister packaging design (two tablets per blister and three blisters per strip) corresponds with the daily dosage and frequency of administration (two tablets three times a day) and according to the review Division this application does not provide for variations from this dosing. However, the blister packaging as currently labeled may lead to overdoses or dosing errors. Patients may misunderstand the packaging configuration and think each blister contains 375 mg of telaprevir and will take four tablets for each dose rather than a single blister of 2 tablets. Due to this concern, on March 30, 2011, DMEPA requested data from Vertex to evaluate the comprehension and usability of the blister packaging design. Vertex Pharmaceuticals

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

submitted a summary report of packaging research they have conducted since 2007 which assessed compliance, portability, privacy, package size, and ease of opening four different packaging configurations (pouch, (b) (4) blister, bottle, and (b) (4) blister) in support of the blister strip packaging configuration currently under review. However, since only a summary report was provided, DMEPA held a teleconference with Vertex on April 19, 2011, to request raw data from the research study that demonstrates the design of the proposed blister packaging configuration improves compliance without introducing dosing errors. During the teleconference, Vertex acknowledged that the research data pertained to previous iterations of the blister package labeling and that no additional comprehension testing was conducted on the proposed labeling of the blister packaging submitted for review. On April 20, 2011, Vertex submitted transcripts from their research studies in response to DMEPA's request. DMEPA's ability to assess the data was limited by the fact that the responses provided in the transcripts pertained to earlier iterations and not the final labeled blister packaging configuration submitted for review. Therefore, we have no assurances that the iterations made to the labeling are effective in minimizing the risk of confusion.

#### **4 CONCLUSIONS AND RECOMMENDATIONS**

The proposed blister packaging design is vulnerable to confusion that may result in wrong dosing errors and overdose. We provide recommendations for the blister labels, and carton labeling in Section 4.1 *Comments to the Applicant*. In addition, we provide comments on the proposed insert to improve the clarity of information in Section 4.2, *Comments to the Division*. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

(b) (4)

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact the OSE Regulatory Project Manager, Brantley Dorch, at 301-796-0150.

#### **4.1 COMMENTS TO THE APPLICANT**

##### **A. Blister Label (2 X 375 mg)**

1. Ensure the established name is at least ½ the size of proprietary name and has a commensurate prominence with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See 21 CFR 201.10(g)(2).

2. Delete the statement, [REDACTED] (b) (4) to provide adequate space for implementation of the following comments.

a. It is not clear to users whether the entire blister contains 375 mg. Therefore, we request you revise the presentation of the strength statement on each blister to read :

750 mg                      OR                      750 mg  
(375 mg per tablet)    (2 X 375 mg tablets)

b. Revise the statement, ‘Take With Food’, to read, ‘Take With Meals’, to be consistent with the statements in the package insert labeling.

B. Blister Carton Labeling (42 tablets)

1. See comments A.1 above.
2. Revise the font color for the presentation of the strength statement to a darker color to provide for a better color contrast that will increase readability and prominence of the statement.
3. Revise the statement ‘Take with food’ presented under the food pictogram on the bottom panel to read, ‘Take with meals’ to be consistent with the statements in the package insert labeling.
4. Revise the statement, [REDACTED] (b) (4), to read, ‘Tradename must only be taken with both peginterferon alfa and ribavirin’. As currently presented the statement is intended to prescribers and may be confusing to patients.
5. Delete the [REDACTED] (b) (4) fields. As currently presented it is unclear how these fields will be useful to patients or healthcare providers given this is a fixed dose.

C. Blister Carton Labeling (168 tablets)

1. See comments A.1, B.2, and B.4 above.
2. Revise the statement ‘Take with food’ presented under the food pictogram on the inside of the top flap to read ‘Take with meals’, to be consistent with the statements in the package insert labeling.
3. Increase the prominence (i.e. bold) of the dosing instructions, ‘Take 2 tablets three times a day (7 to 9 hours apart)’ under the tablet pictograms.
4. Revise the Medication Guide statement to read “ATTENTION PHARMACIST: Dispense the enclosed Medication Guide to each patient.”

D. Container Label (168 tablets) for Institutional Use

1. See comments A.1 and A.2.b above.

2. Ensure that the net quantity statement '168 tablets' is presented away from the strength statement.

3. Delete the inactive ingredients contained in the statement that begins (b) (4)

Revise the statement to read 'Each Incivek (telaprevir) tablet contains 375 mg of telaprevir.'

#### 4.2 COMMENTS TO THE DIVISION

A. In Section 16 'How Supplied/Storage and Handling', revise the statement (b) (4), to read (b) (4) 'Unit-dose bottles containing ...'.

This section should describe how the product is supplied (b) (4).

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CARLOS M MENA-GRILLASCA on behalf of WALTER L FAVA  
05/03/2011

CARLOS M MENA-GRILLASCA  
05/03/2011

CAROL A HOLQUIST  
05/04/2011

**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**

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**CLINICAL INSPECTION SUMMARY**

DATE: April 26, 2011

TO: Myung-Jo Patricia Hong, Regulatory Health Project Manager  
Russell Fleischer, PA-C., 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: 201-917

APPLICANT: Vertex Pharmaceuticals, Inc.

DRUG: Telaprevir

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of chronic hepatitis C in adult patients

CONSULTATION REQUEST DATE: December 9, 2010

DIVISION ACTION GOAL DATE: May 23, 2011

PDUFA DATE: May 23, 2011

## **I. BACKGROUND:**

Vertex Pharmaceuticals submitted this application for the use of telaprevir in the treatment of chronic hepatitis C in adults. Two clinical trials were submitted in support of the application: Study VX07-950-108 and Study VX-950-TiDP24-C216.

Telaprevir is an inhibitor of HCV NS3-4A protease which is essential in viral replication. Clinical trials demonstrated that the combination of telaprevir and pegylated interferon with or without ribavirin resulted in a sustained virologic response (SVR); i.e., a substantial decrease in the presence of HCV RNA.

The Applicant has provided data from two studies, Study VX07-950-108 and Study VX-950-TiDP24-C216, in support of the approval of the new protease inhibitor. These studies are summarized in the following sections.

**Protocol VX07-950-108**, entitled: “A Phase 3 Study of 2 dose Regimen of Telaprevir in Combination with Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment – Naïve Subjects with Genotype 1 Chronic Hepatitis C”.

The objective of this study was to demonstrate the efficacy of telaprevir in combination with Peg-IFN-alfa-2a) and ribavirin in treatment-naïve subjects with genotype 1 chronic hepatitis C.

The primary endpoint was the proportion of subjects achieving a sustained viral response (SVR) as demonstrated by undetectable HCV RNA 24 weeks after the last planned dose of study treatment.

**Protocol VX-950-TiDP24-C216**, entitled: “A Randomized, Double-Blind, Placebo-Controlled, Phase III Trial of 2 regimens of Telaprevir (with and without delayed start) Combined with Pegylated Interferon alfa-2a (Pegasys) and Ribavirin (Copegus) in Subjects with Chronic Genotype 1 Hepatitis C Infection who Failed Prior Pegylated Interferon Plus Ribavirin Treatment”.

The primary objective of this study was to demonstrate the superior efficacy of telaprevir in combination with Peg-IFN alfa-2a and ribavirin compared to standard treatment of subjects with chronic HCV genotype 1 infection who failed prior treatment with Peg-IFN plus ribavirin. Failed subjects were those subjects who were non-responders (those subjects whose viral loads were not undetectable after treatment) or relapsers (those subjects with detectable HCV RNA during the follow-up period after demonstrating previously undetectable HCV RNA at the end of treatment).

The primary efficacy parameter was the proportion of subjects in each treatment group achieving SVR which is defined as having undetectable HCV RNA levels (10 IU/mL) 24 weeks after the last planned dose of study medication. Treatment success was those subjects who complete their treatment regimens and achieve SVR or those subjects who terminate treatment early for reasons other than virologic failure and achieve SVR.

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 VX07-950-108 and Study VX07-950-C216) as data from the two protocols are considered essential to the approval process and the limited experience with this product has been at foreign sites. 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 and 2) site specific protocol violations. Vertex Pharmaceutical, Inc. the Sponsor of this application was also inspected.

## II. RESULTS (by protocol/site):

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
John Vierling, M.D. St. Lukes Episcopal Hospital Baylor College of Medicine Advanced Liver Therapies 6620 Main St.1505 Houston, TX 77030 Site# 169	Protocol VX07-950-108 Number of subjects listed 31	1/31-2/2/11	NAI
Peter Ferenci, M.D. Univ.Klinik fur Inner Medizin III Abeiling for Gastroenterologie and Hepatologie Aahringer Gurtel 18-20 Vienna, Austria 1090 Site# 201	Protocol VX07-950-108 Number of subjects listed 22	2/28-3/4/11	Pending  Preliminary: VAI
Michel Ryan, M.D. 1 Digestive and Liver Disease Specialist 885 Kempsville Rd #114 Norfolk, VA 23502 Site# US00133	Protocol VX-950-C216 Number of subjects listed 4	2/11-23/11	Pending  Preliminary: VAI
Pietro Andrecone, M.D. Universita degli Study di Bologna Via Massarenti9 Dipartimento de Medicina Clinica Bologna, Italy 40138 Site# IT00146	Protocol VX07-950-C216 Number of subjects listed 25	3/7-11/11	Pending  Preliminary: VAI
Sponsor Vertex Pharmaceuticals, Inc. Cambridge, MA 02139 Sites# 201&133	Protocols VX07-950-108 and C216 Number of subjects listed 26	11/14-26/11	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 3 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 VX07-950-108

1. **John Vierling, M.D.**  
**Houston, TX 77030**

**a. What Was Inspected:** At this site, a total of 31 subjects were screened, six subjects were reported as screen failures. Twenty five (25) subjects were randomized and 24 subjects completed the study. There were no deaths and no under-reporting of adverse events. Review of Informed Consent Documents for 25 subjects records reviewed, verified that subjects signed prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 25 random subjects were reviewed, including drug accountability records, vital signs, laboratory test results, IRB records, use of concomitant medications; 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. Vierling. The medical records reviewed were found to be in order and the data verifiable. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.

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

2. **Peter Ferenci, M.D.**  
**Vienna, Austria**

**a. What Was Inspected:** At this site, a total of 22 subjects were screened, twenty two (22) subjects were randomized and 20 subjects completed the study. Two subjects were discontinued shortly after randomization due to the use of prohibited drugs (heroin and

sedatives). There were no deaths and no under-reporting of adverse events (exceptions noted below). Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 13 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 2 item Form FDA 483 was issued to Dr. Ferenci. Our investigation found protocol violations and inadequate record keeping.

**Protocol Violations:**

- Two subjects did not meet inclusion criteria in that Subjects 201012 and 201013 lacked evidence of hepatitis C chronicity as specified by the protocol. The two subjects were randomized in error and went unreported to the sponsor until approximately six months; when retrospective exemption requests were submitted to the sponsor. These two subjects should be excluded from final analyses.

**Record Keeping Violations:**

Review of source documents revealed the clinical investigator did not maintain adequate accountability records. For example,

- Lot numbers for the Copegus and Pegylsus kits dispensed to subjects were not recorded, as specified for dispensing by the interactive Web Response System (IWRS) for the approved medications.

DSI Reviewer Note: Per discussions with the field investigator, there is no evidence to suggest that subjects did not receive appropriate randomized treatment.

- Study records did not identify who dispensed study drugs to subjects. The identity of the dispensing individuals could only be determined through handwriting recognition by study personnel.
- Study drugs were required to be stored under refrigerated conditions (2-8) degrees centigrade. Some instances of temperature excursions were noted outside of this range. Note: Per CMC reviewer, isolated instances of being below 2 degrees C are probably not a concern. In addition, 18 dosing kits were inadvertently stored at room temperature for 6 days. Further, the CMC reviewer noted that in the context of a 3 year shelf life when stored at 2 degrees C, this temperature excursion is not considered significant.

The clinical investigator acknowledged the inspectional findings in a written response dated March 17, 2011, in which the clinical investigator promised to implement corrective and preventive measures will be taken to avoid such deviations from occurring in future studies. DSI finds his response acceptable.

**c. Assessment of Data Integrity**

Although regulatory violations were noted, the findings are not likely to affect data integrity. However, the review division may wish to exclude the two subjects who did not meet inclusion criteria from the final analysis. The study appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the pending application.

**Protocol VX07-950-C216**

**3. Michael Ryan, M.D.  
Norfolk, VA 23502**

**a. What Was Inspected:** At this site, a total of 4 subjects were screened, 3 subjects were reported as screen failures (for not meeting inclusion criteria), one subject was randomized into the study and completed the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for all 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 and no discrepancies were noted.

**b. General Observations/Commentary:** At the conclusion of the inspection, a 1 item Form FDA 483 was issued to Dr. Ryan. Our investigation found protocol violations in terms of drug storage under temperature controlled conditions. Study drugs were required to be stored under refrigerated conditions (2-8) degrees centigrade. Some instances of temperature excursions were noted outside of this range. Note: Per CMC reviewer isolated instances of being below 2 degrees centigrade are probably not a concern; in the context of a 3 year shelf life when stored at 2 degrees Centigrade, this finding is not considered significant. An additional finding noted was that informed consent did not note specifically the possibility that the FDA may inspect records rather than the wording of “Regulatory Authorities” may have access to and review the records.

The clinical investigator acknowledged the inspectional finding and verbally stated in the future will exercise more care in his future studies.

**c. Assessment of Data Integrity:** The medical records (limited number) 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. There were no known limitations to this inspection. The data generated from Dr. Ryan’s site are considered reliable and appear acceptable in support of the application.

**4. Pietro Andrecone, M.D.  
Bologna, Italy**

- a. What was Inspected:** At this site, a total of 25 subjects were screened, one (1) subject was reported as screen failure. 23 subjects were randomized and 16 subjects completed the study. Three (3) subjects were discontinued from the study and the reasons were documented. Review of Informed Consent Documents, for 14 subjects reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for 14 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 for selected subjects 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, a two item Form FDA 483 was issued to Dr. Andrecone. Our investigation found protocol deviations and inadequate drug accountability records.

**Protocol Violations:**

- The clinical investigator did not follow inclusion criteria in that the medical records for two subjects did not include HCV RNA values for end-of-treatment and follow-up testing for a prior failed treatment. Medical records for subjects 216-0046 and 216-0804 included only “qualitative” HCV RNA as “presente” with a number code. This is contrary to protocol inclusion criteria.

**Inadequate Record Keeping:**

- Study records did not identify who dispensed study drugs to subjects. The identity of the dispensing individual(s) who carried the drug package from the pharmacy to the Clinical Medicine Department (CMD), did not include the time of receipt, who received the package, and who place the drug into a controlled-temperature storage condition at the CMD. However, review of other source records did not raise concerns regarding adequate dispensation.
- Study drugs were required to be stored under refrigerated conditions (2-8) degrees centigrade. There were no records of the location where the study drugs were stored. Note: Per CMC reviewer, the storage at ambient conditions is not a concern. As such, this finding is unlikely to impact data reliability.

The clinical investigator acknowledged the inspectional findings in a written response (Not dated) received late March, 2011 in which the clinical investigator promised to implement corrective actions to prevent the recurrence of the inspectional findings in future studies. DSI find his response acceptable.

The medical records reviewed disclosed no other adverse findings that would negatively on the reliability of the data. With the exception of the items noted above (protocol deviations for the two subjects), the records reviewed were found to be organized and the data verifiable. There were no known limitations to this inspection.

- c. Assessment of Data Integrity:** Although regulatory violations were noted, the findings are considered isolated in nature and/or unlikely to significantly impact data reliability. However, the review division may wish to exclude the two subjects, as described above, in their assessment of safety and the efficacy of the drug. The data from Dr. Andrecone's site are considered reliable and appear acceptable in support of the pending application.

**5. Vertex Pharmaceuticals, Inc.  
Cambridge, MA 02139**

- a. What was Inspected:** The inspection audited Protocols VX07-950-108 and VX07-950-C216 and focused on the following clinical investigators: Drs. Ryan and Ferrenci during the course of this sponsor/monitor inspection. Vertex Pharmaceutical Incorporated was established in 1989 and went public in 1991. Vertex Pharmaceutical Incorporated then partnered with Johnson & Johnson Pharmaceutical Research & Development LLC (J7JPRD) in 2006 for the development of Telaprevir. Vertex acquired ViroChem of Canada in 2008 and in 2010 submitted its first NDA to the Agency for telaprevir. Vertex delegated various study functions, via contract, to [REDACTED] <sup>(b)(4)</sup>, who was the CRO for Study VX07-950-108. Similarly for Study VX-950-TiDP24-C216, Vertex delegated the majority of study functions, via contract to Tibotex, Inc.

During the inspection the following areas were reviewed: Company history and officers responsibilities, Sponsor's obligations, Monitoring plan, training program, site monitoring, manufacturing/design operation, selection of clinical investigators, quality control and assurance practices, including identification of systemic errors and issues of significant and /or persistent noncompliance, and evaluation of suspected scientific misconduct on the part of the clinical investigators. In addition, protocol development and site specific documents associated with the clinical investigators noted above. The inspection also focused on other select clinical trials activities to determine whether adequate controls (such as written procedures and policies, training, monitoring, auditing and governance) were in order. The clinical trial activities reviewed included: study monitoring procedures, data review reports, protocol adherence, sponsor adequate oversight of clinical sites, monitors report, IRB documentation, CRFs, data collection, 100 % of AE's were checked. No significant violations were noted and a Form FDA 483 was not issued. Both the primary efficacy endpoints were verifiable, electronic data capture systems were used for all data from the eCRFs to data lock, no issues were found and the records were found to be adequate.

- b. **General Observations/Commentary:** The inspection found that the sponsor adhered to their SOPs regarding proper monitoring of their clinical investigators. The activities included, but not limited to, trial drug records, subject records, electronic database for entry of study data, protocol adherence, case report forms/source documents and adverse events reporting. No Form FDA 483 was issued following the inspection.
- c. **Assessment of Data Integrity:** The sponsor monitoring procedures appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication. In general, the sponsor appears to have fulfilled their regulatory obligations for the two studies indentified above. Therefore, data from these studies in support of the requested indication are considered reliable.

### **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. Vierling, Ferenci, Ryan, Andrecone and the sponsor revealed no significant problems that would adversely impact data acceptability. Overall the data submitted from these sites and submitted by the sponsor from the above four sites are acceptable in support of the pending application.

**Note: Observations noted above for at least 3 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  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

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

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/s/  
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ANTOINE N EL HAGE  
04/28/2011

TEJASHRI S PUROHIT-SHETH  
04/28/2011

MEMORANDUM

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

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DATE: April 15, 2011

TO: Debra B. Birnkrant, M.D.  
Division Director.  
Division of Antiviral Products  
Office of Antimicrobial Products

John Lazor, Pharm.D.  
Division Director,  
Division of Clinical Pharmacology 4  
Office of Clinical Pharmacology

FROM: Jyoti B. Patel, Ph.D.  
GLP and Bioequivalence Branch  
Division of Scientific Investigations

THROUGH: Martin K. Yau, Ph.D. \_\_\_\_\_  
Acting Team Leader, Bioequivalence  
GLP and Bioequivalence Branch  
Division of Scientific Investigations

SUBJECT: (b)(4) of EIR Covering NDA 201-917,  
(b)(4) (Telaprevir) Tablets, 375 mg  
r: Vertex Pharmaceuticals, Inc., Cambridge, MA

At the request of the Division of Antiviral Products (DAVP), Office of Antimicrobial products (OAP) and the Division of Clinical Pharmacology 4, Office of Clinical Pharmacology (OCP), the Division of Scientific Investigations (DSI) conducted an audit of the clinical and bioanalytical portions of the following bioequivalence study.

**Study Number:** VX07-950-017

**Study Title:** "A Phase I, open-label, randomized, single dose escalation, and relative bioavailability study of Telaprevir in healthy subjects"

The inspections of the clinical and analytical portions of Study VX07-950-017 were conducted at Covance Clinical Research Unit, Dallas, TX (02/28/11 to 03/03/11) and at (b)(4) (02/28/11 to 03/04/11), respectively. Please note that the Covance Clinical Research Unit, at Austin, TX

(where the study was conducted) closed for business on June 30, 2010. David Carter, M.D. Clinical Investigator is no longer associated with Covance and the custody of records has been transferred to Stephen D. Flach, M.D., Executive Medical Director at Covance Clinical Research Unit, Dallas, TX. Following the inspections, no objectionable issues were found at the clinical site and no Form FDA-483 was issued; however Form FDA-483 was issued at the analytical site (Attachment 1).

(b)(4) (analytical site) responded to the Form FDA-483 observations in the letter dated March 17, 2011 (Attachment 2). The Form FDA-483 observations, discussion items, written response by the analytical site, and our evaluations are as follows:

**Form FDA-483 Analytical Observations issued at (b)(4)**

**Analytical Observation 1:**

**Failure to detect and correct errors in records and reports, concerning origin of clinical samples, receipt dates, protocol number and condition of samples.**

- A) The Final Report; issue date 11 April 2008, did not contain accurate and complete information regarding the samples received. Under the Sample Analysis section, (b)(4) "(samples) were received from (b)(4)". This is not accurate in that samples were received from Covance - Clinical Research Unit Austin, TX.
- B) Sample Analysis section of the Final Report contains a listing of samples received, by date and the number of samples received. This information is not complete in that it does not include the receipt of 90 samples received on Oct. 24, 2007.
- C) Sample receipt paper work is not accurate in that several of the Specimen Inventory Forms and Receipt of Shipment Fax forms list the incorrect protocol number as VX07-950-117. The last three digits should be 017.
- D) Human plasma samples received on Oct. 16, 2007 contained a Sample Issue Worksheet completed by the clinical site. This document states "Period 4, 24 HR post samples were stored ambient in error. Samples were placed in -70 (° C) freezers on 15 Oct 2007 @ 11:08". There was no indication whether the samples should be analyzed. Additionally, there was no follow-up with the clinical site or sponsor to determine if samples should be analyzed.
- E) Human plasma samples received on Nov. 28, 2007 contained a Sample Issue Worksheet completed by the clinical site. This

document states that at least 4 samples are hemolyzed or slightly hemolyzed. There was no indication whether the samples should be analyzed. Additionally, there was no follow-up with the clinical site or sponsor to determine if samples should be analyzed.

**Response:**

- In response to FDA-483 observations 1A and 1B, (b)(4) acknowledges that the final report was incorrect. (b)(4) amendment to the final report with the correct information was provided with the response (Attachment 2).
- (b)(4) accepts the discrepancies of their 'Received Sample Receipt System' as cited in FDA-483 observations 1C, 1D and 1E. The firm has a SOP (SOP NA-BAC 102) in place that defines discrepancies in the process focused on the demographic and label information of each individual sample received for which, a Discrepancy Information form (DIF) is (b)(4) as part of the corrective action, as of June 30, 2011, (b)(4) will review and revise the SOP as necessary to enhance (b)(4) process, increasing focus on all aspects of sample receipt.
- In regards to FDA-483 observation 1D, (b)(4) contacted the clinical site and the sponsor. (b)(4) reviewed the data of the plasma samples that were (b)(4) properly stored and is currently amending a report that clearly identifies the samples and describes the impact of the storage conditions on the analytical results. According to the draft amendment (Attachment 2) provided with the response, plasma samples for period 4 from subjects 01014, 01015, 01016, 01017, 01018, 01019 and 01020 collected 24 hours post-dose were stored at room temperature for approximately 8 days. As the stability of telaprevir under these conditions was not evaluated, these plasma samples are likely compromised.
- Regarding FDA-483 observation 1E, the firm responded that at the time when the study was conducted, the decision to assay or not assay hemolyzed samples was based on the scientific judgment of the Principal Investigator and the bioanalytical chemist. The samples were analyzed without any validation. The updated current SOP for hemolyzed samples focuses on validation of assay performances in hemolyzed samples. The firm has initiated a more detailed review of this issue and will respond with the proposed changes by June 30, 2011.

**Evaluation:**

After evaluating the firm's response to FDA-483 observation 1, DSI recommends the Review Division to discard the plasma sample data from subjects 01014, 01015, 01016, 01017, 01018, 01019 and 01020 collected 24 hours post-dose in period 4, as these plasma samples are likely to be compromised following storage at room temperature for approximately 8 days (FDA-483 observation 1D). Most of the slightly hemolyzed samples (FDA-483 observation 1E) were from a duplicate set of samples, which were not analyzed; this should not impact the study outcome. The other findings under FDA-483 observation 1 are errors in documentation and should not significantly affect the study outcomes.

**Analytical Observation 2:**

Failure to establish stability of internal standard (ISTD) stock solution at the specified storage temperature. Specifically, the ISTD was stored at (b)(4) expiration date assigned as (b)(4); however, stability was only performed at room temperature for 6 hours.

(b)(4)

(b)(4). However, (b)(4) has agreed to review current client requests, benchmark current industry practices and consult both internally and externally on this observation and complete this process improvement work by June 30, 2011.

**Evaluation:**

DSI has found (b)(4) response to be reasonable. Due to the rationales mentioned above, this observation should not have significant impact on the study outcomes.

**Analytical 483 Observation 3:**

**Failure to follow or be consistent with established, written SOPs.**

A

- (b)(4)
- B) Training files for bioanalytical employees revealed that the SOP required annual review was not conducted and/or documented in 2006, 2007, 2008, or 2009 for (b)(6); and not documented in 2009 or 2010 for (b)(6).

**Response:**

- (b)(4) is in agreement that the information in the final report pertaining to observation 3A is incorrect. A report amendment to correct this error was included in the response (Attachment 2).
- In response to FDA-483 observation 3B, as part of corrective action, (b)(4) management team will implement by the end of April, 2011 a system of positive affirmation by supervisors for training record reviews triggered by a calendar based alert to perform the annual training record review. Effective March 30, 2011, a revised form used to document annual review of an employee training file will be in place (Attachment 2).

**Evaluation:**

DSI accepts the firm's response.

**Other findings:**

In addition to the Form FDA-483 observations, the following items were discussed with the firm's management (please see attachment# 4 for details). These findings are not likely to have significant impact on the study outcomes.

- 1) Aliquot History Report (b)(4) that documents sample tracking, movement and storage information requires improvement.
- 2) Sample receipt paperwork did not include information on the anticoagulant used during the collection and processing of the samples at the clinical site.
- 3) Shipping Request for Samples and Test Articles that document the final disposition of samples was not accurate.

4) Reintegration of individual chromatographic peaks for calibration standards, QCs and blank matrix samples along with subject samples was performed. Though proper justification was provided for the reintegration, the current SOP requires to be updated.

### Conclusion

Following the inspection of Covance Clinical Research Unit (clinical site) and (b)(4) (analytical site), DSI recommends acceptance of analytical data of Study VX07-950-017 for review with the exception of the following two items:

- Plasma sample data from subjects 01014, 01015, 01016, 01017, 01018, 01019 and 01020 collected 24 hours post-dose in period 4, should be discarded because the integrity of these samples was likely compromised. These plasma samples were stored at room temperature for approximately 8 days, and the stability under these conditions was not evaluated.
- The telaprevir plasma concentration for subject 01011, Period 2, 1.5 hrs post-dose, should be 27.4 ng/mL and not 28.1 ng/mL.

The Ower should also be aware of the corrective actions that (b)(4) has agreed to implement by June 30, 2011. After you have read this transmittal memo, please append it to the original NDA submission.

Jyoti B. Patel, Ph.D.  
Staff Fellow (Pharmacologist)

### **DSI Final Classification:**

**NAI** - Covance Clinical Research Unit, Austin, TX

**VAI** - (b)(4)

cc:

CDER DSI PM TRACK

OC DSI/Ball/Haidar/Yau/Patel/Dejernett/CF

HFR-SW1515/Alanna L. Bias (BIMO)

HFR-SW1540/Joel Martinez (BIMO)/Tricia Martinez

HFR-SW150/Susan Turcovski (DIB)

HFR-CE8590/Constance Richard-Math (BIMO)

HFR-CE850 Sharon Matson (BIMO), Cheryl A. Bigam (DIB)

HFR-CE8585/Scott Laufenberg

HFD-530/OAP/DAVP/Myung-Joo Patricia Hong  
HFD-580/OCP/DCP4/Shirley Seo/Sarah Robertson  
Draft: JBP 4/02/2011, 4/06/2011, 4/14/2011  
Edit: MKY 4/05/2011, 4/13/2011, 4/15/2011  
File:6174 O:\BE\EIRCOVER\201917cov.tel.doc  
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/s/  
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JYOTI B PATEL  
04/15/2011

MARTIN K YAU  
04/15/2011



## MEMORANDUM

Date: April 1, 2011

From: Brenda Carr, M.D./Medical Officer, Dermatology

Through: Jill Lindstrom, M.D./ Clinical Team Leader, Dermatology  
Susan Walker, M.D./Director, Division of Dermatology and Dental Products

To: Debra Birnkrant, M.D./Director, Division of Antiviral Products (DAVP)

Cc: Margo Owens, Project Management Staff Team Leader  
Barbara Gould, Chief, Project Management Staff

Re: Division of Dermatology and Dental Products (DDDP) Consult #1326  
Subject of consult: NDA 201-917 (telaprevir)

Material Reviewed: Primary review materials: clinical study report for VX07-950-108, the Dermatology Expert Panel (DEP) report, photographs appended to the DEP report; Summary of Clinical Safety

Background: The Division of Antiviral Products (DAVP) consulted the Division of Dermatology and Dental Products (DDPP) on NDA 201-917. The product proposed for marketing is telaprevir (tablet dosage form), a new molecular entity intended for treatment of chronic hepatitis C virus infection. The applicant was granted a "rolling submission," and the final unit, the clinical section, was received by the Agency on November 23, 2010. The application was granted priority review. An Advisory Committee meeting is scheduled for April 28, 2011.

From the consult request form dated December 10, 2010:

"Telaprevir is a NS3/4 protease inhibitor developed for treatment of chronic hepatitis C virus infection. The drug is administered for up to 12 weeks in combination with pegylated interferon and ribavirin. During development, it was noted that telaprevir caused rash and pruritis that in some cases was severe and treatment limiting. The Applicant devised a special search criteria to evaluate the safety data base for rash and pruritis. In addition, they established a category of events of special interest to capture Grade 3 and 4 rash, discontinuations due to rash and cases of Stevens Johnson Syndrome; which there were a few. The Applicant convened a Dermatology Expert Panel to evaluate clinical cases, photographs and skin biopsies. Additionally, the

Applicant states they have attempted to investigate the mechanism of the rash but have not found anything definitive. The pivotal trials for this NDA are Studies 108 and C216. The Expert Panel review with photos are in Section 5.3.5.3 of the NDA. Biopsy slides have been requested.”

Per the applicant’s draft labeling (Highlights), the product is proposed for use “. . .in combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers.”

The intended dosage is “750 mg taken 3 times a day (7-9 hours apart) with food, and it must be administered with both peginterferon alfa and ribavirin for all patients for 12 weeks (i.e., it is not intended as monotherapy). The 12-week telaprevir course should be “followed by a response-guided regimen of either 12 or 36 weeks of peginterferon alfa and ribavirin depending on viral response and prior response status” (from the draft label, Highlights).

## **Background**

Severe cutaneous eruptions were first reported in telaprevir-treated subjects during the placebo-controlled Phase 2 trials. The applicant’s approach to assessment and management of cutaneous adverse events evolved over the development program, with the heightened awareness of the potential for such adverse events generated by the occurrence of severe cutaneous events in Phase 2 trials.

By Phase 3, the applicant had both refined and expanded the approach to the handling of rash-type events from what was done in Phase 2. The protocols for the pivotal Phase 3 trials provided for (additional details provided below in the discussion of study VX07-950-108):

- a grading scale specific for mucocutaneous adverse events
- guidance on management of study drugs relative to the severity grading of the mucocutaneous event
- formal designation of select adverse events as “Events of Special Interest” (ESI)
- procedures to be performed for subjects with ESI

Protocol-specified procedures for subjects with ESI were similar in the pivotal trials VX07-950-108 (108) and VX07-950-TiDP24-C216 (C216). However, only in study 108 were all of the following required for ESI (Section 13.1.2.3.2 of the protocol for study 108):

- photographs of the skin reaction
- consultation with a dermatologist for further characterization of the rash and skin biopsy
- Laboratory tests: WBC w/differential, ALT/AST, serum creatinine, CPK (creatinine phosphokinase), and LDH (lactate dehydrogenase)
- a blood sample for pharmacokinetic analysis (only at the sites that have the technical capability to process the samples, as close to the time of onset of rash as possible, and if possible, prior to the discontinuation of study drugs).

The definition of an ESI was the same in study C216 as in study 108. However, in study C216, photographs and biopsy of ESI were at the discretion of the evaluating dermatologist, i.e. these procedures were not required as they were in study 108.

In an effort to characterize the cutaneous eruptions, the applicant convened a Dermatology Expert Panel (DEP) and an expert dermatopathologist (adjunct member of the DEP). The primary charge of the DEP was to characterize the ESI that occurred in study 108 with a particular focus on those events that might represent severe cutaneous adverse reactions (SCAR). Study 108 was the primary focus of the DEP because this study provided the most comprehensive data about cutaneous events (because of procedures specified only in the protocol for study 108). The DEP report is discussed later in this consult.

The primary focus of this consult will be on the pivotal trial VX07-950-108, the primary database for cutaneous adverse events, and on the DEP report.

\*\*\*\*\*

**VX07-950-108:** “A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination With Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C”

**Primary Objective:**

To demonstrate the efficacy of telaprevir in combination with peginterferon alfa-2a (Peg-IFN-alfa-2a) and ribavirin (RBV) in treatment-naïve subjects with genotype 1 chronic hepatitis C

**Secondary Objective:**

To evaluate the safety of telaprevir in combination with Peg-IFN-alfa-2a and RBV in treatment-naïve subjects with genotype 1 chronic hepatitis C

**Methodology:**

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in treatment-naïve subjects with genotype 1, chronic hepatitis C virus (HCV) infection. The study compared 2 regimens of telaprevir dosed with Peg-IFN-alfa-2a and RBV against standard treatment, Peg-IFN-alfa-2a and RBV.

The treatment regimens that included telaprevir were either 24 or 48 weeks in duration. Telaprevir was dosed orally at 750 mg every 8 hours in combination with Peg-IFN-alfa-2a and RBV for either:

- the first 8 weeks (T8/PR group) or
- the first 12 weeks (T12/PR group).

