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*APPLICATION NUMBER:*

**201917Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	May 2, 2011
<b>From</b>	Linda L. Lewis, M.D. Medical Team Leader Division of Antiviral Products, CDER, FDA
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	201917/000
<b>Supplement#</b>	Original submission
<b>Applicant</b>	Vertex Pharmaceuticals, Inc. 130 Waverly Street Cambridge, MA 02139-4242
<b>Date of Submission</b>	November 22, 2010
<b>PDUFA Goal Date</b>	May 23, 2011
<b>Proprietary Name / Established (USAN) names</b>	Incivek™/telaprevir
<b>Dosage forms / Strength</b>	Tablets/375 mg
<b>Proposed Indication(s)</b>	1. Telaprevir, in combination with peginterferon alfa and ribavirin, is indicated 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, including prior null responders, partial responders, and relapsers.
<b>Recommended:</b>	<i>Approval – with modifications to proposed labeling</i>

### 1. Introduction

[**Note:** This CDTL Review was written prior to the Antiviral Drugs Advisory Committee meeting held on April 28, 2011 and reflects the findings of each discipline review and the inter-disciplinary discussions of the FDA review team. Sections 9, 12, and 13 incorporate the discussions and recommendations of the Advisory Committee.]

Telaprevir, a novel direct-acting antiviral drug, 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. This NDA contains the results of the nonclinical and clinical development program conducted by Vertex Pharmaceuticals. The submission contains study reports characterizing the chemistry/manufacturing processes, nonclinical toxicology, in vitro and clinical virology, clinical pharmacology (including multiple drug-drug interaction studies), in addition to clinical safety and efficacy, and dose recommendations in a wide variety of patients at different stages

of disease and with different prior treatment history. This review will summarize the findings of the FDA team of reviewers and describe the conclusions and recommendations of all disciplines.

In particular, this NDA proposes a new approach to determining the optimal duration of treatment for patients with chronic HCV infection known as “response-guided therapy” (RGT). This strategy allows patients with early evidence of viral suppression to receive a shorter course of Peg-IFN/ribavirin therapy than those who do not achieve an early virologic response and thus minimize potential toxicity. This review will describe the data supporting the use of RGT and the patient populations for which it may be appropriate.

## 2. Background

Chronic HCV infection represents a significant global public health problem with an estimated 180 million people infected worldwide. In the U.S., about 4 million people were estimated to be seropositive for HCV antibodies in a 2002 review, with about 80% of those developing chronic infection. Chronic HCV is the leading cause of death from liver disease and the leading indication for liver transplantation in the U.S. Primary modes of transmission are those related to blood exposure, such as illicit injection drug use, occupational exposure, and receipt of a blood product prior to universal donor screening. Sexual transmission accounts for a small proportion of cases and pediatric patients may acquire infection through perinatal transmission from an infected mother. In the U.S., Blacks/African Americans and other minorities have higher rates of chronic HCV than Caucasians and have historically been under-represented in clinical trials of new treatments.

The current standard of care for the treatment of chronic HCV infection includes a regimen of Peg-IFN/ribavirin for 24 to 48 weeks, depending on HCV genotype. While the once weekly injections of Peg-IFN are an improvement over earlier interferon regimens, the toxicity profile of Peg-IFN is daunting for both prescribers and patients. Adverse drug reactions commonly associated with Peg-IFN include fatigue, headache, nausea, chills, insomnia, fever, flu-like symptoms, neutropenia, depression, irritability, alopecia, and pruritus, to name only a few. As stated in the Boxed Warning of a representative alpha interferon product label, “alpha interferons may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders.” In addition, ribavirin use is associated with hemolytic anemia and is considered teratogenic and potentially carcinogenic. Thus, a treatment regimen that shortens the duration of Peg-IFN/ribavirin treatment and lessens their toxicity has been a key goal for researchers in the field and pharmaceutical sponsors.

Treatment with Peg-IFN/ribavirin can successfully eradicate HCV and provide durable “cure” or Sustained Virologic Response (SVR). SVR has become the standard endpoint for clinical trials and is defined as undetectable HCV RNA documented 24 weeks following the completion of treatment (SVR24). Patients’ prospects for achieving SVR after a course of Peg-IFN/ribavirin are negatively influenced by the HCV genotype (genotype 1, especially subtype 1a), high HCV RNA level at start of treatment, race/ethnicity (Blacks/African Americans), age (older patients), and other demographic and disease factors. HCV genotype 1

accounts for about 70% of the chronic HCV in the U.S. and requires longer therapy (48 weeks) than genotypes 2 and 3 (24 weeks). SVR can be achieved in less than half of patients with genotype 1 who receive a 48 week regimen of Peg-IFN/ribavirin. Thus, a treatment regimen achieving higher rates of SVR in patients with genotype 1 would provide an important public health benefit.

Telaprevir is a linear, peptidomimetic inhibitor of the HCV NS3/4A protease. NS3/4A has become an actively investigated HCV target for antiviral small molecules (b) (4)

This new class of direct-acting antiviral drugs is expected to have a dramatic impact on treatment of chronic HCV by providing improved SVR rates and by decreasing the duration of Peg-IFN/ribavirin required for treatment.

Vertex has partnered with Mitsubishi Tanabe Pharma for development of telaprevir in Asia and with Tibotec for development in other parts of the world. Tibotec is managing the concurrent submission to the European Medicines Agency for marketing authorization in the E.U. To date, telaprevir has not been approved for use in any country.

### 3. CMC/Device

The NDA submission included adequate information to allow the CMC review team to evaluate the characteristics and quality of the drug substance (b) (4), and the drug product. For a complete discussion of these topics, please refer to the full Chemistry Review provided by the CMC review team led by Dr. George Lunn. The following descriptions of key CMC issues are summarized from the Chemistry Review.

- **General product quality considerations**

Telaprevir drug substance (chemical name: (1S,3aR,6aS)-2-[(2S)-2-((2S)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl)amino)-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-1-carboxamide) is a lipophilic, white to yellow (b) (4) powder, poorly soluble in water. As noted in the CMC Review, a Quality by Design approach has been used for the manufacture of telaprevir drug substance. Each step in the procedure has been evaluated and for each parameter a Normal Operating Range (NOR) and a Proven Acceptable Range (PAR) have been determined on the basis of experiments in which the parameter was varied. The critical/non-critical nature of each step was also assessed. Adequate specifications are provided for the starting materials, solvents, and reagents and acceptable drug substance specification with appropriate testing was provided in the NDA.

(b) (4)  
The specifications and dissolution of the (b) (4) were critically evaluated as dissolution is proposed (b) (4) of telaprevir tablets. Review of the data confirmed a correlation between

(b) (4)

Final drug product is formulated as a tablet for oral administration containing 375 mg of telaprevir drug substance. (b) (4)

(b) (4) film coated to form the final drug product. A Quality by Design approach was also used in the drug product manufacturing process and the Applicant provided acceptable descriptions of processes and controls.

The sponsor proposes to package telaprevir tablets in blister packs containing 2 tablets in a single blister, with 3 blisters in a strip. Each blister holds one adult dose and each strip contains one day of dosing. Blister packs are packaged in a carton of 7 strips per carton (a week of dosing) with 4 cartons packed in a 28-day box. Each box will, therefore, provide a 28-day supply of telaprevir for an adult patient. A bottle containing 168 tablets (a 28-day supply for a single patient) will also be supplied for institutional use. The Applicant has requested a shelf-life of 24 months for the tablets, which is well supported by the 24 months of stability data submitted with the NDA.

- ***Facilities review/inspection***

The Office of Compliance has been consulted to complete facilities inspections for drug substance (b) (4). In addition to two inspections already conducted ( (b) (4) ), there are three additional required inspections: (b) (4). Due to difficulties scheduling the international site inspections, the Office of Compliance will not complete the inspections until mid-May, 2011.

- ***Other notable issues (resolved or outstanding)***

At the time of writing this CDTL Review, the CMC review team can not fully recommend approval of telaprevir as the manufacturing site inspections have not been completed. However, no other CMC issues have been identified that would preclude approval.