For subjects who achieved an extended rapid viral response (eRVR, defined as undetectable HCV RNA at Week 4 and Week 12), Peg-IFN-alfa-2a and RBV were dosed for a total of 24 weeks. For subjects who did not achieve eRVR, Peg-IFN-alfa-2a and RBV were dosed for a total of 48 weeks.

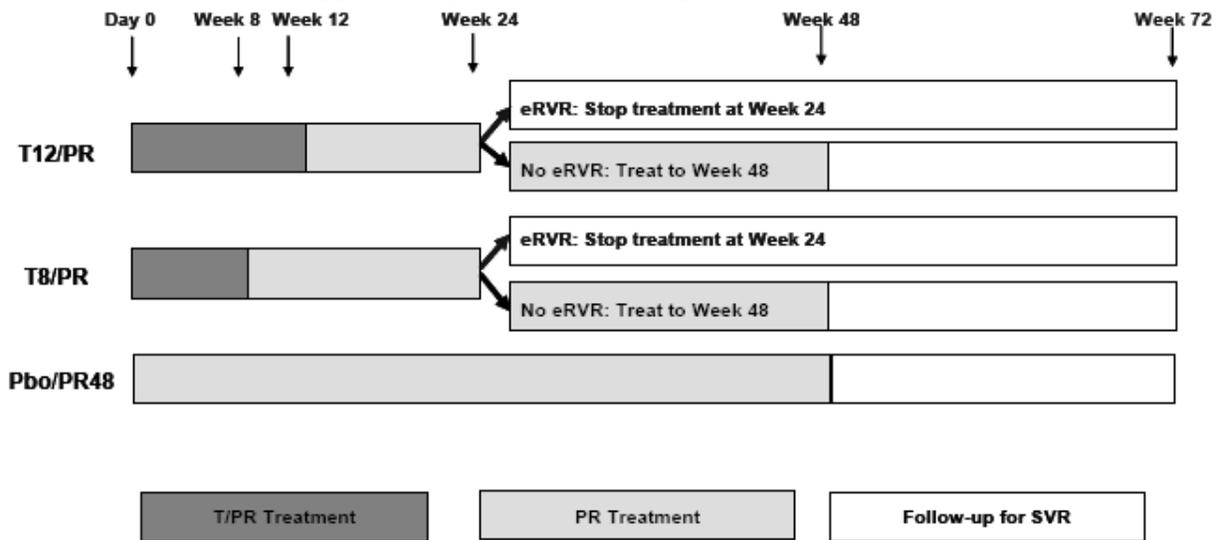
The control group had a total treatment duration of 48 weeks, with telaprevir-matching placebo given for the first 12 weeks and Peg-IFN-alfa-2a and RBV dosed for 48 weeks (Pbo/PR48 group).

**Treatment Groups (Applicant Table 4)**

Treatment			
Treatment Group	Telaprevir Dosing Period	Telaprevir-matching Placebo Dosing Period	Peg-IFN-alfa-2a and RBV Dosing Period
T8/PR	Day 1 through Week 8	Weeks 9 through 12	Day 1 through Week 24–with eRVR Day 1 through Week 48–without eRVR
T12/PR	Day 1 through Week 12	---	Day 1 through Week 24–with eRVR Day 1 through Week 48–without eRVR
Pbo/PR48	---	Weeks 1 through 12	Day 1 through Week 48

T: telaprevir; PR: Peg-IFN-alfa-2a and RBV; Pbo: placebo; eRVR: extended rapid viral response (undetectable HCV RNA at Week 4 and Week 12)

Schematic of Study Design (Applicant Figure 1 from study report)



eRVR: extended rapid viral response (undetectable HCV RNA at Weeks 4 and 12); Pbo: placebo; PR: peginterferon alfa-2a (Pegasys®) and ribavirin (Copegus®); T: telaprevir.

“Rash Assessment: Severity Grading”

Section 13.1.2.1 of the protocol defined the severity grades of cutaneous eruptions as below:

**Grade 1 (mild):** a localized skin eruption and/or a skin eruption with a limited distribution (e.g., up to several isolated sites on the body), with or without associated pruritus. A mild rash would have no target lesions, no signs of systemic involvement, and no involvement of mucous membranes or signs of epidermal detachment.

**Grade 2 (moderate):** a diffuse skin eruption involving up to approximately 50% of the body surface, with or without superficial skin peeling, pruritus, or mucous membranes involvement with no ulceration. A moderate rash would have no signs of target lesions or epidermal

detachment. A moderate rash may have had associated systemic symptoms which were mild and/or limited.

**Grade 3 (severe):** a generalized rash involving over 50% of the body surface; or rash presenting with any of the following characteristics:

- vesicles or bullae
- superficial ulceration of mucous membranes
- epidermal detachment (full thickness epidermal necrosis and separation of epidermis from underlying dermis)
- atypical or typical target lesions
- palpable purpura/non-blanching erythema

“Rash with appearance of significant systemic signs or symptoms that are new and are considered related to the onset and/or progression of rash should be considered to be Grade 3.

“In addition to events meeting the criteria above, any events of Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug-Related Eosinophilia with Systemic Symptoms (DRESS), or Erythema Multiforme (EM) should always be categorized as Grade 3.

“Determination of seriousness of skin rash events will follow the standard ICH criteria for serious adverse events....”

### Events of Special Interest (ESI)

Section 13.1.1.1 of the protocol specified that select cutaneous adverse events were to be formally classified as “Events of Special Interest” (ESI). ESI were “rash or rash-like events” that met any of the following criteria:

- permanent discontinuation of any or all study drugs due to rash
- Grade 3 (severe) rash
- rash which meets the criteria to be a serious adverse event.”

The protocol specified the following procedures for ESI:

- reporting of the event as an ESI to the sponsor within 24 hours
- photographs of the skin reaction
- consultation with a dermatologist for further characterization of the rash and skin biopsy
- Laboratory tests: WBC w/differential, ALT/AST, serum creatinine, CPK (creatinine phosphokinase), and LDH (lactate dehydrogenase)
- a blood sample for pharmacokinetic analysis (only at the sites that have the technical capability to process the samples, as close to the time of onset of rash as possible, and if possible, prior to the discontinuation of study drugs).

### Management of Cutaneous Eruptions

Grade 1 and 2 Eruptions:

- Study products did not have to be discontinued, but discontinuation should have been considered for Grade 2 eruptions
- If the investigator determined that study drug(s) should be discontinued, the applicant recommended permanent discontinuation of telaprevir.

**Note:** Telaprevir could not be resumed if it had been discontinued (irrespective of the severity grade of the eruption, i.e. 1, 2 or 3)

- If the eruption did not improve within seven days, RBV should have next been discontinued (or sooner if the eruption progressed after discontinuation of telaprevir). Peg-IFN-alfa-2a could have been continued (unless interruption was also thought indicated).
- Treatment with Peg-IFN-alfa-2a and/or RBV could have been resumed if the eruption improved within 14 days of discontinuation of the agents. Neither product could be resumed after 14 days. As RBV monotherapy is not permitted, both Peg-IFN-alfa-2a and RBV were to have been restarted were treatment resumed.

Grade 3 Eruptions

- Telaprevir was to have been discontinued immediately.
- If the eruption did not improve within seven days, RBV and Peg-IFN-alfa-2a were to have been handled as per Grade 1 and 2 eruptions.
- The investigator could have discontinued all study drugs simultaneously, if thought clinically indicated. **However, all study drugs were to have been permanently discontinued immediately for any subjects with diagnosed/suspected SJS, TEN, DRESS, EM, or a cutaneous eruption considered life-threatening.**
- Treatment with Peg-IFN-alfa-2a and/or RBV could have been resumed if the eruption improved within 14 days of discontinuation of the agents (protocol was as per for Grade 1 and 2 eruptions; see above)
- Daily follow-up (in person or by telephone), with on-site visits as clinically appropriate. Additionally, subjects were to have been followed until complete resolution of the eruption.

**Comment:** *Cutaneous adverse events were evaluated on a 4-grade scale only in the Phase 2 trial 104EU. On that scale, Grade 4 events were considered “very severe” and reserved for events such as SJS and TEN. The other studies employed 3-grade scales in which Grade 3 events were “severe” and were inclusive of events such as SJS and TEN.*

**RESULTS:**

**Note:** Discussion of safety results will be limited to cutaneous events during the Telaprevir/Placebo treatment phase. Tables of Adverse Events will generally only present cutaneous events. This consult will focus on the Telaprevir/Placebo treatment period, as these data reflect treatment with telaprevir (through weeks 8 or 12 except as below)

and are placebo-controlled. (Data from the Overall Treatment Phase only reflect Peg-IFN-alfa-2a and RBV combination treatment, as treatment with telaprevir was discontinued at either week 8 or 12) and half-life of telaprevir is 9-11 hours.

The consultant reviewed all available photographs of subjects who experienced serious cutaneous adverse events.

### Extent of Exposure

**Excerpted from Table 71 Treatment Duration for Telaprevir/Placebo, Peg-IFN-alfa-2a, and RBV During the Telaprevir/Placebo Treatment Phase, Full Analysis Set**

	<b>T8/PR</b> N = 364	<b>T12/PR</b> N = 363	<b>Pbo/PR48</b> N = 361
<b>Time on Study Drug (weeks)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Telaprevir/Placebo</b>			
0 to ≤4	25 (6.9)	25 (6.9)	12 (3.3)
>4 to ≤8	36 (9.9)	30 (8.3)	6 (1.7)
>8 to ≤12 <sup>a</sup>	299 (82.1)	306 (84.3)	339 (93.9)
<b>Peg-IFN-alfa-2a</b>			
0 to ≤4	17 (4.7)	15 (4.1)	12 (3.3)
>4 to ≤8	16 (4.4)	9 (2.5)	4 (1.1)
>8 to ≤12	9 (2.5)	8 (2.2)	3 (0.8)
>12 to ≤24	123 (33.8)	143 (39.4)	48 (13.3)
>24 to ≤36	123 (33.8)	112 (30.9)	81 (22.4)
>36	76 (20.9)	76 (20.9)	213 (59.0)
<b>RBV</b>			
0 to ≤4	16 (4.4)	16 (4.4)	12 (3.3)
>4 to ≤8	20 (5.5)	9 (2.5)	5 (1.4)
>8 to ≤12	9 (2.5)	10 (2.8)	4 (1.1)
>12 to ≤24	136 (37.4)	150 (41.3)	46 (12.7)
>24 to ≤36	107 (29.4)	102 (28.1)	81 (22.4)
>36	76 (20.9)	76 (20.9)	213 (59.0)

<sup>a</sup> The 12-week treatment duration includes a 1-week window. A total of 10 subjects received telaprevir or placebo for longer than the 12-week treatment duration (>13 weeks): 4 subjects in T8/PR group, 2 subjects in T12/PR group, and 4 subjects in Pbo/PR48 group.

Per Listing 14.3.1.34:

- four subjects in the T8/PR group received telaprevir for >13 Weeks ≤14 Weeks and
- two subjects in the T12/PR group received telaprevir for >13 Weeks ≤14 Weeks.

No subjects in either T/PR group received telaprevir for >14 Weeks.

### Deaths

No deaths occurred from complications of cutaneous eruptions.

### Serious Cutaneous Adverse Events

Serious adverse events were most commonly reported in the Blood and Lymphatic System Disorders system organ classes (SOC). Per Table 14.3.1.9.1c, seven subjects in T/PR treatment groups experienced serious adverse events in the Skin and Subcutaneous Tissue Disorders SOC during the Telaprevir/Placebo Treatment Phase. The events were coded under the preferred terms “rash,” “eczema” and “pruritus”. No subjects in the Pbo/PR48 group experienced a serious cutaneous adverse event. “Rash” was the only serious cutaneous adverse event reported in more than one subject and was the only category of event reported in the T12/PR group per Table 14.3.1.9.1c.

The incidence of “rash” was similar between the T8/PR and T12/PR, with two such reports in each of these treatment groups (0.5% and 0.6%, respectively). A third report of a serious cutaneous adverse event in the T12/PR is included in other tables (e.g., Tables 88 and 14.3.2.2c), but absent from Table 14.3.1.9.1c (below). That third event was “rash maculo-papular.” The overall incidences of serious cutaneous adverse events were similar between the T8/PR group and T12/PR groups (1.1% and 0.8%, respectively), which may suggest that the additional 4 weeks of telaprevir in the T12/PR was not associated with increased risk for serious cutaneous adverse events.

All subjects who experienced serious cutaneous adverse events recovered (“recovered/resolved”). All seven permanently discontinued telaprevir. None of the seven permanently discontinued Peg-IFN-alfa-2a or RBV due to the cutaneous serious adverse event (subject 109006 had RBV interrupted; and subject 166004 had RBV reduced).

**Comment:** “Rash” is a rather vague clinical descriptor that has no specific clinical correlate and allows only for a cutaneous eruption of some sort; it does not permit visualization of a subject.

**Excerpted from Table 14.3.1.9.1c: Number and Percentage of Subjects With Serious Adverse Events During Telaprevir/Placebo Treatment Phase by System Organ Class, Preferred Term, and Treatment Group**  
**Full Analysis Set**

System Organ Class Preferred Term	T8/PR			T12/PR			Pbo/PR48 (N=361) n (%)
	PR24 (N=207) n (%)	PR48 (N=157) n (%)	Total (N=364) n (%)	PR24 (N=210) n (%)	PR48 (N=153) n (%)	Total (N=363) n (%)	
Number of subjects with serious AEs	9 ( 4.3)	9 ( 5.7)	18 ( 4.9)	14 ( 6.7)	5 ( 3.3)	19 ( 5.2)	7 ( 1.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS							
RASH	3 ( 1.4)	1 ( 0.6)	4 ( 1.1)	3 ( 1.4)	-	3 ( 0.8)	-
ECZEMA	2 ( 1.0)	-	2 ( 0.5)	2 ( 1.0)	-	2 ( 0.6)	-
PRURITUS	-	1 ( 0.6)	1 ( 0.3)	-	-	-	-
	1 ( 0.5)	-	1 ( 0.3)	-	-	-	-

Table 88 provided additional information about the subjects who experienced serious cutaneous adverse events:

**Excerpted from Table 88: Serious Adverse Events During the Overall Treatment Phase, Full Analysis Set**

Subject	Adverse Event (Preferred Term)	Day of Onset <sup>a</sup>	Severity	Reported Relationship <sup>b</sup>	Study Drug Action Taken	Outcome
<b>T8/PR:</b>						
109006	Rash	5	Grade 2	Related	T: Discontinued; P, R: Interrupted	Recovered/resolved
166004	Pruritus	15	Grade 3	Related	T: Discontinued; P: None; R: Reduced	Recovered/resolved
214009	Rash	84	Grade 3	Possibly related	T, P, R: N/A	Recovered/resolved
703007	Rash	38	Grade 3	Related	T: Discontinued; P, R: None	Recovered/resolved
<b>T12/PR:</b>						
152010	Rash maculo-papular	54	Grade 3	Possibly related	T: Discontinued; P, R: None	Recovered/resolved
211009	Rash	64	Grade 2	Related	T: Discontinued; P, R: None	Recovered/resolved
214008	Rash	53	Grade 3	Related	T: Discontinued; P, R: None	Recovered/resolved

<sup>a</sup> Day of onset is the time from date of first dose of study drug to the date of onset of the SAE.

<sup>b</sup> Reported relationship is the relationship to study drug regimen, not the relationship to individual study drugs.

The day of onset of the serious adverse event relative to the onset of treatment ranged from 5 to 84 days. (Note: The event reported on Day 84 occurred 21 days after the last dose of telaprevir; subject 214009 is further discussed below.)

Subjects who experienced serious cutaneous adverse events are presented below.

**T/8/PR Group:**

**Subject 109006: “Rash”**

The subject was a 48 y/o male who was randomized to the T8/PR treatment group and received the first dose of study drugs on 25 August 2008. On 28 August 2008, he experienced a rash located on the right knee and right gluteal area. On 29 August 2008, the RBV dose was reduced to 1000 mg/day due to nausea. The eruption progressed over subsequent days and became pruritic. On 31 August 2008, the eruption had progressed to involve the axillae, chest, buttocks, and extremities. On the same day, telaprevir was permanently discontinued (6 days after the first dose) and Peg-IFN-alfa-2a and RBV dosing was interrupted due to rash. Treatment included prednisone. On 02 September 2008, purpura and non-blanching erythema were noted (sites unspecified). A dermatology consult was obtained the same day, which provided for the clinical diagnosis of a drug exanthema. Photographs were obtained; biopsy was not. Treatment included hydrocortisone. On 08 September 2008, Peg-IFN-alfa-2a and RBV dosing was resumed as the rash had improved. On 11 September 2008, RBV dosing was interrupted again due to a recurrence of the rash. On 14 September 2008, the rash resolved after 14 days, and on 15 September 2008, RBV dosing was resumed at 600 mg/day. On 16 December 2009 (473 days after the last dose of telaprevir), the subject withdrew consent and was discontinued from the study.

***Comment:*** Concur with the assessment of drug exanthema. Improvement following discontinuation of telaprevir and tolerance of Peg-IFN and RBV with rechallenge (although the eruption was said to have recurred on initial resumption of RBV, he apparently later tolerated the product well) would appear to implicate telaprevir as causative.

Subject 166004: “Pruritus”

The subject was a 42 y/o male who initiated study treatment on 01 Aug 2008. He developed generalized, severe pruritus on 15 Aug. 2008 (14 days after the first dose of telaprevir). He had no associated cutaneous eruption. The pruritus contributed to insomnia and fatigue. Treatment included doxepin and diphenhydramine and, later, hydroxyzine, cetirizine. On 19 August 2008, the RBV dose was reduced to 800 mg/day due to the severity of the pruritus; however, as the pruritus did not improve, the 1000 mg daily dosing was resumed (?date). He had the Week 8 visit on 25 September 2008, and the last dose of telaprevir was on 01 October 2008. Placebo dosing was permanently discontinued the same day due to pruritus. The pruritus resolved after 62 days on 16 Oct 2008. No action was taken with the PEG; RBV was decreased.

**Comment:** *The timing of onset and resolution relative to telaprevir dosing and in the face of continued dosing with PEG/RBV suggest a possible role for telaprevir.*

Subject 214009: “Rash”

The subject was a 67 y/o female who started study treatment on 28 Oct 2008. Concomitant medications at study entry included metformin and glimepiride (diabetes mellitus) and carvedilol (hypertension). She had the Week 8 visit on 22 December 2008 and the last dose of telaprevir on 30 December 2008.

On 22 December 2008, RBV dosing was permanently discontinued due to anemia. On 26 December 2008, she experienced the onset of pruritus and exanthema. She received desloratadine for pruritus. On 30 December 2008, placebo and Peg-IFN-alfa-2a were permanently discontinued (reason not found, but was not due to the anemia). On 31 December 2008, 01 January 2009, and 12 January 2009, treatment included dimetindene, oral prednisolone, and diflucortolone (route not specified), respectively for exanthema. On 19 January 2009, the pruritus and exanthema worsened, and a Grade 3 rash was reported (21 days after the last dose of telaprevir). She was evaluated by a dermatologist (date unclear, but may have been the same day) who described the eruption as “pruritic, generalized, macular and urticarial involving the arms and trunk.” The clinical diagnosis was a medication-induced exanthema. Treatment included topical corticosteroids. That day, the absolute eosinophil count was  $0.10 \times 10^9/L$ , eosinophil percentage was 4.2%. Although not listed among the concomitant medications, “(a)llopurinol was noted as relevant predisposing risk factor” for the skin eruption. A skin biopsy was done. Histopathological findings included an essentially normal epidermis with sub-epidermal “slight lymphocytic infiltrate, pronounced in the perivascular areas” and was considered consistent with the clinical diagnosis of drug-induced exanthema. On [REDACTED] (b)(6), she experienced edema of legs and rash had progressed to involve her face. She was hospitalized for treatment with corticosteroids. On [REDACTED] (b)(6), the rash had resolved (29 days duration).

**Comment:** *Concur with the diagnosis of drug exanthema, based on the clinical presentation and the histopathological findings. Cannot exclude telaprevir as perhaps causative. Although the event was reported 21 days after the last dose of the product, the onset of signs and symptoms was while she was on therapy. Drug eruptions may initially manifest after a medication has been discontinued.*<sup>1</sup>

Subject 70300: “Rash”

The subject was a 48-year-old Caucasian male who received the first dose of study drugs on 27 October 2008. The subject had the Week 8 visit on 22 December 2008 and the last dose of telaprevir/placebo on 23 December 2008.

On 30 October 2008, he experienced a mild red rash with pruritus. The rash was of erythematous, papular lesions on the forearms, legs, and neck. Treatment included betamethasone. On 24 November 2008, the rash resolved after 25 days with unspecified sequelae.

He developed a new generalized (trunk/limbs), pruritic rash on 03 December 2008, of Grade 2 severity. He was treated with topical corticosteroids and an oral antihistamine. The pruritus worsened and was accompanied by insomnia. On 16 December 2008, a dermatology consult was obtained, and the rash was described as “pruriginous maculopapular rash with pseudo-urticarial peripheral erythematous enhancement, fixed, and localized on the trunk, thighs, and arms.” A skin biopsy revealed a “perivascular lymphocytic infiltrate compatible with induced (*sic*) maculopapular erythematous rash.” On 23 December 2008, (57 days after the first dose of telaprevir), he experienced pruritus of Grade 3 intensity that caused “total insomnia,” and placebo dosing was permanently discontinued that day due to skin rash. No action towards Peg-IFN-alfa-2a or RBV was taken. On 26 December 2008 (60 days after the first dose of telaprevir), a second dermatology consult was obtained, and a Grade 2 erythematous, maculopapular rash was described. By 29 December 2008, the pruritus had resolved. On 15 March 2009, the rash was resolved after 42 days.

**Comment:** *The clinical presentation and biopsy findings are consistent with a drug exanthema. Onset and time to resolution relative to telaprevir dosing would not appear to strongly implicate this product.*

**T12/PR Group:**

Subject 15201: (“Rash maculo-papular”)

The subject was a 45 y/o female who received the first dose of study drugs on 26 June 2008. Her last dose of telaprevir was on 17 August 2008.

On 17 July 2008 (21 days after the first dose of telaprevir), she developed a pruritic, erythematous rash. She did not improve on treatment with hydroxyzine and topical betamethasone. On 18 August 2008 (52 days after the first dose of telaprevir), she experienced a Grade 3 rash, described as generalized, papular and erythematous; it was considered a serious adverse event. The rash was estimated to cover > 60% of the body surface area (BSA). She was also described as having non-blanching erythema and purpura. She experienced pruritus, but no systemic symptoms. She was seen by a dermatologist the same day, and the dermatologist concurred with the investigator’s clinical description. Biopsy was done and revealed a mixed-cell inflammatory infiltrate with eosinophils and interface changes. These changes were concluded to be consistent with a morbilliform drug eruption. Treatment included topical corticosteroids and systemic antihistamines. Pruritus diminished, but the rash worsened. Her eosinophil count was within the reference range. Telaprevir dosing was permanently discontinued on 18 August 2008. No modifications were made to Peg-IFN-alfa-2a or RBV dosing due to rash. On 10 December 2008, the rash had resolved with no residual effects after 115 days.

**Comment:** *Concur with the assessment of drug eruption; however, the persistence for months after discontinuation of telaprevir suggests it may not have been the offending agent. It is possible that one of the other products was causative, e.g. RBV. Pruritus and rash are among the adverse reactions reported in the labels for both Peg-IFN-alfa-2a and ribavirin (in combination with Peg-IFN-alfa-2a)<sup>2,3</sup> Drug eruptions may resolve even if the offending agent is continued<sup>4,5</sup> (although continuation of the offending agent is not generally the recommendation).*

Note: Subject 211009: “Rash” is discussed in the Dermatology Expert Panel report

Subject 214008 “Rash”

The subject was a 50 y/o male who received the first dose of study drugs on 21 October 2008. His last dose of telaprevir was on 12 December 2008. On 12 December 2008 (52 days after the first dose of telaprevir), the subject experienced a Grade 3 skin rash.

On 28 October 2008, he developed a generalized exanthema (head, trunk, limbs); he was treated with a topical corticosteroid. On the same day, he apparently developed a second rash which was pruritic. The rash (unclear which one) progressively worsened through 12 December 2008. He additionally experienced intense pruritus, fever and joint pains (shoulders, hips, and knees). Telaprevir was discontinued the same day. Eosniophil counts were not reported. A dermatology consult was obtained (apparently on the same day), and the eruption was described as a “generalized red-brownish confluent macular, but primarily, papular exanthema and partly exhibiting lesions with pseudovesicular appearance that involved the whole body.” The clinical diagnosis was drug eruption, and a biopsy was taken. The pathology report read: “perivascular dermatitis with mild interface dermatitis and slightly increased eosinophilic involvement...consistent with drug eruption” and presumed to be to telaprevir. He was hospitalized on (b) (6) because of worsening of rash. Treatment included desloratadine, dimetindene, diazepam, prednisolone, hydroxyzine. On (b) (4), the joint pain skin rash(?es) had resolved.

**Comment:** *Concur with the assessment of a drug eruption possibly due to telaprevir. The presence of a generalized papular eruption, fever and joint pains could perhaps bring an early stage severe cutaneous adverse reaction into consideration.*

Additional Subject 129002: Stevens Johnson Syndrome (SJS)

One subject in the T8/PR group developed SJS during the Peg-IFN-alfa-2a and RBV treatment phase. Subject 129002 completed treatment with telaprevir/placebo. Approximately 48 days after the last dose of telaprevir/placebo, he discontinued treatment with Peg-IFN-alfa-2a and RBV due to SJS. The serious adverse event resolved after 31 days and was considered unlikely related to telaprevir/placebo and possibly related to Peg-IFN-alfa-2a and RBV by the investigator.

**Comment:** *The consultant concurs with this conclusion given the time of onset of the SJS, in relation to the completion of telaprevir dosing and the drug’s half life of 9 to 11 hours.*

**Discontinuation of Telaprevir/Placebo Due to Adverse Events**

Per Table 14.3.1.25c, events leading to discontinuation only of telaprevir/placebo during the Telaprevir/Placebo Treatment Phase were most commonly reported in the Skin and Subcutaneous Tissue Disorders SOC. The percentages of subjects discontinuing from T/PR groups was noticeably higher than from the Pbo/PR48 group approximately  $\geq 6\%$  in T/PR groups versus approximately 1% in the Pbo/PR48 group. The percentages were similar between T8/PR and T12/PR groups: approximately 6% and 7%, respectively. Similar to the pattern seen with serious cutaneous adverse events, the most common event leading to discontinuation of telaprevir was “rash,” and the second most common event was “pruritus.” The percentages of subjects discontinuing telaprevir for “rash” were similar between T/PR groups, at approximately 3% in each group and were  $>$  than the  $< 1\%$  observed in the Pbo/PR48 group. The second most common event was “pruritus.” The percentages of subjects discontinuing telaprevir for “pruritus” were similar between T/PR groups, at approximately 1% in each group compared to none in the Pbo/PR48 group. One subject in the T8/PR group ( $<1\%$ ) discontinued telaprevir specifically for “drug eruption;” three subjects in the T12/PR group (1%) discontinued for this reason. Single subjects discontinued telaprevir for variants on the “rash” preferred term, e.g. “rash exfoliative,” “rash macular.” See Table 14.3.1.25c below.

**Excerpted from Table 14.3.1.25c: Number and Percentage of Subjects With Adverse Events Leading to Permanent Discontinuation of Telaprevir/Placebo Only During Telaprevir/Placebo Treatment Phase by System Organ Class, Preferred Term, and Treatment Group Full Analysis Set**

System Organ Class Preferred Term	T8/PR			T12/PR			Pbo/PR48 (N=361) n (%)
	PR24 (N=207) n (%)	PR48 (N=157) n (%)	Total (N=364) n (%)	PR24 (N=210) n (%)	PR48 (N=153) n (%)	Total (N=363) n (%)	
Number of subjects with AEs Leading to Permanent Discontinuation of Telaprevir/Placebo	18 ( 8.7)	9 ( 5.7)	27 ( 7.4)	25 ( 11.9)	16 ( 10.5)	41 ( 11.3)	3 ( 0.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	12 ( 5.8)	8 ( 5.1)	20 ( 5.5)	13 ( 6.2)	11 ( 7.2)	24 ( 6.6)	2 ( 0.6)
RASH	8 ( 3.9)	4 ( 2.5)	12 ( 3.3)	5 ( 2.4)	6 ( 3.9)	11 ( 3.0)	1 ( 0.3)
PRURITUS	2 ( 1.0)	1 ( 0.6)	3 ( 0.8)	1 ( 0.5)	1 ( 0.7)	2 ( 0.6)	-
DRUG ERUPTION	-	1 ( 0.6)	1 ( 0.3)	2 ( 1.0)	1 ( 0.7)	3 ( 0.8)	-
RASH PRURITIC	1 ( 0.5)	1 ( 0.6)	2 ( 0.5)	1 ( 0.5)	-	1 ( 0.3)	-
RASH GENERALISED	-	-	-	1 ( 0.5)	1 ( 0.7)	2 ( 0.6)	-
RASH MACULO-PAPULAR	-	-	-	1 ( 0.5)	1 ( 0.7)	2 ( 0.6)	-
URTICARIA	-	1 ( 0.6)	1 ( 0.3)	-	-	-	1 ( 0.3)
EXFOLIATIVE RASH	-	-	-	1 ( 0.5)	-	1 ( 0.3)	-
HYPERKERATOSIS	1 ( 0.5)	-	1 ( 0.3)	-	-	-	-
HYPOAESTHESIA FACIAL	-	1 ( 0.6)	1 ( 0.3)	-	-	-	-
RASH ERYTHEMATOUS	-	-	-	1 ( 0.5)	-	1 ( 0.3)	-
RASH MACULAR	-	-	-	-	1 ( 0.7)	1 ( 0.3)	-
RASH PAPULAR	-	-	-	1 ( 0.5)	-	1 ( 0.3)	-
RASH VESICULAR	-	1 ( 0.6)	1 ( 0.3)	-	-	-	-
SKIN IRRITATION	-	-	-	-	1 ( 0.7)	1 ( 0.3)	-
SWELLING FACE	-	-	-	-	1 ( 0.7)	1 ( 0.3)	-

Per Table 14.3.1.23.3c, no subjects had Peg-IFN-alfa-2a dose decreased during the Telaprevir/Placebo Treatment Phase due to a cutaneous event. Per Table 14.3.1.23.2c, five subjects in the T/PR groups had dose reduction of RBV during Telaprevir/Placebo Treatment Phase due to cutaneous events (rash and pruritus). Per the same tables, no subjects in the Pbo/PR48 group had dose reduction of Peg-IFN-alfa-2a or RBV during Telaprevir/Placebo Treatment Phase due to a cutaneous event.

**Adverse Events Leading to Discontinuation of Telaprevir/Placebo by Time Period During the Telaprevir/Placebo Treatment Phase**

Adverse events in the Skin and Subcutaneous Tissue Disorders SOC most commonly led to permanent discontinuation of telaprevir/placebo during each four-week interval of the Telaprevir/Placebo Treatment Phase. The incidence of discontinuation of telaprevir for an adverse event in the Skin and Subcutaneous Tissue Disorders SOC was generally similar for each four-week interval. The incidence of discontinuation from the Pbo/PR48 group for events in this SOC was very low for each four-week interval (0 to < 1%).

Rash-type events (e.g. “rash”, “rash maculopapular” and “rash pruritic”) were the most commonly reported event types to lead to permanent discontinuation in T/PR treated subjects in all three intervals (they received the same telaprevir regimens through Week 8 at which point telaprevir was discontinued for subjects in the T8/PR group). The incidence of “rash” was similar in the T/PR-treated subjects for all intervals (1% during each interval). Somewhat interestingly, two cutaneous events were formally classified as drug eruptions, and both events occurred in the T12/PR group during the Week 8 through Week 12 interval. One subject discontinued during the Week 4 through Week 8 interval in the Pbo/PR48 group (<1%), and the event was “urticaria” (per Table 14.3.1.25.2cN). One subject discontinued in the Pbo/PR48 group during the Week 8 through Week 12 interval (<1%), and the event was “rash.”

In the T8/PR, two subjects (1%) discontinued due to “rash” in the Week 8 through Week 12 interval, i.e., in the four weeks following completion of telaprevir dosing. Per Table 98, two subjects in the T12/PR (< 1%) discontinued for “rash generalized” during the Week 12 through Week 24 interval i.e., in the four weeks following completion of telaprevir dosing in this group.