## **4. Nonclinical Pharmacology/Toxicology**

The Applicant submitted a portfolio of nonclinical study reports describing the results of acute and chronic toxicity studies, genotoxicity studies, and reproductive toxicology studies. For a complete discussion of the in vitro safety assessments and animal toxicology studies, please

refer to the Pharmacology/Toxicology Review performed by Dr. Mark Powley. Key points from his review are summarized in this section.

- ***General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise)***

Oral bioavailability of telaprevir varies by species, from < 22% in rabbits, to 33-52% in rats, to 43-67% in fasted dogs and 70-95% in fed dogs. Animal toxicokinetic studies identified the marked food effect on exposure that is also observed in humans receiving telaprevir. Following oral dosing in rats, radio-labeled telaprevir is distributed widely in tissues with highest concentrations in gastrointestinal and liver tissue. The metabolic profile was similar in rats, dogs, and humans. Telaprevir is extensively metabolized by CYP3A4 in vitro and in vivo. Three major metabolites (VRT-127934, VRT-922061, and pyrazinoic acid) reached exposures > 10% of total drug exposure in humans.

In the pivotal 6-month, repeat-dosing studies in rats, the target organs for toxicity were bone marrow/hematologic system, liver, spleen, and testes. Decreases in hemoglobin (Hgb) and hematocrit were identified in rats with compensatory increases in circulating reticulocytes. Minor bone marrow changes were thought to be part of the compensatory response to decreases in circulating red blood cells. Increased spleen weight and histologic changes in the spleen were also consistent with compensatory response to red blood cell changes. Increased liver weight was accompanied by increases in liver transaminases and hepatocellular hypertrophy and single-cell hepatocellular necrosis. These changes may be related to the induction of CYP3A4 isoenzyme activity (CYP3A4 activity not induced in human hepatocytes). Decreased weight of testes and epididymis were accompanied by degeneration of the germinal epithelium, degeneration/necrosis of individual germ cells, increased exfoliated germ cells, decrease in proportion of motile sperm, and hypospermia/aspermia. Most of these changes were reversible, although the indicators of hepatotoxicity persisted during the recovery period.

The pivotal toxicology study in dogs, a 9-month, repeat-dosing study, identified similar target organs for toxicity (bone marrow/hematology and liver). Red blood cell parameters such as Hgb, hematocrit, MCH, and MCHC were decreased significantly and accompanied by increased circulating reticulocytes. Increased liver weight was accompanied by histologic changes of mixed perivascularitis, sinusoidal hypercellularity, and increased eosinophilic pigmentation in Kupffer cells. Chronic active vasculitis affecting multiple organs was observed in dogs with lesions identified in stomach, epididymis, heart, and ovary but was thought to be consistent with canine polyarteritis and may have limited relevance in humans. Overall, the histologic changes in dogs were reversible and limited to the higher two doses studied.

As noted in Dr. Powley's review, no adverse drug-related effects on neurological activity or respiratory parameters were detected in rats. Minor effects occurred in the in vitro cardiotoxicity evaluations (hERG channel study and Purkinje fiber study) but lacked in vivo correlates in either dogs or humans.

- ***Carcinogenicity***  
Telaprevir is not thought to be genotoxic based on negative findings in the Ames assay, in vitro chromosomal aberration assay, and in vivo rat micronucleus assay. Because the genotoxicity battery was negative and because telaprevir will only be given for 12 weeks, the Applicant was not required to perform carcinogenicity studies.
- ***Reproductive toxicology***  
No adverse drug effects on embryofetal development were identified in rats or mice. In rats, perinatal/postnatal findings were limited to a decrease in pup weight/litter in offspring of dams receiving telaprevir. As noted in the summary of general toxicology considerations above, male rats developed gross and histologic findings in the testes. A fertility study in rats identified male reproductive toxicity and effects on % preimplantation loss, % nonviable embryos, and % nonviable conceptuses/litter. These fertility effects are presumed to be due to the male reproductive system toxicity but the contribution of female reproductive toxicity can not be completely ruled out due to limitations of study design. The Applicant suggested that the testicular toxicity observed in rats is species-specific and may have questionable relevance for humans. Because the species specificity of testicular findings was not completely established, assessment of hormonal markers of testicular toxicity (FSH, LH, inhibin-B) was incorporated into the Phase 2 clinical trials.
- ***Other notable issues (resolved or outstanding)***  
Multiple impurities have been identified in the final telaprevir drug substance or drug product. The proposed specifications appear to be acceptable based on a rat toxicology study and the evaluation of genotoxic potential of the process impurities.

Based on the reproductive toxicology studies, telaprevir is considered a Pregnancy Category B drug (no studies in pregnant women but no significant embryofetal toxicity in animal studies). However, telaprevir must be administered in combination with ribavirin, a Pregnancy Category X drug, and Peg-IFN, a known abortifacient, so adequate contraception is critical. The telaprevir label will include information regarding the teratogenic potential of ribavirin and prescribers will be instructed to counsel patients regarding the potential harm to pregnant women and fetuses and the need for adequate contraception (see also Section 5, Clinical Pharmacology/Biopharmaceutics, Drug-drug interactions).

## 5. Clinical Pharmacology

Telaprevir was extensively evaluated to assess its clinical pharmacologic characteristics, to determine dose- and exposure-response relationships, and to identify relevant drug-drug interactions. For a complete discussion of the clinical pharmacology issues, please refer to the Clinical Pharmacology Review submitted by Dr. Shirley Seo and the collaborating team of reviewers (Dr. Jiang Liu, Pharmacometrics Reviewer and Dr. Shashi Amur, Pharmacogenomics Reviewer). The following points summarize the conclusions of the Clinical Pharmacology reviewers.

- ***General clinical pharmacology/biopharmaceutics considerations***

Telaprevir was evaluated at doses ranging from 450 mg to 1875 mg in healthy volunteers. Telaprevir exhibits greater than dose proportional increases in exposure within the therapeutic dose range; it has time-dependent pharmacokinetics (PK), accumulating 2-fold at steady-state. At the proposed therapeutic dose, telaprevir exposure was slightly lower in subjects with chronic HCV infection compared to healthy volunteers. Following multiple-dose administration of telaprevir in HCV-infected patients, pyrazinoic acid, VRT-127394 (R-diastereomer of telaprevir), and VRT-0922061 are the predominant metabolites, present at >10% of total drug-related material at steady-state. However, the major metabolites demonstrated significantly lower antiviral activity compared to the parent drug.

Telaprevir appears to be absorbed in the small intestine. Exposure is significantly affected by food, with a 3- to 4-fold increase in exposure when drug is administered with a standard test breakfast. Higher fat content appears to further increase exposure. Exposure may not be adequate when telaprevir is administered in the fasted state and patients were instructed to take doses with a non-low fat meal; consequently, the drug will be labeled to be taken with meals.

- ***Pathway of elimination***

Telaprevir is metabolized primarily by cytochrome P450 CYP3A4; it is a strong inhibitor of CYP3A4 and it is a substrate of P-glycoprotein (P-gp). Approximately 82% of a telaprevir dose is excreted through feces (as both unchanged drug and metabolites), with minimal renal elimination.

- ***Drug-drug interactions***

Based on the determination that telaprevir is metabolized by CYP3A4 and P-gp, and is an inhibitor of CYP3A4, clinically relevant drug interactions were anticipated by the Applicant and multiple drug-drug interaction studies were conducted. Drug interaction studies were conducted characterizing telaprevir's effect on various CYP3A4 substrates and on medications commonly used in patients with chronic HCV infection including: methadone, escitalopram, a combined oral contraceptive, digoxin, multiple HIV antiretrovirals, immunosuppressants, atorvastatin, and midazolam. In addition, the effects of potent CYP3A induction (rifampin) and inhibition (ketoconazole) on telaprevir PK were assessed in vivo. These studies provided adequate information to allow dosing recommendations for telaprevir and potentially interacting drugs used in this population. No drug-drug interactions were identified between telaprevir and ribavirin, however, coadministration with Peg-IFN increased telaprevir exposure about 30%. Telaprevir had no effect on the exposures of these products with which it will be used in combination.

Adjustments will be required in dosing of some drugs and additional clinical monitoring recommended for other drugs during co-administration with telaprevir. The product label will include tables identifying known or anticipated effects on exposure of concomitant medications and the corresponding recommended monitoring or dose adjustment. For example, prescribers will be advised to use caution when coadministering antiarrhythmic drugs because of the potential for increased exposure of these drugs. Telaprevir will be contraindicated in combination with certain drugs that are highly dependent on CYP3A

clearance and that are associated with serious or life-threatening complications at high exposures or that significantly decrease telaprevir exposure, such as ergot derivatives (potential for acute ergot toxicity) and rifampin (potential for loss of effectiveness due to reduced telaprevir levels).

Coadministration of telaprevir and ethinyl estradiol resulted in about 25% decreased exposure of the estradiol. Because ribavirin is teratogenic (Pregnancy Category X), effective contraception during treatment for chronic HCV is critical. The interaction between telaprevir and ethinyl estradiol raised concerns that low-dose oral contraceptives may fail and this issue was referred to our colleagues in the Division of Reproductive and Urologic Products. The consultants from DRUP concluded that although contraceptive efficacy is more closely linked to the progestin component of combined oral contraceptives, the clinical impact of this drug interaction is unknown. Until more data are available, alternative, non-hormonal contraceptive methods will be recommended when patients are taking telaprevir.

- ***Critical intrinsic factors potentially affecting elimination: age, gender, race, hepatic insufficiency, and renal impairment.***

Although not evaluated in specific PK studies, the Applicant evaluated the effects of age, gender, and race on telaprevir exposure across the clinical development program. The Applicant conducted a population PK analysis across selected Phase 2 and Phase 3 trials to assess the impact of these covariates on telaprevir clearance. Race and gender were not found to have significant impact on clearance, however, the population PK model predicted that patients 65 years and older were likely to have the highest exposure, probably due to age-related reduction in renal function.

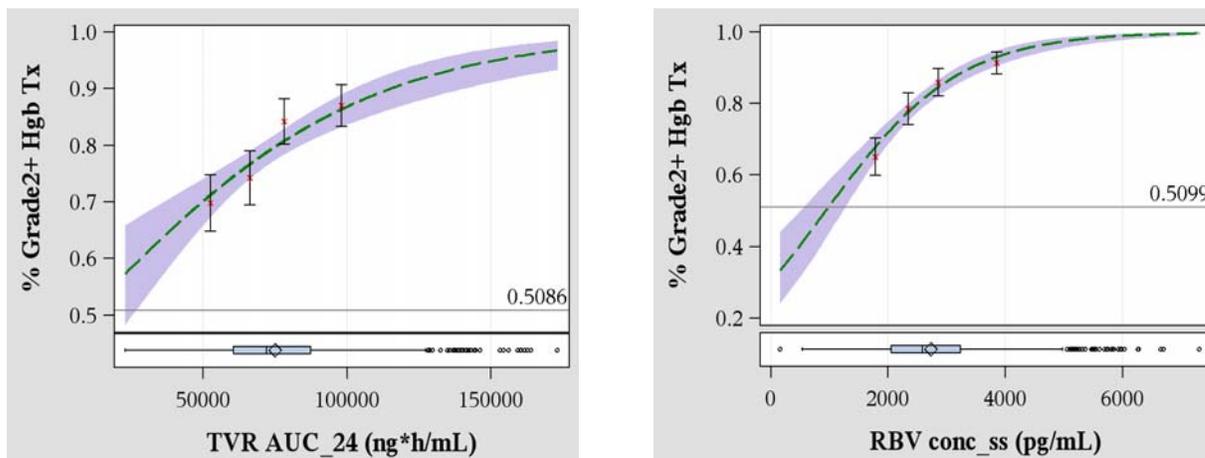
Telaprevir exposure was evaluated in subjects with mild and moderate hepatic impairment. Compared to healthy volunteers, subjects with mild (Child-Pugh class A) impairment were found to have telaprevir exposure decreased by about 15%, while those with moderate (Child-Pugh class B) impairment had telaprevir exposure decreased by greater than 50%. Because the exposure of telaprevir was significantly reduced in subjects with Child-Pugh class B, subjects with Child-Pugh class C have not been studied. The Clinical Pharmacology reviewers agree with the Applicant's recommendation that telaprevir should not be administered to patients with moderate to severe hepatic impairment.

As noted in Dr. Seo's review, "The results of the renal impairment study (reduced study design) conducted by the Applicant were inconclusive. The renal impairment study included only a single dose of telaprevir. The results from this study indicate that following a single dose of telaprevir in patients with severe renal impairment, mean telaprevir  $AUC_{inf}$  increased by 21% and  $C_{max}$  increased by 3%, compared to subjects with normal renal function. Due to telaprevir's non-linear PK, a multiple-dose study would have more accurately characterized the effect of renal impairment on telaprevir steady-state exposure." However, after extensive internal discussion, the Clinical Pharmacology team determined that an additional study is not needed. They concluded that the magnitude of increase in telaprevir exposure following multiple doses was not likely to be great enough to require a dose adjustment in patients with renal impairment.

- ***Relevant issues related to clinical pharmacology arising from investigations by gender, age, including pediatrics and geriatrics, and other demographic-based investigations.***  
Telaprevir has not been specifically evaluated in either pediatric or geriatric patients, although patients 65 years and older are expected to have reduced clearance and higher exposure. PK studies in pediatric patients have been discussed with the Applicant but have not yet been conducted. As noted in the section summarizing critical intrinsic factors, neither gender nor race had an impact on telaprevir clearance based on the Applicant's population PK analysis. No additional demographic interactions or special populations are expected to influence telaprevir exposure.
- ***Thorough QT study or other QT assessment***  
The Applicant conducted two thorough QT studies, one using ketoconazole to boost the telaprevir exposure and one without ketoconazole and also including female subjects. These studies were reviewed by the FDA's Interdisciplinary Review Team for QT Studies (IRT) and found to represent an adequate evaluation of the highest exposures expected in the clinical setting. The IRT concluded telaprevir's effect on QTc prolongation did not reach the threshold for regulatory concern and there appeared to be no clinically relevant effects on PR and QRS intervals.
- ***Other notable issues (resolved or outstanding)***  
Both the Clinical Pharmacology Genomics Group and the Pharmacometrics Group provided valuable analyses and recommendations regarding issues for which there was incomplete clinical trials data. The Pharmacometrics Reviewer evaluated three key issues related to dose selection and treatment duration of telaprevir. The Genomics Reviewer analyzed retrospective genetic substudy data to assess the impact of *IL28B* variants on response to treatment.

For the Pharmacometrics analyses, Dr. Liu first analyzed the telaprevir exposure-response data supporting efficacy and safety of the proposed dose of 750 mg taken thrice daily. Overall, the proposed dosing regimen appears to adequately balance efficacy and safety. The relationships between telaprevir exposure and multiple efficacy endpoints including sustained virologic response (SVR), rapid virologic response (RVR), extended rapid virologic response (eRVR), and viral breakthrough were explored. In general, these exposure-efficacy relationships were not statistically significant, although higher telaprevir exposure was weakly associated with increased SVR24.

On the other hand, higher telaprevir exposure was significantly associated with increased risk of anemia or hemoglobin (Hgb) toxicity defined as Hgb < 10 g/dL or a decrease of 3.5 g/dL from baseline. In a multivariate analysis, the odds ratio of Hgb toxicity associated with a doubling of telaprevir exposure was 2.4 (95% CI: 1.6, 3.6) after adjusting for Peg-IFN and ribavirin exposure. A similar analysis of ribavirin exposure revealed an even more significant relationship, with the odds ratio of Hgb toxicity increasing to 5.2 (95% CI: 3.6, 7.5) with a doubling of ribavirin exposure. These exposure-response relationships are displayed in Figure 1, excerpted from Dr. Liu's review.