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**Table 96: Incidence of Adverse Events Leading to Permanent Discontinuation of Telaprevir/Placebo Only in At Least 2 Subjects by System Organ Class and Preferred Term From Baseline Through Week 4, Week 4 Through Week 8, and Week 8 Through Week 12 During the Telaprevir/Placebo Treatment Phase, Full Analysis Set**

System Organ Class Preferred Term	T8/PR n (%)	T12/PR n (%)	T/PR n (%)	Pbo/PR48 n (%)
<b>Baseline through Week 4</b>	<b>N = 364</b>	<b>N = 363</b>	<b>N = 727</b>	<b>N = 361</b>
<b>Number of subjects with adverse events leading to discontinuation of telaprevir/placebo only</b>	<b>11 (3.0)</b>	<b>10 (2.8)</b>	<b>21 (2.9)</b>	<b>0</b>
<b>Skin and subcutaneous tissue disorders</b>	<b>9 (2.5)</b>	<b>6 (1.7)</b>	<b>15 (2.1)</b>	<b>0</b>
Rash	5 (1.4)	4 (1.1)	9 (1.2)	0
Pruritus	1 (0.3)	1 (0.3)	2 (0.3)	0
<b>Blood and lymphatic system disorders</b>	<b>2 (0.5)</b>	<b>2 (0.6)</b>	<b>4 (0.6)</b>	<b>0</b>
Anaemia	2 (0.5)	2 (0.6)	4 (0.6)	0
<b>Gastrointestinal disorders</b>	<b>0</b>	<b>2 (0.6)</b>	<b>2 (0.3)</b>	<b>0</b>
<b>Week 4 through Week 8</b>	<b>N = 340</b>	<b>N = 338</b>	<b>N = 678</b>	<b>N = 349</b>
<b>Number of subjects with adverse events leading to discontinuation of telaprevir/placebo only</b>	<b>12 (3.5)</b>	<b>17 (5.0)</b>	<b>29 (4.3)</b>	<b>1 (0.3)</b>
<b>Skin and subcutaneous tissue disorders</b>	<b>8 (2.4)</b>	<b>8 (2.4)</b>	<b>16 (2.4)</b>	<b>1 (0.3)</b>
Rash	5 (1.5)	3 (0.9)	8 (1.2)	0
Pruritus	2 (0.6)	0	2 (0.3)	0
Rash maculopapular	0	2 (0.6)	2 (0.3)	0
Rash pruritic	1 (0.3)	1 (0.3)	2 (0.3)	0
<b>Blood and lymphatic system disorders</b>	<b>4 (1.2)</b>	<b>7 (2.1)</b>	<b>11 (1.6)</b>	<b>0</b>
Anaemia	4 (1.2)	7 (2.1)	11 (1.6)	0
<b>General disorders and administration site conditions</b>	<b>1 (0.3)</b>	<b>1 (0.3)</b>	<b>2 (0.3)</b>	<b>0</b>
<b>Week 8 through Week 12</b>	<b>N = 305</b>	<b>N = 308</b>	<b>N = 613</b>	<b>N = 343</b>
<b>Number of subjects with adverse events leading to discontinuation of telaprevir/placebo only</b>	<b>4 (1.3)</b>	<b>15 (4.9)</b>	<b>19 (3.1)</b>	<b>2 (0.6)</b>
<b>Skin and subcutaneous tissue disorders</b>	<b>3 (1.0)</b>	<b>10 (3.2)</b>	<b>13 (2.1)</b>	<b>1 (0.3)</b>
Rash	2 (0.7)	4 (1.3)	6 (1.0)	1 (0.3)
Drug eruption	0	2 (0.6)	2 (0.3)	0
<b>Blood and lymphatic system disorders</b>	<b>1 (0.3)</b>	<b>4 (1.3)</b>	<b>5 (0.8)</b>	<b>0</b>
Anaemia	1 (0.3)	4 (1.3)	5 (0.8)	0
<b>Gastrointestinal disorders</b>	<b>0</b>	<b>3 (1.0)</b>	<b>3 (0.5)</b>	<b>0</b>

### Common Adverse Events

Adverse events were most frequently reported in the General disorders and administration site conditions.

In the Skin and subcutaneous tissue disorders SOC, 79% of subjects in the T8/PR group, 78% in the T12/PR group and 58% in the Pbo/PR48 group experienced an adverse event. Thus, the incidences were similar between both T/PR groups and  $\geq 20\%$  higher in these groups than in the Pbo/PR48 group. “Pruritus” was the most common adverse event in all groups: 42% of subjects in T8/PR, 46% T12/PR and 28% Pbo/PR. The other cutaneous events that occurred in  $> 10\%$  of subjects in all three groups were “rash” (34%, 32% and 17%, respectively) and “dry skin” (12%, 12% and 13%, respectively). Adverse events that occurred in  $\geq 5\%$  of subjects in any treatment group, i.e. T8/PR, T12/PR or Pbo/PR48, are presented in an excerpt from Table 14.3.1.2c below. The following events occurred at  $\geq$  twice the incidence in the T12/ group, when T8/PR and T12/PR are compared: “rash maculo-papular” (3% and 6%, respectively), “rash erythematous” (1% and 4%) and “rash generalized” (1% and 4%). “Alopecia” occurred in  $\geq 5\%$  in all groups and in the highest incidence Pbo/PR48 group (8%) compared to the T8/PR (5%) and T12/PR (6%) groups. Alopecia could be related to the Peg-IFN/RBV as it is labeled as an adverse reaction in both labels.<sup>2,3</sup>

**Excerpted from Table 14.3.1.2c: Number and Percentage of Subjects with Adverse Events During Telaprevir/Placebo Treatment Phase By System Organ Class, Preferred Term and Treatment Group Full Analysis Set**

System Organ Class Preferred Term	T8/PR			T12/PR			Pbo/PR48 (N=361) n (%)
	PR24 (N=207) n (%)	PR48 (N=157) n (%)	Total (N=364) n (%)	PR24 (N=210) n (%)	PR48 (N=153) n (%)	Total (N=363) n (%)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	185 ( 89.4)	138 ( 87.9)	323 ( 88.7)	184 ( 87.6)	136 ( 88.9)	320 ( 88.2)	310 ( 85.9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	165 ( 79.7)	124 ( 79.0)	289 ( 79.4)	167 ( 79.5)	117 ( 76.5)	284 ( 78.2)	210 ( 58.2)
PRURITUS	84 ( 40.6)	68 ( 43.3)	152 ( 41.8)	97 ( 46.2)	70 ( 45.8)	167 ( 46.0)	102 ( 28.3)
RASH	69 ( 33.3)	53 ( 33.8)	122 ( 33.5)	68 ( 32.4)	47 ( 30.7)	115 ( 31.7)	62 ( 17.2)
DRY SKIN	26 ( 12.6)	17 ( 10.8)	43 ( 11.8)	22 ( 10.5)	20 ( 13.1)	42 ( 11.6)	48 ( 13.3)
ALOPECIA	13 ( 6.3)	6 ( 3.8)	19 ( 5.2)	14 ( 6.7)	8 ( 5.2)	22 ( 6.1)	30 ( 8.3)
PRURITUS GENERALISED	11 ( 5.3)	8 ( 5.1)	19 ( 5.2)	9 ( 4.3)	11 ( 7.2)	20 ( 5.5)	11 ( 3.0)
RASH PAPULAR	13 ( 6.3)	5 ( 3.2)	18 ( 4.9)	12 ( 5.7)	7 ( 4.6)	19 ( 5.2)	10 ( 2.8)
RASH MACULO-PAPULAR	5 ( 2.4)	5 ( 3.2)	10 ( 2.7)	15 ( 7.1)	6 ( 3.9)	21 ( 5.8)	6 ( 1.7)
ERYTHEMA	4 ( 1.9)	5 ( 3.2)	9 ( 2.5)	4 ( 1.9)	5 ( 3.3)	9 ( 2.5)	18 ( 5.0)
RASH PRURITIC	11 ( 5.3)	4 ( 2.5)	15 ( 4.1)	7 ( 3.3)	5 ( 3.3)	12 ( 3.3)	4 ( 1.1)
RASH ERYTHEMATOUS	4 ( 1.9)	1 ( 0.6)	5 ( 1.4)	13 ( 6.2)	2 ( 1.3)	15 ( 4.1)	9 ( 2.5)
HYPERHIDROSIS	6 ( 2.9)	2 ( 1.3)	8 ( 2.2)	3 ( 1.4)	2 ( 1.3)	5 ( 1.4)	12 ( 3.3)
RASH MACULAR	3 ( 1.4)	2 ( 1.3)	5 ( 1.4)	9 ( 4.3)	3 ( 2.0)	12 ( 3.3)	8 ( 2.2)
RASH GENERALISED	1 ( 0.5)	1 ( 0.6)	2 ( 0.5)	11 ( 5.2)	4 ( 2.6)	15 ( 4.1)	7 ( 1.9)

**Adverse Events by Time Period**

**Table 80 Incidence of Adverse Events in At Least 10% of Subjects in any Treatment Group by System Organ Class and Preferred Term from Baseline through Week 4, Week 4 Through Week 8, and Week 8 through Week 12 During the Telaprevir/Placebo Treatment Phase, Full Analysis Set**

System Organ Class Preferred Term	T8/PR n (%)	T12/PR n (%)	T/PR n (%)	Pbo/PR48 n (%)
<b>Baseline Through Week 4</b>	<b>N = 364</b>	<b>N = 363</b>	<b>N = 727</b>	<b>N = 361</b>
Number of subjects with adverse events	355 (97.5)	356 (98.1)	711 (97.8)	338 (93.6)
<b>Skin and subcutaneous tissue disorders</b>	<b>220 (60.4)</b>	<b>215 (59.2)</b>	<b>435 (59.8)</b>	<b>138 (38.2)</b>
Pruritus	103 (28.3)	104 (28.7)	207 (28.5)	61 (16.9)
Rash	83 (22.8)	76 (20.9)	159 (21.9)	31 (8.6)
<b>Week 4 Through Week 8</b>	<b>N = 340</b>	<b>N = 338</b>	<b>N = 678</b>	<b>N = 349</b>
<b>Skin and subcutaneous tissue disorders</b>	<b>104 (30.6)</b>	<b>119 (35.2)</b>	<b>223 (32.9)</b>	<b>73 (20.9)</b>
Pruritus	42 (12.4)	45 (13.3)	87 (12.8)	18 (5.2)
Rash	35 (10.3)	27 (8.0)	62 (9.1)	19 (5.4)
<b>Week 8 Through Week 12</b>	<b>N = 305</b>	<b>N = 308</b>	<b>N = 613</b>	<b>N = 343</b>
<b>Skin and subcutaneous tissue disorders</b>	<b>86 (28.2)</b>	<b>104 (33.8)</b>	<b>190 (31.0)</b>	<b>83 (24.2)</b>
Pruritus	23 (7.5)	43 (14.0)	66 (10.8)	32 (9.3)
Rash	19 (6.2)	34 (11.0)	53 (8.6)	20 (5.8)

The table indicates that most adverse events in the Skin and subcutaneous tissue disorders SOC were captured from Baseline through Week 4 of treatment (specifically as pertains to the most common of events of “pruritus” and “rash.”)

**Other Significant Adverse Events**

The applicant performed special analyses to more comprehensively assess certain categories of adverse events observed in the clinical development program:

1. Special Search Categories

The sponsor created Special Search Categories (SSC) by performing comprehensive analyses on grouped select MedDRA preferred terms (including from the same or different SOCs). Each subject with a predefined SSC was counted once. The SSC included analyses of cutaneous adverse events by MedDRA preferred terms used for identifying rash and pruritus.

## 2. Event of Special Interest

An Event of Special Interest (ESI) was “a clinical event for which the sponsor implemented special reporting procedures for surveillance, monitoring, and management purposes” (Section 12.3.1.6 of the study report). The sponsor designated one ESI for study 108: All “rash or rash-like events” that occurred during the study that met any of the following three criteria:

- permanent discontinuation of any or all study drugs due to rash
- Grade 3 (severe) rash
- rash which met the criteria for a serious adverse event

### Rash Special Search Category

Under these analyses, more than 50% of telaprevir-treated subjects experienced a rash event, 53% in the T8/PR group and 57% in the T12/PR group, compared to 37% of subjects in the Pbo/PR48 group (Table 108). Reactions were most commonly of Grade 1 (mild) severity in all treatment groups: T8/PR at 41%, with 38% in the T12/PR group and 31% in the Pbo/PR48 group. The highest incidence of Grade 2 (moderate) rashes occurred in the T12/PR at 13% which is an approximately one third higher incidence than the 9% in the T8/PR group and an approximately 2.5 times higher incidence compared to the 5% in the Pbo/PR48. A similar, but more pronounced pattern was observed with Grade 3 (severe) events: The highest incidence was again in the T12/PR group at 6% which was twice the incidence of that in the T8/PR group and six times the 1% incidence in the Pbo/PR48 group. This analysis could suggest a possible correlation between the duration of telaprevir treatment and rash severity (the only differential between the telaprevir treatment groups was the duration of treatment). See Table 108 below.

**Excerpted from Table 108: Incidence of Rash Special Search Category (SSC) Events during the Telaprevir/Placebo, Full Analysis Set**

Severity	T8/PR N = 364 n (%)	T12/PR N = 363 n (%)	T/PR N = 727 n (%)	Pbo/PR48 N = 361 n (%)
<b>Telaprevir/placebo treatment phase</b>				
<b>Total</b>	<b>193 (53.0)</b>	<b>205 (56.5)</b>	<b>398 (54.7)</b>	<b>132 (36.6)</b>
Grade 1	148 (40.7)	137 (37.7)	285 (39.2)	111 (30.7)
Grade 2	34 (9.3)	48 (13.2)	82 (11.3)	19 (5.3)
Grade 3	11 (3.0)	20 (5.5)	31 (4.3)	2 (0.6)

From Table 109 (below), most Grade 3 eruptions were not considered to be serious adverse events. In both T/PR groups, 1% of subjects experienced serious adverse events; no correlation with duration of treatment was evidenced. No subjects in the Pbo/PR48 group with Grade 3 eruptions were considered to have experienced a serious adverse event. Rash events most impacted telaprevir dosing: < 1% of subjects in T/PR groups had a reduction in Peg-IFN-alfa-2a and/or RBV dosing; 6% of subjects in T/PR groups had telaprevir/placebo permanently discontinued. The percentage of subjects who under these analyses had telaprevir/placebo only discontinued was generally similar between T/PR groups, albeit slightly higher in the T/12 group. Approximately 1% of subjects in each T/PR group had permanent discontinuation of the entire treatment regimen, and none did in the Pbo/Pr48 group. See Table 109 below.

**Excerpted from Table 109 Summary of Rash Special Search Category (SSC) Events During the Telaprevir/Placebo and Overall Treatment Phases, Full Analysis Set**

Subjects with:	T8/PR N = 364 n (%)	T12/PR N = 363 n (%)	T/PR N = 727 n (%)	Pbo/PR48 N = 361 n (%)
<b>Telaprevir/placebo treatment phase</b>				
At least 1 adverse event of rash SSC	193 (53.0)	205 (56.5)	398 (54.7)	132 (36.6)
At least 1 Grade 3 adverse event of rash SSC	11 (3.0)	20 (5.5)	31 (4.3)	2 (0.6)
At least 1 serious adverse event of rash SSC	3 (0.8)	3 (0.8)	6 (0.8)	0
Rash SSC that led to reduction of dose of any study drug <sup>a</sup>	2 (0.5)	1 (0.3)	3 (0.4)	0
Rash SSC that led to permanent discontinuation of telaprevir/placebo only	17 (4.7)	24 (6.6)	41 (5.6)	2 (0.6)
Rash SSC that led to permanent discontinuation of treatment regimen	2 (0.5)	5 (1.4)	7 (1.0)	0

<sup>a</sup> Dose reduction and interruption was for Peg-IFN-alfa-2a and/or RBV only.

“Rash” was the most commonly reported event under the SSC (Table 110 below). One-third of subjects in T/PR groups (33%) experienced “rash,” and that is approximately twice that that was seen in the Pbo/PR48 group (17%). Seven of the eight most commonly-reported cutaneous adverse events were recorded as some variant of the preferred term “rash”, e.g. “rash papular”, “rash pruritic.” If all events coded as “rash” or rash with some descriptive term, e.g. “exfoliative

rash,” are considered, 54% of subjects in the T/PR group experienced some event of this sort compared with 29% in the Pbo/PR 48 group. Five events (1%) were formally recorded as “drug eruption,” and all of these events occurred in T/PR subjects (one in T8/PR and four in 12/PR). Approximately 1% of subjects in the T/PR and Pbo/PR48 groups experienced “photosensitivity reaction,” and it is possible that this may be related to ribavirin with for which photoallergic reaction has been reported. <sup>6</sup> The single reports of angioedema and erythema multiforme (<1%) each occurred in the Pbo/PR48 group.

**Table 110 Incidence of Rash Search Special Category (SSC) Events by Preferred Term During the Telaprevir/Placebo Treatment Phase, Full Analysis Set**

Preferred Term	T8/PR	T12/PR	T/PR	Pbo/PR48
	N = 364 n (%)	N = 363 n (%)	N = 727 n (%)	N = 361 n (%)
Rash	122 (33.5)	115 (31.7)	237 (32.6)	62 (17.2)
Rash papular	18 (4.9)	19 (5.2)	37 (5.1)	10 (2.8)
Rash maculo-papular	10 (2.7)	21 (5.8)	31 (4.3)	6 (1.7)
Erythema	9 (2.5)	9 (2.5)	18 (2.5)	18 (5.0)
Rash pruritic	15 (4.1)	12 (3.3)	27 (3.7)	4 (1.1)
Rash erythematous	5 (1.4)	15 (4.1)	20 (2.8)	9 (2.5)
Rash macular	5 (1.4)	12 (3.3)	17 (2.3)	8 (2.2)
Rash generalised	2 (0.5)	15 (4.1)	17 (2.3)	7 (1.9)
Eczema	8 (2.2)	5 (1.4)	13 (1.8)	8 (2.2)
Cheilitis	6 (1.6)	5 (1.4)	11 (1.5)	7 (1.9)
Dermatitis	4 (1.1)	6 (1.7)	10 (1.4)	6 (1.7)
Skin exfoliation	3 (0.8)	6 (1.7)	9 (1.2)	4 (1.1)
Photosensitivity reaction	3 (0.8)	2 (0.6)	5 (0.7)	4 (1.1)
Urticaria	5 (1.4)	0	5 (0.7)	2 (0.6)
Drug eruption	1 (0.3)	4 (1.1)	5 (0.7)	0
Exfoliative rash	2 (0.5)	3 (0.8)	5 (0.7)	0
Prurigo	3 (0.8)	1 (0.3)	4 (0.6)	1 (0.3)
Skin irritation	1 (0.3)	3 (0.8)	4 (0.6)	0
Dermatitis atopic	0	3 (0.8)	3 (0.4)	0
Blister	0	1 (0.3)	1 (0.1)	1 (0.3)
Palmar erythema	1 (0.3)	0	1 (0.1)	1 (0.3)
Skin burning sensation	0	2 (0.6)	2 (0.3)	0
Skin lesion	0	1 (0.3)	1 (0.1)	1 (0.3)
Toxic skin eruption	1 (0.3)	1 (0.3)	2 (0.3)	0
Acrodermatitis	0	0	0	1 (0.3)
Angioedema	0	0	0	1 (0.3)
Dermatitis exfoliative	0	1 (0.3)	1 (0.1)	0
Erythema multiforme	0	0	0	1 (0.3)
Erythema of eyelid	1 (0.3)	0	1 (0.1)	0
Rash vesicular	1 (0.3)	0	1 (0.1)	0

### Pruritus Special Search Category

During the telaprevir/placebo treatment phase, “pruritus” (SSC) was experienced by approximately half (49%) of subjects in the T/PR group compared to approximately a third (31%) in the Pbo/PR48 group. The one subject who experienced pruritus as a serious adverse

event was in a T/PR group (T8), as were all of the subjects who experienced it as a Grade 3 event (approximately 1%). The same was true of all for whom “pruritus” led to permanent discontinuation of telaprevir/placebo only (Table 115):

**Table 115 Summary of Pruritus Special Search Category (SSC) Events During the Telaprevir/Placebo and Overall Treatment Phases, Full Analysis Set**

Subjects with:	T8/PR N = 364 n (%)	T12/PR N = 363 n (%)	T/PR N = 727 n (%)	Pbo/PR48 N = 361 n (%)
<b>Telaprevir/placebo treatment phase</b>				
At least 1 pruritus SSC	169 (46.4)	184 (50.7)	353 (48.6)	111 (30.7)
At least 1 serious adverse event of pruritus SSC	1 (0.3)	0	1 (0.1)	0
At least 1 Grade 3 adverse event of pruritus SSC	2 (0.5)	3 (0.8)	5 (0.7)	0
Pruritus SSC that led to reduction of dose of any study drug	1 (0.3)	1 (0.3)	2 (0.3)	0
Pruritus SSC that led to permanent discontinuation of telaprevir/placebo only	3 (0.8)	2 (0.6)	5 (0.7)	0
Pruritus SSC that led to permanent discontinuation of treatment regimen	0	2 (0.6)	2 (0.3)	1 (0.3)

### Events of Special Interest (ESI)

ESI for study 108 underwent comprehensive analysis by a panel of expert dermatologists convened by the applicant (their report is reviewed later in this consult).

All “rash or rash-like” events that met any one of the following criteria were ESI:

- permanent discontinuation of any or all study drugs due to rash
- Grade 3 (severe) rash
- rash which met the criteria for a serious adverse event

Per Tables 113 and 14.3.1.29c, a total of 53 ESI occurred during the telaprevir/placebo treatment phase, and these events occurred in 51 (7%) of T/PR subjects compared to 2(1%) in the Pbo/PR48 group. The percentages of T/PR subjects with ESI progressively increased in parallel with the severity grade of the eruption: 1% of T/PR subjects had Grade 1 events, 2% had Grade 2 events and 4% had Grade 3 events. This may reflect that Grade 3 events were one of the criteria for defining an ESI. No subjects in the Pbo/PR group experienced ESI in the Grade 1 or 2 categories of severity; 1% of these subjects had ESI of Grade 3 severity. Most ESI in T/PR subjects were of Grade 3 severity (31 of 51; 61%) and the two ESI reported in the Pbo/PR48 group were both of Grade 3 severity. The percentage of Grade 3 ESI in the T12/PR group was approximately twice that of the T8/PR group: 3% in the T8/PR group and 6% in the T12/PR group, and these incidences were 3 and 6 times higher than the 1% in the Pbo/PR48 group. (See Table 113 below):

**Excerpted from Table 113: Incidence of Rash Events of Special Interest (ESI) by Severity during the Telaprevir/Placebo Treatment Phase, Full Analysis Set**

Severity	T8/PR	T12/PR	T/PR	Pbo/PR48
	N = 364 n (%)	N = 363 n (%)	N = 727 n (%)	N = 361 n (%)
<b>Telaprevir/placebo treatment phase</b>				
Total	21 (5.8)	30 (8.3)	51 (7.0)	2 (0.6)
Grade 1	2 (0.5)	3 (0.8)	5 (0.7)	0
Grade 2	8 (2.2)	7 (1.9)	15 (2.1)	0
Grade 3	11 (3.0)	20 (5.5)	31 (4.3)	2 (0.6)

From review of Tables 88 and 14.3.2.6c, 6 of the 53 subjects with ESI (11%) were assessed as having serious adverse events, and all were reported in subjects in T/PR groups (3 in each TP/PR group). Five of these 6 ESI were coded as “rash,” and the 6<sup>th</sup> as “rash maculo-papular.”

From Table 14.3.1.28c, the median time to onset of rash ESI (days) was:

- T8/PR: 37 (range: 3 to 77)
- T/12/PR: 54 (range: 1 to 126)
- Pbo/PR: 48 (range: 35 to 61)

The ESI events resolved in all but 1 subject; this subject (Subject 116001 in the T12/PR group) discontinued the study due to withdrawal of consent before the ESI resolved.

From Table 14.3.1.28c, the median duration of rash ESI (days):

- T8/PR: 37 (range: 3 to 276)
- T/12/PR: 23 (range: 5 to 445)
- Pbo/PR: 30 (range: 8 to 52)

Per Table 14.3.2.6c, six subjects with ESI received treatment with systemic corticosteroids: 5 subjects in T/PR groups (9%) and one in the Pbo/PR48 group (2%). A total of 4 subjects (8%) received treatment only with topical medications (not otherwise specified), and all were in T/PR groups. A total of 14 subjects with rash ESI (26%) received treatment only with oral antihistamines. The remaining subjects received combination treatment e.g. systemic steroid and topical medication, antihistamine and a topical.

Per Table 14.3.2.6c, of the 53 ESI, 31 (58%) were coded by the MedDRA preferred term “rash.” An additional 13 cases were coded as rash with some descriptor, e.g. “pruritic rash” or “maculo-papular rash.” Thus, 83% of rash ESI were recorded as rash ± a descriptor (consistent with the definitions of ESI as applying to “rash or rash-type” events).

Per Section 11.6.3 of the study report (“Pharmacokinetics Following Events of Special Interest Results”), the dataset for the analysis of the pharmacokinetics following ESI (PK/ESI) included;

- 34 telaprevir ESI PK samples from 32 subjects,
- 40 Peg-IFN-alfa-2a ESI PK samples from 38 subjects, and
- 39 RBV ESI PK samples from 37 subjects.

In Section 11.6.4, the sponsor states, “The distribution of telaprevir, Peg-IFN-alfa-2a, and RBV concentrations in the ESI PK assessments are contained within the observed concentration

distribution (Section 11.4.2.1), suggesting no apparent correlation between acute drug exposure and the occurrence of an ESI.”

### **VX-950-TiDP24-C216 (C216)**

This was the sponsor’s other pivotal trial.

Title: “A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of telaprevir (with and without delayed start) combined with pegylated interferon alfa-2a (Pegasys®) and ribavirin (Copegus®) in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment.”

Design: This was a randomized, double-blind, placebo-controlled Phase 3 study with telaprevir in subjects with genotype 1 chronic hepatitis C infection who failed prior treatment with pegylated interferon (Peg- IFN; Peg-IFN-alfa-2a or Peg-IFN-alfa-2b) plus ribavirin (RBV).

The study was designed to compare the efficacy, safety, and tolerability of 2 regimens of telaprevir (with and without delayed start (DS) of telaprevir) combined with Peg-IFN-alfa-2a and RBV versus standard treatment (Peg-IFN-alfa-2a and RBV). Telaprevir was administered at a dose of 750 mg every 8 hours (q8h) and Peg- IFN-alfa-2a and RBV at standard doses, i.e., 180 µg once weekly and 1000 or 1200 mg/day (weight-based), respectively.

There were three treatment groups in this study:

- Treatment group A: telaprevir in combination with Peg-IFN-alfa-2a and RBV for 12 weeks; followed by placebo in combination with Peg-IFN-alfa-2a and RBV for 4 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.
- Treatment group B (260 subjects: 140 prior relapsers and 120 prior non-responders): placebo in combination with Peg-IFN-alfa-2a and RBV for 4 weeks; followed by telaprevir in combination with Peg-IFN-alfa-2a and RBV for 12 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.
- Treatment group C (control group, 130 subjects: 70 prior relapsers and 60 prior non-responders): placebo in combination with Peg-IFN-alfa-2a and RBV for 16 weeks; followed by Peg-IFN-alfa-2a and RBV for 32 weeks.

### **Special Search Categories (SSC) in Study VX-950-TiDP24-C216(C216)**

Per Section 4.6.2.6.5 of the study report, the applicant created SSC by grouping select adverse from the same or different SOCs, to ensure that each subject with an event included within a predefined SSC, was counted only once (i.e., the same approach as was used in study 108). For cutaneous events, the sponsor created the following SSC:

- Rash SSC
- Pruritus SSC
- Rash and/or pruritus SSC.

**Table 142: Summary Table of Rash SSC Events During the Telaprevir/Placebo Treatment Phase (C-216)**

<b>Adverse Event, n (%)</b>	<b>T12/PR48 N = 266</b>	<b>T12(DS)/PR48 N = 264</b>	<b>Pooled T/PR48 N = 530</b>	<b>Pbo/PR48 N = 132</b>
Any AE	135 (50.8)	137 (51.9)	272 (51.3)	36 (27.3)
Any SAE	2 (0.8)	3 (1.1)	5 (0.9)	0
At least grade 3	9 (3.4)	8 (3.0)	17 (3.2)	0
Any AE leading to permanent discontinuation of telaprevir/placebo	12 (4.5)	10 (3.8)	22 (4.2)	0
Any AE at least possibly related to telaprevir/placebo	124 (46.6)	122 (46.2)	246 (46.4)	25 (18.9)

More than half of subjects in the pooled T12/PR48 group (51%) experienced an adverse event in the rash SSC compared to approximately one quarter of subjects (27%) in the Pbo/PR48 group (Table 142 above). Approximately 1% of subjects in the pooled T12/PR48 group experienced a serious adverse event under this search (none in the Pbo/PR48 group); 3% in the pooled group experienced a rash of at least Grade 3 (none in the Pbo/PR48 group); 4% in the pooled group experienced an adverse event leading to permanent discontinuation of telaprevir (none in the Pbo/PR48 group).

**Sponsor Table 144: Summary Table of Pruritis SSC Events During the Telaprevir/Placebo Treatment (C-216)**

<b>Adverse Event, n (%)</b>	<b>T12/PR48 N = 266</b>	<b>T12(DS)/PR48 N = 264</b>	<b>Pooled T/PR48 N = 530</b>	<b>Pbo/PR48 N = 132</b>
Any AE	144 (54.1)	135 (51.1)	279 (52.6)	36 (27.3)
Any SAE	1 (0.4)	0	1 (0.2)	0
At least grade 3	3 (1.1)	4 (1.5)	7 (1.3)	0
Any AE leading to permanent discontinuation of telaprevir/placebo	1 (0.4)	3 (1.1)	4 (0.8)	0
Any AE at least possibly related to telaprevir/placebo	128 (48.1)	115 (43.6)	243 (45.8)	32 (24.2)

The proportions of subjects who experienced an adverse event in the pruritus SSC were greater in the pooled T/PR48 group (53%) relative to the Pbo/PR48 group (27%). Less than 1% in the pooled group (one subject) experienced a serious adverse event under this SSC (none in the Pbo/PR48 group); 1% in the pooled T12/PR48 group experienced pruritus at least Grade 3 (none in the Pbo/PR48 group) and 1% in the pooled T12/PR48 group experienced an adverse event leading to permanent discontinuation of telaprevir (none in the Pbo/PR48 group). See Table 144.

**Table 146: Summary Table of Rash SSC and Pruritus SSC Events During the Telaprevir/Placebo Treatment Phase (C-216)**

Adverse Event, n (%)	T12/PR48 N = 266	T12(DS)/PR48 N = 264	Pooled T/PR48 N = 530	Pbo/PR48 N = 132
Any AE	192 (72.2)	190 (72.0)	382 (72.1)	62 (47.0)
Any SAE	3 (1.1)	3 (1.1)	6 (1.1)	0
At least grade 3	11 (4.1)	11 (4.2)	22 (4.2)	0
Any AE leading to permanent discontinuation of telaprevir/placebo	13 (4.9)	11 (4.2)	24 (4.5)	0
Any AE at least possibly related to telaprevir/placebo	175 (65.8)	174 (65.9)	349 (65.8)	47 (35.6)

During the telaprevir/placebo treatment phase, rash and/or pruritus SSC events were reported in 72% of subjects in the pooled T/PR48 group compared to 47.0% in the Pbo/PR48 group. In the pooled group, 1% of subjects experienced serious adverse event ((none in the Pbo/PR48 group); 4% in the pooled group had at least Grade 3 (none in the Pbo/PR48 group); 5% in the pooled group experienced an event under this SSC that lead to permanent discontinuation of telaprevir/placebo (none in the Pbo/PR48 group).

Events of Special Interest (ESI) in Study VX-950-TiDP24-C216 (C216)

ESI were defined as in Study 108. Management procedures were similar to those in study 108; however, neither biopsy nor photographs were required (Section 5.4.8.2.3.3 of the protocol).

A total of 28 of 520 telaprevir-treated subjects (5%) experienced ESI during the Telaprevir/Placebo Treatment Phase. There were no reports of ESI among the 132 subjects in the Pbo/PR48 during this period. ESI that occurred during the Telaprevir/Placebo Treatment Phase are presented in the following table (Table 148):

The remainder of this page is left intentionally blank.

**Sponsor Table 148: Events of Special Interest Reported During the Telaprevir/Placebo Treatment Phase by Body System and Preferred Term (C216)**

Body System Preferred Term, n (%)	T12/PR48 N = 266	T12(DS)/PR48 N = 264	Pooled T/PR48 N = 530	Pbo/PR48 N = 132
<i>Any event of special interest</i>	14 (5.3)	14 (5.3)	28 (5.3)	0
Skin and subcutaneous tissue disorders	14 (5.3)	14 (5.3)	28 (5.3)	0
Rash	5 (1.9)	5 (1.9)	10 (1.9)	0
Dermatitis	3 (1.1)	1 (0.4)	4 (0.8)	0
Pruritus	2 (0.8)	1 (0.4)	3 (0.6)	0
Rash generalised	1 (0.4)	1 (0.4)	2 (0.4)	0
Rash maculo-papular	1 (0.4)	1 (0.4)	2 (0.4)	0
Toxic skin eruption	0	2 (0.8)	2 (0.4)	0
Drug rash with eosinophilia and systemic symptoms <sup>b</sup>	1 (0.4)	0	1 (0.2)	0
Dry skin	0	1 (0.4)	1 (0.2)	0
Erythema	0	1 (0.4)	1 (0.2)	0
Erythema multiforme	1 (0.4)	0	1 (0.2)	0
Pustular psoriasis	0	1 (0.4)	1 (0.2)	0
Pyoderma gangrenosum	0	1 (0.4)	1 (0.2)	0
Swelling face	1 (0.4)	0	1 (0.2)	0
Urticaria	1 (0.4)	0	1 (0.2)	0

<sup>b</sup>this event was reported as a drug eruption

**Comment:** The cases listed as DRESS and erythema multiforme were reviewed by the dermatology expert panel, and the panel suspect either of these reported diagnose in their review of the cases.

### **Dermatology Expert Panel Report**

In July 2008, the applicant convened a Dermatology Expert Panel (DEP) and a dermatopathologist (as an adjunct member). The primary charge of the DEP was to characterize the ESI in study 108, with a particular focus on events that might represent severe cutaneous adverse reactions (SCAR). The experts conducted a final review after study unblinding. The DEP committee members were:



*Comment: The members of the DEP are qualified to serve as experts.*

The DEP relied on study 108 as the primary data source for ESI review, as this was the only study that for ESI required:

- dermatology consultation,
- photographs,
- skin biopsies, (the affiliated dermatopathologist received, processed and evaluated all rash ESI biopsy samples, blinded to treatment assignment)
- central histopathology review, and
- specific hematology and chemistry laboratory tests

The DDDP consultant agrees that Study 108 provided the most comprehensive information.

The scope of the DEP review evolved over the course of the Phase 3 trials and was broadened to include review of some data from other studies and literature. However, as only study 108 required the above procedures, the DEP considered data from studies other than Study 108 to be supportive, i.e. those were not considered primary data and were not included in the primary analyses. The DEP requested dermatopathologic review of select non study-108 cases.

Per Section 6.5.3, the DEP members reviewed each case independently and arrived at consensus at meetings of the full panel.

The DEP ultimately characterized ESI by:

1. Histopathology assessment

Biopsies were each categorized as one of the following patterns below (Section 6.5.3.1):

- 1 = Spongiotic dermatitis, predominantly lymphocyte-mediated
- 2 = Spongiotic dermatitis with patchy low-grade vacuolar interface dermatitis, predominantly lymphocyte-mediated
- 3 = Spongiotic/urticarial reaction +/- marked subepidermal edema
- 4 = Spongiotic dermatitis with eosinophil-rich dermal infiltrate
- 5 = Mild vacuolar interface dermatitis without significant keratinocyte necrosis
- 6 = Severe vacuolar interface dermatitis with abundant keratinocyte apoptosis/necrosis

2. Systematic assessment of skin photographs

Per Section 6.5.3.2, the DEP assessed photographs (if of adequate quality) by:

- Morphology: eczematous, papular-lichenoid, and/or morbilliform/maculopapular (all that were applicable)
- BSA involvement: <10%, 10-30%, >30-50%, or >50%

### 3. Characterizing and scoring suspected SCARs

The DEP scored events using a modification of the assessment criteria of the RegiSCAR-group (the consultant could not find a statement of how the criteria were modified) in determining which cutaneous adverse events might represent a Severe Cutaneous Adverse Reaction (SCAR).