**Figure 1: Effect of Telaprevir (TVR) and Ribavirin (RBV) Exposure on Hemoglobin Toxicity<sup>a</sup>**

<sup>a</sup> Hemoglobin toxicity of Grade 2+ (Grade 2+ Hgb Tx) was defined as Hgb < 10 g/dL or any decrease from baseline > 3.5 g/dL.

Exposure-Hgb toxicity analysis was conducted in the pooled patients with T12/PR.

Vertical bars represent rates of Hgb toxicity in each quartile of AUC. The horizontal bar along the AUC axis represents the distribution of AUC (5-95%, 1<sup>st</sup> to 3<sup>rd</sup> quartile, mean, median).

Source: Clinical Pharmacology Review, Pharmacometric Review, NDA 201917.

The exposure-response analyses led to the conclusion that increasing the dose of telaprevir would have only modest impact on increasing SVR but would be expected to have a negative impact on rate of anemia. The exposure-Hgb toxicity analysis also suggested that ribavirin dose reduction is likely to be most effective in managing anemia since the exposure-response relationship is greater than for telaprevir.

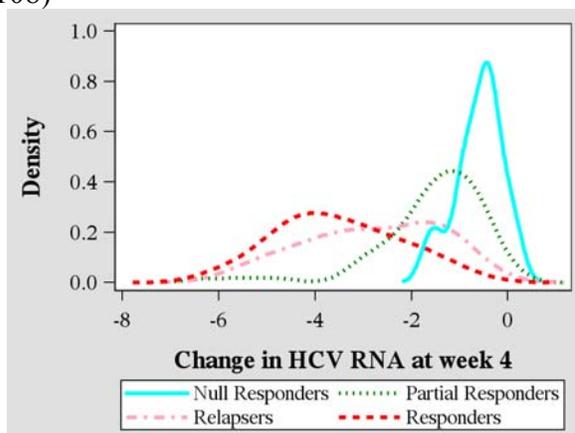
Next, Dr. Liu evaluated the Applicant's proposal to extend the recommendation for RGT to patients who have previously relapsed after completing a standard course of Peg-IFN and ribavirin (prior relapsers). The Applicant submitted adequate and well-controlled clinical trials providing evidence that treatment naïve patients who achieve eRVR can be effectively treated with 24 weeks of Peg-IFN/ribavirin (see Section 7, Clinical/Statistical-Efficacy). Although RGT was not evaluated in prior relapsers in a controlled trial, a small amount of clinical data from earlier trials suggested that prior relapsers achieving eRVR might also respond well to shortened treatment with Peg-IFN/ribavirin. Also, prior relapsers might be expected to respond very much like patients in the treatment naïve population based on the presumed lack of virologic resistance to Peg-IFN and emerging genetic evidence that response to Peg-IFN is dependent, in large part, on host factors (eg. *IL28B*) rather than viral factors.

The Pharmacometrics Review provides a description of evidence from three sources supporting RGT in prior relapsers. A small group of prior relapsers received RGT in one of the Phase 2 trials (Study 107) and another small group were assigned to a T12/PR24 regimen in another Phase 2 trial (Study 106). Across all the Phase 2 and Phase 3 clinical trials, the subgroup of prior relapsers who achieved eRVR had SVR rates > 90%,

regardless of the whether they received 24 or 48 weeks of Peg-IFN/ribavirin. Also, based on Week 4 HCV RNA levels, treatment-naïve subjects receiving Peg-IFN/ribavirin in Study 108 demonstrated similar response patterns compared to treatment-experienced subjects in Study C216 when matched for treatment outcomes (final outcome of Study 108 matched to prior response at entry to Study C216). Figure 2 shows plots of HCV RNA at Week 4 for treatment naïve (Panel A) and treatment experienced (Panel B). In fact, the outcome groups demonstrate remarkably similar HCV RNA profiles at Week 4 regardless of whether they received Peg-IFN/ribavirin for the first time or the second time.

**Figure 2: Distribution of Change in HCV RNA at Week 4 in Cohorts receiving Peg-IFN/ribavirin**

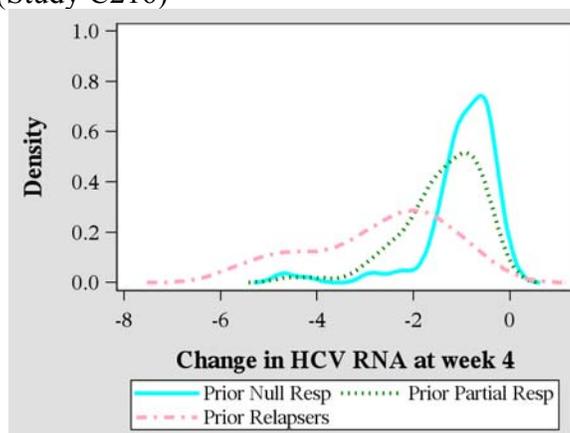
A. Treatment-naïve subjects receiving PR48 according to final treatment outcome (Study 108)



Log change in HCV RNA at week 4

	Mean	Q1	Median	Q3
Relapsers	-2.8	-3.6	-2.9	-1.5
Partial Responders	-1.6	-2.0	-1.4	-0.9
Null Responders	-0.6	-0.9	-0.5	-0.4

B. Treatment-experienced subjects receiving PR according to prior response to treatment (Study C216)



Log change in HCV RNA at week 4

	Mean	Q1	Median	Q3
Relapsers	-2.7	-3.6	-2.4	-1.7
Partial Responders	-1.4	-1.8	-1.3	-0.8
Null Responders	-1.0	-1.2	-0.9	-0.5

Source: Clinical Pharmacology Review, Pharmacometric Review, NDA 201917.

Finally, using the concept that any treatment-naïve population can be theoretically divided into would-be responder, relapser, partial responder, and null responder subgroups, Dr Liu’s analyses suggested that prior relapser subjects, in this case, can be considered a subset of treatment-naïve subjects. Additional analyses bridged information from the treatment-naïve population to the treatment-experienced population.

The Applicant’s proposal to use the RGT approach to dosing in prior relapsers was a source of discussion within the review team. Whether or not to approve this strategy remains an unresolved issue. Because the Pharmacometrics analyses suggest that RGT should be effective in prior relapsers but the controlled clinical trial in this population tested a different dosing regimen (only T12/PR48), use of RGT will be discussed at the Advisory Committee.

Finally, the Pharmacometrics Review addresses when treatment with telaprevir and Peg-IFN/ribavirin should be discontinued when there is little likelihood of achieving SVR. Because resistance mutations may accumulate if telaprevir is continued in a patient failing treatment, the Applicant proposed discontinuing telaprevir if HCV RNA levels were (b) (4) at Week 4 and discontinuing all treatment if HCV RNA levels were (b) (4) at Week 12. However, the “stopping rules” followed in the Phase 3 clinical trials recommended discontinuing telaprevir treatment if HCV RNA > 1000 IU/mL at Weeks 4 or 12. Dr. Liu pooled data from Studies 108 and 111 in treatment-naïve subjects and identified 50 subjects (about 4%) with HCV RNA above 1000 IU/mL at either Week 4 or 12. None of these subjects achieved SVR even if Peg-IFN/ribavirin was continued. To evaluate the Applicant’s proposal for futility, he identified 31 subjects (about 2%) with HCV RNA between 100 IU/mL and 1000 IU/mL at Week 4 or Week 12. Of these subjects, 8/31 (26%) ultimately achieved SVR. These data support a recommendation to discontinue telaprevir (and possibly all treatment) at Week 4 if HCV RNA is > 1000 IU/mL cut-off and to discontinue Peg-IFN/ribavirin at Week 12 if HCV RNA is > 1000 IU/mL.