The RegiSCAR scoring system is intended to aid in the diagnosis of SCAR.<sup>7</sup> Point values were assigned to the following clinical characteristics fever, lymphadenopathy, eosinophilia, skin rash (including extent of involvement), internal organ involvement, and time to resolution (> 15 days). The sum total yielded a score corresponding to a categorization of “no case,” “possible,” “probable” or “definite.” The DEP appeared to follow this approach. The DEP acknowledged that no worldwide consensus exists for the definition or scoring for SCAR (Section 6.5.3.3).

The DEP considered the following as possible SCAR:

- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Drug reaction with eosinophilia and system symptoms (DRESS)
- Acute generalized exanthematous pustulosis (AGEP)

*Comment: The RegiSCAR-group is “a multinational collaborative research team...operating as a registry collecting detailed clinical data and biological samples on 3 varieties of SCAR, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and system symptoms (DRESS), also called drug induced hypersensitivity syndrome (DIHS) and acute generalized exanthematous pustulosis (AGEP).”<sup>7</sup> As of January 2009, countries in which the group was active included France, Germany, the United Kingdom, Taiwan and South Africa.*

Per Section 6.2, DEP meeting participants included representatives from Vertex, Mitsubishi (per the Background and Overview Section of the Summary of Clinical Safety, Mitsubishi Pharma retains commercial rights to telaprevir in South East Asia, China, and Japan) and Tibotec (?developing product in Europe?).

## RESULTS

The DEP reviewed 221 rash cases that occurred in unique subjects in the clinical development program, 208 of whom (94%) had received telaprevir. Of the 221 subjects, 59 were from Study 108 and served as the data source for the DEP primary analyses. Of those 59, 56 subjects (95%) received telaprevir. Of the 56 subjects in the primary database who received telaprevir (Per Table 7-2 of the DEP report):

- 47 had dermatology consultation.
- 45 had photographs of the ESI.
- 36 had biopsies of the ESI and review of the biopsy by the DEP-affiliated dermatopathologist.

From Listing 6.1, 36 telaprevir-treated subjects from Study 108 had the following protocol-specified ESI evaluations: dermatology consultation, photographs, and biopsy (an additional subject also had these evaluations, but did not receive telaprevir treatment).

### Rash Morphology and BSA Involvement

The DEP assessed rash morphology and BSA involvement by review of photographs of the 45 subjects in study 108 who had photographs of their cutaneous eruptions. Per Table 7-4, there were no photographs of ESI of Grade 1 severity (perhaps reflective of the definition of ESI). Per Table 113 from the study report for study 108, five subjects had ESI reported as Grade 1 severity.

Rash morphologies were classified as being:

- eczematous,
- papular-lichenoid, or
- morbilliform/maculopapular.

From Table 7-4: The DEP concluded that the majority of subjects (60%) had  $\geq 2$  morphological components to the eruptions, with 13% of subjects having 2 assessable components and 47% having 3 assessable components. The proportions of subjects with 2 components were similar between the Grade 2 (15%) and Grade 3 (13%) groups. The proportion of subjects with 3 components was higher in the Grade 2 group (54%) relative to Grade 3 (44%). Of the sets of photographs from study 108 reviewed by the DDDP consultant (those of subjects who also had dermatology consultation and central review of biopsy), mixed morphologies were noted.

For the 41 subjects for whom the DEP could make a determination, they concluded that an eczematous component was the most common of the morphological features to manifest in cutaneous eruptions (39 subjects; 95%). An eczematous component was present in all subjects with Grade 2 eruptions (12; 100%) and most with Grade 3 eruptions (27; 93%). The DDDP consultant agrees with the morphological categorizations of the DEP and that those generally adequately capture the clinical features of the ESI represented in the series of photographs reviewed (the consultant might have also included “urticarial”). The consultant also agrees that an eczematous reaction pattern was a common feature. Two of the subjects who did not receive telaprevir had only an eczematous component assessable.

The DEP could assess BSA involvement in 42 of the 56 telaprevir-treated subjects and concluded that most (98%) had  $\leq 30\%$  BSA involved (Table 7-4). Of these, 8 (67%) of Grade 2 eruptions had  $< 10\%$  BSA involvement and 13 (43%) of Grade 3 eruptions had  $< 10\%$  BSA affected. Table 7-5 in the DEP report suggests that some investigators considered some eruptions to involve a greater extent of BSA than did the DEP. (The DDDP consultant did not find that investigators received training in estimation of BSA.) For example, the DEP considered none of 19 subjects assessed by investigators as having  $> 50\%$  BSA affected to have had disease of this extent. The DEP assessed no subjects as having  $> 50\%$  BSA affected. Further, the DEP assessed 7 of those 19 as having  $< 10\%$  BSA affected. The most extensive eruption, as assessed by the DEP, involved  $>30\text{-}50\%$  BSA, and this occurred in one subject with a Grade 3 eruption (Subject 158009 per p. 29). Having  $> 50\%$  BSA affected was a criterion on which investigators could rely to assess an ESI as being of Grade 3 severity. Therefore, the DDDP consultant considers it possible that some ESI categorized by investigators as Grade 3 (severe) may have been of lesser severity, if investigators overestimated the extent of BSA involvement to be  $> 50\%$  (and graded the event based solely on this criterion). However, in their analyses, the DEP considered the severity grade as provided by the investigator (Section 7.1, “the DEP did not re-evaluate investigator reported rash severity.”).

**Excerpted from Table 7-4 Primary Review (Study 108 ESIs): Number (%) of Subjects by Rash Morphology Component and BSA Involvement**

Parameter	Telaprevir-based Regimen N = 56			Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	
Number of subjects with photographs	0	13	32	45
0 component assessable by the DEP <sup>a</sup>	0	1 (8)	3 (9)	4 (9)
1 component assessable by the DEP <sup>a</sup>	0	3 (23)	11 (34)	14 (31)
2 components assessable by the DEP <sup>a</sup>	0	2 (15)	4 (13)	6 (13)
3 components assessable by the DEP <sup>a</sup>	0	7 (54)	14 (44)	21 (47)
At least 1 component assessable by the DEP <sup>a</sup>	0	12 (92)	29 (91)	41 (91)
Eczematous component present <sup>b</sup>	0	12 (100)	27 (93)	39 (95)
Papular-Lichenoid component present <sup>b</sup>	0	1 (8)	3 (10)	4 (10)
Maculopapular component present <sup>b</sup>	0	4 (33)	3 (10)	7 (17)
BSA assessable by the DEP <sup>a</sup>	0	12 (92)	30 (94)	42 (93)
BSA <10% <sup>c</sup>	0	8 (67)	13 (43)	21 (50)
BSA 10-30% <sup>c</sup>	0	4 (33)	16 (53)	20 (48)
BSA >30-50% <sup>c</sup>	0	0	1 (3)	1 (2)
BSA >50% <sup>c</sup>	0	0	0	0

<sup>a</sup> Percentages based on number of subjects with photographs available.

<sup>b</sup> Percentages based on number of subjects with at least 1 component assessable by the DEP.

<sup>c</sup> Percentages based on number of subjects with BSA assessable by the DEP.

### Histopathology Patterns

As previously stated, biopsies were each categorized as one of the following patterns:

- 1 = Spongiotic dermatitis, predominantly lymphocyte-mediated
- 2 = Spongiotic dermatitis with patchy low-grade vacuolar interface dermatitis, predominantly lymphocyte-mediated
- 3 = Spongiotic/urticarial reaction +/- marked subepidermal edema
- 4 = Spongiotic dermatitis with eosinophil-rich dermal infiltrate
- 5 = Mild vacuolar interface dermatitis without significant keratinocyte necrosis
- 6 = Severe vacuolar interface dermatitis with abundant keratinocyte apoptosis/necrosis

Of the 56 subjects in study 108 who received telaprevir and experienced an ESI, 36 (64%) had a centrally-reviewed biopsy. Per Table 7-6, most of these biopsies were of eruptions of Grade 3 severity (29; 81%); the remaining 6 biopsies were of ESI of Grade 2 severity. There were no biopsies of Grade 1 ESI in the analyses.

Most of the 36 biopsies were categorized as being of histological patterns 1 (44%) and 2 (36%). In the consultant's opinion, Pattern 1 histology is consistent with an eczematous clinical picture.<sup>8</sup> Absent the spongiosis, Patterns 2 through 5 could be consistent with a drug eruption, the histology of which can be non-specific, requiring clinical-pathological correlation.<sup>8,9</sup> A higher percentage of subjects with Grade 2 eruptions had pattern 1 histology (4; 57%) compared

to those categorized as Grade 3 (12; 41%). The reverse pattern was seen with pattern 2 histology: 2 (29%) of Grade 2 compared to 11 (38%) of Grade 3 eruptions. The percentages of biopsies of ESI of Grade 3 severity reported as patterns 1 and 2 were similar: 41% and 38%, respectively. Generally, biopsies of Patterns 3 through 6 were of eruptions of Grade 3 severity (with the one exception being a Grade 2 eruption that was classified as showing Pattern 5 histology).

Spongiosis was present in 94% of the specimens and would correlate clinically with the observations of eruptions with eczematous features<sup>8</sup>. One case was reported as Pattern 6, the most severe category, and the DEP classified this subject (129002) as “definite” SJS, a clinical diagnosis with which the Pattern 6 histology is consistent.<sup>10</sup>

**Excerpted from Table 7-6 Primary Review (Study 108 ESIs): Number (%) of Subjects by Rash Histopathology Pattern**

Rash Histopathology Pattern	Telaprevir-based Regimen N = 56			
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total n (%)
Number of subjects with centrally reviewed biopsy	0	7	29	36
Rash histopathology pattern <sup>a</sup>				
Pattern 1: Spongiotic dermatitis, predominantly lymphocyte-mediated	0	4 (57)	12 (41)	16 (44)
Pattern 2: Spongiotic dermatitis with patchy low-grade VID, predominantly lymphocyte-mediated	0	2 (29)	11 (38)	13 (36)
Pattern 3: Spongiotic/urticarial reaction ± marked subepidermal edema	0	0	4 (14)	4 (11)
Pattern 4: Spongiotic dermatitis with eosinophil-rich dermal infiltrate	0	0	1 (3)	1 (3)
Pattern 5: Mild vacuolar interface dermatitis without significant keratinocyte necrosis	0	1 (14)	0	1 (3)
Pattern 6: Severe vacuolar interface dermatitis with abundant keratinocyte apoptosis/necrosis	0	0	1 (3) <sup>b</sup>	1 (3)

<sup>a</sup> Percentages are based on number of subjects with centrally reviewed biopsy.

<sup>b</sup> The case assessed by the central dermatohistopathologist as having pattern 6 (severe vacuolar interface dermatitis with abundant keratinocyteapoptosis/necrosis) was scored by the DEP as definite SJS (Subject 129002)

### Pruritus

Pruritus was reported in 53 of 56 subjects in the telaprevir group (95%), but was also reported in all three subjects (100%) in the non-telaprevir group. Pruritus was clinically evidenced by the prominence of excoriations in many of the photographs.

### Resolution

A total of 53 of 56 ESI (95%) resolved. In the remaining three cases, subjects withdrew consent and terminated the study; information on resolution status is not available.

### Supportive Reviews

The report also provided data from 4 supportive reviews: data from Phase 2 and Phase 3 studies, Phase 1 studies, Mitsubishi-sponsored studies, and a literature review.

Data from Phase 2 and 3 studies were pooled for the supportive analyses and included the data from study 108. Per Table 7-9, an additional 51 subjects had photographs available for DEP review (based on comparison to Table 7-4 which reflected data only from study 108). Based on photographic review, the DEP assessed an additional 8 subjects as having BSA >30-50%, and 2 subjects were assessed as having > 50% (there were none in study 108). Most subjects had > 3 components assessable and most had an eczematous component to the eruption.

**Table 7-9 Supportive Review (Phase 2 and Phase 3 Studies [including Study 108 ESIs]): Number (%) of Subjects by Rash Morphology Component and BSA Involvement**

Parameter	Telaprevir-based Regimen N = 165			Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	
Number of subjects with photographs <sup>a</sup>	2	33	61	96
0 component assessable by the DEP <sup>b</sup>	1 (50)	3 (9)	5 (8)	9 (9)
1 component assessable by the DEP <sup>b</sup>	0	4 (12)	12 (20)	16 (17)
2 components assessable by the DEP <sup>b</sup>	0	9 (27)	10 (16)	19 (20)
3 components assessable by the DEP <sup>b</sup>	1 (50)	17 (52)	34 (56)	52 (54)
At least 1 component assessable by the DEP <sup>b</sup>	1 (50)	30 (91)	56 (92)	87 (91)
Eczematous component present <sup>c</sup>	1 (100)	29 (97)	53 (95)	83 (95)
Papular-Lichenoid component present <sup>c</sup>	0	1 (3)	5 (9)	6 (7)
Maculopapular component present <sup>c</sup>	1 (100)	7 (23)	15 (27)	23 (26)
BSA assessable by the DEP <sup>b</sup>	1 (50)	29 (88)	53 (87)	83 (86)
BSA <10% <sup>d</sup>	0	14 (48)	14 (26)	28 (34)
BSA 10-30% <sup>d</sup>	1 (100)	14 (48)	29 (55)	44 (53)
BSA >30-50% <sup>d</sup>	0	1 (3)	8 (15)	9 (11)
BSA >50% <sup>d</sup>	0	0	2 (4)	2 (2)

<sup>a</sup> The Phase 2 and 3 studies include Study 108.

<sup>b</sup> Percentages based on number of subjects with photographs available.

<sup>c</sup> Percentages based on number of subjects with at least 1 component assessable by the DEP.

<sup>d</sup> Percentages based on number of subjects with BSA assessable by the DEP.

Per Table 7-10, an additional 10 subjects had central review of biopsies relative to study 108. Most biopsies were assessed as having Grade 1 or 2 histology.

**Table 7-10 Supportive Review (Phase 2 and Phase 3 Studies [including Study 108 ESIs]): Number (%) of Subjects by Rash Histopathology Pattern<sup>a</sup>**

Rash Histopathology Pattern	Telaprevir based Regimen N = 165			Total n (%)
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	
Number of subjects with centrally reviewed biopsy <sup>c</sup>	0	8	38	46
Rash histopathology pattern <sup>b</sup>				
Pattern 1: Spongiotic dermatitis, predominantly lymphocyte-mediated	0	5 (63) <sup>c</sup>	18 (47) <sup>d</sup>	23 (50)
Pattern 2: Spongiotic dermatitis with patchy low-grade VID, predominantly lymphocyte-mediated	0	2 (25)	12 (32) <sup>e</sup>	14 (30)
Pattern 3: Spongiotic/urticarial reaction ± marked subepidermal edema	0	0	6 (16) <sup>f</sup>	6 (13)
Pattern 4: Spongiotic dermatitis with eosinophil-rich dermal infiltrate	0	0	1(3)	1 (2)
Pattern 5: Mild vacuolar interface dermatitis without significant keratinocyte necrosis	0	1 (13)	0	1 (2)
Pattern 6: Severe vacuolar interface dermatitis with abundant keratinocyte apoptosis/necrosis	0	0	1(3) <sup>g</sup>	1 (2)

<sup>a</sup> The Phase 2 and 3 studies include Study 108.

<sup>b</sup> Percentages are based on number of subjects with centrally reviewed biopsy.

<sup>c</sup> 1 subject from Study 111 with histopathology pattern 1.

<sup>d</sup> 2 subjects from Study 111 and 4 subjects from Study C216 with histopathology pattern 1.

<sup>e</sup> 1 subject from Study 111 with histopathology pattern 2.

<sup>f</sup> 2 subjects from Study 111 with histopathology pattern 3.

<sup>g</sup> The case assessed by the central dermatohistopathologist as having pattern 6 (severe vacuolar interface dermatitis with abundant keratinocyte apoptosis/necrosis) was scored by the DEP as definite SJS (Subject 129002)

Of the nine ESI reviewed from the Phase 1 studies, seven were of Grade 1 severity, and the remaining two were Grade 2. Eight subjects had 3 morphologic components to their ESI (the 9<sup>th</sup> had no components assessable).

#### Mitsubishi-sponsored Studies

Of the 33 telaprevir-treated subjects who photographs available for review in the Mitsubishi-sponsored, 6 had biopsies centrally reviewed (Tables 7-14 and 7-15, respectively).

Of the 33 subjects assessed, 82% had 3 assessable components, 87% had an eczematous component present and 54% had >30-50% BSA involvement. Of the seven subjects who did not receive telaprevir, four had 2 or 3 components to their ESI, and six of the seven had an eczematous component.

Six biopsies were reviewed, four of which were of Pattern 1 histology. One biopsy showed a mixed pattern that was assessed as Pattern “4 + ?6.”

### Literature Review

The sponsor conducted a literature search. On review of the provided literature, the DEP noted the association of rash with Peg-IFN treatment for chronic hepatitis C and that frequency of rash reports increased when RBV was added to the Peg-IFN monotherapy. There were literature reports of cutaneous eruptions that appear to be similar to those seen in the setting of telaprevir treatment, i.e. eczematous eruptions with spongiotic dermatitis reported on histology.

### Assessment for Severe Cutaneous Adverse Reactions

The DEP assessed each of the 221 cases for the possibility of being a Severe Cutaneous Adverse Reaction (SCAR). The DEP considered the following a possible SCAR:

- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Drug reaction with eosinophilia and system symptoms (DRESS)
- Acute generalized exanthematous pustulosis (AGEP)

Investigators reported 6 cases as SCARs (3 as SJS and 3 as DRESS), and the DEP concurred with the assessment of suspected SCAR in 4 of these cases. One SCAR was reported by an investigator in Study 108 in a telaprevir-treated subject (Subject 129002); however, the subject completed treatment with telaprevir/placebo and developed SJS during the Peg-IFN-alfa-2a and RBV treatment phase approximately 48 days after the last dose of telaprevir/placebo. The subject discontinued treatment with Peg-IFN-alfa-2a and RBV due to the serious adverse event of SJS. The consultant concurs with the conclusion that given the time of onset of the SJS, in relation to the completion of telaprevir dosing of approximately 9 to 11 hours (per draft label), that the SJS was not likely related to the telaprevir. The following table presents the DEP assessment of SCARs and other important events as reported by investigators:

**Table 7-16 Listing of Investigator-Reported SCAR and/or Important Dermatological Conditions**

Study	Case No.	Subject No.	MedDRA Preferred term (based on Investigator- Reported Event Term)	SCAR Score or Comment, per DEP			Important Dermatological Conditions Comment	Site Biopsy Performed/ Central Rash Histo- pathology Pattern <sup>1</sup>	Photos Reviewed	Resolved
				DRESS Score	SJS Score	AGEP Score				
<b>Study 108</b>										
	AE-2008-0087	129002	Stevens-Johnson syndrome	NA	Definite	NA	NA	Y/6	Y	Y
	AE-2010-0050	406005	Erythema multiforme	NA	NA	NA	Not suspected	N/NA	Y	Y
<b>Other Phase 2 and 3 Studies (excluding Study 108)</b>										
C216	AE-2009-0173 <sup>b</sup>	KC-0644	Drug rash with eosinophilia and systemic symptoms	Not suspected	NA	NA	NA	Y/NA	Y	Y
	AE-2009-0211	NSP-0516	Erythema multiforme	NA	NA	NA	Not suspected	Y/1	Y	Y
	AE-2009-0234	GS-0791	Pustular psoriasis <sup>c</sup>	Possible	NA	Possible	Not suspected	N/NA	N	Y
107	AE-2008-0043	2212202	Drug rash with eosinophilia and systemic symptoms	Possible	NA	NA	NA	Y/NA	Y	Y
<b>Mitsubishi-sponsored Studies</b>										
A6	AE-2009-0170	A63803	Erythema multiforme	NA	NA	NA	Not suspected	Y/1	Y	Y
	AE-2009-0205	A62607	Stevens-Johnson syndrome	Possible	Probable	NA	NA	Y/4+6	Y	Y
	AE-2009-0207	A60603	Drug rash with eosinophilia and systemic symptoms	Definite	NA	NA	NA	Y/1	Y	Y
A8	AE-2009-0127	A82401	Stevens-Johnson syndrome	NA	Not suspected	NA	NA	Y/1	Y	Y

Of the three cases reported as DRESS by investigators, the DEP on their review of these cases (including review of photographs and the site biopsies for all three subjects):

- did not suspect this diagnosis in Subject KC-0644 (this subject was not suspected by the DEP as having any SCAR),
- considered the diagnosis possible in Subject 2212202 and
- considered the diagnosis definite in Subject A60603 (this subject also had central review of the biopsy specimen).

Of the three cases reported as SJS by investigators, the DEP on their review of these cases (including review of photographs and the site biopsies and central review of biopsies for all three subjects):

- considered the diagnosis definite in Subject 129002
- considered the diagnosis probable in Subject A62607 (The DEP also scored this subject as “possible” DRESS)
- did not suspect this diagnosis in Subject A82401 (this subject was not suspected by the DEP as having any SCAR)

Independent of investigator-reported term, the DEP reviewed all 221 cases for potential SCARs. Per Table 7-18, the DEP assessed 13 subjects as having experienced 15 suspected SCAR: 11 DRESS, three SJS and one AGEP. Two subjects were scored for two suspected SCAR:

- Subject GS-0791: “possible” DRESS and “possible” AGEP (no other cases were as suspected AGEP).
- Subject A62607: “probable” SJS and “possible” DRESS.

The DEP suspected two cases as “definite” SCAR:

- one SJS case in Study 108 (Subject 129002 discussed above) and
- one DRESS case in Mitsubishi Study A6 (Subject A60603).

Table 7-18 (below) presents suspected SCAR per assessment of the DEP.

For four of the subjects assessed as having suspected SCAR, the DEP arrived at this conclusion without review of photographs.

**Table 7-18 Listing of Suspected SCARs per DEP Assessment**

Study	Case No.	Subject No.	SCAR Type Score			MedDRA Preferred term (based on Investigator-Reported Event Term)	Rash Details			
			DRESS	SJS/TEN	AGEP		Central Rash Histopathology Pattern <sup>a</sup>	Photographs Reviewed	Site Biopsy Reviewed	Resolved
<b>Study 108</b>										
	AE-2008-0087	129002	NA	Definite	NA	Stevens-Johnson syndrome	6	Y	Y	Y
	AE-2009-0026	211009	Possible	NA	NA	Rash, Respiratory tract infection, Anaemia	NA	Y	N	Y
	AE-2009-0027	702008	Possible	NA	NA	Rash	1	Y	Y	Y
<b>Other Phase 2 and 3 Studies (excluding Study 108)</b>										
111	AE-2009-0138	111002	Possible	NA	NA	Rash	NA	N	Y	Y
111	AE-2009-0264	111005	Possible	NA	NA	Rash maculo-papular	NA	N	N	Y
C216	AE-2009-0156	MLW-0635	Possible	NA	NA	Drug eruption	1	Y	Y	N
C216	AE-2009-0234	GS-0791	Possible	NA	Possible	Pustular psoriasis	NA	N	N	Y
104EU	AE-2007-0012	204001	Probable	NA	NA	Drug eruption	NA	Y	N	Y
104EU	AE-2007-0037	301004	Possible	NA	NA	Subcutaneous abscess, rash erythematous	NA	Y	Y	Y
107	AE-2008-0043	2212202	Possible	NA	NA	Drug rash with eosinophilia and systemic symptoms	NA	Y	Y	Y
<b>Mitsubishi-sponsored Studies</b>										
A5	AE-2008-0047	A50207	NA	Possible	NA	Drug eruption	3	Y	Y	Y
A6	AE-2009-0205	A62607	Possible	Probable	NA	Stevens-Johnson syndrome	4 + 6	Y	Y	Y
A6	AE-2009-0207	A60603	Definite	NA	NA	Drug rash with eosinophilia and systemic symptoms	1	Y	Y	Y

<sup>a</sup> Rash histopathology patterns are as follows:

- 1 = Spongiotic dermatitis, predominantly lymphocyte-mediated
- 2 = Spongiotic dermatitis with patchy low-grade vacuolar interface dermatitis, predominantly lymphocyte-mediated
- 3 = Spongiotic/urticarial reaction ± marked subepidermal edema
- 4 = Spongiotic dermatitis with eosinophil-rich dermal infiltrate
- 5 = Mild vacuolar interface dermatitis without significant keratinocyte necrosis
- 6 = Severe vacuolar interface dermatitis with abundant keratinocyte apoptosis/necrosis
- NA = not applicable due to biopsy and/or photomicrographs were unavailable for central histopathology review

Of the the suspected SCAR, six had biopsies reviewed by the DEP dermatopathologist (adjunct member) with histopathology pattern assessment as below:

- Pattern 1: two cases of possible DRESS; one case of definite DRESS
- Pattern 3: one case of possible SJS
- Pattern “4 + 6”: one case of probable SJS which was also considered possible DRESS
- Pattern 6: one case of definite SJS

Of the 13 subjects suspected as having SCAR by the DEP, nine (69%) were not among those reported by investigators as SCAR (Tables 17-16 and 17-18). The DEP suspected three cases of SJS, two of which were also suspected by investigators (67%). The DEP suspected 11 cases of DRESS, two of which were also suspected by investigators (18%). The four subjects who were assessed by investigators and the DEP as suspected SCAR were (DEP assessment in parentheses):

- 129002: (definite SJS)
- 2212202: (possible DRESS)
- A62607: (possible SJS)
- A60603: (definite DRESS)

Investigators appeared to report ten of the 13 subjects (77%) as having experienced serious adverse events, four of whom were the subjects whom investigators suspected of having a SCAR.

Ten of the 11 DRESS events were resolved at last follow-up (the 11<sup>th</sup> was resolving); all of SJS events resolved.

### **Presentation of DEP Suspected Possible SCAR Cases**

Note: The DDDP consultant reviewed the available photographs of subjects with suspected SCAR.

#### **Study VX05-950-108**

**Note:** Subject 129002 has been previously discussed (above). This subject developed SJS during treatment with Peg-IFN and RBV.

#### **Subject 211009: "Rash"**

The subject was a 43 y/o female who received the first dose of study drugs on 31 October 2008. Her last dose of telaprevir was on 05 January 2009. On 24 December 2008, she developed a "drug-induced exanthema" that was considered to be a Grade 2 rash. The eruption was generalized and diffuse, present on the limbs and trunk. It was described as a macular exanthema with sizeable areas of confluence, "livid red lichenification," and excoriations on the dorsa of hands and the extensor aspects of the forearms. She experienced pruritus. Treatment included methylprednisolone "or" prednicarbate. On [REDACTED]<sup>(b) (6)</sup>, she presented with "pyrexia up to 36.8°C" with dry cough and "general physical health deterioration". Laboratory tests, chest x-ray, and computed tomography (CT) of the thorax had no significant findings. On [REDACTED]<sup>(b) (6)</sup>, dyspnea on exertion, anemia, respiratory tract infection, and rash were reported. On [REDACTED]<sup>(b) (6)</sup>, laboratory results included an eosinophil percentage of 16.0% (reference range: 0.0-5.0%). On [REDACTED]<sup>(b) (6)</sup>, pyrexia persisted and a respiratory tract infection was suspected. The thoracic CT scan revealed no infiltrate, bronchiolitis in the lower right lobe, no significant pleural effusions, no pathological mediastinal lymph nodes. She was transfused for her anemia. Telaprevir was permanently discontinued on the same day ([REDACTED]<sup>(b) (6)</sup>); no action was taken with Peg-IFN-alfa-2a and RBV. On [REDACTED]<sup>(b) (6)</sup>, the eosinophil percentage was 24.7%. On [REDACTED]<sup>(b) (6)</sup>, she was discharged with diagnoses that included febrile infection and anemia, and treatment included levofloxacin. On the same day, "general physical health deterioration" was reported as resolved (7 days duration). On 09 January 2009, dyspnoea on exertion resolved after 8 days. On 15 January 2009, the rash was reported as resolved (22 days duration), and topical steroids were discontinued. On [REDACTED]<sup>(b) (6)</sup>, she was again hospitalized for respiratory tract infection, pyrexia of up to 38.8°C, weakness. Chest x-ray revealed "slight indications" of pulmonary congestion. On [REDACTED]<sup>(b) (6)</sup>, respiratory tract infection resolved [REDACTED]<sup>(b) (6)</sup>.

**Comment:** *Concur with the assessment of possible DRESS in this subject with fever, eosinophilia, generalized cutaneous eruption and a somewhat vague history of a persistent and respiratory tract infection (?pneumonitis).*

Subject 702008: “Rash”

The subject was a 67-year-old male who was randomized to the T12/PR treatment group who received the first dose of study drugs on 08 October 2008. On 09 January 2009 (93 days after the first dose of telaprevir), he experienced a severe rash that was an event of special interest.

On 17 December 2008, he experienced pruritus on the thighs. On 20 December 2008, the subject developed a moderate pruritic rash on the legs. On 30 December 2008, eosinophilia was first noted. On 31 December 2008, telaprevir dosing was permanently discontinued due to thrombocytopenia. He was revealed to have longstanding known thrombocytopenia. On 05 January 2009, laboratory results revealed eosinophilia due to an eosinophil count of 1222 eosinophils/mm<sup>3</sup> (reference range: 47-188/mm<sup>3</sup>). 06 January 2009, the subject developed a rash and edema of the hands that progressed to involve the face and legs. On 07 January 2009, the Peg-IFN-alfa-2a dose was reduced to 135µg weekly due to thrombocytopenia. On 09 January 2009, the rash progressed to severe intensity and appeared on the trunk and limbs. The subject also developed axillary lymphadenopathy (only site specified, reference to having lymphadenopathy generally. The investigator estimated that the rash covered 60% BSA. The rash progressed to involve "all of the integuments" and was extremely pruritic associated with slight edema of the face and extremities. He had no systemic symptoms.

On 09 January 2009, dermatology consult was obtained. The dermatologist noted “disseminated, erythematous, maculopapular, and eczematous-like lesions with skin edema.” The dermatologist considered that the long delay between study drug initiation and manifestation of symptoms, lymphadenopathy, eosinophilia, and edematous lesions, was suggestive of an atypical DRESS syndrome. Histopathological findings were reported to be “compatible with DRESS.” Treatment with topical corticosteroids was instituted. On 14, 2209, the rash and edema apparently progressed, and a (?2<sup>nd</sup>) dermatology consult was obtained with skin biopsy. Laboratory results revealed an absolute eosinophil count of 0.32 x 10<sup>9</sup>/L and an eosinophil percentage of 7.6% (no reference ranges). On 15 January 2009, “angioedema” of the hands, face, and legs, pruritis and eosinophilia were noted. On 21 January 2009, the Peg-IFN-alfa-2a dose was resumed to 180 µg weekly. On 28 January 2009, the edema resolved completely after 22 days. On 17 March 2009, the eosinophilia had resolved (the eosinophil count was 107.3 mm). On 26 January 2009, the rash resolved completely after 17 days. No action towards RBV or Peg-IFN-alfa-2a was taken due to rash.

**Comment:** *Concur with the DEP assessment of possible DRESS in this subject who had an apparent generalized eruption with biopsy findings “compatible with DRESS,” eosinophilia, facial edema, lymphadenopathy; however, of note he had no systemic symptoms nor was he hospitalized.*

Study VX05-950-104EU

Subject 204001: “Drug eruption”

This 53-year-old male, was randomized to T12/PR12 treatment. He received his first dose of study drugs on 23 November 2006. He experienced a “drug eruption” on 08 January 2007. Treatment included oral antihistamines. On [REDACTED] (b) (6), he experienced the serious adverse event of drug eruption for which he was hospitalized. He also presented with fever (39 °C), facial edema and eosinophilia (eosinophils >1200 mm<sup>3</sup>; reference range not listed). All study drugs were discontinued on [REDACTED] (b) (6). Treatment included topical and systemic corticosteroids and oral antihistamines. The eruption was said to have “initiated as erythematous lesions that then evolved into plaques, some purpuric, affecting approximately 75% of total skin surface area and being more prominent on the trunk and limbs without mucosal involvement.” No biopsy was done. By [REDACTED] (b) (6) the lesions were no longer evolving, and he was discharged [REDACTED] (b) (6). The eruption resolved with unspecified sequelae on [REDACTED] (b) (6). The investigator considered the drug eruption serious, severe, and related to treatment with telaprevir, Peg-IFN-alfa-2a, and RBV.

**Comment:** *Concur with assessment of probable DRESS in this subject with fever, facial edema eosinophilia, apparent extensive cutaneous eruption.*

Subject 301004: “Erythematous rash”

The subject was a 35-year-old female was randomized to the T12/PR12 treatment and received her first dose of study drugs on 04 January 2007. On 06 January 2007 (Day 3), she experienced a maculo-papular rash of moderate severity that persisted 27 days. Treatment included systemic antihistamines and topical corticosteroids. No action was taken with study drug.

She experienced moderate generalized pruritus beginning on 02 February 2007 (Day 30 of treatment) and persisting for 63 days and a mild macular rash in localized areas beginning on 03 February 2007 and lasting 36 days. No action was taken with study drug.

On 10 March 2007 (Day 66 of treatment), she developed a diffuse erythematous eruption (face, trunk, limbs). All study drugs were discontinued on 15 March 2007 due to this serious adverse event, and she was hospitalized on [REDACTED] (b) (6). Treatment included topical betamethasone. A skin biopsy was described as “consistent with a drug eruption with eosinophils and a spongiotic inflammatory infiltrate.” Peripheral eosinophilia (not otherwise specified) was also observed. The erythematous rash resolved on [REDACTED] (b) (6). She withdrew consent for study participation.

**Comment:** *Concur with assessment of possible DRESS in this subject with an exanthematous cutaneous eruption of [REDACTED] (b) (4) duration (with biopsy described as being consistent with a drug eruption) and eosinophilia.*

Study VX08-950-111

Note: No photographs were reviewed for the two subjects from this study nor were the biopsies centrally-reviewed.

Subject 111002: “Rash”

The subject was a 52-year-old female who was randomized to the T12/PR treatment group and received the first dose of study drugs on 23 January 2009. On 13 March 2009 (80 days after the first dose of telaprevir), she experienced a severe rash.

On 30 December 2008, she developed a mild rash which became pruritic on 02 February 2009. It was described a “fine, red, raised rash over the trunk and extremities. On 13 January 2009, her temperature was normal, but at some unspecified date she began experiencing intermittent fevers (not otherwise specified). On 03 March 2009, she experienced flu-like symptoms (e.g. fatigue and headaches). Teleaprevir was discontinued on the same day due to rash and anemia. Peg-IFN $\alpha$ -2a was interrupted on the same day (and not restarted). RBV dosing was later discontinued due to anemia. On 06 March 2009, the rash progressed to involve the entire body (occurred during and following a transfusion), described as severe, erythematous, maculopapular, pruritic eruption involving extremities, face and trunk. She had periorbital urticaria and facial edema and edema of the lower extremities. She was febrile at 38.2°C. She was treated with oral antihistamines. The rash did not improve. On 10 March 2009, her temperature was 99.9°F (unclear why temperature is reported in Celsius and Fahrenheit). On 13 March 2009, a dermatology consult was obtained. She was described as erythrodermic with salmon-colored papules coalescing into plaques on the upper torso and confluent erythematous plaques on the legs. Crust was noted on the chin and right ear and thought to perhaps represent impetiginization. Small erosions and fissures were noted on the body and palms and soles exhibited blanching erythema. Biopsies revealed acute dermatitis with eosinophilic spongiosis with small numbers of eosinophils in the superficial dermal inflammatory infiltrate. Treatment included tapering course of oral prednisone, trimacinalone and hydrocortisone creams, and cephalexin. On 13 March 2009, the absolute eosinophil count was 1.41 and the percentage was 17.1% (reference ranges not provided). On significantly 19 March 2009, the pruritus had improved significantly and the periorbital edema had decreased. The skin lesions persisted. On 26 March 2009, a dermatology consult was obtained; her condition was noted to have improved; lesions were resolving. On April 2009, two days after completing the prednisone taper, she developed edema, erythema and pruritus on scalp which was treated with the topical steroids (above). On 09 April 2009, salmon-colored “skin” was noted on scalp and papules of similar coloration were noted on the upper torso and upper extremities. The dermatologist assessed her as experiencing a mild rebound flare after completion of the systemic and topical steroids. She received treatment with wet dressings. On 14 April 2009, the rash resolved after 32 days. No action was with RBV due to rash.

***Comment:*** Concur with the assessment of possible DRESS in this subject who had fever, generalized eruption with biopsy findings consistent with a drug eruption, facial edema and rebound after completion of a course of systemic steroids.

Subject 111005: “Rash maculo-papular”

The subject was a 60-year-old male who was randomized to the T12/PR treatment group and received the first dose of study drugs on 12 January 2009. At screening, he was noted to have tinea corporis (on back) and a rash on the abdomen which resolved with topical hydrocortisone.

On 23 March 2009, he “had new rash symptoms” not otherwise described. He was treated with “hydrazine” with no improvement. On 25 March 2009, telaprevir was permanently discontinued due to the rash. On 26 March 2009 (73 days after the first dose of telaprevir) the rash apparently graded as mild and formally declared to be an event of special interest. The rash was described as a diffuse macular and papular rash, confluent in areas and involving the “entire body.” He had fever (unspecified) and eosinophilia of with absolute count of  $0.65 \times 10^9/L$  (reference range:  $0-0.5 \times 10^9/L$ ) and percentage of 21.3% (reference range: 0 -7%). He was treated with topical hydrocortisone and hydroxyzine and had improved by 30 March 2009. Dermatology consult, biopsy and photographs were not obtained. On 09 April 2009, the rash and fever had resolved after 14 days. He reportedly continued to experience periodic recurrence of rash, but no episodes were considered to be ESI. No action was taken with RBV or Peg-IFN-alfa-2a due to rash.

***Comment:** Concur with the DEP assessment of possible DRESS in this subject who had fever, diffuse cutaneous eruption, albeit of mild severity, and eosinophilia. However, he otherwise had no systemic signs, he was not hospitalized, and the cutaneous eruption resolved with most conservative treatment: topical hydrocortisone and hydroxyzine.*

#### **Study VX-950-TiDP24-C216:**

##### **Subject 216-0635: “Drug eruption”**

The subject was a 60 year-old female who was randomized to the T12/PR48 treatment group and received the first dose of study drugs on 19 January 2009. Her last dose of telaprevir/placebo was on 20 March 2009.

On 20 March 2009 (61 days after first dose of telaprevir/placebo), she presented with a Grade 3 rash (an ESI) leading to permanent discontinuation of telaprevir/placebo. The dose of Peg-IFN-alfa-2a had been reduced to 135 µg weekly from 5 February 2009 to 13 April 2009 and the RBV reduced to 1000 mg/day from 17 February 2009 onwards (due to anemia). The subject had been on a ciprofloxacin from 3 to 12 March 2009 for bronchitis, and on Bactrim from 14 to 20 March 2009 for lymphadenitis.

A dermatology consult was obtained. The eruption had progressed to involve her trunk and extremities (including palms and soles). She had purplish discoloration on her legs. She was febrile (100-102 °F). On 20 March 2009, rash involvement was more than 50% of BSA with no mucosal involvement. Itch persisted. The clinical differential diagnosis was drug exanthem versus vasculitis. Biopsy was done on 23 March 2009. Microscopic examination findings included, moderate perivascular and interstitial inflammation in the papillary dermis, of lymphocytes, histiocytes, neutrophils and eosinophils. No vascular mural damage or fibrin microthrombi were identified. The histological findings were considered suggestive of a hypersensitivity or urticarial-type process; a drug-induced reaction was thought possible.

At an unscheduled visit on 23 March 2009, % eosinophils and absolute eosinophil count were 11.0% and 0.59, respectively. Telaprevir/placebo was permanently discontinued due to the Grade 3 rash on 20 March 2009. No action towards the other study drugs (Peg-IFN-alfa2a/RBV). The eruption improved and was scored as Grade 1 on 11 May 2009.

**Comment:** *Concur with assessment of possible DRESS in this subject with fever, an exanthematous cutaneous eruption, biopsy suggesting possible drug reaction, and eosinophilia.*

**Subject 216-0791**

The subject was a 63-year-old male, randomized to the T12(DS)/PR48 treatment group (placebo in combination with Peg-IFN-alfa-2a and RBV for the first 4 weeks, followed by telaprevir in combination with Peg-IFN-alfa-2a and RBV in the subsequent 12 weeks, followed by Peg-IFN-alfa-2a and RBV for 32 weeks) and received the first dose of study drugs on 19 February 2009. He had the Week 4 visit on 19 March 2009 and the last intake of telaprevir/placebo on 21 May 2009.

On 21 May 2009 (92 days after the first dose of telaprevir/placebo) he presented with “pustular psoriasis,” considered an event of special interest (Grade 3 rash). It was recorded as a serious adverse event and led to permanent discontinuation of all study drugs (21 May 2009). On the same day, he experienced “strong itching and dermatitis” and presented to a dermatologist who was reported to have made a preliminary diagnosis of pustular psoriasis. He was hospitalized on [REDACTED] (b)(6) with a persistent fever of 39°C, facial edema, and “widespread” pustular psoriasis. Eosinophils were 1630/mm<sup>3</sup>. He reportedly progressively improved over the hospital course, receiving treatment with tetracosactide, cefotaxime, and ebastine. There were no reports of lesion cultures. Lymphadenopathy was present but said to have been related to his hepatitis C. He recovered from the pustular eruption (without sequelae) by [REDACTED] (b)(6) and was discharged the same day. The discharge diagnosis was “diffuse erythematous pustular skin manifestation on the face and on the trunk.” Neither photographs nor biopsy were obtained.

**Comment:** *From the available information, concur with the assessment of possible DRESS and possible AGEP in this subject with fever, facial edema, eosinophilia and apparently a widespread pustular eruption of some sort. The clinical description and course and treatment do not suggest “pustular psoriasis.” n. The consultant is unfamiliar with the use of tetracosactide in the treatment of pustular psoriasis. The description of the lymphadenopathy is rather vague.*

**Study VX06-950-107**

**Subject 2212202: DRESS**

The subject was a 57 year-old-female who received the T12/PR24 treatment regimen with the first dose of study drugs on 20 May 2008. Prior to enrollment in study 107, she participated in Study 104EU and was classified as a relapser. During participation in the control arm (Peg-IFN/RBV) of Study 104EU, she experienced a moderate cutaneous eruption, with onset after 12 weeks on therapy and duration of approximately 6 weeks. Treatment included hydrocortisone (by unspecified route), hydroxyzine and levocetirizine. She remained on study treatment (placebo, peg-interferon alfa-2a, and RBV), and the event resolved. She continued on treatment for an additional 6 months.

On 01 July 2008 (Day 42), she experienced severe pruritus on the trunk and face. The only concomitant medication at this time was escitalopram (for depression). She received

levocetirizine (01 to 07 July 2008) and desloratadine (08 to 10 July 2008) for pruritus. The subject also started oxazepam (08 to 10 July 2008) for depression.

She presented to the investigator on 11 July 2008 (Day 53) for evaluation of worsening pruritus. Physical examination revealed a “moderate cutaneous rash” on the trunk and face. She had moderate facial edema and severe cervical adenopathy on 12 July 2008 (Day 54). She remained on escitalopram. She received antihistamines for the cutaneous eruption and prednisolone (12 July to 15 July 2008) for the edema and did not improve. Study drugs were permanently discontinued on 12 July 2008 (Day 54) due to the rash, edema, and lymphadenopathy.

She was hospitalized for the serious adverse event of DRESS on [REDACTED] (b)(6). She was febrile (not otherwise specified). She had eosinophilia: 100/mm on day of admission with increase to 2400/mm<sup>3</sup> by [REDACTED] (b)(6). The skin findings progressed to a maculo-papular eruption with vesicles on the palms and “red points” on the tongue with no oral ulcerations, facial edema and vaginal and anlb “burning.”

Skin biopsy findings included “focal spongiosis...(t)he superficial dermis contained moderately inflamed infiltrates, arranged in pericapillary cuffs”. Lymphocytes were noted and “(s)light, very focal basal lymphocytic margination was found in the periphery.” The findings were concluded to be consistent with “toxicodermatitis.”

On [REDACTED] (b)(6), she had moderate arthralgia and pyrexia (maximum temperature of 39.5 °C. On [REDACTED] (b)(6), she developed lesions on the buccal mucosa and experienced dysphagia. Edema resolved by [REDACTED] (b)(6), adenopathy after [REDACTED] (b)(6) and arthralgia after [REDACTED] (b)(6). The DRESS was considered resolved on 07 Oct 2008 (Day 141).

***Comment:*** Concur with the assessment of possible DRESS in this subject with fever, an exanthematous cutaneous eruption, biopsy suggesting possible drug reaction, and eosinophilia. She also had adenopathy, but only cervical sites were specified.

**Study G060-A5 (from submitted study synopsis):**

**Subject AE-2008-004: “Drug eruption”**

The subject was a 56 year-old-female who began treatment with telaprevir, (1500 mg/day), PEG-IFN (100 mcg/week) and RBV (800 mg/day) on 17 June 2008. She was noted to have a “reddening” at injection site of peg-interferon on 14 July 2 (Day 28) with increased warmth, edema and pruritus. On 19 July 2008, the eruption appeared on the face, trunk and limbs. Blisters were noted on the left arm at injection site on 20 July 2008 (Day 34). On 22 July 2008 (Day 36), she had marked pruritus and facial edema. Her temperature was 39.1 degrees. PEG-IFN dose was not given. On 23 July 2008 (Day 23), she was examined in the Dermatology Department and also found to have erosions on the mouth/lips and target lesions on limbs and trunk with estimated BSA involvement of 50%. She was diagnosed with a severe drug eruption (SJS was considered because of the mucosal lesions). Study drugs were discontinued that day. Biopsy (24 July 2008) findings included “blistering in epidermal basal cells to dermal junction...minimal necropsy of keratinocytes...lymphocytes and histiocytes observed in the blisters, as well as...lymphocytes in the epidermal basal layer...Erythema multiforme was present. Did not contradict with Stevens-Johnson syndrome findings.” Prednisolone was begun on 25 July 2008. She progressively improved and prednisolone was progressively decreased.

The lesions were “disappearing” by 03 Sept 2008 and only resolving pigmentary changes were being described by 17 Sept 2008. Her final diagnosis was severe drug eruption.

**Comment:** *Concur with the assessment of probable SJS in this subject with fever, widespread targetoid lesions, and mucosal lesions. Agree too that the presence of facial edema in the context of the other findings makes DRESS a consideration, i.e. “possible” (favor SJS based on available information).*

**Study G060-A6 (from submitted study synopsis)**

**Subject A60603: drug-induced hypersensitivity syndrome (DIHS)**

The subject was a 60-year-old female who received the first dose of study drugs on 10 February 2009.

On 16 April 2009 (64 days after the first dose of telaprevir), the serious adverse event of drug-induced hypersensitivity syndrome (DIHS) was reported.

On 10 February 2009, the subject was said to have developed pyrexia (however, the temperature was reported as “around 37°C”) and a headache. On 16 February 2009, mild erythema was noted on her ankles and calves and right forearm (at injection site). On 24 March 2009, the erythema on the ankles had disappeared, but persisted on the right forearm.

On 31 March 2009, a dermatology consult was obtained. Treatment included clobetasol (working diagnosis not stated). On 06 April 2009, the subject’s skin signs worsened and erythema was accompanied by intense pruritus on the trunk and extremities. Her temperature ranged from 37.4°C to more than 38.0°C. By 13 April 2009 she was noted to have erythema on face and facial edema for which she received topical prednisolone. Telaprevir, Peg-IFN-alfa-2b, and RBV were discontinued 14 April 2009. On [REDACTED]<sup>(b) (6)</sup>, she was hospitalized due to DIHS. She also had oral mucosal ulcerations/erosions (timepoint is unclear). Treatment included topical corticosteroids and nutritional support. Eosinophils were 13.0% on hospital admission. Other lab values included: leukocyte count of 15.8 x 1000/μL (reference range: 3.0-7.8 x 1000/μL), creatinine level of 1.16 mg/dL (reference range: 0.40-0.90 mg/dL), gamma glutamyl transferase level of 88 IU/L (reference range: 5-32 IU/L), lactate dehydrogenase level of 417 IU/L (reference range: 119-229 IU/L), C-reactive protein level of 6.82 mg/dL (reference range: 0.01-0.43 mg/dL), and erythrocyte sedimentation rate of 93.

On [REDACTED]<sup>(b) (6)</sup>, she had a dermatology evaluation and was diagnosed with suspected DIHS. She, at an unclear timepoint, was noted to have atypical lymphocytes of 23.3%, eosinophil of 45.7%. A skin biopsy was taken and reported as being consistent with drug-induced eruption. On 23 April 2009, she was noted to have subject erythema with “a” target lesion covering more than 70% of the body surface area, Grade 3 severity, pruritus, pyrexia (38-39°C), oral erosions and ulcerations, and purpura on the lower extremities. Treatment included systemic corticosteroids. On [REDACTED]<sup>(b) (6)</sup>, lymphadenopathy was noted in the occipital, “auricular”, and inguinal regions. She had intermittent fever with maximum of 39.2°C. On [REDACTED]<sup>(b) (6)</sup>, the eruption on the subject’s face had improved and the eruption on the extremities was described as “pigmented”. On [REDACTED]<sup>(b) (6)</sup>, the subject received the last dose of prednisolone and the investigator considered that the DIHS had resolved (date of hospital discharge not found).

**Comment:** *Concur with the assessment of DRESS for this subject with fever, facial edema, lymphadenopathy at 3 sites, generalized eruption biopsy consistent with drug eruption eosinophilia, and evidence suggesting other organ involvement (kidneys, liver).*

Subject A62607: “Stevens-Johnson syndrome”

The subject was a 50-year-old female, received the first dose of study drugs on 04 March 2009. The study drug regimen at study entry was telaprevir 750 mg q8h, Peg-IFN-alfa-2b 80 µg weekly, and RBV 600 mg/day.

On 14 April 2009, a Grade 1 drug eruption with fever (38.3 C) was reported. Treatment included a topical corticosteroid. Her skin worsened on 15 April 2009. On (b) (6), she was hospitalized for the suspected serious adverse event of SJS. Physical examination revealed erythema on the trunk, extremities, and face (estimated to cover 30% BSA). She also had oral mucosal erosions, cervical and inguinal lymphadenopathy and a temperature of 38.5°C and eosinophil percentage of 22%. Treatment included intravenous and topical corticosteroids. Telaprevir, Peg-IFN-alfa-2b, and RBV dosing was discontinued the same day.

On (b) (6), skin biopsy (date done not found) findings included interface dermatitis with epidermal necrosis, “periangitis based on lymphocytes, and ‘spallation’ image of neutrophil and eosinophil infiltration in the superficial dermis.” Her skin condition progressed, and on (b) (6), she was reported to have erythema on > 50% of the body surface area. “Optical mucosal symptoms” were reported. Systemic steroids were increased. By (b) (6), erythema and symptoms were improving; itching had resolved. On (b) (6), she was discharged in improved condition. On 23 May 2009, treatment with prednisolone was discontinued. On 06 June 2009, the SJS was reported resolved.

**Comment:** *Concur with the assessment of probable SJS in this febrile subject with generalized targetoid papules, erosions of oral mucosa, conjunctival injection (with exudates), and biopsy findings interface dermatitis with epidermal necrosis. Concur with assessment of possible DRESS in this subject who also had lymphadenopathy at at least 2 sites and eosinophilia.*

DEP Conclusions

The following are among the reported DEP conclusions of the primary rash data (study 108):

- Primarily a pruritic, eczematous rash ± a maculopapular component with onset anytime during dosing with telaprevir.
- 66% were assessed by investigators as Grade 3, but the severe eruptions would not be considered SCAR
- Per DEP-assessable cases, 98% involved ≤ 30% BSA
- Investigators assessed % BSA involvement higher than did the DEP
- Eruption fully resolves after discontinuation of telaprevir, but require supportive treatment and may take weeks
- No fatal outcomes; no toxic epidermal necrolysis; no erythema multiforme

Histopathology of primary data:

- Histopathologic features: spongiosis (94%); lymphocytic perivascular infiltration (81%); consistent with eczematous process

- Predominant feature was dermal spongiosis
- Includes epidermal changes, e.g. spongiosis
- Vasculitis was not suggested in any of the biopsies

SCAR and/or important dermatological conditions:

- No cases were suggestive of vasculitis or other important dermatologic conditions.
- Cases suggestive of urticaria were very infrequent; none appeared to be life-threatening type I hypersensitivity reactions and/or anaphylactic reactions.

There was a high incidence of rash of all severities in telaprevir-based regimens.

The rash occurs at a higher incidence and is more severe relative to the rash seen with the Peg-IFN/RBV regimen.

Except for the greater severity and extent of BSA involvement, the telaprevir rash appears to be “virtually indistinguishable” clinically from Peg-IFN/RBV regimen rash (based on photograph and literature review). The histopathology is also similar (“consistent”).

### **Consultant Summary and Discussion**

In the Skin and subcutaneous tissue disorders SOC, nearly 80% of subjects in the telaprevir groups and 58% in the Pbo/PR48 group reported an adverse event. “Pruritus” was the most commonly reported adverse event in all treatment groups, but was reported at higher incidences in T/PR groups compared to the Pbo/PR48 group (42-46% compared to 28%, respectively). “Rash” was the second most commonly-reported adverse event, occurring in approximately a third of subjects in T/PR groups compared to 17% in the Pbo/PR48 group. Several other cutaneous adverse events were reported as “rash” with some descriptor (e.g. “rash pruritic”). “Rash” is a vague term and permits little more than a conclusion of a cutaneous eruption of some sort. The addition of a descriptor does little to increase the clinical interpretability of the term. However, the numbers of serious adverse events and the numbers of discontinuations for “rash”-type events relative to the overall numbers of these events reported suggest that most of these events may have been of a relatively benign sort. Additionally, most events in the rash special search category were of mild severity. Further, those analyses permit a conclusion that most events graded as severe events were not considered to be serious adverse events.

The data suggest that most adverse events would be captured in the first four weeks of treatment, and this is well within the time frame for most drug eruptions,<sup>1,4,5,11,12</sup> and pruritus may be a prominent feature of drug eruptions.<sup>11,13</sup> When adverse events are considered by time period, most adverse events that were reported in the Skin and subcutaneous tissue disorders SOC were reported in the interval from Baseline through Week 4, suggesting that adverse events in this SOC may generally be likely to present in the first month of therapy. However, during the interval of Week 4 to Week 8, approximately one third of subjects reported adverse events in this SOC who continued treatment (and the same holds for the interval from Week 8 to Week 12).

Seven subjects in T/PR treatment groups experienced serious adverse events in the Skin and Subcutaneous Tissue Disorders SOC during the Telaprevir/Placebo treatment period. The categories of events were “rash,” “eczema” and “pruritus”. No subjects in the Pbo/PR48 group

experienced a serious cutaneous adverse event. “Rash” was the only serious cutaneous adverse event reported in more than one subject. All subjects who experienced serious cutaneous adverse events recovered.

The percentages of subjects discontinuing from T/PR groups in the Skin and Subcutaneous Tissue Disorders SOC was approximately 6% compared to approximately 1% in the Pbo/PR48 group. Similar to the pattern seen with serious cutaneous adverse events, the most common event leading to discontinuation of telaprevir was “rash,” and the second most common event was “pruritus.” Given that SCAR may begin as morbilliform eruptions<sup>12,14</sup>, it is possible that some among those who discontinued telaprevir because of a “rash” type event may have been in the earliest stage of a SCAR in evolution.

Generally, incidences for events were similar between the T8 and T12 groups, suggesting that the safety of the additional four weeks of telaprevir provided in the 12-week course compared favorably with the safety of the 8-week treatment course.

The special analyses (SSC, ESI) revealed no new pattern to events. Most ESI in telaprevir-treated subjects were reported as Grade 3 (severe) events (31 of 51; 61%), and this may be reflective of the definition of ESI for which one defining criterion was a Grade 3 rash. In telaprevir-treated subjects, 12 % of ESI (6 of 51) were reported as serious adverse events.

The incidence of cutaneous adverse events in the Peg-IFN/RBV group in the telaprevir trials is higher than the incidence reported for Peg-IFN/RBV in their respective labels (cross-study comparisons notwithstanding). It is possible that incidences of cutaneous adverse events in all treatment groups in the telaprevir development program reflect the applicant’s deliberate efforts and specific procedures for capturing such events, enhancing detection.

The occurrence of cutaneous adverse events in the Peg-IFN/RBV group is consistent with what is known about these therapies. Peg-IFN as monotherapy is associated with adverse reactions similar to those reported in the telaprevir-treated subjects (see Peg-IFN package insert). RBV with Peg-IFN (i.e., Peg-IFN/RBV; RBV should not be administered as monotherapy) is associated with adverse reactions similar to those reported in the telaprevir-treated subjects (see ribavirin and Peg-IFN package inserts), and that RBV may have an independent contributory effect to the occurrence of these events is suggested by the higher incidences of all of these events (“except “Sweating increased”) in combination treatment compared to the incidences reported with Peg-IFN monotherapy. It is possible that a similar phenomenon is manifesting with the addition of telaprevir to the Peg-IFN/RBV combination regimen, i.e. the addition of the new therapy increases events of this sort further still: cutaneous adverse events with triple therapy (Telaprevir/Peg-IFN/RBV) > dual therapy (Peg-IFN/RBV) > monotherapy (Peg-IFN).

The following pertain to the potentially life-threatening events of severe cutaneous adverse reactions (SCAR) in the context of the three products:

- Peg-IFN label (label approved 02/23/2011): Stevens-Johnson syndrome (SJS) is listed in Warnings and Precautions; “serious skin reactions” reported in Postmarketing Experience
- Ribavirin label (reflecting study of Peg-Ifn/RBV; label approved: 12/21/2010): SJS is listed in Warnings and Precautions; SJS and TEN reported in Postmarketing Experience
- Telaprevir development program (i.e. *in the clinical trials database*): 11 suspected Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), 3 suspected SJS

In the Peg-INF label, the Warnings and Precautions section (where SJS is described) cross-references the Adverse Reactions section, and the only suggested reference to a SCAR (e.g. SJS)

in the latter section is in the Postmarketing Experience section where “serious skin reactions” are said to have been identified post-approval. In the RBV label, the Warnings and Precautions section (5.4 where SJS is described) specifically cross-references the Postmarketing Experience section of the Adverse Reactions section, where SJS and TEN are reported as having been identified post-approval.

The detection of suspected SCAR events (11 DRESS and 3 SJS) in the clinical trials with telaprevir may be noteworthy, given that SCAR are generally considered to be rare<sup>14</sup> and sample sizes of clinical trials intended to support marketing approval are generally not powered to detect rare events.<sup>15,16,17</sup> However, we acknowledge that the majority of the SCAR events in the telaprevir program (particularly as relates to DRESS) were suspected on case review by expert dermatologists and not by investigators. Therefore, it is possible that reports of SCAR with Peg-IFN ± RBV may have been under reported in the development programs (as it appears would have been the case in the telaprevir program were it not for the Dermatology Expert Panel review) and may be under reported in the marketplace.

The cutaneous adverse event data support a telaprevir effect.

#### Dermatology Expert Panel

The primary charge of the DEP was to characterize ESI from Study 108, with a particular focus on events that might represent SCAR.

Most ESI (95%) had an eczematous *component* (emphasis added). However, it is not clear to the consultant that that necessarily translates to “typically...eczematous rash,” the description proposed in the draft package insert (Section 6.2). Per the DEP review, 60% of subjects had at least 2 assessable morphological components to their rashes (47% of whom had 3 components assessable). The consultant also agrees that an eczematous reaction pattern was a common feature and that some eruptions had mixed morphologies. In Study 108, 2% of telaprevir-treated subjects were reported as “eczema” (compared to 33% reported as “rash”; Table 14.3.1.2c). This may suggest that either the cutaneous eruptions were not “typically...eczematous”, or that “eczema” was under reported (if present or recognized), perhaps raising a question of the meaningfulness of “eczematous” to likely prescribers of telaprevir. We do not believe that the cutaneous eruption(s) has been sufficiently characterized to have clinicians limit their focus and concern to “severe rash,” described as “primarily eczematous, pruritic and involves more than 50% body surface area.”

Of the biopsies reviewed, 94% showed some degree of spongiosis, which would correlate with a clinical presentation of an eruption with an eczematous component. In the consultant’s opinion, absent the spongiosis, several of the histological patterns (2 through 5) could be consistent with drug eruption, the histology of which can be non-specific, requiring clinical-pathological correlation.<sup>9</sup> However, spongiosis would not be a typical feature of the morbilliform eruption, the most common presentation of a drug eruption.<sup>9</sup>

Investigators estimated the extent of BSA to be greater than did the DEP. Thus, it is possible that some ESI categorized by investigators as Grade 3 (severe) may have been of lesser severity, if investigators overestimated the extent of BSA involvement to be > 50% and graded the event based solely on this criterion as was permitted by the protocol. Thus, it is not clear that inclusion of a % BSA involvement would necessarily be useful to prescribers.

A possible limitation of the DEP review is that it may have been biased towards characterizing only the more severe events (reflective of the definition of ESI which constituted

the primary database). One might argue that it is the more severe eruptions that should be characterized as completely as possible, since it is those events with which morbidity and mortality may be most closely correlated. However, the extent to which the conclusions about the eruptions from the DEP review might apply to the broader population of telaprevir-treated subjects who experience cutaneous eruptions is unclear. For example, from the primary database (study 108), the DEP reviewed photographs of 45 subjects with ESI who received treatment with telaprevir, 32 of whom (71%) had reactions of Grade 3 severity. The DEP and affiliated dermatopathologist reviewed biopsies from 36 subjects with ESI who received treatment with telaprevir, 29 of whom (81%) had reactions of Grade 3 severity. The DEP reviewed no photographs or histopathology of Grade 1 (mild) rashes (from study 108), and 285 of 398 rashes (in the telaprevir group) in the Special Search Category were Grade 1 (72%). From the limited data regarding Grade 1 rashes in the supportive studies (i.e. non-108 studies), an eczematous component was also common; no biopsies were reviewed of Grade 1 rashes.

Investigators reported 6 cases as SCAR (3 as SJS and 3 as DRESS), and the DEP concurred with the assessment of SCAR in 4 of these cases. For the remaining 2 cases (1 DRESS, 1 SJS), the DEP did not suspect any SCAR event. Thus, when investigators suspected SCAR, the DEP concordance with those assessments was 67%.

The DEP assessed 13 subjects as having experienced 15 suspected SCAR (11 DRESS, 3 SJS and 1 AGEP). Of the 13 subjects, investigators suspected SCAR in 4 (31%). Thus, when the DEP suspected SCAR, investigators did not suspect the same in 69% of these subjects. The discordance by diagnosis was:

- Investigators did not suspect DRESS in 9 of the 11 cases (82%).
- Investigators did not suspect SJS in 1 of the 3 cases (3%).
- Investigator did not suspect the 1 case of AGEP (nor did the consulting dermatologist apparently).

Of the 9 subjects for whom DRESS was not suspected, 3 (33%) were also not reported as serious adverse events. One of the 3 had no systemic symptoms (nor was he hospitalized) making this presentation unusual (perhaps distinctly so). He was, however, assessed by the consulting dermatologist as having “an atypical DRESS syndrome” and biopsy was “compatible with DRESS.” The clinical diagnosis was based on the presence of other “classic” signs, including a cutaneous eruption, eosinophilia, and facial edema. All other subjects suspected by the DEP as having DRESS presented with findings which might have brought the diagnosis into consideration, assuming some familiarity with the diagnosis and how it may present. Among the subjects’ presenting signs was some combination of the following (not intended as an exhaustive list): generalized eruption, facial edema, fever, eosinophilia, lymphadenopathy. This is somewhat concerning because of the life-threatening nature of DRESS and the importance of early intervention. However, it was reassuring that although the diagnosis of DRESS was not suspected, most investigators appeared to perceive a significant problem (reported as serious adverse event) and proper care was administered.

Some suggest challenges to the diagnosis of DRESS are posed by both the absence of universal diagnostic criteria and the lack of a broad awareness of DRESS among practitioners outside of the dermatology community, a so-called “practice gap.”<sup>18</sup>

### Severe Cutaneous Adverse Reactions (SCAR) with Emphasis on Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Severe Cutaneous Adverse Reactions (SCAR) have been described as having the common characteristics of being:<sup>14</sup>

- severe, usually resulting in hospitalization and usually associated with significant morbidity and mortality
- idiosyncratic reactions that are probably immune mediated
- most often drug-induced.

In the context of a suspected adverse drug reaction, signs which should heighten the clinician's suspicion of a possible SCAR include "urticaria, blisters, mucosal involvement, facial edema, ulcers, purpura, fever or lymphadenopathy."<sup>14</sup> Immediate withdrawal of the suspected drug and urgent dermatology consultation should be considered for an individual who presents with any combination of these signs if an adverse drug reaction is under consideration.

The following serious cutaneous eruptions are among those generally considered to be SCAR:<sup>7</sup>

- Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Acute Generalized Exanthematous Pustulosis (AGEP)

"DRESS" was proposed as the acronym for a syndrome presenting with a certain constellation of clinical findings, i.e. Drug *Rash* with Eosinophilia and Systemic Symptoms (emphasis added) in an article published in 1996 and co-authored by one of the members of the DEP. (b) (4).<sup>19</sup> While the skin is usually involved, the extent of involvement may vary, and the "R" is therefore taken by some to represent "reaction" rather than "rash."<sup>20</sup> Similarly, eosinophils are not always present, some therefore employ the moniker Drug-Induced Hypersensitivity Syndrome (DIHS) for this entity.<sup>21</sup>

The onset of the syndrome is generally described as being within the first 2 to 6 weeks of onset of treatment with the offending agent (i.e., later than the typical drug eruption), with fever and skin eruption often as the presenting signs.<sup>7,14,19,20,21</sup> The skin usually presents a morbilliform eruption/maculopapular eruption<sup>14,19,20</sup> (may also be the initial presentation of other life-threatening SCAR such as SJS/TEN<sup>12,14</sup>). Additional clinical features may include lymphadenopathy, facial edema (which may represent an important diagnostic clue), hepatitis and/or indications of other visceral involvement.<sup>7,14,19,20</sup> In addition to eosinophilia, hematologic abnormalities may include atypical lymphocytes.<sup>7,19,20</sup> Histopathological findings may include a dense diffuse or superficial lymphocytic infiltrate<sup>19</sup>, although the histopathology has not been fully characterized.<sup>7</sup> While other viscera may be affected (e.g. lungs, kidneys, heart)<sup>20,21,22</sup>, the liver is said to be most commonly involved, and it is the hepatitis that may be most concerning, as it may, in the most severe cases, eventuate in hepatic failure, which has been reported as the principle cause of death.<sup>19,20,21</sup> The mortality rate is said to be approximately 10%.<sup>7,19,20</sup> The hepatitis, however, is reported by some as typically manifesting as an isolated elevation of transaminases.<sup>19</sup>

While the above clinical features (or some combination thereof) are frequently reported as describing DRESS, there is no consensus on the diagnostic criteria or severity scoring for this

syndrome.<sup>18,19,22,23</sup> It is thought to perhaps represent a disease spectrum.<sup>20,22</sup> Estimates are of occurrence in approximately 1 in 10,000 drug exposures.<sup>7</sup>

The pathogenesis is not fully understood.<sup>24,25</sup> However, accumulation of drug metabolites from alterations in metabolism of those metabolites possibly resulting in aberrations in T-cell function may play some pathogenic role.<sup>22,25</sup> Aromatic anticonvulsants (e.g. phenytoin, phenobarbital, carbanazepine) have been reported as being most-commonly causative<sup>21,25</sup>, but many other drugs have been implicated, including sulfonamides<sup>23,25</sup>, allopurinol<sup>23,25</sup> and antiretrovirals (e.g. abacavir).<sup>20,25</sup> Reactivation of the human herpesvirus 6 may play some pathogenic role<sup>7,20</sup>, and viral reactivation may contribute to the long latency and the prolonged clinical course.<sup>7</sup>

Withdrawal of the offending agent is the first step in management.<sup>12,14,23,26,27</sup> Systemic corticosteroids may effectively treat this syndrome,<sup>14,19,22</sup> but outcomes may vary.<sup>20</sup> Recovery after discontinuation of the offending agent is typical, but may take weeks.<sup>14,19</sup> Relapses may occur during steroid taper.<sup>14</sup>

**Conclusions/Recommendations:** The applicant appears to have made a conscientious effort to characterize the more severe cutaneous adverse events observed in the development program for telaprevir. Their efforts included:

- Modifying the protocol to refine criteria for assessment of cutaneous adverse events (severity grading)
- Establishing criteria for discontinuation of telaprevir
- Modifying the protocol to specify categorization of certain cutaneous adverse events as events of special interest (ESI)
- Creating special search categories for analyses of cutaneous adverse events
- Convening a panel of expert dermatologists and a dermatopathologist to characterize the ESI and identify potential Severe Cutaneous Adverse Reactions (SCAR)

The observation of suspected SCAR [11 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and 3 Stevens-Johnson syndrome (SJS)] in the clinical trials with telaprevir may be significant, given that SCAR are generally considered to be rare,<sup>7,14</sup> and the sample sizes of clinical trials intended to support marketing approval are generally not powered to detect rare events.<sup>15,16,17</sup> SCAR have been estimated to occur in 1 of every 1000 hospitalized patients.<sup>14</sup> Documentation of even a few cases in association with a particular product may have regulatory implications<sup>14</sup> (e.g. labeling, REMS).