While the telaprevir clinical trials were in progress, researchers identified a genetic polymorphism, rs12979860, near the *IL28B* gene encoding interferon-lambda 3 (the “*IL28B* genotype”) to be a strong predictor of SVR in patients receiving therapy with Peg-IFN/ribavirin. Over the last year, multiple studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype. The Applicant conducted a retrospective analysis of *IL28B* genotype in available samples from two Phase 2 and two Phase 3 studies. The total number of subjects included in the analysis was 1374: 610 treatment-naïve and 764 treatment-experienced subjects. These investigations were not performed prospectively and the cohort of subjects consenting to genetic testing may not be representative of the full study population. Specifically, the genetic substudy population included very few Black/African American subjects.

As noted in Dr. Amur’s Genomics review, the *IL28B* genetic substudy confirms previous reports that *IL28B* genotype affects Peg-IFN/ribavirin responses; subjects with C/T and T/T genotype had significantly lower SVR rates in the Peg-IFN/ribavirin control arms. A similar genetic effect was apparent in the telaprevir arms. In both Study 108 and C216, subjects with the C/T and T/T genotypes had higher SVR rates with telaprevir-containing regimens than PegIFN/RBV alone. In Study 108, treatment-naïve C/C subjects responded favorably to PegIFN/RBV alone, but SVR rates were higher for all of the telaprevir regimens even in this favorable *IL28B* genotype. Table 1 summarizes the response rates by *IL28B* genotype in Studies 108 and C216. Although the overall study results and the genetic substudy results were relatively similar, these results should be interpreted with caution because the sample size of some subgroups was small and the cohort may not fully represent the study population.

**Table 1: SVR Rates by *IL28B* Genotype, Treatment Arm, and Trial**

Trial	Treatment	SVR, % (n/N)				
		Overall	Substudy	IL28B C/C	IL28B C/T	IL28B T/T
<b>Treatment-naïve</b>						
108	PR48	44% (158/361)	38% (61/161)	64% (35/55)	25% (20/80)	23% (6/26)
	T8/PR24-48 RGT	69% (250/364)	67% (102/153)	84% (38/45)	57% (43/76)	59% (19/32)
	T12/PR24-48 RGT	75% (271/363)	78% (109/140)	90% (45/50)	71% (48/68)	73% (16/22)
<b>Treatment-experienced</b>						
C216	PR48	17% (22/132)	17% (18/105)	29% (5/17)	16% (9/58)	13% (4/30)
	T12/PR48	64% (250/364)	57% (120/212)	76% (31/41)	63% (84/134)	57% (21/37)
	T12 (DS)/PR48	66% (175/264)	54% (114/210)	83% (29/35)	58% (76/132)	65% (28/43)

Source: Clinical Pharmacology Review, Genomics Group Review, NDA 201917.

## 6. Clinical Microbiology

The Applicant submitted multiple studies and analyses evaluating the antiviral mechanism of action of telaprevir, the emergence of resistance substitutions, and the persistence of these substitutions. Genotypic data of the entire NS3/4A coding region and treatment response outcomes from 2,260 subjects' baseline isolates and post-baseline and follow-up isolates from 628 subjects not achieving SVR in Studies 108, 111, and C216 were submitted to support the clinical virology analysis. In addition, the Applicant submitted interim virology data from Study 112, an observational cohort study following subjects who completed treatment (both those who did and did not achieve SVR) in one of the telaprevir Phase 2 clinical trials. Please refer to the Virology Review performed by Dr. Lisa Naeger for a detailed discussion of these data and analyses. The main conclusions of her review are summarized below.

- **General considerations**

HCV is a single-stranded RNA virus, in the *Flaviviridae* family. Of the major genotypes, genotypes 1, 2, 3, and 4 are most common among patients with chronic HCV, with genotype 1 accounting for > 70% of chronic infection in the U.S. and Europe. Genotype 1 infection has the poorest response to treatment and subtype 1a appears to respond more poorly than subtype 1b.

Telaprevir is a peptidomimetic inhibitor of HCV NS3/4A serine protease, an enzyme critical for production of mature forms of the nonstructural proteins NS4A, NS4B, NS5A, and NS5B and for viral replication. (b) (4)

Telaprevir appears to be selective for the HCV NS3 protease domain and does not interfere with human serine proteases such as kallikrein, thrombin, and plasmin.

Anti-HCV activity was assessed in two assays, primary human hepatocytes infected with patient-derived infectious virus and the HCV replicon assay in Huh7 cells. Telaprevir's EC<sub>50</sub> against wild-type HCV was 354 nM in an HCV subtype 1b replicon assay and was 280 nM in a subtype 1a infectious virus assay. Antiviral activity was decreased about 10-fold in the presence of 40% human serum. In comparison, the cytotoxic CC<sub>50</sub> value was 83 μM, providing a favorable toxic/therapeutic ratio. In addition, combination of telaprevir with interferon alfa or ribavirin did not demonstrate evidence of antagonism in reducing HCV RNA in the HCV replicon assay.

- ***Discussion of primary and secondary reviewers' comments and conclusions***

Dr. Naeger's analysis of pooled subjects who did not achieve SVR from the Phase 3 studies confirmed that NS3 amino acid substitutions V36M, A or L, T54A or S, R155K or T, A156S, T or V and D168N emerged frequently on telaprevir treatment. The pattern of resistance substitutions was different in subjects with subtype 1a (V36M and R155K and combination of both most frequent) and subjects with subtype 1b (V36A, T54A or S and A156T most frequent). In replicon-based and enzymatic phenotypic assays using site-directed mutants, the V36M/A, T54A or S, R155K or T, A156S amino acid substitutions were shown to confer 4- to 20-fold reduced susceptibility to telaprevir and substitutions V36M+R155K, A156T, or A156V were shown to confer >60-fold reduced susceptibility to telaprevir. Variants at position D168, known to confer decreased susceptibility to the macrocyclic NS3/4A protease inhibitors, have not been previously associated with telaprevir resistance.

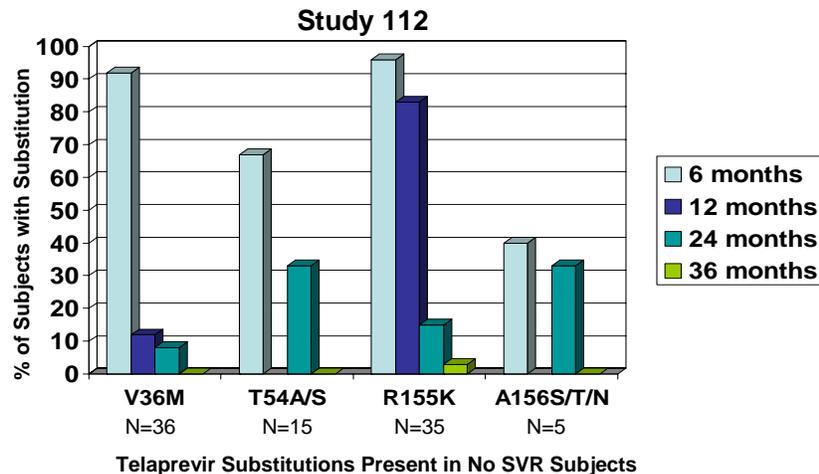
Telaprevir-associated resistance substitutions (substitutions at positions V36, T54, R155, A156 or D168) were present at baseline in 5% (117/2239) of the subjects in the combined Phase 3 Studies. Given the small number of subjects with baseline telaprevir resistance substitutions, definitive conclusions on response outcomes when these specific substitutions are present at baseline can not be made. However, the limited data indicate that even when these telaprevir resistance-associated substitutions are present at baseline, some patients can still achieve SVR with a T/PR regimen.

Review of the three controlled clinical trials revealed additional information regarding emergence of resistance substitutions. In Study 108, the proportion of telaprevir resistance substitutions emerging on treatment was comparable between the T8/PR and T12/PR arms; more substitutions emerged in subtype 1a than 1b treatment failures. Almost all subjects who failed during telaprevir dosing (Week 12 or earlier) had treatment-emergent substitutions and 60% of isolates from subjects who failed while on Peg-IFN/ribavirin (after Week 12) or who relapsed had treatment-emergent substitutions. In Study 111, a high percentage of telaprevir treatment failures had treatment-emergent substitutions. Of those who failed after Week 12 on Peg-IFN/ribavirin or who relapsed, 90% (46/51) had treatment-emergent substitutions. In Study C216, 70% of subject failing to achieve SVR had treatment-emergent substitutions when they experienced failure on treatment or relapsed. The proportion of treatment-emergent substitutions was similar between the immediate and delayed telaprevir start arms. Over half the treatment-failure subjects in Study 216 were prior null responders and this subgroup had the most treatment-emergent substitutions.

- **Other notable issues (resolved or outstanding)**

One of the critical outstanding virology issues is the duration of persistent resistance-associated substitutions in patients failing treatment and the impact on future treatment options. The Applicant has attempted to characterize resistance by following subjects failing treatment during the Phase 2 and Phase 3 clinical trials. Study 112, “A 3-year, virology follow-up study in subjects previously treated with telaprevir in select clinical studies,” documented durability of response and persistence of telaprevir resistance-associated substitutions among subsets of subjects who did or did not achieve SVR with a telaprevir regimen. This study confirmed previous observations that once SVR is achieved, it represents a durable response (i.e., cure); 122/123 (99%) of subjects achieving SVR remained HCV RNA undetectable for a median follow-up of 22 months. In addition, 56 subjects who had failed a telaprevir regimen were followed for a median of 25 months and had paired samples available for resistance analysis. Figure 3, excerpted from Dr. Naeger’s review, shows the persistence of selected telaprevir resistance-associated substitutions in subjects followed in Study 112 for up to 36 months.

**Figure 3: Persistence of Telaprevir Resistance-Associated Substitutions**



As noted in Dr. Naeger’s review, V36M, T54A/S, R155K and A156S/T/N may persist in significant proportions of treated subjects for 24 to 36 months and this study used a population sequencing method that only detects variants representing about 25% of the viral population. More sensitive detection methods might identify substitutions at lower frequency persisting for longer periods. The clinical implications of this prolonged persistence of resistance-associated substitutions are unknown. To date, no clinical trials have attempted to re-treat subjects failing a telaprevir regimen with another course of a telaprevir regimen or with another HCV protease inhibitor. However, data from other HCV NS3/4A inhibitor development programs suggest substitutions at V36, T54, R155, A156, or D168 confer cross-resistance across this class of drugs.

## 7. Clinical/Statistical- Efficacy

Vertex initiated the U.S. clinical development program for telaprevir in December, 2005 when the IND was opened and the telaprevir development program was granted Fast Track designation. Since that time, 40 clinical trials have been completed and several more remain in progress or in follow-up. In August, 2007 a Type C clinical development meeting was held during which FDA and Vertex discussed dose selection, treatment duration, rash and anemia management plans, virology “stopping rules” and other aspects of proposed clinical trials. In January, 2008 a formal End of Phase 2 meeting was held to finalize study design for the Phase 3, registrational trials. At that meeting FDA, agreed with the overall design of Study 108 to evaluate both 8- and 12-week courses of telaprevir and a shortened duration of Peg-IFN/ribavirin (24 weeks) for subjects with undetectable viral load at Weeks 4 and 12. We recommended the Applicant evaluate in a clinical trial whether extending Peg-IFN/ribavirin to 48 weeks in patients with early virologic response would provide additional benefit. This recommendation was later incorporated into the development plan as Study 111. Later communications with Vertex provided agreement on the design of Study C216 evaluating telaprevir treatment in patients who had failed prior treatment with Peg-IFN/ribavirin. In accordance with the Fast Track guidance, the Applicant proposed a schedule for submission of a rolling NDA review with CMC and nonclinical data to be submitted first, followed by the clinical study report for Study 108 and finally the clinical study reports for Studies 111 and C216 and the bulk of the integrated NDA review.

The proposed dosing regimen for telaprevir is 750 mg given three times daily for 12 weeks (T12) in combination with Peg-IFN/ribavirin for 24 weeks (T12/PR24) or 48 (T12/PR48) weeks, depending on treatment response. The Applicant proposes treatment naïve patients and patients with relapse after prior treatment who achieve an extended rapid virologic response (eRVR), defined as undetectable HCV RNA at Weeks 4 and 12, will receive the T12/PR24 regimen. The Applicant’s plan to administer a shortened duration of Peg-IFN/ribavirin treatment in patients who achieve undetectable HCV RNA at Weeks 4 and 12 (RGT), represents an evolution in HCV treatment. Treatment-naïve subjects who fail to achieve eRVR and patients with null response (< 2 log decrease in HCV RNA at Week 12 of prior treatment) and partial response (> 2 log decrease in HCV RNA at Week 12 of prior treatment but never achieved undetectable HCV RNA on treatment) will receive the T12/PR48 regimen.

To support the proposed indication, the Applicant conducted three adequate and well-controlled Phase 3 trials: Studies 108 and 111 in treatment-naïve subjects and Study C216 in treatment-experienced subjects. The primary efficacy endpoint in all clinical trials was the proportion of subjects achieving SVR24. For a detailed description of the registrational trial designs, please refer to the Clinical Review provided by Senior Clinical Analyst Russell Fleischer.

Overall, the Clinical and Statistical reviewer’s independent analyses confirmed the Applicant’s primary efficacy findings and many secondary endpoint analyses for all pivotal clinical trials. Dr. Thomas Hammerstrom, the Statistical Reviewer, conducted numerous analyses using different methods of imputing missing data and different HCV RNA cut-off values to assess the robustness of the SVR24 endpoint. In general, all of these methods produced very similar

results. The following points summarize the key findings of the FDA's clinical and statistical reviewers.

For Study 108, the FDA reviewers confirmed the overall SVR rates of 73% for T8/PR and 79% for T12/PR compared to 46% for the PR48 control arm. Compared to the T8/PR regimen, the T12/PR regimen produced slightly higher overall SVR rates, and higher SVR rates among subjects with demographic or disease characteristics associated with poorer response: genotype 1a, high baseline viral load ( $\geq 800,000$  IU/mL) and cirrhosis. Using the RGT approach, 58% of naïve subjects in the study achieved eRVR, and 90% of those achieved SVR. Only 8% (29/361) of PR48 subjects achieved eRVR but this subgroup had a high success rate with 97% (28/29) achieving SVR. For subjects without eRVR, extending the duration of Peg-IFN/ribavirin treatment to 48 weeks (T12/PR48) resulted in a higher SVR rate (61%) than the corresponding subgroup in the control arm receiving treatment with PR48 alone (42%). Table 2 summarizes eRVR and SVR results for Study 108.

**Table 2: FDA Analysis of SVR24 by eRVR Status and Regimen - Study 108**

	T8			T12			PR48
	All (n=364)	eRVR (PR24) (n=207)	No eRVR (PR48) (n=157)	All (n=363)	eRVR (PR24) (n=213)	No eRVR (PR48) (n=150)	(n=361)
<b>SVR Rate</b>	73%	87%	55%	79%	92%	62%	46%

Source: Abstracted from Clinical Review, NDA 201917.

For Study 111, the FDA reviewers confirmed the overall SVR rate of all study participants was 72%. No significant differences in SVR rates were identified between subjects achieving eRVR who were randomized to receive either T12/PR24 or T12/PR48. Approximately 60% of subjects achieved eRVR and were randomized to 24 or 48 weeks of Peg-IFN/ribavirin, and 90% of those receiving either treatment duration achieved SVR. Of the 40% of subjects not achieving eRVR and assigned to receive T12/PR48, about 64% achieved SVR.

FDA analyses confirmed the primary efficacy conclusions of Study C216. In general, no differences were observed in SVR, virologic failure, virologic breakthrough, or relapse rates between the immediate and delayed start telaprevir regimens. The SVR rates for the pooled T12/PR48 groups were significantly higher than for re-treatment with Peg-IFN/ribavirin alone, 66% and 16%, respectively, and SVR rates varied according to prior treatment response (see Table 3).