(b) (4) (two of the three voting members of the Dermatology Expert Panel) stated that:

“Because of the low frequency of such severe reactions (usually less than 1 reaction per 5000 exposed patients), they are unlikely to be detected in premarketing clinical trials.”<sup>14</sup>

Additionally, the DEP stated that the likelihood of SCAR may have been underestimated in a case with incomplete information.

We recommend that the review division consider encouraging the applicant to continue their investigatory efforts to characterize the cutaneous eruptions associated with their product post-

marketing. We recommend that the investigations include efforts to establish etiology and to identify risk factors, including for SCAR.

We concur with the applicant's proposal for a REMS consisting of a Medication Guide and a communication plan. However, given the number of suspected SCAR in the development program, the discordance between the DEP observation of these events and the investigators, and that the DEP could have underestimated the likelihood of SCAR in some cases, we recommend that the communication plan be enhanced to include a specific discussion of SCAR, particularly DRESS, to increase clinicians awareness of this potentially life-threatening category of events. It is our opinion that the proposed general discussion of "severe rashes" is inadequate in this regard. The discussion does not convey that SCAR were observed in the clinical trials nor does it address the possible risk of SCAR and attendant risk of morbidity and mortality. Given the observations in the clinical trials database, we believe it important that clinicians become familiar with SCAR and recommend use of the acronyms: "SCAR" has specific implications pertaining to morbidity and mortality that may not attach to the simple descriptor "severe." For example, an allergic contact dermatitis to poison ivy (rhus dermatitis) may be "severe," but would not be a "SCAR."

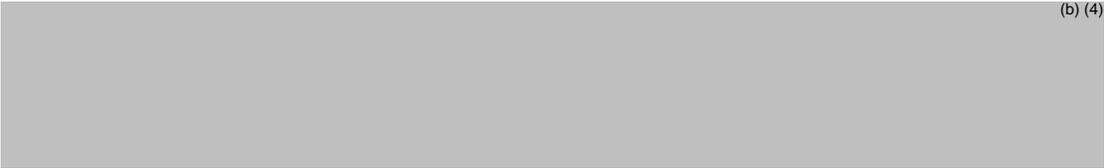
In light of the background rate of cutaneous adverse events with telaprevir and that SCAR may initially present as benign-appearing morbilliform eruptions, we believe it important that clinicians (and patients) have a heightened awareness of the potential for SCAR. A high index of suspicion may be required for DRESS in particular because of its long latency<sup>21</sup> and absence of pathognomonic features.<sup>20,23</sup> Early recognition may allow for what is probably the most critical first step: prompt withdrawal of the offending agent (with appropriate medical and supportive care as indicated).<sup>12,14,23,26,27</sup> A heightened awareness may also allow for early dermatology consultation<sup>23</sup> (for which we believe there should be a low threshold).

1

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/s/  
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BRENDA CARR  
04/01/2011

JILL A LINDSTROM  
04/05/2011

SUSAN J WALKER  
04/06/2011

## CDER/DRUP Consultation Response (Tracking No. 226)

<b>Division Consult #</b>	226
<b>To</b>	Sherly Abraham, RPh Office of Antimicrobial Products Division of Antiviral Products
<b>From</b>	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
<b>Names of drug products</b>	Boceprevir (IND 69027; NDA 202-258) Telaprevir (IND 71832; NDA 201-917)
<b>Class of drugs</b>	Protease inhibitors
<b>Sponsors</b>	Merck (previously Schering-Plough) for Boceprevir Vertex for Telaprevir
<b>Re:</b>	Drug interactions with Oral Contraceptives
<b>Date of consult request</b>	February 7, 2011
<b>Desired completion date</b>	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<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> 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<sub>0-24hr</sub> remains unchanged for DRSP administered under fed or fasting conditions, it decreases 20% for ethinyl estradiol under fed conditions. C<sub>max</sub> 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/  
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GERALD D WILLETT  
03/31/2011

LISA M SOULE  
03/31/2011

SCOTT E MONROE  
03/31/2011

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

<b>NDA</b>	201917
<b>Generic Name</b>	Telaprevir (TVR) or VX-950
<b>Sponsor</b>	Vertex Pharmaceuticals
<b>Indication</b>	In combination with peginterferon alfa and ribavirin, for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease, including cirrhosis, who are treatment naïve or who have been previously treated, including prior null responders, partial responders, and relapsers
<b>Dosage Form</b>	Tablets
<b>Drug Class</b>	Protease inhibitor
<b>Therapeutic Dosing Regimen</b>	750 mg q8h
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Not established
<b>Submission Number and Date</b>	SDN 007 23 Nov 2010
<b>Review Division</b>	DAVP / HFD 530

**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

No significant QTc prolongation effect of telaprevir (750 mg and 1875 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between telaprevir (750 mg and 1875 mg) and placebo were 7.0 ms and 9.9 ms in QTcF. In addition, no significant concentration-QT relationship (P = 0.35) was established from the study. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

A double-blind, double-dummy, randomized, placebo and active controlled, 4 period crossover trial, 44 healthy subjects received telaprevir 750 mg, telaprevir 1875 mg, placebo, and a single oral dose of moxifloxacin 400 mg. 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 Telaprevir (750 mg and 1875 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Telaprevir 750 mg	3	4.2	(1.3, 7.0)
Telaprevir 1875 mg	3	7.0	(4.2, 9.9)
Moxifloxacin 400 mg*	4	9.4	(6.7, 12.1)

\* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 3 time points is 5.9 ms.

The suprathreshold dose (1875 mg q8h, i.e., 2.5 times the therapeutic dose, 750 mg q8h) is the maximum dose which has been tested in the entire clinical development. This suprathreshold dose showed 40% increases in  $C_{\text{max}}$  and  $\text{AUC}_{(0,8\text{h})}$  values compared with 750 mg drug. Telaprevir must be administered with both peginterferon alfa and ribavirin in clinical situation. Telaprevir exposure is approximately 40% higher in  $C_{\text{max}_{\text{ss}}}$  and  $\text{AUC}_{(0,8\text{h})}$  in the presence of Peg-IFN coadministration. Therefore, the studied suprathreshold dose provided the comparable exposures in the current clinical situation.

In principle, the worst-case scenario for telaprevir exposure would be a subject with severe renal impairment (10% increase in  $C_{\text{max}}$  and 21% increase in AUC) who takes telaprevir (in combination with Peg-IFN and ribavirin) with a high-fat meal. The test plasma concentration in the current TQT study might be insufficient to cover the worst case scenario at steady state expected due to severe renal impairment. However, telaprevir should not be administered to patients with creatinine clearance <50 mL/min based on current ribavirin's label. Therefore, the expected worst case scenario will be unlikely. Moreover, the exposure-response analysis did not detect a significant and positive relationship, which provides additional assurance QT effect will be unlikely even under the high exposure scenario.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- There appear to be no clinically relevant effects on the PR and QRS intervals in this study. While there appears to be trend for mean increase of PR interval with both doses of telaprevir (maximum upper bound-7 ms) between hour 3 and 6, on review of the categorical data (absolute values over 200 ms), the majority of subjects on telaprevir had an elevated PR interval at baseline. Only one subject had a change from baseline that was around 24% at an isolated time point (213 ms at hour 3).

## **2 PROPOSED LABEL**

### **2.1 THE SPONSOR PROPOSED LABEL**

*The sponsor has the following labeling language. We consider that section 5.6 is not needed. In addition, we provide alternative language for Section 12.2 (Please see 2.2).*

(b) (4)



## 2.2 QT-IRT RECOMMENDED LABEL

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

The effect of telaprevir 750 and 1875 mg on QTc interval was evaluated in a double-blind, double-dummy, randomized, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT study in 44 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 Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 1875 mg is adequate to represent the high exposure clinical scenario.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Telaprevir is an inhibitor of the HCV NS3•4A protease under clinical development by Vertex Pharmaceuticals for the treatment of genotype 1 chronic hepatitis C (CHC) infection in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have previously been treated with interferon alpha (pegylated or non-pegylated) alone or in combination with RBV, including prior relapsers, partial responders, and null responders.

In a previous TQT study (VX06-950-008) conducted under IND 71832 (see IRT review dated May 6, 2008). The effects of VX-950 1250 mg plus a single dose of ketoconazole 400 mg was used to evaluate supra-therapeutic exposures. The QT-IRT concluded that while results were below the threshold of regulatory concern, the maximum exposures achieved in this study may not be sufficient to cover increases in plasma concentration expected due to moderate or severe hepatic impairment and known drug-drug interactions, such as: 1.) maximum enzyme inhibition following multiple dose of ketoconazole in combination with VX-950, and 2.) 2.2- fold increase in maximum exposure following co-administration of ritonavir. Hence we recommended additional ECG monitoring in clinical studies enrolling patients with hepatic impairment or on concomitant potent CYP3A4 inhibitors. The sponsor has now conducted another TQT study evaluating a supra-therapeutic dose of 1875 mg.

### 3.2 MARKET APPROVAL STATUS

Telaprevir is not approved for marketing in any country.

### 3.3 PRECLINICAL INFORMATION

#### Source-Pharmacology Tabulated Summary (eCTD 2.6.3)

Organ Systems Evaluated	GLP	Species / Strain	Method of Administration	Dose <sup>a</sup> (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number	Location in CTD
Cardiovascular (hERG channel)	No	Cloned hERG channels in HEK293 cells	In vitro	0.1, 0.3, 1, 3, 10, 100 µM	5 to 7 cells at 0.1 Hz; 6 cells at 3 Hz	0.1 Hz: Concentration-dependent inhibition of hERG current: 3.7%, 7.7%, 13.6%*, 17.1%*, 23.7%, 43.9%* at 0.1, 0.3, 1, 3, 10, 100 µM IC <sub>50</sub> > 100 µM 3 Hz: Minimal rate-dependent block of hERG current at 1 µM	VERT-01/01	4.2.1.3
Cardiovascular (hERG channel)	Yes	Cloned hERG channels in HEK293 cells	In vitro	3, 10, 30, and 100 µM	≥ 3 cells	Concentration-dependent inhibition of hERG current: 13.8%, 21.3%, 36.8%, and 49.0% at 3, 10, 30 and 100 µM, respectively. IC <sub>25</sub> = 12.24 µM; IC <sub>50</sub> estimated at 100.6 µM	VRT-108720-TX-006	4.2.1.3
Cardiovascular (Purkinje fiber)	Yes	Purkinje fibers from Beagle Dog	In vitro	1, 10, and 100 µM	4 fibers	No statistically significant effects on cardiac action potentials (APD <sub>90</sub> , APD <sub>60</sub> , RMP, APA, and Vmax)	VRT-108720-TX-005	4.2.1.3

<sup>a</sup> - Single dose unless specified otherwise.

\* Indicates value was significantly different from control.

Cardiovascular (telemetry)	Yes	Dog / Beagle	Oral	25, 75, and 250	4M (Latin square)	≤ 250: No effect on cardiovascular (blood pressure or heart rate) or ECG (RR, PR, QRS, QT, QTc, or RA) parameters for up to 22 h post-dose	VRT-108720-TX-007	4.2.1.3
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### 3.4 PREVIOUS CLINICAL EXPERIENCE

#### Source: Summary of Clinical Safety-eCTD 2.7.4

In the pooled placebo-controlled Phase 2-3 studies, 2012 subjects received at least one dose of telaprevir, including:

- 1346 subjects who received a regimen of 750 mg telaprevir q8h for 12 weeks in combination with Peg-IFN and RBV (T12/PR group) and
- 1823 subjects who received a regimen of telaprevir for 8, 12, or 24 weeks in combination with Peg-IFN and RBV (Any T/PR group).

Placebo in combination with Peg-IFN and RBV was received by 764 subjects (pooled control group, Pbo/PR group).

In addition, the Phase 2-3 placebo-controlled pooling also contains data from 364 subjects who received at least one dose of telaprevir in a regimen of 750 mg telaprevir

q8h for 8 weeks in combination with Peg-IFN and RBV (T8/PR group) and 189 subjects in a regimen of telaprevir in combination with Peg-IFN, without RBV (Any T/P group).

In the pooled placebo-controlled Phase 2-3 studies, 5 of the 2012 subjects in the telaprevir groups and 4 of the 764 subjects in the placebo group died. Of these 9 deaths, none occurred during treatment with telaprevir/placebo. The sponsor reports no deaths within 30 days after last intake of telaprevir.

A special search category (SSC) was developed by the sponsor with the intention of comprehensively identifying any events that could signal a potential proarrhythmic effect of telaprevir. The incidence of potential proarrhythmic effect SSC events was 1.3% in the T12/PR group and 0.8% in the Pbo/PR group. The sponsor reports that syncope was the most frequently observed event within this SSC but an association with arrhythmia was not documented. No ECG abnormalities were reported for any of the subjects experiencing syncope, with the exception of one subject (CRF ID C216-0191) who had QTcF interval between 450 and 480 ms at baseline, Day 1 5h post-dose, and Week 12 (461, 452, and 461 ms, respectively) and syncope on Day 9.

**Table 41: Placebo-Controlled Phase 2-3 Studies: Incidence of Potential Proarrhythmic Effect SSC Events by Preferred Term - Telaprevir/Placebo Treatment Phase**

SSC Preferred Term, n (%)	T12/PR (750 mg q8h) N = 1346	Any T/PR N = 1823	Pbo/PR N = 764
Any potential proarrhythmic effect SSC	17 (1.3)	20 (1.1)	6 (0.8)
Syncope	17 (1.3)	20 (1.1)	3 (0.4)
Loss of consciousness	1 (<0.1)	1 (<0.1)	1 (0.1)
Convulsion	0	0	2 (0.3)
Epilepsy	0	0	1 (0.1)

N: number of subjects with data, n: number of subjects with observation  
Source: [Module 5.3.5.3/VX-950-SCS/Display ADD.B7](#)

In the Phase 2 and Phase 3 studies, a subset of studies collected ECG data both at baseline and at an on-treatment time point (Studies 104, C208, C209, C210, and C216). In these studies, the treatments administered, the population studied, and the timing of ECG collection were different. Three (0.4%) subjects in the T12/PR group of the pooled placebo-controlled Studies 104 and C216, compared to none of the subjects in the Pbo/PR group, had a treatment-emergent QTcF interval >500 ms (see table below). One subject had not yet started telaprevir and was receiving Peg-IFN/RBV only when the QTcF interval >500 ms was observed. None of these 3 subjects experienced ECG-related AEs. Increases in QTcF relative to baseline >60 ms were observed in 3.0% of the subjects in the T12/PR group and in 2.9% of the subjects in the Pbo/PR group. Most of these increases in QTcF >60 ms did not result in prolonged QTcF values (>480 ms).

**Table 42: Treatment-Emergent Abnormalities in Heart Rate and QTc (Worst Abnormality) in the Pooled Studies 104 and C216 - Telaprevir/Placebo Treatment Phase**

ECG parameters, n (%)	T12/PR (750 mg q8h) N = 705	Pbo/PR N = 207
Heart rate (bpm), N	696	207
Abnormally low	9 (1.3)	4 (1.9)
Abnormally high	1 (0.1)	0
QTc (Bazett, ms), N	696	207
]450 ms, 480 ms]	54 (7.8)	25 (12.1)
]480 ms, 500 ms]	5 (0.7)	1 (0.5)
More than 500 ms	14 (2.0)	1 (0.5)
QTc (Fridericia, ms), N	696	207
]450 ms, 480 ms]	20 (2.9)	5 (2.4)
]480 ms, 500 ms]	4 (0.6)	1 (0.5)
More than 500 ms	3 (0.4)	0
QTc (Bazett, ms), N	695	206
Increase by 30-60 ms	148 (21.3)	35 (17.0)
Increase by >60 ms	40 (5.8)	7 (3.4)
QTc (Fridericia, ms), N	695	206
Increase by 30-60 ms	75 (10.8)	14 (6.8)
Increase by >60 ms	21 (3.0)	6 (2.9)

N: number of subjects with data; n: number of subjects with the abnormality

Source: [Module 5.3.5.3/VX-950-SCS/Display SAF.B196](#) and [Display SAF.B198](#)

The sponsor reports that in subjects in the uncontrolled study C208 had treatment-emergent QTcF interval >500 ms, 1 subject had QTcF interval between 480 and 500 ms, and 3 subjects had increases in QTcF relative to baseline >60 ms during the telaprevir treatment phase.

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of telaprevir's clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT have reviewed the study report for VX06-950-08 previously and recommended additional ECG monitoring in clinical studies enrolling patients with hepatic impairment or on concomitant potent CYP3A4 inhibitors. Currently, the sponsor submitted the study report for VX-950-TIDP24-C136, including electronic datasets and waveforms to the ECG warehouse.

### 4.2 TQT STUDY

#### 4.2.1 Title

A double-blind, double-dummy, randomized, placebo- and active-controlled, 4 period crossover trial to evaluate the effect of telaprevir (TVR) on the QT/QTc interval in healthy subjects

#### 4.2.2 Protocol Number

VX-950-TiDP24-C136-CTP

### 4.2.3 Study Dates

Start: 15-Sep-2009 / End: 19-Jan-2010

### 4.2.4 Objectives

#### Primary:

“The primary objective was to evaluate the effect of administration of telaprevir 750 mg q8h and 1875 mg q8h, both at steady-state, versus placebo on the QT and QTc interval in healthy subjects.”

#### Secondary:

“The secondary objectives of the study were:

- To evaluate study sensitivity (i.e., to evaluate the effect of a positive control, a single 400-mg dose of moxifloxacin, on the QT/QTc interval in healthy subjects);
- To evaluate the effect of 2 different regimens of telaprevir on non-QT interval electrocardiogram (ECG) parameters (RR interval, heart rate [HR], PR interval, and QRS interval) in healthy subjects;
- To evaluate the pharmacokinetics of 2 dose regimens of telaprevir, 750 mg q8h and 1875 mg q8h, at steady-state in healthy subjects;
- To explore the concentration-effect relationship for QT/QTc for telaprevir in healthy subjects;
- To evaluate the short-term safety and tolerability of 2 dose regimens of telaprevir, 750 mg q8h and 1875 mg q8h, in healthy subjects. ”

### 4.2.5 Study Description

#### 4.2.5.1 Design

This was a Phase I, double-blind, double-dummy, randomized, placebo- and active-controlled, 4-period crossover study. There was a washout period of 8 days between subsequent sessions. The study population consisted of 44 healthy subjects (20 females and 24 males).

#### 4.2.5.2 Controls

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

#### 4.2.5.3 Blinding

All treatment arms including moxifloxacin were administered blinded using a double dummy approach.

### 4.2.6 Treatment Regimen

#### 4.2.6.1 Treatment Arms

44 healthy subjects (20 females and 24 males) were received the following treatment in 4 sessions in a random order (Table 2). In each treatment session, the subjects were admitted to the testing facility in the evening of Day -2 and stayed in the unit until the

morning of Day 6 after the assessments of that day. There was a washout period of 8 days between subsequent sessions.

**Table 2: Dosing Schedule**

	Treatment A	Treatment B	Treatment C	Treatment D
telaprevir, 375 mg tablet (F004)	Days 1-4: 2 tablets q8h; Day 5: 2 tablets in the morning	Days 1-4: 5 tablets q8h; Day 5: 5 tablets in the morning	-	-
telaprevir, placebo tablet (F003)	Days 1-4: 3 tablets q8h; Day 5: 3 tablets in the morning	-	Days 1-4: 5 tablets q8h; Day 5: 5 tablets in the morning	Days 1-4: 5 tablets q8h; Day 5: 5 tablets in the morning
moxifloxacin, 400 mg over-encapsulated film-coated tablet (8000-G001)	-	-	Day 5: 1 capsule in the morning	-
moxifloxacin, placebo capsule (F301)	Day 5: 1 capsule in the morning	Day 5: 1 capsule in the morning	-	Day 5: 1 capsule in the morning

(Source: Sponsor's Study Report, Table 1. on Page 42)

*Reviewer's Comment: The mean elimination half-life after single-dose oral administration of 750 mg telaprevir is 4-5 hours. At steady state, the effective half-life is approximately 9 to 11 hours. The 5-day treatment duration was reasonable to ensure that steady-state telaprevir plasma concentrations were achieved prior to the ECG assessments on Day 5. A washout period of 8 days was sufficient in order to avoid carry-over effects of drug/moxifloxacin.*

#### 4.2.6.2 Sponsor's Justification for Doses

Two doses of telaprevir, a therapeutic and a suprathereapeutic dose, 1875 mg q8h, (i.e., 2.5 times the therapeutic dose, 750 mg q8h), were tested. The therapeutic dose has been shown to be generally safe and well tolerated. Based on a previous study evaluating the pharmacokinetics of telaprevir after single doses up to 1875 mg, this dose was expected to result in about a 2-fold higher exposure to telaprevir compared to the 750-mg q8h regimen. The exposure likely to be achieved with a dose of 1875 mg q8h telaprevir was expected to be generally safe and well tolerated.

*Reviewer's Comment: The tested doses are acceptable. The suprathereapeutic dose (1875 mg q8h, i.e., 2.5 times the therapeutic dose, 750 mg q8h) is the maximum dose which has been tested in the entire clinical development. This suprathereapeutic dose was expected to result in about a 2-fold higher exposure to telaprevir compared to the 750-mg q8h regimen. However, the PK results from the current TQT study only showed 40% increases in  $C_{max}$  and  $AUC_{(0,8h)}$  values following administration of 1875 mg compared with 750 mg drug. Even though the 750-mg dose is the intended clinical dose, telaprevir must be administered with both peginterferon alfa and ribavirin in clinical situation. Telaprevir exposure is higher in the presence of Peg-IFN coadministration. In Study 103, there was a trend for higher telaprevir exposure on Day 14 in the presence of Peg-IFN:*

$C_{max,ss}$  approximately 43% higher, AUC approximately 38% higher, and  $C_{min,ss}$  approximately 22% higher. Therefore, the studied suprathreshold dose provided the comparable exposures in the current clinical situation.

While the AUC and  $C_{max}$  of telaprevir after a single dose of 750 mg increased (20-30% for  $C_{max}$ ) in the presence of co-administered ketoconazole (400-mg single dose) or ritonavir (100-mg single dose), due to the strong inhibition of CYP3A by telaprevir itself, no substantial increase in telaprevir exposure at the steady state by other CYP3A inhibitors like ketoconazole and ritonavir has been observed. For 750-mg q8h regimen, the mean accumulation ratio was approximately 2.2 fold, which is higher than any increases caused by drug-drug interaction at single dose of 750 mg. Therefore, in principle, the worst-case scenario for telaprevir exposure would be a subject with severe renal impairment (10% increase in  $C_{max}$  and 21% increase in AUC) who takes telaprevir (in combination with Peg-IFN and ribavirin) with a high-fat meal. The test plasma concentration in the current TQT study might be insufficient to cover the worst case scenario at steady state expected due to severe renal impairment. However, telaprevir should not be administered to patients with creatinine clearance <50 mL/min based on current ribavirin's labeling. Therefore, currently the expected worst case scenario will not be a clinical situation. Moreover, the exposure-response analysis did not detect strong relationship which might further suggest a mild QT prolongation.

#### 4.2.6.3 Instructions with Regard to Meals

Telaprevir will be taken with standardized meals.

*Reviewer's Comment:* Acceptable. The conduct of the trial reflects the clinical practice due to higher bioavailability with food. Compared to a standard breakfast (533 kcal), telaprevir exposure ( $C_{max}$ ,  $AUC_{(0,t)}$ , and  $AUC_{\infty}$ ) decreased by 73% to 83% when telaprevir was administered under fasting conditions; 25% to 26% when telaprevir was administered after a low-calorie, high-protein breakfast (260 kcal); and 38% to 39% when telaprevir was administered after a low-calorie, low-fat breakfast (249 kcal).

#### 4.2.6.4 ECG and PK Assessments

Blood samples for PK were collected on Day -1 (-0.5 h), and on Day 5 (-0.5, 1, 2, 3, 4, 5, 6, and 8 h).

The 24-hour ECG recordings on Day -1 and Day 5 were performed by 12-lead Holter. The time points (-0.5 h, 1, 2, 3, 4, 5, 6, 8 and 24 h) were extracted and used in the analyses.

*Reviewer's Comment:* The ECG/PK sampling schedule is acceptable to cover the  $T_{max}$  (~4 hours) and PK profile of telaprevir at steady state.

#### 4.2.6.5 Baseline

Time-matched QTc on Day -1 before dosing day in each period was used as baseline.

#### **4.2.7 ECG Collection**

The 24-hour ECG recordings on Day -1 and Day 5 were performed by 12-lead Holter. Subjects rested in bed (supine) for at least 10 minutes prior to each safety ECG recording or ECG extraction time point from the Holter.

Triplicate 10-second recordings, collected at 60-second intervals, were extracted from the Holter recordings at several time points as indicated in the flowchart (Day -1 and Day 5 at -0.5 h, 1, 2, 3, 4, 5, 6, and 8 h) and were used in the analyses. The average QT and RR intervals were calculated to the nearest millisecond and these values were used in the analysis.

Safety ECG recordings were performed according to the flowchart.

The 24-hour 12-lead Holter recordings were blinded for the cardiologist of the ECG vendor for subject ID, sex, time and treatment, and were taken according to the flowchart and processed, handled and identified according to the central ECG reader manual. The inter-reader variability of this study was assessed with a small subset of ECG recordings (3 to 5%) read by a second reader.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

In this study, 44 healthy subjects were enrolled and received at least one dose of study medication. 37 subjects completed the study.

- One subject (CRF ID 136-0021) was withdrawn due to non-compliance on Day 1 of Session 3 (telaprevir 750 mg q8h), after taking only 3 of the 5 tablets of the morning dose of telaprevir/placebo despite intake supervision.
- Three subjects in treatment sequence discontinued study medication (telaprevir 1875 mg q8h) due to AEs. One subject (CRF ID 136-0007) discontinued due to an AE on Day 4 of Session 2, after the morning dose of telaprevir. One subject (CRF ID 136-0070) discontinued due to an AE on Day 4 of Session 4 (telaprevir 1875 mg q8h), after the second dose of telaprevir. One subject (CRF ID 136-0071) discontinued study medication after the last intake of Day 2 of Session 1 due to an AE.
- One subject (CRF ID 136-0065) withdrew consent on Day 3 of Session 2, after the morning dose of telaprevir (1875 mg q8h).
- One subject (CRF ID 136-0094) was withdrawn after the last medication intake on Day 5 of Session 1 (placebo) because not all entry criteria were met.
- One subject discontinued study medication after the last intake on Day 5 of Session 2 (placebo) due to an AE.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

“Summary statistics (n, mean, 90% CI for telaprevir; 97.5% CI for moxifloxacin) of the treatment-difference with placebo in time-matched changes from reference in QTcF interval for telaprevir and for moxifloxacin computed from mixed model are provided in following table.

“A summary of the mixed effects model results for LSmeans of the time-matched changes on drug minus time-matched changes on placebo at the time point of highest CI upper limit for telaprevir regimens and highest CI lower limit (on predefined time points of interest and overall) for moxifloxacin is provided in Table 11.

“For the telaprevir 750 mg q8h regimen, the results of the mixed effects model support the conclusion based on observed data that this telaprevir dose regimen was not associated with a clinically significant effect on QTcF interval: the highest upper limit of the 90% CI was below 10 ms (see Table 11).

“In contrast with the observed data, the highest upper limit of the 90% CI estimated in the mixed effects model for the telaprevir 1875 mg q8h regimen was below 10 ms.”

**Table 3: Mixed Model Analysis on Time-Matched Changes on Drug Minus Time-Matched Changes on Placebo (Double Delta) in QTcF Interval (Sponsor’s Results)**

Time Point	Telaprevir 750 mg q8h		Telaprevir 1875 mg q8h		Moxifloxacin 400 mg	
	LSMean	(90% CI) <sup>a</sup>	LSMean	(90% CI) <sup>a</sup>	LSMean	(97.5% CI) <sup>a,b</sup>
Day 5						
-0.5h	2.7	(0.39; 4.94)	3.7	(1.37; 5.96)	-0.9	(-4.01; 2.13)
1h	<b>4.8</b>	<b>(2.50; 7.09)</b>	6.1	(3.82; 8.38)	1.3	(-1.71; 4.39)
2h	2.9	(0.65; 5.24)	5.1	(2.79; 7.34)	5.7	(2.68; 8.78)
3h	2.9	(0.59; 5.14)	5.9	(3.66; 8.22)	8.9	(5.87; 12.00)
4h	3.9	(1.68; 6.21)	6.7	(4.38; 8.93)	<b>10.1</b>	<b>(7.01; 13.11)</b>
5h	2.3	(0.02; 4.57)	<b>7.5</b>	<b>(5.22; 9.80)</b>	8.5	(5.38; 11.52)
6h	3.0	(0.69; 5.24)	4.2	(1.90; 6.48)	8.9	(5.88; 12.01)
8h	1.9	(-0.41; 4.17)	3.0	(0.73; 5.34)	8.1	(5.03; 11.21)
24h	3.7	(1.42; 5.94)	6.4	(4.07; 8.66)	5.4	(2.30; 8.44)

<sup>a</sup> Linear mixed model including subject as a random effect and including the following fixed effects: period, treatment sequence, time-dependent reference QTc, time, treatment and the interaction between time and treatment.

<sup>b</sup> For moxifloxacin, 4 time points of interest were defined in the protocol: 2h, 3h, 4h and 5h. The 97.5% CI (Bonferroni correction) is shown to account for multiplicity.

Source: Sponsor’s report Table 11.

Reviewer’s Comments: FDA reviewer’s results were similar to the sponsor’s. The upper bound in QTcF for the high dose was 9.9 ms. Please see the results in section 5.2.

#### 4.2.8.2.2 Assay Sensitivity

“As a sensitivity analysis, a mixed effects model was planned, adjusting for sequence, treatment, period, reference QTcF interval, time, and the interaction of time and treatment as fixed effects, and subject as a random effect. At 3 of the 4 predefined time points of interest, the lower limit of the 97.5% CI estimated in the mixed effects model was above 5 ms, with the highest lower limit of the 97.5% CI at one of the four predefined time

points of interest observed at 4h after administration (mean [97.5% CI]: 10.01 ms [7.01, 13.11])”

#### 4.2.8.2.3 Categorical Analysis

None of the subjects had a QTcF value above 480 ms and none of the subjects had a QTcF increase versus reference of more than 60 ms. Absolute QTcF values between 450 and 480 ms were observed for 1 subject (2.4%) each during telaprevir 1875 mg q8h, moxifloxacin, and placebo treatment phases. QTcF increases from reference between 30 and 60 ms were noted for 2 subjects (5.0%) during the telaprevir 750-mg q8h treatment phase, for 6 subjects (14.6%) during the telaprevir 1875 mg-q8h treatment phase, for 2 subjects (4.9%) during the moxifloxacin treatment phase, and for 1 subject (2.4%) during the placebo treatment phase. All corresponding QTcF actual values were  $\leq$  450 ms.

#### 4.2.8.2.4 Additional Analyses

The results of the mixed effects model for other QT corrections for both telaprevir regimens were also mainly in line with those of the mixed effects model for QTcF (see Table 15). The only exceptions were QTcB interval for both telaprevir regimens, and QTc non-linear and QTc individual non-linear for the telaprevir 1875-mg q8h regimen.

**Table 4: Mixed Model Analysis on Time-Matched Changes on Drug Minus Time-Matched Changes on Placebo (Double Delta) with other QT-RR corrections (Sponsor’s Results)**

QT Correction (ms)	Telaprevir 750 mg q8h		Telaprevir 1875 mg q8h		Moxifloxacin 400 mg	
	Time point	LSMean (90% CI) <sup>a</sup>	Time point	LSMean (90% CI) <sup>a</sup>	Time point	LSMean (97.5% CI) <sup>a,b</sup>
QTcF	1h	4.8 (2.50; 7.09)	5h	7.5 (5.22; 9.80)	4h	10.1 (7.01; 13.11)
QTcB	1h	10.4 (7.33; 13.43)	5h	12.9 (9.90; 16.00)	4h	9.3 (5.22; 13.33)
QTcS	1h	5.2 (2.86; 7.53)	5h	7.5 (5.16; 9.83)	4h	9.7 (6.63; 12.85)
QTcL	1h	5.0 (2.66; 7.27)	24h	7.0 (4.72; 9.32)	4h	9.7 (6.68; 12.80)
QTcNL	1h	5.7 (3.34; 8.01)	5h	8.3 (6.00; 10.67)	4h	10.1 (6.99; 13.19)
QTcIL	1h	4.3 (2.01; 6.51)	5h	6.8 (4.53; 9.03)	4h	9.3 (6.35; 12.33)
QTcINL	1h	5.2 (2.82; 7.55)	5h	7.8 (5.40; 10.13)	4h	9.8 (6.65; 12.94)

QTcS: QTc (Sagie); QTcL: QTc linear; QTcNL: QTc non-linear; QTcIL: QTc individual linear; QTcINL: QTc individual non-linear

<sup>a</sup> Linear mixed model including subject as a random effect and including the following fixed effects: period, treatment sequence, time-dependent reference QTc, time, treatment and the interaction between time and treatment.

<sup>b</sup> For moxifloxacin, 4 time points of interest were defined in the protocol: 2h, 3h, 4h and 5h. The 97.5% CI (Bonferroni correction) is shown to account for multiplicity.

Source: Sponsor’s report Table 15.

### 4.2.8.3 Safety Analysis

There were no deaths or SAEs in this study.

In total, 4 subjects permanently discontinued study medication due to one or more AEs. For 3 subjects, these AEs occurred during telaprevir 1875-mg q8h treatment; for 1 subject, they were reported during placebo administration.

- Subject 136-0071 discontinued study medication due to grade 2 nausea starting during telaprevir 1875-mg q8h treatment (in the first treatment session).
- Subject 136-0007 discontinued study medication due to grade 1 diarrhoea, grade 2 anorectal discomfort, and grade 2 headache all starting during telaprevir 1875-mg q8h treatment (in the second treatment session).
- Subject 136-0070 discontinued study medication due to grade 2 decreased appetite, grade 1 nausea, and grade 2 vomiting all starting during telaprevir 1875-mg q8h treatment (in the fourth treatment session).
- Subject 136-0054 discontinued study medication due to rash and pruritus of severity grade 2 starting during placebo administration

For Subject 136-0081, the AE dizziness was reported on the same day as QTcF values between 450 and 480 ms during the moxifloxacin phase: dizziness was reported from Day 2 till Day 7 and QTcF values of 453 ms and 454 ms were observed on Days 2 and 5, respectively. None of the other subjects reporting dizziness experienced QTcF values above 450 ms, according to the sponsor.

### 4.2.8.4 Clinical Pharmacology

#### 4.2.8.4.1 Pharmacokinetic Analysis

The PK results are presented in Table 5.  $C_{max}$  and  $AUC_{(0,8h)}$  values in the thorough QT study were 40% higher following administration of 1875 mg telaprevir compared with 750 mg telaprevir, the intended clinical dose.

**Table 5: Summary of Plasma Pharmacokinetic Parameters of Telaprevir**

Parameter	LSmeans <sup>a</sup>		LSmeans ratio	90% CI <sup>c</sup>	p-value	
	Telaprevir 750 mg q8h (reference)	Telaprevir 1875 mg q8h (test)			Period	Sequence
$C_{min}$ , ng/mL	1881	2628	1.40	1.33 - 1.46	0.6033	0.6134
$C_{max}$ , ng/mL <sup>b</sup>	2949	4106	1.39	1.33 - 1.46	0.6898	0.3973
$AUC_{8h}$ , ng.h/mL	19270	26940	1.40	1.35 - 1.45	0.5119	0.6848

<sup>a</sup> n=39 for reference and n=36 for test

<sup>b</sup> n=37 for test

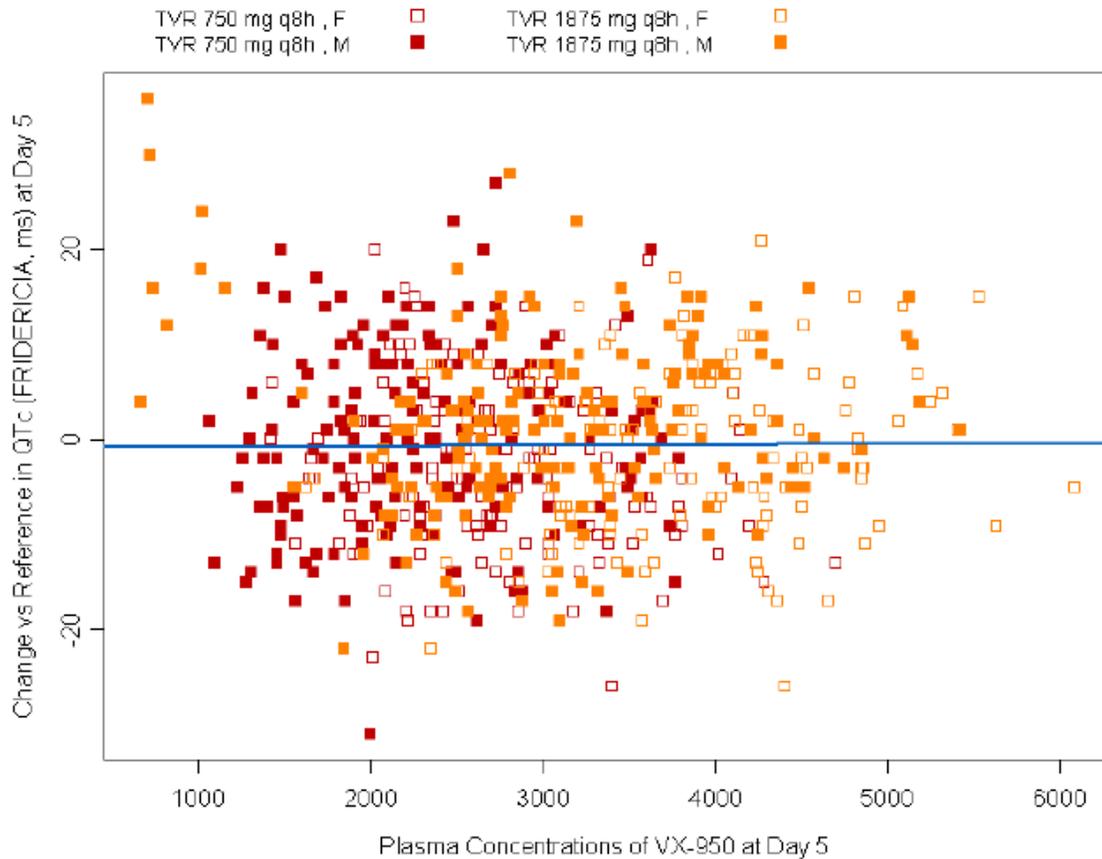
<sup>c</sup> 90% confidence intervals

(Source: Sponsor's Study Report, Table 8 on Page 77)

#### 4.2.8.4.2 Exposure-Response Analysis

The concentration- $\Delta$ QTc analysis results show the relationship between the change from baseline in QTcF and telaprevir concentrations is flat (Figure 1).

**Figure 1: Changes (ms) from Baseline in QTcF versus the Telaprevir Concentrations**



Line: linear regression; estimated slope= 0.0001, p=0.8695

(Source: Sponsor’s Study Report, Figure 13 on Page 97)

*Reviewer’s Analysis: The reviewer performed independent analyses to explore the relationship between the telaprevir concentration and  $\Delta\Delta QTc$  (See section 5.3). Consistent with the sponsor’s results, the slope of the concentration-response relationship is relatively flat and non-significant from zero.*

## 5 REVIEWERS’ ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods QTcF , QTcS (Framingham correction), linear and non-linear regression modeling on the pooled study data (QTcL, QTcN), and linear and non-linear regression modeling on the individual subject data (QTIL, QTIN). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We first used 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 6, it appears that only QTcIL, QTIN and QTcN are comparable to QTcF, we then compare each correction methods with QTcF using mixed model.

**Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

method	Treatment									
	Moxifloxacin 400 mg		Placebo		Telaprevir 1875 mg		Telaprevir 750 mg		All	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTIL	41	0.0021	41	0.0019	38	0.0023	39	0.0019	43	0.0013
QTIN	41	0.0021	41	0.0023	38	0.0030	39	0.0022	43	0.0015
QTcF	41	0.0014	41	0.0021	38	0.0024	39	0.0026	43	0.0015
QTcL	41	0.0016	41	0.0024	38	0.0024	39	0.0029	43	0.0018
QTcN	41	0.0013	41	0.0020	38	0.0026	39	0.0025	43	0.0014
QTcS	41	0.0016	41	0.0023	38	0.0025	39	0.0029	43	0.0017

QTcF and other correction methods identified by MSSS were then included in the mixed model by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF vs. others), and the interaction term of RR and correction type. The slopes of QTcF and others versus RR are compared in magnitude as well as statistical significance in difference. As shown in the following tables, QTcF produced the smallest slope (except in the placebo group for the QTcF and QTcIL comparison as shown in Table 8). This reviewer used QTcF as the primary outcome, which is also consistent with the sponsor's choice.

**Table 7: Comparison of QTcF and QTcN Using the Mixed Model**

Treatment Groups	Slope of QTcF	Slope of QTcN	diff_p_value
Moxifloxacin 400 mg	0.00524	-.00565	0.00084
Overall	0.00364	-.00746	0.00000
Placebo	0.00699	-.00372	0.00117
Telaprevir 1875 mg	0.00028	-.01141	0.00512
Telaprevir 750 mg	-.00179	-.01323	0.00324

**Table 8: Comparison of QTcF and QTcIL Using the Mixed Model**

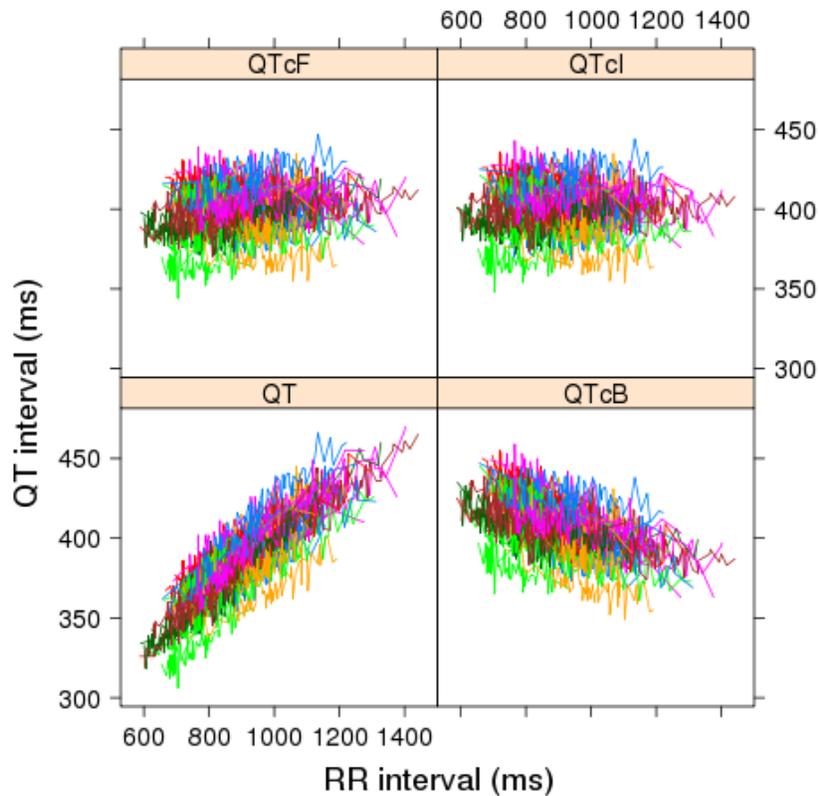
Treatment Groups	Slope of QTIL	Slope of QTcF	diff_p_value
Moxifloxacin 400 mg	0.00853	-.00819	0.00000
Overall	0.00932	-.00613	0.00000
Placebo	0.01192	-.00494	0.00000
Telaprevir 1875 mg	0.00735	-.00892	0.00023
Telaprevir 750 mg	0.00613	-.00837	0.00046

**Table 9: Comparison of QTcF and QTcIN Using the Mixed Model**

Treatment Groups	Slope of QTIN	Slope of QTcF	diff_p_value
Moxifloxacin 400 mg	0.00574	-.00714	0.00024
Overall	0.00487	-.00692	0.00000
Placebo	0.00811	-.00261	0.00231
Telaprevir 1875 mg	0.00007	-.01263	0.00465
Telaprevir 750 mg	-.00008	-.01151	0.00641

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 Telaprevir

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect. The model includes time point, sequence, and period 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 10: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Telaprevir 750 mg**

	Telaprevir 750 mg $\Delta$ QTcF	Placebo $\Delta$ QTcF	$\Delta\Delta$ QTcF	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-1.2	-6.0	4.8	(2.6, 7.1)
2	-1.9	-5.3	3.4	(0.7, 6.1)
3	-0.8	-5.0	4.2	(1.3, 7.0)
4	-2.0	-5.7	3.7	(1.0, 6.5)
5	-2.1	-4.3	2.2	(0.0, 4.4)
6	-1.4	-5.1	3.7	(1.2, 6.2)
8	-0.6	-2.9	2.4	(-0.5, 5.2)
24	-1.1	-4.9	3.8	(1.1, 6.6)

**Table 11: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Telaprevir 1875 mg**

	Telaprevir 750 mg $\Delta$ QTcF	Placebo $\Delta$ QTcF	$\Delta\Delta$ QTcF	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	0.1	-6.0	6.2	(3.9, 8.4)
2	0.6	-5.3	5.9	(3.2, 8.6)
3	2.1	-5.0	7.0	(4.2, 9.9)
4	0.3	-5.7	6.1	(3.3, 8.8)
5	3.2	-4.3	7.5	(5.2, 9.7)
6	-0.5	-5.1	4.6	(2.1, 7.1)
8	0.4	-2.9	3.3	(0.5, 6.2)
24	1.7	-4.9	6.6	(3.8, 9.4)

The largest upper bounds of the 2-sided 90% CI for the mean difference between telaprevir 750 mg and placebo, and between telaprevir 1875 mg and placebo were 7.0 ms and 9.9 ms at 3 hour after dose, 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 12. The largest unadjusted 90% lower confidence interval is 6.7 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 5.9 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

**Table 12: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Moxifloxacin 400 mg**

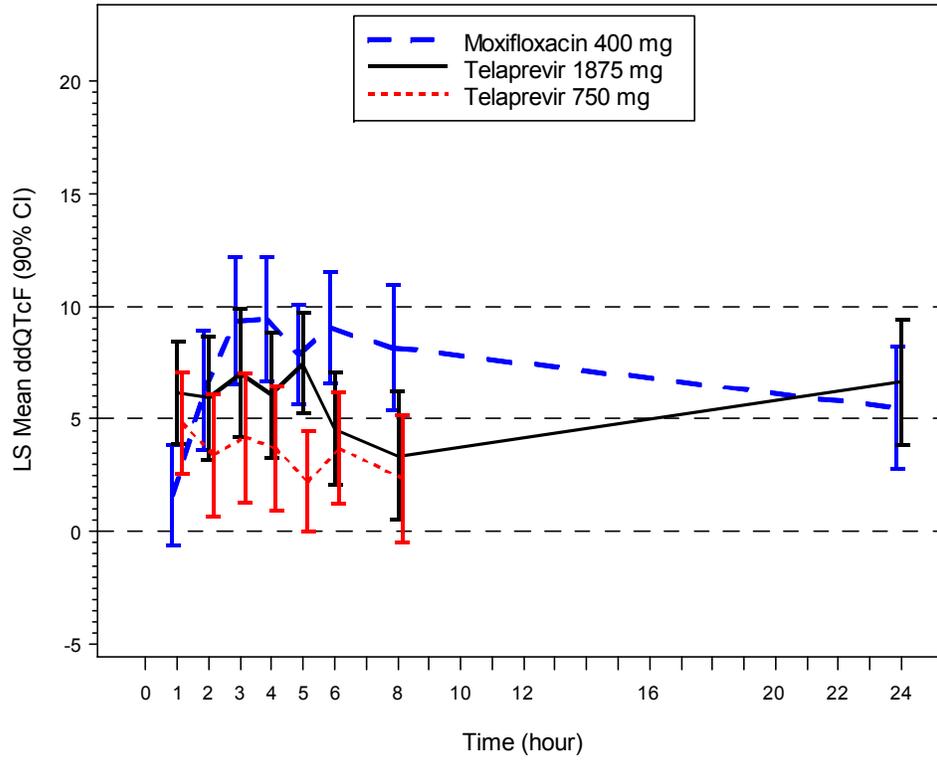
	Moxifloxacin 400 mg $\Delta$ QTcF	Placebo $\Delta$ QTcF	$\Delta\Delta$ QTcF	
		Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
Time/(hr)	Mean (ms)	Mean (ms)	Mean (ms)	90% CI (ms)
1	-4.4	-6.0	1.6	(-1.3, 4.5)
2	0.9	-5.3	6.2	(2.8, 9.7)
3	4.4	-5.0	9.4	(5.7, 13.0)
4	3.7	-5.7	9.4	(5.9, 12.9)
5	3.6	-4.3	7.9	(5.0, 10.7)
6	3.9	-5.1	9.0	(5.9, 12.2)
8	5.2	-2.9	8.2	(4.5, 11.8)
24	0.6	-4.9	5.5	(1.9, 9.1)

\* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

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

Figure 3: Mean and 90% CI  $\Delta\Delta Q_{TcF}$  Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

#### 5.2.1.4 Categorical Analysis

In this study, there is no subject's QTcF was above 450 ms. Table 13 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 13: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin 400 mg	41	326	40 (97.6%)	325 (99.7%)	1 (2.4%)	1 (0.3%)
Placebo	41	324	41 (100%)	324 (100%)	0 (0.0%)	0 (0.0%)
Telaprevir 1875 mg	38	303	37 (97.4%)	302 (99.7%)	1 (2.6%)	1 (0.3%)
Telaprevir 750 mg	39	307	39 (100%)	307 (100%)	0 (0.0%)	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 between telaprevir 750 mg and placebo and telaprevir 1875 mg and placebo are 6.2 ms and 7.0 ms, respectively.

The outlier analysis results for PR are presented in Table 16.

**Table 14: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = Telaprevir 750 mg**

	Telaprevir 750 mg $\Delta$ PR	Placebo $\Delta$ PR	$\Delta\Delta$ PR	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-1.2	-0.6	-0.6	(-3.4, 2.3)
2	-0.7	-1.5	0.9	(-1.8, 3.6)
3	1.0	-0.6	1.7	(-0.9, 4.2)
4	2.2	-0.7	3.0	(0.8, 5.2)
5	1.6	-0.0	1.6	(-0.7, 3.9)
6	1.2	-2.5	3.7	(1.2, 6.2)
8	0.8	0.4	0.4	(-1.6, 2.4)
24	0.6	0.6	-0.0	(-2.4, 2.4)

**Table 15: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = Telaprevir 1875 mg**

	Telaprevir 1875 mg $\Delta$ PR	Placebo $\Delta$ PR	$\Delta\Delta$ PR	
Time/(hr)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	1.4	-0.6	2.1	(-0.8, 4.9)
2	1.4	-1.5	2.9	(0.2, 5.6)
3	3.8	-0.6	4.4	(1.9, 7.0)
4	4.0	-0.7	4.7	(2.5, 7.0)
5	4.3	-0.0	4.3	(2.0, 6.6)
6	2.0	-2.5	4.5	(2.0, 7.0)
8	2.2	0.4	1.7	(-0.3, 3.7)
24	2.3	0.6	1.6	(-0.8, 4.0)

**Table 16: Categorical Analysis for PR**

Treatment Group	Total		Value<=200 ms		Value>200 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	43	1264	36 (83.7%)	1246 (98.6%)	7 (16.3%)	18 (1.4%)
Moxifloxacin 400 mg	41	327	37 (90.2%)	322 (98.5%)	4 (9.8%)	5 (1.5%)
Placebo	41	324	38 (92.7%)	321 (99.1%)	3 (7.3%)	3 (0.9%)
Telaprevir 1875 mg	38	304	34 (89.5%)	297 (97.7%)	4 (10.5%)	7 (2.3%)
Telaprevir 750 mg	39	310	35 (89.7%)	300 (96.8%)	4 (10.3%)	10 (3.2%)

**Table 17: Outliers Analysis for PR>200 ms**

ID	Treatment	time 1	time 2	time3	time4	time5	time8	time24
136-0043	Telaprevir 750 mg							201
136-0043	Baseline							199
136-0047	Telaprevir 1875 mg		204					
136-0047	Baseline		188					
136-0047	Telaprevir 750 mg	202	204	203	205	202	203	201
136-0047	Baseline	200	195	200	204	192	190	191
136-0051	Telaprevir 1875 mg			200	202			204
136-0051	Baseline			183	183			192
136-0051	Telaprevir 750 mg		208					
136-0051	Baseline		190					
136-0074	Telaprevir 1875 mg	215	208	213				
136-0074	Baseline	200	177	171				

136-0074	Telaprevir 750 mg		203					
136-0074	Baseline		215					
136-0101	Telaprevir 1875 mg	202		200				
136-0101	Baseline	201		180				

### 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 18 and Table 19. The largest upper limits of 90% CI for the QRS mean differences between telaprevir 750 mg and placebo and telaprevir 1875 mg and placebo are 2.0 ms and 3.4 ms, respectively. There is no subject who experienced QRS interval greater than 110 ms in any treatment groups.

**Table 18: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = Telaprevir 750 mg**

	Telaprevir 750 mg $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-0.3	-1.1	0.8	(-0.2, 1.8)
2	0.2	-0.7	0.9	(-0.1, 1.9)
3	0.5	-0.6	1.1	(0.3, 1.9)
4	0.7	-0.6	1.3	(0.5, 2.0)
5	0.9	-0.3	1.2	(0.4, 2.0)
6	0.1	-0.7	0.7	(-0.1, 1.6)
8	0.1	-0.5	0.6	(-0.3, 1.5)
24	-0.0	-0.4	0.3	(-0.5, 1.2)

**Table 19: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = Telaprevir 1875 mg**

	Telaprevir 1875 mg $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	1.0	-1.1	2.1	(1.1, 3.0)
2	1.0	-0.7	1.7	(0.8, 2.7)
3	1.3	-0.6	1.8	(1.0, 2.7)
4	1.5	-0.6	2.1	(1.4, 2.8)
5	1.3	-0.3	1.6	(0.8, 2.4)
6	1.8	-0.7	2.5	(1.7, 3.3)
8	2.0	-0.5	2.5	(1.5, 3.4)
24	1.8	-0.4	2.2	(1.3, 3.1)

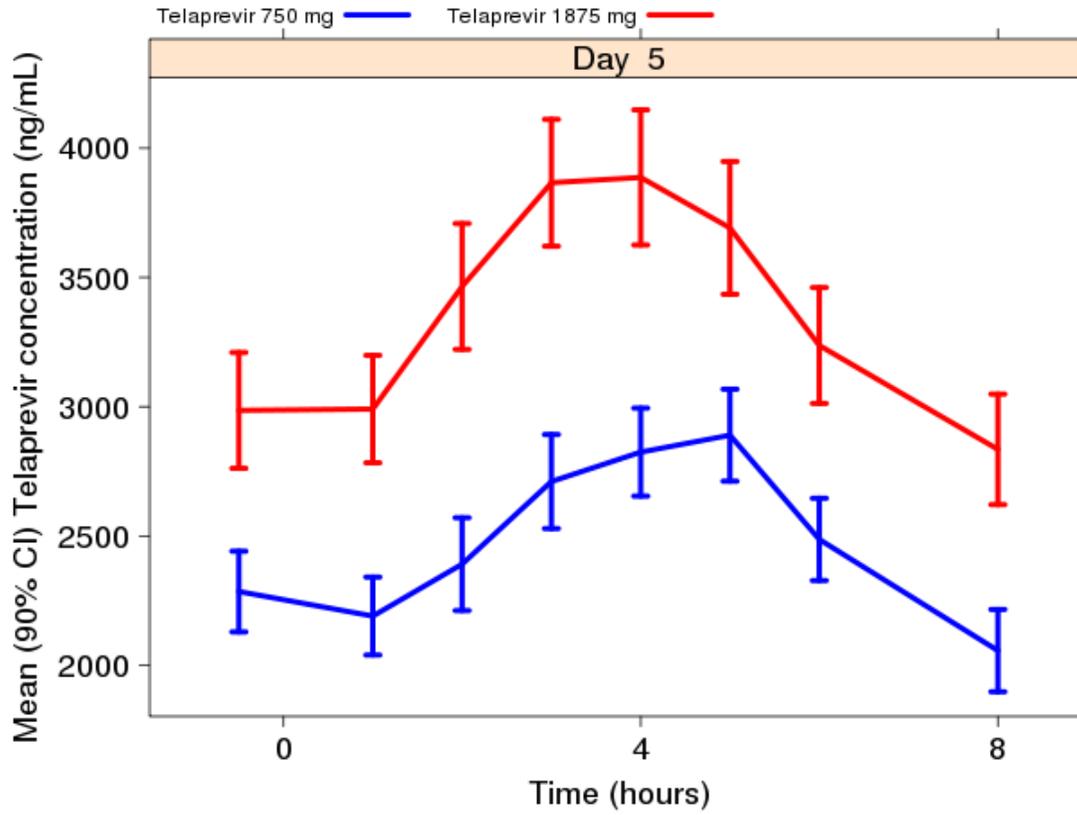
**Table 20: Categorical Analysis for QRS**

Treatment Group	Total		Value<=100 ms		100 ms<Value<=110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	43	1265	33 (76.7%)	1144 (90.4%)	10 (23.3%)	121 (9.6%)
Moxifloxacin 400 mg	41	327	36 (87.8%)	304 (93.0%)	5 (12.2%)	23 (7.0%)
Placebo	41	325	36 (87.8%)	298 (91.7%)	5 (12.2%)	27 (8.3%)
Telaprevir 1875 mg	38	304	29 (76.3%)	276 (90.8%)	9 (23.7%)	28 (9.2%)
Telaprevir 750 mg	39	310	32 (82.1%)	271 (87.4%)	7 (17.9%)	39 (12.6%)

**5.3 CLINICAL PHARMACOLOGY ASSESSMENTS**

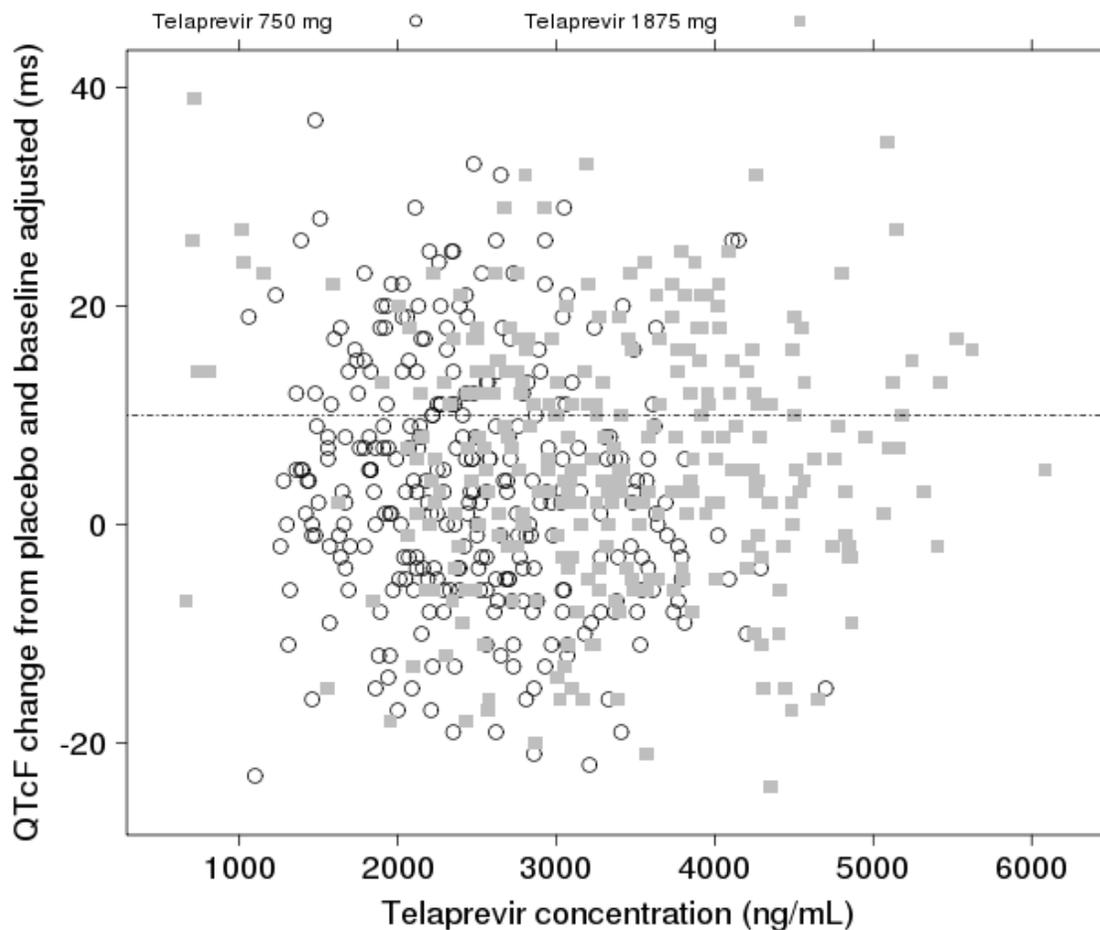
The mean drug concentration-time profile is illustrated in Figure 4.

**Figure 4: Mean Concentration-time Profiles for 750 mg (Blue Line) And 1875 mg (Red Line) Telaprevir (Red Line)**



The relationship between  $\Delta\Delta\text{QTcF}$  and telaprevir concentrations is visualized in Figure 5 with no significant exposure-response relationship (slope = 0.000625 with p-value: 0.3514).

**Figure 5:  $\Delta\Delta$  QTcF vs. Telaprevir 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. Based on review of a subset of ECGs, Lead V2 was annotated for QRS and lead II for PR and QT measurements. According to ECG warehouse automated algorithm, only 0.01% of the ECGs were reported to have significant QT bias. Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

There appear to be no clinically relevant effects on the PR and QRS intervals. There appears to be trend for mean increase of PR interval with both doses of telaprevir (maximum upper bound-7 ms) between hour 3 and 6. However, on review of the categorical data (absolute values over 200 ms), the majority of subjects on telaprevir had an elevated PR interval at baseline. Only one subject had a change from baseline that was around 24% at an isolated time point (213 ms at hour 3).