**Table 3: FDA Analysis of SVR24 by Regimen and Prior Response Status - Study C216**

	All T12/PR48 combined*	T12/PR48	T12(DS)/PR48	PR48
<b>Overall</b>	66%	65%	67%	16%
<b>Prior Null</b>	32%	30%	33%	5%
<b>Prior Partial</b>	59%	61%	56%	15%
<b>Prior Relapse</b>	86%	84%	88%	22%

\*Includes both T12/PR48 immediate (T12/PR48) and delayed start [T12(DS)/PR48] groups.

Source: Abstracted from Clinical Review, NDA 201917.

The addition of telaprevir to Peg-IFN/ribavirin for 24 or 48 weeks increased SVR rates 30-40% compared to PR48 across a broad spectrum of demographic and disease characteristic subgroups, including subgroups associated with poorer response to PR (i.e., older age, minorities, subjects with high BMI or diabetes, subjects with high baseline viral load, and genotype 1a). For some subgroups, the numbers of subjects enrolled in the clinical trials were relatively low, but the treatment benefit of adding telaprevir to PR appeared to be consistent. For details of the subgroup analyses, please refer to the Clinical Review provided by Mr. Fleischer and the Statistical Review provided by Dr. Hammerstrom.

A few subgroups deserve specific comment. As in earlier studies of HCV treatment, Blacks/African Americans in the telaprevir clinical trials had SVR rates approximately 20% lower than Caucasians. Enrollment of this subgroup was relatively low; Blacks/African Americans made up 9% (158/1797) of telaprevir subjects and 8% (39/493) of PR48 subjects. Even based on small numbers enrolled, treatment with T/PR significantly improved response rates among Blacks/African Americans compared to those treated with PR48: SVR in 65% overall (range; 50% to 94%) among those receiving T/PR compared to 31% (range; 29% to 36%) among those receiving PR48. Similarly, Latino/Hispanic subjects made up 10% (185/1797) of telaprevir subjects and 12% (58/493) of PR48 subjects. SVR rates for Latino/Hispanic subjects were also significantly improved; 79% overall (range; 70% to 94%) in subjects receiving T/PR and 31% (range; 10% to 42%) for PR48.

Telaprevir also appeared to provide a treatment benefit among subjects with cirrhosis. Among telaprevir-treated subjects, 8% (108/1267) of naïve and 26% (139/530) of treatment-experienced subjects had cirrhosis at baseline. Among cirrhotic subjects treated with telaprevir, SVR was achieved in 50% overall (range; 33% to 92%) among those receiving T/PR compared to 24% (range; 13% to 33%) among those treated with PR48. In Study 108, it appeared that T12/PR provided somewhat better SVR than T8/PR, and in Study 111, it appeared that T12/PR48 provided somewhat better SVR than T12/PR24. However, the number of treatment naïve cirrhotic subjects in these trials was small. Because the limited data suggest a difference in treatment duration may be of benefit in some cirrhotic patients, the Advisory Committee will be asked to comment on the adequacy of these data or whether additional data are needed to determine appropriate duration of treatment in cirrhotic patients.

- ***Other notable efficacy issues (resolved and outstanding)***

The submitted clinical trials data provide evidence of telaprevir's treatment efficacy in subjects representing a wide range of demographic and disease characteristics. The trial results are consistent and robust across subgroups. The only unresolved issues related to efficacy pertain to the adequacy of data to guide treatment recommendations in some key subgroups under-represented in the clinical trials (i.e., Blacks/African Americans and patients with cirrhosis). The most appropriate treatment regimen in these subgroups may not be clearly identified at this time and may require additional investigation. The Advisory Committee will be asked to discuss this issue.

## **8. Safety**

The Applicant provided an adequate safety database compiled during the Phase 2 and Phase 3 clinical trials. In general, Vertex's integrated safety analysis was conducted using pooled data from the placebo-controlled Phase 2 and Phase 3 clinical trials (1346 subjects receiving T12/PR and 764 subjects receiving PR48). The FDA clinical safety review provided by Mr. Fleischer was conducted using pooled data from the three Phase 3 trials (1433 subjects receiving T/PR and 364 subjects receiving PR48). Both safety analyses focused on the first 12-16 weeks of treatment while subjects were receiving telaprevir or the matched placebo in combination with Peg-IFN/ribavirin. In general, these different approaches to the safety evaluation identified similar safety signals.

- ***General safety issues: deaths, discontinuations, serious adverse events, common adverse events***

At the time of the NDA submission, 11 deaths had been reported during the telaprevir clinical development program, 7 among subjects receiving T/PR and 4 among subjects receiving PR48. None of the deaths in subjects who had received telaprevir occurred during the telaprevir dosing period and many occurred weeks to months after completing telaprevir (range 9 to 403 days after). The Applicant notes two of these deaths were considered possibly related to study drug and summaries of these are included below.

A 62-year-old male, prior relapser, treated with T/PR in a non-IND study sponsored by Mitsubishi. On day 72 he had anemia, severe malaise, chills and impaired appetite and telaprevir was discontinued. He was treated for urinary sepsis and recovered. On day 81 after the first dose of telaprevir and 9 days after the last dose of telaprevir, the subject was admitted to hospital for delirium. Peg-IFN/ribavirin was discontinued. On day 82, he had chest pain and dyspnea, had cardiopulmonary arrest, and was resuscitated. A thoracoabdominal CT scan with contrast revealed pulmonary artery embolism. An inferior vena cava filter was placed, and the clots were removed. However, the subject's blood pressure decreased and he died. The delirium and pulmonary embolism were considered possibly related to telaprevir and probably related to Peg-IFN/ribavirin.

A 59-year old male was enrolled in Study C216 and randomized to T12(DS)/PR48. Medical history included a 40-year history of smoking. He was diagnosed with

bronchopulmonary carcinoma and died 138 days after completing telaprevir. The death was considered possibly related to telaprevir.

Discontinuations due to adverse events were more common among subjects receiving telaprevir than among those receiving Peg-IFN/ribavirin alone. As noted in the Clinical Review, between 8-14% of subjects treated with a telaprevir-containing regimen in the Phase 2 and 3 trials discontinued telaprevir due to adverse events compared to about 3% of those treated with PR. The most common events leading to discontinuation of telaprevir were rash, pruritus, anemia, and fatigue. Similarly, in the Phase 3 trials, 10% (180/1797) of subjects who received telaprevir experienced serious AEs compared to 6% (28/493) of those who received PR48. Of these, 62% (111/180) of telaprevir subjects and 39% (11/28) of PR subjects had serious AEs during the telaprevir/placebo dosing period. The most frequently reported serious AEs during telaprevir dosing were anemia (35%, 39/111) and skin reactions (15%, 17/111).

The safety profile of Peg-IFN/ribavirin treatment in patients with chronic HCV infection has been well characterized over many years. The most common adverse events associated with Peg-IFN/ribavirin treatment include: fatigue, headache, myalgia, rigors, fever, nausea, anorexia, insomnia, anxiety/emotional lability, depression, and alopecia. Neutropenia and anemia are also commonly reported. These events were also the most commonly reported adverse reactions associated with telaprevir use. Table 4 displays the adverse drug reactions reported at a frequency at least 5% higher among subjects receiving T/PR than among those receiving PR48. This information will be displayed in the product label.

**Table 4: Adverse Drug Reactions Occurring with  $\geq 5\%$  Higher Frequency in Subjects Treated with Telaprevir - Phase 3 Trials**

	<b>Combined T/PR N=1797</b>	<b>Combined PR48 N=493</b>
Rash	1009 (56%)	158 (32%)
Fatigue	998 (55%)	245 (50%)
Pruritus	840 (47%)	137 (28%)
Nausea	704 (39%)	138 (28%)
Anemia	590 (33%)	66 (14%)
Diarrhea	458 (25%)	86 (17%)
Vomiting	241 (13%)	40 (8%)
Hemorrhoids	220 (12%)	9 (2%)
Ano-rectal discomfort	191 (11%)	13 (3%)
Dysgeusia	178 (10%)	15 (3%)

Source: Excerpted from Clinical Review, NDA 201917.