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	750 mg every 8 hours (q8h) orally for 12 weeks (in combination with pegylated interferon (Peg-IFN) and ribavirin (RBV). At the completion of telaprevir dosing, Peg-IFN/RBV dosing continues for an additional 12 or 36 weeks, depending on early virologic response and, if applicable, prior response to Peg-IFN/RBV.	
Maximum tolerated dose	All doses studied in clinical studies were well-tolerated. No maximum tolerated dose was established in humans.	
Principal adverse events	The majority of the adverse drug reactions (ADRs) reported during treatment with telaprevir combination treatment were mild in severity. In subjects who received telaprevir combination treatment, the most common adverse drug reactions ( $\geq 5\%$ ) of at least moderate intensity were anemia, pruritus, rash, nausea, and diarrhea. 10.4% of subjects discontinued telaprevir due to ADRs (in the pooled controlled trials: N = 1346) (see proposed USPI for summary of adverse events; Module 2.7.4 for detailed discussion).	
Maximum dose tested	Single Dose	1875 mg (Study 017)
	Multiple Dose	Telaprevir alone: 1875 mg q8h for 4 days, followed by a single dose on the morning of Day 5 (Study 136)
Exposures Achieved at Maximum Tested Dose	Single Dose	Study 017 (1875 mg): Mean (SD) $C_{max}$ : 3259 (1662) ng/mL Mean (SD) $AUC_{0-\infty}$ : 34944 (22575) ng·h/mL
	Multiple Dose	Study C136 (telaprevir alone, healthy subjects, 1875 mg q8h): Mean (SD) $C_{max}$ : 4228 (825) ng/mL Mean (SD) $AUC_{0-24}$ : 27750 (5688) ng·h/mL Study 108 (750 mg q8h in combination with Peg-IFN and RBV, treatment naïve subjects): Mean (SD) $C_{max}$ : 3510 (1280) ng/mL Mean (SD) $AUC_{0-24}$ : 22300 (8650) ng·h/mL Study C216 (750 mg q8h in combination with Peg-IFN and RBV, treatment failure subjects): Mean (SD) $C_{max}$ : 5087 (1577) ng/mL Mean (SD) $AUC_{0-24}$ : 33840 (11010) ng·h/mL
Range of linear PK	<p><b>Single Dose:</b> In Study 017, doses of 375 to 1875 mg resulted in AUC and <math>C_{max}</math> of telaprevir increasing slightly greater than proportional to dose (Module 2.7.2/Section 3.2.2).</p> <p><b>Multiple Dose:</b> In Study C136, an increase in telaprevir dose from 750 mg q8h to 1875 mg q8h resulted in a less than proportional increase in telaprevir exposure (i.e., <math>C_{max}</math> and <math>AUC_{0-24}</math> increased by approximately 40% with a 2.5-fold increase in dose) (Module 2.7.2/Section 3.2.2).</p> <p>In Study 008, mean telaprevir <math>C_{max}</math> and <math>AUC_{0-24}</math> following the suprathreshold TVR/KETO regimen (3 doses of telaprevir 1250 mg q8h followed by a single 400-mg dose of ketoconazole co-administered</p>	

	with a fourth and final 1250-mg dose of telaprevir) were about 20% higher than those of the therapeutic TVR regimen (a single dose of 1250 mg followed by 3 doses of 750 mg q8h). Thus, a 67% increase in dose and the addition of ketoconazole with the last dose resulted in less than proportional increase in exposure to telaprevir.	
Accumulation at steady state	For 750 mg q8h regimen, the mean (SD) accumulation ratio ( $AUC_{0-\infty}$ after steady-state to $AUC_{0-\infty}$ after single dose) was approximately 2.21 (0.81) (Study 006) to 2.52 (0.61) (Study 009).	
Metabolites	<p>Following a single oral administration of 750 mg telaprevir, all telaprevir metabolite exposures were less than 10% of the total drug-related material (TDM), with the exception of VRT-127394 (R-diastereomer of telaprevir) (Module 2.7.2/Section 3.1.3). The metabolism of <math>^{14}C</math>-telaprevir involved oxidation, reduction, and hydrolysis to produce numerous metabolites and their isomers (Study 005). In plasma, <math>^{14}C</math>-telaprevir and <math>^{14}C</math>-VRT-127394 were the main circulating compounds detected at 5 hours postdose. The major hydrolysis metabolites M12 isomers were detected in the 12- and 24-hour plasma samples but not in the 48-hour postdose sample. Minor hydrolysis/oxidation metabolites M3, M4, and M8/M9 isomers were also detected in plasma at all time points.</p> <p>In Phase 2 Study 104EU, at steady state following repeated oral administration of telaprevir (750 mg q8h, coadministered with Peg-IFN and RBV), VRT-127394, pyrazinoic acid, and VRT-0922061 were found to be the predominant metabolites; mean steady-state concentrations of all other metabolites evaluated were much less than 10% of the total drug-related material (see Table 1). The analyte to TDM relative concentrations remained consistent from Days 8 to 85. Day 85 <math>C_{max}</math> and <math>AUC_{0-\infty}</math> percentages relative to TDM were 37% to 38% for telaprevir, 22% to 23% for pyrazinoic acid, 20% to 22% for VRT-127394, and 10% to 11% for VRT 0922061 (Module 2.7.2/Section 3.1.3.2).</p> <p>The majority of metabolites were not predicted to be active against the HCV protease, based on their chemical structure. Three metabolites that either were present in relatively high amounts in plasma in multiple dose studies (VRT-127394 [R-diastereomer of telaprevir] and VRT-0922061 [an isomer of M3]) or were potentially active against the HCV protease based on chemical structure (M12) were tested for inhibitory activity in the HCV protease enzyme and replicon assays and found to have at least 30-fold-lower activity than telaprevir (Module 2.6.2/Section 2.2</p>	
Absorption	Absolute/Relative Bioavailability	not determined
	$T_{max}$	Single dose 750 mg (Study C121; after standard breakfast): Median (range) 4.0 (1.5, 6.0)
Distribution	$V_d/F$ or $V_d$	The typical apparent volume of distribution ( $V_d/F$ ) was estimated to be 252 L, with an inter-individual variability of 72% (Module 2.7.2/Section 3.1.2).
	% bound	Telaprevir is approximately 59% to 76% bound to plasma proteins (Module 2.7.2/Section 3.1.2).
Elimination	Route	Following administration of a single oral dose of

		750 mg <sup>14</sup> C-telaprevir in healthy subjects, the median recovery of the administered radioactive dose was approximately 82% in the feces, 9% in exhaled air and 1% in urine (Study 005).
	Terminal t <sub>1/2</sub>	The mean elimination half-life after single-dose oral administration of telaprevir 750 mg typically ranged from about 4.0 to 4.7 hours. At steady state, the effective half-life is approximately about 9 to 11 hours (Module 2.7.2/Sections 3.2.1 and 3.2.4).
	CL/F or CL	The apparent total clearance (CL/F) was estimated to be 32.4 L/h with an inter-individual variability of 27.2% (Module 2.7.2/Section 3.2.5.5).
Intrinsic Factors	Age	No apparent effect (Module 2.7.2/Section 3.7.1).
	Sex	No apparent effect (Module 2.7.2/Section 3.7.1).
	Race	No apparent effect (Module 2.7.2/Section 3.7.1).
	Hepatic & Renal Impairment	<p><b>Renal impairment (Study C132):</b> After administration of a single dose of 750 mg to HCV-negative subjects with severe renal impairment (CrCl &lt; 30 ml/min), the mean telaprevir C<sub>max</sub> and AUC<sub>∞</sub> were increased by 10% and 21%, respectively, compared to healthy subjects.</p> <p><b>Hepatic impairment (Study 006 and 012):</b></p> <p>After a single dose, the C<sub>max</sub> and AUC<sub>0-24</sub> of telaprevir was reduced by approximately 18% and 11 % in HCV-negative subjects with mild (Child-Pugh Class A) hepatic impairment and by 41% and 37% in subjects with moderate (Child-Pugh Class B) hepatic impairment, respectively, compared to healthy subjects.</p> <p>Steady-state C<sub>max</sub> and AUC<sub>0-24</sub> of telaprevir was reduced by approximately 10% and 15 % in HCV-negative subjects with mild (Child-Pugh Class A) hepatic impairment and by 49% and 46% in subjects with moderate (Child-Pugh Class B) hepatic impairment, respectively, compared to healthy subjects.</p>
Extrinsic Factors	Drug interactions	See attached Table 2 and Table 3.  Telaprevir exposure is higher in the presence of Peg-IFN coadministration. In Study 103, there was a trend for higher telaprevir exposure on Day 14 in the presence of Peg-IFN: C <sub>max,ss</sub> approximately 43% higher, AUC approximately 38% higher, and C <sub>min,ss</sub> approximately 22% higher (Module 2.7.2, section 3.2.5.2).
	Food Effects	In Study C121, when compared to a standard breakfast (533 kcal), telaprevir exposure (C <sub>max</sub> ,

		<p>AUC<sub>last</sub>, and AUC<sub>∞</sub>) decreased by 73% to 83% when telaprevir was administered under fasting conditions; 25% to 26% when telaprevir was administered after a low-calorie, high-protein breakfast (260 kcal); and 38% to 39% when telaprevir was administered after a low-calorie, low-fat breakfast (249 kcal). Compared to a standard breakfast, administration of telaprevir with a high-fat breakfast (928 kcal) resulted in a moderate increase in AUC<sub>∞</sub> (approximately 20% increase). Based on these results, it is recommended to take telaprevir with food.</p> <p>See <a href="#">Table 4</a>.</p>
Expected High Clinical Exposure Scenario	<p>While the AUC and C<sub>max</sub> of telaprevir after a single dose of 750 mg increased in the presence of co-administered ketoconazole or ritonavir, due to the strong inhibition of CYP3A by telaprevir itself, telaprevir exposure after multiple doses is not likely to be affected to any significant degree by other CYP3A inhibitors like ketoconazole and ritonavir. This has been shown for ketoconazole (<a href="#">Study 008</a> – discussed above), ritonavir (<a href="#">Study 009</a>), boosted atazanavir or lopinavir (<a href="#">Study C122</a>), boosted fosamprenavir or darunavir (<a href="#">Study C124</a>). <a href="#">Table 2</a> below summarizes the effect of these drugs on the PK parameters of telaprevir.</p> <p>Therefore, in principle, the worst-case scenario for telaprevir exposure would be a subject with severe renal impairment (10% increase in C<sub>max</sub> and 21% increase in AUC) who takes telaprevir (in combination with Peg-IFN and ribavirin) with a high-fat meal (20% increase in AUC but not C<sub>max</sub>; see <a href="#">Table 4</a>). Given the variability in the PK parameters of telaprevir, the supratherapeutic dose used in <a href="#">Study C136</a> (2.5-fold increase over the therapeutic dose) represents the range of exposures expected from the worst case scenario.</p>	

Note: data sources given in blue text; the following attached Tables are referred to in above text.

## 6.2 TABLE OF STUDY ASSESSMENTS

### Screening

Day	Blood Sample		Urine Sample	ECG <sup>b</sup> , Vital Signs <sup>c</sup>	Other <sup>d</sup>
	Drug	Safety <sup>a</sup>			
Screening (≤ 21 days prior to Day 1 of the first treatment session)		X	X	X	Informed consent, subject characteristics and demographics, inclusion/exclusion criteria, medical and surgical history and concomitant diseases, smoking habits, HIV-1 and HIV-2 and hepatitis A, B, and C test, coagulation tests, urine drug screening, alcohol breath test, physical examination <sup>e</sup> , serum pregnancy test (if applicable).

<sup>a</sup> Biochemistry sample had to be taken fasted for at least 7 hours.

<sup>b</sup> Safety ECG: ECG had to be performed in supine position, after at least 10 minutes rest in supine position.

<sup>c</sup> Blood pressure (BP) and pulse (supine, after at least 5 minutes rest, and standing, after at least 1 minute standing) had to be measured just before the 10-minute rest period prior to start of the ECG recording.

<sup>d</sup> Adverse events and concomitant medication were monitored throughout the study from the signing of the ICF onwards until the last study-related activity.

<sup>e</sup> Physical examination included skin examination.

**Treatment A, B, C and D:**

Day	Time	Blood sample		Urine sample <sup>l</sup>	Safety ECG <sup>g</sup>	Holter Extracted ECG <sup>c</sup>	Vital Signs <sup>d</sup>	Other <sup>e</sup>
		Drug <sup>a</sup>	Safety <sup>b</sup>					
-2								Admission to the unit in the evening; Physical examination <sup>f</sup> ; Urine drug screening; alcohol breath test; Urine pregnancy test (if applicable)
-1	-2.5 h							Start water restriction 2 hours before start of breakfast
	-0.5 h	X <sup>g,h</sup>	X <sup>g</sup>	X		X <sup>k</sup>	X	Start 24-hour ECG registration by Holter; Standard breakfast
	0 h							
	1 h	X <sup>h</sup>				X		
	2 h	X <sup>h</sup>				X		Resume water intake
	3 h	X <sup>h</sup>				X		
	4 h	X <sup>h</sup>				X		Standard lunch <sup>l</sup>
	5 h	X <sup>h</sup>				X		
	6 h	X <sup>h</sup>				X		
	8 h	X <sup>h</sup>				X		Resume diet; Randomization (only in first treatment session) <sup>i</sup>
1	24 h / predose					X <sup>k</sup>	X	Stop 24-hour ECG registration by Holter; Intake study medication q8h with standard meals <sup>m</sup>
	4 h				X			
2		X <sup>g,h</sup>			X <sup>k</sup>		X	Intake study medication q8h with standard meals <sup>m</sup>
3		X <sup>g,h</sup>			X <sup>k</sup>		X	Intake study medication q8h with standard meals <sup>m</sup>
4		X <sup>g,h</sup>			X <sup>k</sup>		X	Intake study medication q8h with standard meals <sup>m</sup>
5	-2.5 h							Start water restriction 2 hours before start of breakfast
	-0.5 h / predose	X <sup>g,h</sup>	X <sup>g</sup>	X		X <sup>k</sup>	X	Start 24-hour ECG registration by Holter; Standard breakfast
	0 h							Intake study medication <sup>m</sup>
	1 h	X <sup>h</sup>				X		
	2 h	X <sup>h</sup>				X		Resume water intake
	3 h	X <sup>h</sup>				X		
	4 h	X <sup>h</sup>			X <sup>n</sup>	X		Standard lunch <sup>l</sup>
	5 h	X <sup>h</sup>				X		
	6 h	X <sup>h</sup>				X		
	8 h	X <sup>h</sup>				X		Resume diet
6	24 h		X <sup>g</sup>	X	X <sup>k,n</sup>	X <sup>k</sup>	X	Stop 24-hour ECG registration by Holter
								Discharge from unit after morning assessments; Day 6 is the first day of the washout period, if applicable

*Flowchart continues on next page*

**Treatment A, B, C and D, cont'd:**

- <sup>a</sup> Pharmacokinetic sample had to be drawn within 5 minutes after safety ECG recording or Holter extraction time point.
- <sup>b</sup> Biochemistry sample had to be taken fasted for at least 7 hours, before breakfast.
- <sup>c</sup> Safety ECG and 12-lead Holter extracted ECG had to be performed in supine position, after at least 10 minutes rest in supine position. For Holter extracted ECG: triplicate 10-second recording collected at 60-second intervals. For safety ECG: single 12-lead ECG.
- <sup>d</sup> Blood pressure and pulse (supine, after at least 5 minutes rest, and standing, after at least 1 minute standing) had to be measured just before the start of the 10-minute rest period prior to safety ECG recording or Holter extraction time point.
- <sup>e</sup> Adverse events and concomitant medication were monitored throughout the study from the signing of the ICF onwards until the last study-related activity.
- <sup>f</sup> Physical examination included skin examination.
- <sup>g</sup> Before the start of breakfast, within 5 minutes after safety ECG recording or Holter extraction time point.
- <sup>h</sup> For determination of telaprevir and moxifloxacin concentrations, as appropriate.
- <sup>i</sup> Randomization could be performed from the 8 hour time point on Day -1 onwards, but had to be done before the first intake of study medication on Day 1 (only applicable for the first treatment session).
- <sup>j</sup> Within 2 hours before the start of Holter monitoring on Day -1; within 2 hours before study medication intake on Day 5; within 2 hours before the stop of Holter monitoring on Day 6.
- <sup>k</sup> Approximately 10 minutes before the start of breakfast. On Day 6: before the start of breakfast.
- <sup>l</sup> Start standard lunch immediately after 4-hour pharmacokinetic sampling on Day -1 and Day 5.
- <sup>m</sup> Intake of study medication had to be within 30 minutes after the start of the meal.
- <sup>n</sup> Within 5 to 15 minutes before planned time point for Holter extracted ECG.

There had to be a washout period of 8 days between subsequent treatment sessions. Day 6 of a treatment session was the first day of the washout period and Day 8 of the washout period was Day -2 of the next session.

**Flowchart for Follow-up Period After Last Session, and in Case of Dropout Other Than Withdrawal of Consent<sup>a</sup>:**

Day	Blood sample		Urine sample	ECG <sup>c</sup>	Vital Signs <sup>d</sup>	Other <sup>e</sup>
	Drug	Safety <sup>b</sup>				
In case of dropout: at time of dropout or the following morning	X <sup>f</sup>	X	X	X	X	Physical examination <sup>g</sup> , Urine pregnancy test (if applicable)
5, 6 or 7 days after last study medication intake or after dropout		X	X	X	X	Physical examination <sup>g</sup>
30, 31, or 32 days after last study medication intake or after dropout		X	X	X	X	Physical examination <sup>g</sup> Urine pregnancy test (if applicable)

- <sup>a</sup> If a subject withdrew from the study (i.e., withdrawal of consent), he/she could still agree to participate in the safety follow-up procedures/visits.
- <sup>b</sup> Biochemistry sample had to be taken fasted for at least 7 hours. In case of dropout, the biochemistry sample taken at the time of dropout had to preferably be taken fasted for at least 7 hours.
- <sup>c</sup> Safety ECG: ECG had to be performed in supine position, after at least 10 minutes rest in supine position.
- <sup>d</sup> Blood pressure and pulse (supine, after at least 5 minutes rest, and standing, after at least 1 minute standing) had to be measured just before the start of the 10-minute rest period prior to the ECG recording.
- <sup>e</sup> Adverse events and intake of concomitant medication were monitored throughout the study from the signing of the ICF onwards until the last study-related activity.
- <sup>f</sup> For determination of telaprevir and moxifloxacin concentrations, as appropriate.
- <sup>g</sup> Physical examination included skin examination.

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/s/  
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JOANNE ZHANG  
03/15/2011

QIANYU DANG  
03/15/2011

JIANG LIU  
03/15/2011

HAO ZHU  
03/15/2011

SUCHITRA M BALAKRISHNAN  
03/15/2011

NORMAN L STOCKBRIDGE  
03/15/2011

# DSI CONSULT

## Request for Biopharmaceutical Inspections

**DATE:** January 13, 2011

**TO:** Associate Director for Bioequivalence  
Division of Scientific Investigations, HFD-48

**THROUGH:** John Lazor, Pharm.D., Division Director  
Division of Clinical Pharmacology 4  
Office of Clinical Pharmacology

**FROM:** Myung-Joo Patricia Hong, Regulatory Health Project Manager/DAVP

**SUBJECT: Request for Biopharmaceutical Inspections**  
NDA 201-917  
(b)(4) (proposed) – telaprevir, 375 mg tablet  
Vertex Pharmaceuticals

### Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available) (b)(4)
VX07-950-017: A Phase 1 Single Dose Escalation, & Relative Bioavailability Study of Telaprevir in Healthy Subjects	David Carter, MD Covance Clinical Research Unit 313 East Anderson Lane, Bldg 3, Suite 200 Austin, TX 78752	(b)(4)

### Note to DSI:

This study was not designed as a traditional “pivotal BE” study. It was designed to assess the relative bioavailability of the film-coated tablet (proposed commercial formulation) to the uncoated tablet (Phase 3 formulation) and was built into a dose proportionality study. However, it is currently being reviewed and evaluated as a BE study, as it contains the only PK data available to bridge the intended commercial formulation to the formulation used in the Phase 3 studies.

In addition to not following a traditional BE study design, the results of the formulation comparison indicate the criteria for BE acceptance were not met. The clinical pharmacology reviewer will address the study design deficiencies in the course of her review. In addition, the failure to meet BE acceptance criteria and the clinical impact of differences in BA for the commercial formulation will be a review issue.

Please contact the primary clinical pharmacology review, Shirley Seo, or the team leader, Sarah Robertson, for further discussion or clarification of these issues.

**International Inspections:**

**(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)**

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **April 1, 2011**. We intend to issue an action letter on this application by **May 23, 2011**.

Should you require any additional information, please contact Shirley Seo (6-1447) or Sarah Robertson (6-1637).

Concurrence:

Shirley Seo, PhD

Sarah Robertson, PharmD

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/s/  
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MYUNG JOO P HONG  
01/14/2011

KELLIE S REYNOLDS  
01/14/2011

I am signing this request as acting DCP4 director. The division director (John Lazor) is aware of the request and provided comments.



CDER Consult Request  
Vertex Corporation, NDA-201,917

Date: December 23, 2010

From: Lisa Naeger, PhD, CPH  
To: CDRH

NDA: 201,917  
Sponsor: Vertex, Inc.  
Product: Telaprevir  
RE: COBAS® TaqMan® HCV Test, v2.0 with HPS  
Completion Requested Date: January 21, 2011

**BACKGROUND:**

Two NDA applications, telaprevir and boceprevir, have come in to our Division for the treatment of chronic HCV using the COBAS® TaqMan HCV Test, v2.0 (for use with The High Pure System). In telaprevir viral load results in Studies 108 and 111, we have seen much fluctuation or “blipping” (jumping around of results from below limit of detection [BLOD; <10 IU/mL] and below limit of quantification [BLOQ; <25 IU/mL]. This viral load fluctuation is not necessarily unexpected for patients currently on anti-HCV therapy at the time of measurement. However, what is unexpected in this case is that the fluctuations are frequently observed in patients who have been off anti-HCV therapy and are currently several weeks into their treatment-free follow-up phase. This does not appear to be the case in a third study, Study 216. The vendor for Studies 108 and 111 was (b) (4) and the vendor for Study 216 was (b) (4). Furthermore, in the other NDA for boceprevir, which used the vendor (b) (4), blipping back and forth from BLOD and BLOQ in the treatment-free follow-up phase was a relatively rare occurrence.

The primary endpoint for efficacy in these studies and for previously approved products is defined as SVR24 (sustained virologic response at Week 24) using BLOD. However, BLOD is a different value depending on which assay was used. Achievement of an SVR24 with standard-of-care has been interpreted as the subject clearing the virus and long term follow-up has been consistent with this based on previous studies with standard-of-care. The current NDA applications add telaprevir or boceprevir onto the standard-of-care, which significantly increase SVR rates. Given that the package insert for the COBAS assay indicates the lower limit of quantification is 23 IU/mL and the fact that prior products for treatment of chronic HCV were approved using <50 IU/mL, we are considering using <25 IU/mL or BLOQ for the primary endpoint efficacy analysis.

## CONSULT QUESTIONS:

1. Do you agree with changing the criteria for the primary endpoint efficacy analysis from <10 IU/mL BLOD to <25 IU/mL BLOQ?
2. We have two NDA applications and studies within an application with different variability in the viral load results in the <25 IU/mL range over time, despite the same assay being used. We are not yet sure what if anything this means clinically. Having reviewed the assay, how would you interpret results at the lower end of quantification <25 IU/mL – specifically viral load results that bounce from <10 IU/mL to <25 IU/mL back to <10 IU/mL? Is this a true measure of detectable HCV, an artifact of the assay, operator or run variability? How often would you expect to obtain a result of HCV RNA detectable but BLOQ in a panel of plasma samples from a patient population with no history of HCV infection?
3. In the COBAS label, Section E, Tables 5-8, the component of Variance %CV results seem to indicate that reproducibility is variable on the lower end of viral load 23-50 IU/mL. Is this a correct interpretation? If so, should caution be used in interpreting test results <50 IU/mL?
4. Does the fact that different vendors performed the HCV viral load assays in the different studies seem a plausible explanation for the difference in “blipping” from BLOD and BLOQ in the different studies and applications? If so, what are the potential factors (e.g., differences in assay setup, differences in data analysis, contamination, etc.) that might explain why two different sites using the same standardized assay have different frequencies of these observations?

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/s/  
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STACEY MIN  
12/23/2010



CDER Consult Request  
Vertex Corporation, NDA-201,917

Date: December 22, 2010

From: Lisa Naeger, PhD, CPH  
To: CDRH

NDA: 201,917  
Sponsor: Vertex, Inc.  
Product: Telaprevir  
RE: COBAS® TaqMan® HCV Test, v2.0 with HPS  
Completion Requested Date: January 21, 2011

**BACKGROUND:**

Two NDA applications, telaprevir and boceprevir, have come in to our Division for the treatment of chronic HCV using the COBAS® TaqMan HCV Test, v2.0 (for use with The High Pure System). In telaprevir viral load results in Studies 108 and 111, we have seen much fluctuation or “blipping” (jumping around of results from below limit of detection [BLOD; <10 IU/mL] and below limit of quantification [BLOQ; <25 IU/mL]. This viral load fluctuation is not necessarily unexpected for patients currently on anti-HCV therapy at the time of measurement. However, what is unexpected in this case is that the fluctuations are frequently observed in patients who have been off anti-HCV therapy and are currently several weeks into their treatment-free follow-up phase. This does not appear to be the case in a third study, Study 216. The vendor for Studies 108 and 111 was (b) (4) and the vendor for Study 216 was (b) (4). Furthermore, in the other NDA for boceprevir, which used the vendor (b) (4), blipping back and forth from BLOD and BLOQ in the treatment-free follow-up phase was a relatively rare occurrence.

The primary endpoint for efficacy in these studies and for previously approved products is defined as SVR24 (sustained virologic response at Week 24) using BLOD. However, BLOD is a different value depending on which assay was used. Achievement of an SVR24 with standard-of-care has been interpreted as the subject clearing the virus and long term follow-up has been consistent with this based on previous studies with standard-of-care. The current NDA applications add telaprevir or boceprevir onto the standard-of-care, which significantly increase SVR rates. Given that the package insert for the COBAS assay indicates the lower limit of quantification is 23 IU/mL and the fact that prior products for treatment of chronic HCV were approved using <50 IU/mL, we are considering using <25 IU/mL or BLOQ for the primary endpoint efficacy analysis.

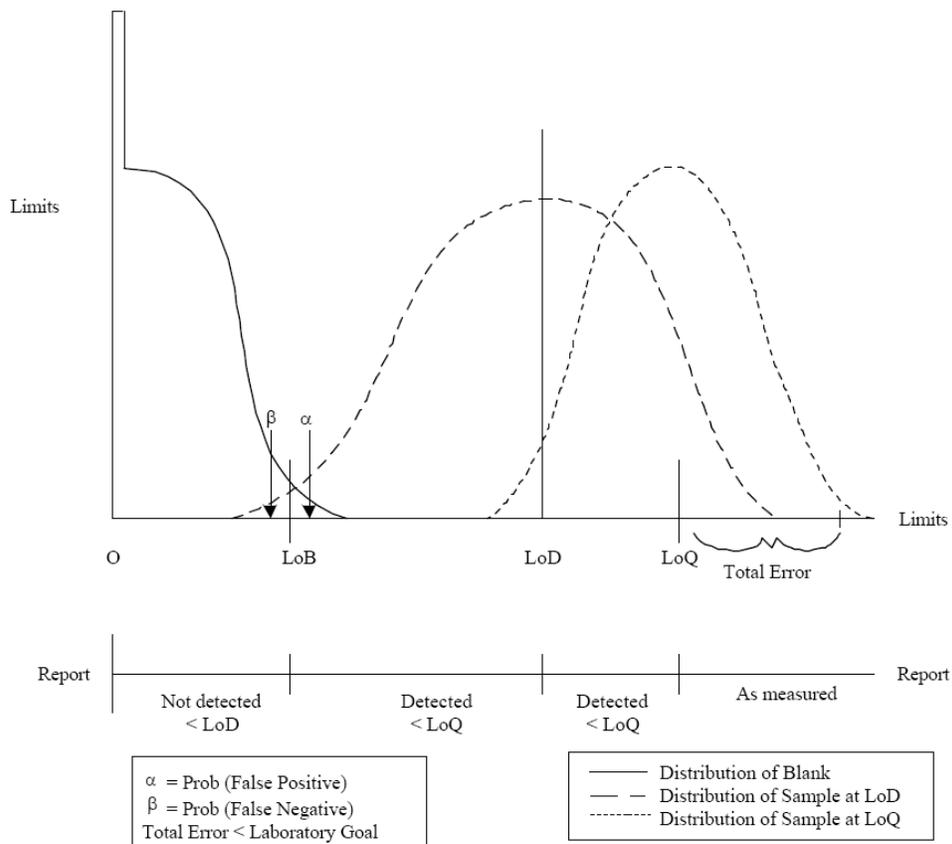
**CDER CONSULT QUESTIONS / CDRH/OIVD Response:**

1. Do you agree with changing the criteria for the primary endpoint efficacy analysis from <10 IU/mL BLOD to <25 IU/mL BLOQ?

*Current recommendations from the AASLD recognize below 50 IU/ml as “undetectable” and sufficient for defining SVR. The assay has only been approved for an LoQ of 25 IU/ml. Below this is an unquantifiable measurement and should not be used for determining SVR. Samples will be positive at varying rates below this measurement. A truly negative sample will be below the LoD.*

*We have done analyses for several studies using less than 50 IU/ml or less than 25 IU/ml (no numerical assignments) to define SVR and have seen no difference in the percentage of patients assigned an SVR status.*

*Please see the description below on the relationship between the limit of blank, the LoB, the LoD, and the LoQ. The LoQ represents the lowest limit of the accurate measuring range. Truly negative samples should not be above the LoD however you can see that a sample with LoD has a bell shaped distribution (see EP-17P for more information on this figure).*



**Figure 5. Distribution of Results for Blank, Low Positive at LoD, and Low Positive at LoQ.** Report recommendations are shown for results at various points relative to Limits.

2. We have two NDA applications and studies within an application with different variability in the viral load results in the <25 IU/mL range over time, despite the same assay being used. We are not yet sure what if anything this means clinically. Having reviewed the assay, how would you interpret results at the lower end of quantification <25 IU/mL – specifically viral load results that bounce from <10 IU/mL to <25 IU/mL back to <10 IU/mL?

*As noted above, clinically any result below 50 IU/ml is used to define SVR. If a sample falls between the LoD and the LoQ one would expect some variability in the absolute value of that sample. The sample is positive (above the LoD) but not quantifiable (below the LoQ). See the figure above.*

Is this a true measure of detectable HCV, an artifact of the assay, operator or run variability?

*There is an inherent variability in this portion of the assay (10 – 25 IU/ml) and thus results in this area of the assay are not reliable for determining SVR.*

How often would you expect to obtain a result of HCV RNA detectable but BLOQ in a panel of plasma samples from a patient population with no history of HCV infection?

*In our specificity studies using patients with signs and symptoms similar to those of viral hepatitis we have not seen any samples with RNA detectable but below the LoQ. Please refer back to the graph in response to question #1. A truly negative HCV sample should not test above the LoD. If truly negative samples are testing positive, there is a problem with assay performance due to operator error, machine calibration, or contaminated assay reagents.*

3. In the COBAS label, Section E, Tables 5-8, the component of Variance %CV results seem to indicate that reproducibility is variable on the lower end of viral load 23-50 IU/mL. Is this a correct interpretation?

*NO,  $\%CV = (SD/Mean) * 100$ . Since the mean is much lower at the lower concentrations, the CV is higher even though the SD is also lower.*

If so, should caution be used in interpreting test results <50 IU/mL?

*AASLD considers values below 50 IU/ml to be sufficient for determining SVR. Samples falling between the LoD and LoQ are only positive, not a specific viral load, but they are positive. Samples testing with values below the LoD are negative.*

4. Does the fact that different vendors performed the HCV viral load assays in the different studies seem a plausible explanation for the difference in “blipping” from BLOD and BLOQ in the different studies and applications?

*Yes. Again, it could be machine build, machine calibration, or operator associated. Refer to the figure above and note the variability of results with a sample at LoD.*

If so, what are the potential factors (e.g., differences in assay setup-sample handling, improper cleaning, improper workflow, differences in data analysis-no, contamination-yes, etc.) that might explain why two different sites using the same standardized assay have different frequencies of these observations?

*There are many factors that can contribute to the perceived differences. These include but are not limited to sample handling, improper cleaning, and improper workflow. Data analysis should not affect the results unless machine settings have been changed. Proper controls should be in place to detect contamination (i.e. negative controls run on each plate, changes in standard curve values).*

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/s/  
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MYUNG JOO P HONG  
02/03/2011

# DSI CONSULT: Request for Clinical Inspections

**Date:** December 9, 2010

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

**Through:** *Debra Birnkrant, M.D.*  
*Director, Division of Antiviral Products*  
*Russell Fleischer, PA-C, MPH*  
*Medical Reviewer*

**From:** *Myung-Joo Patricia Hong, Regulatory Health Project Manager/DAVP*

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 201-917

Applicant/ Applicant contact information: Vertex Pharmaceuticals, Inc.

Drug Proprietary Name: (b) (4) (proposed)

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 virus infection in adults

PDUFA: May 23, 2011

Action Goal Date: May 23, 2011

Inspection Summary Goal Date: March 1, 2011 (if possible)

**II. Protocol/Site Identification**

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

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
169-John Vierling, MD St. Lukes Episcopal Hospital Baylor College of Medicine Advanced Liver Therapies 6620 Main Street #1505 Houston, Texas 77030 Ph: 832-355-8966 Fax: 832-355-8965 vierling@bcm.edu	<b>VX07-950-108:</b> A Phase 3 study of 2 dose regimens of TVR in Pegasys® and Copegus® in treatment-naïve subjects with genotype 1 CHC	31	Treatment of chronic hepatitis C in adults
201-Peter Ferenci, MD Univ. Klinik für Innere Medizin III Abteilung für Gastroenterologie und Hepatologie Währinger Gürtel 18-20 Vienna Austria 1090 Ph: 43-1404006589 Fax: 43-1404004735 <a href="mailto:peter.ferenci@meduniwien.ac.at">peter.ferenci@meduniwien.ac.at</a>	<b>VX07-950-108:</b> A Phase 3 study of 2 dose regimens of TVR in Pegasys® and Copegus® in treatment-naïve subjects with genotype 1 CHC	22	Treatment of chronic hepatitis C in adults

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
<p>IT00146-Pietro Andrecone, MD                      Universita Degli Study di Bologna                      Via Masserenti 9                      Dipartimento de Medicina Clinica                      Bologna, Italy 40138                      Ph: 39-0516363618                      Fax: 39-051345806                      pietro.andreone@unibo.it</p>	<p><b>VX-950-C216:</b> A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of TVR (with and without delayed start) combined Pegasys® and Copegus® in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment</p>	<p>25</p>	<p>Treatment of chronic hepatitis C in adults</p>
<p>US0073-Michael Ryan, MD                      Digestive and Liver Disease Specialist                      885 Kempsville Road,                      # 114                      Norfolk, Virginia 23502                      Ph: 757-466-0165                      Fax: 757-466-7504                      mryandlds@yahoo.com                      AND                      mjrresearch@DLDS.org</p>	<p><b>VX-950-C216:</b> A randomized, double-blind, placebo-controlled, Phase III trial of 2 regimens of TVR (with and without delayed start) combined Pegasys® and Copegus® in subjects with chronic genotype 1 hepatitis C infection who failed prior pegylated interferon plus ribavirin treatment</p>	<p>15</p>	<p>Treatment of chronic hepatitis C in adults</p>

### **III. Site Selection/Rationale**

*Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.*

**This is a new molecular entity. The sites were selected because they all had relatively high enrollment. Also, the trials were conducted primarily in the US and EU. Therefore, it seems important to evaluate at least one US and one ex-US site for each trial.**

#### **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):

#### **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 (Enrollment of large numbers of study subjects. This would be the first approval of this new drug and much of the limited experience has been at foreign sites, so it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

#### **Five or More Inspection Sites (delete this if it does not apply):**

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *N/A*

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

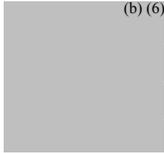
### **IV. Tables of Specific Data to be Verified (if applicable)**

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

Page 5-Request for Clinical Inspections

Should you require any additional information, please contact *Myung-Joo Patricia Hong* at 301-796-0807 or *Russell Fleischer* at 301-796-1500.

Concurrence: (as needed)



(b) (6)

Medical Team Leader

Medical Reviewer

12/9/10

Division Director (for foreign inspection requests or requests for 5 or more sites only)

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MYUNG JOO P HONG  
12/09/2010

# REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

**\*\*Please send immediately following the Filing/Planning meeting\*\***

TO: <b>CDER-DDMAC-RPM</b>	FROM: (Name/Title, Office/Division/Phone number of requestor) <b>Myung-Joo Patricia Hong Regulatory Project Manager OND/OAVP/DAVDP 301-796-0807</b>
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REQUEST DATE 12/2/10	IND NO.	NDA/BLA NO. 201-917	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG <b>Telaprevir</b>	PRIORITY CONSIDERATION Priority review by May 23, 2011	CLASSIFICATION OF DRUG Antiviral	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) <b>April 15, 2011</b>
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NAME OF FIRM: <b>Vertex Pharmaceuticals, Inc.</b>	PDUFA Date: <b>May 23, 2011</b>
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## TYPE OF LABEL TO REVIEW

<b>TYPE OF LABELING:</b> (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input checked="" type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<b>TYPE OF APPLICATION/SUBMISSION</b> <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	<b>REASON FOR LABELING CONSULT</b> <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION
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**EDR link to submission:**

EDR Location: <\\CDSESUB1\EVSPROD\NDA201917\201917.enx>

**Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.**

**COMMENTS/SPECIAL INSTRUCTIONS:**

Vertex Pharmaceuticals, Inc. submitted a new NDA application for telaprevir. Telaprevir, in combination with peginterferon alfa and ribavirin, is being proposed for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease including both patients who are treatment naïve and those who have been treated previously with interferon alfa alone or in combination with ribavirin. Telaprevir is a NME product.

Please review promotional materials: PI, cartons and container labeling, and MG, etc.

Mid-Cycle Meeting: February 22, 2011  
GAM # 1: January 24, 2011  
GAM # 2: March 22, 2011  
GAM # 3: April 22, 2011  
Labeling Meetings: TBD  
Wrap-Up Meeting: TBD  
Advisory Committee Meeting: April 28, 2011  
**Reference ID: 2871975**

SIGNATURE OF REQUESTER Myung-Joo Patricia Hong, RPM	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> e-MAIL <input type="checkbox"/> HAND

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MYUNG JOO P HONG  
12/03/2010