- ***Safety issues of special interest***

The major safety risks of telaprevir use are associated with two key toxicities: skin reactions (rash and pruritus) and anemia, events that were common, sometimes severe, and in some cases treatment-limiting. Other events of interest include ano-rectal disorders and hyperuricemia. These events will be discussed in more detail in this review and will be highlighted in product labeling.

Skin reactions were identified as a telaprevir-associated toxicity relatively early in the drug development program. With input from the FDA review team, the Applicant developed a comprehensive rash monitoring and management plan for use in the Phase 3 and future clinical trials. Study subjects with significant rash were to be evaluated by dermatologists and were to have photographs and skin biopsies performed. This management plan allowed good characterization of the presentations of rash and appeared to decrease the number of subjects who had treatment discontinued because of rash but it did not mandate specific treatment. The Applicant pursued several analyses and nonclinical evaluations to identify a mechanism or predisposing factors for severe rash including a case-control study to explore a potential association with HLA alleles, animal toxicology studies to assess the skin sensitizing potential of some telaprevir metabolites, an exposure-response analysis to explore a possible association with higher exposure of telaprevir, Peg-IFN, or ribavirin, and an exploratory analysis of pyrazinoic acid as a potential contributor to rash. None of these investigations provided an explanation for the increased incidence of rash.

In addition, the Applicant convened a Dermatology Expert Panel (DEP) to review and categorize rash events post hoc. The DEP concluded that the rash associated with telaprevir was similar in appearance and histologic characteristics to the rash associated with Peg-IFN/ribavirin but was more severe and more extensive. Telaprevir rash is most often eczematous, maculopapular, or papular-lichenoid (and may have multiple components), and in many cases accompanied by pruritus. Histologically, the rash appeared as spongiform dermatitis, with predominantly lymphocytic or eosinophilic perivascular infiltration. Telaprevir-associated rash occurred early, usually within the first 16 to 20 days of treatment. Rash was reported in 56% of subjects receiving telaprevir compared to 32% of subjects receiving PR48. In most subjects, the rash was mild to moderate in severity, but it was severe in 1% and resulted in discontinuing telaprevir in about 6% of subjects. Fewer than 1% subjects experienced Stevens-Johnson syndrome (SJS) or drug reaction with eosinophilia and systemic symptoms (DRESS). No subjects experienced toxic epidermal necrolysis and none died of rash-related complications. Many subjects received intervention for rash events including discontinuation of treatment, treatment with oral antihistamines, topical steroids and/or systemic corticosteroids (see Table 5). No data are available to assess effectiveness of these interventions.

**Table 5: Rash Management Strategies – Phase 3 Trials**

	<b>Combined T/PR (N=1797)</b>	<b>Combined PR48 (N=493)</b>
Discontinued telaprevir or placebo	7%	<1%
Discontinued regimen	<1%	0
Use of oral antihistamines	5%	2%
Use of topical steroids	4%	2%
Use of systemic steroids	3%	1%

Source: Excerpted from Antiviral Drug Advisory Committee presentation, NDA 201917.

As part of the safety review process, DAVP requested consultation from our colleagues in the Division of Dermatologic and Dental Products to confirm the dermatologic findings of the Applicant and the DEP. Dr. Brenda Carr provided DDDP expertise and focused her review on the safety data in Study 108 and the report from the DEP. In general, Dr. Carr confirmed the findings of the DEP. The DEP evaluated cases from 221 subjects with rash, many including photographs and biopsies. The DEP suspected SJS in 3 subjects, 2 of whom were suspected by the local investigators, and 11 cases of DRESS, 2 of whom were suspected by the investigators. As noted in Dr. Carr's consult review, this frequency of SJS and DRESS may be important since these serious skin reactions are generally thought to be rare and clinical trials are not usually large enough to identify rare events. She acknowledged that most of the cases of serious skin reactions were suspected by the DEP, not the local investigators, suggesting that these events may have been under-diagnosed in the telaprevir clinical trials. Because earlier Peg-IFN/ribavirin clinical trials (and clinical trials in general) did not have such intensive rash monitoring, it is likely that those trials also under-diagnosed serious skin reactions. She also confirmed the DEP's findings that local investigators frequently over-estimated the extent of rashes and on reviewing the cases, the DEP determined that > 90% of the evaluable rashes covered  $\leq$  30% body surface area. The symptoms of serious skin reactions (also called serious cutaneous adverse reactions) include vesicles, bullae, ulceration of the mucosa, epidermal detachment, target lesions, purpura, or any generalized rash with facial edema, fever, eosinophilia, or lymphadenopathy and should prompt health care providers to immediately stop telaprevir and Peg-IFN/ribavirin and consult a dermatologist. This warning will be included in the telaprevir label.

Anemia is another telaprevir-associated adverse event previously reported in patients receiving Peg-IFN/ribavirin. Ribavirin is recognized to cause a reversible hemolytic anemia which typically develops during the first 2 to 4 weeks of treatment and Peg-IFN use may exacerbate this effect. Reduction or discontinuation of ribavirin dosing may have a negative impact on a patient's likelihood of achieving SVR.

As described in the Clinical Review, subjects receiving telaprevir had a higher frequency of anemia clinical adverse events (36% compared to 15%), a higher frequency of hemoglobin reductions to Grade 3 levels (defined as <8.9 g/dL or >4.5 g/dL decrease from baseline; 55% compared to 27%), more anemia-related serious AEs (2.5% compared to <1%), and a higher frequency of anemia-related discontinuations (3% compared to <1%). Time to onset of any anemia was faster among telaprevir-treated subjects (median 11 days compared to 29 days). In subjects treated with telaprevir, hemoglobin values generally decreased steeply through Weeks 4 to 8, were stable between Weeks 8 and 20, and then began to rise to levels similar to or higher than those of subjects in the PR48 group. Overall, telaprevir increased the drop in hemoglobin levels by 1.0-1.5 g/dL more than observed in PR-treated subjects. Across Phase 3 trials, 801/1797 (45%) of telaprevir and 134/493 (27%) of PR subjects had hemoglobin levels <10 g/dL, and 14% (245/1797) and 5% (25/493) had levels <8.5 g/dL. Table 6 summarizes the interventions used to manage anemia during the Phase 3 clinical trials. It should be noted that erythropoiesis stimulating agents were prohibited during the Phase 3 trials and their use was considered a protocol

violation. Although ribavirin dose reductions and interruptions had limited impact on SVR rates, early discontinuation of ribavirin did have a negative impact on treatment response.

**Table 6: Anemia Management Strategies – Phase 3 Trials**

	<b>Combined T/PR N=1797</b>	<b>Combined PR48 N=493</b>
Discontinue telaprevir or placebo	4%	<1%
Ribavirin dose reduction	23%	10%
Ribavirin interruption	6%	1%
Discontinue ribavirin	2%	<1%
Discontinue all drugs	1%	<1%
Blood transfusions	6%	1%
ESA* use	1%	<1%

\*ESA – erythropoiesis stimulating agent

Source: Excerpted from Antiviral Drug Advisory Committee presentation, NDA 201917.

Interpreting rates and severity of anemia as a reported clinical adverse event is difficult as the criteria for reporting varied and investigators used different criteria for initiating anemia management strategies. Ribavirin dose reductions are recommended at Hgb < 10 g/dL but these recommendations were not followed consistently during the clinical trials. In addition, the evaluation of anemia is confounded by the Applicant's analysis that did not account for baseline differences in Hgb between male and female subjects. In analyses conducted by Dr. Charles Cooper, FDA Computational Science Center reviewer, the difference between male and female subjects with regard to Hgb toxicity is substantially smaller when an attempt is made to control for baseline Hgb. Table 7 shows the results of this analysis using the placebo-controlled Studies 108 and C216 (anemia analysis population). In the anemia analysis population, female subjects had smaller mean and median declines in Hgb but were more likely to reach the < 10 g/dL cut-off at which an intervention was recommended because they started at a lower value. Also, in the anemia analysis population, ribavirin dose modifications were made in about 71% of female subjects compared to about 52% of male subjects regardless of study treatment group. The relevance of this finding to final treatment outcome (SVR) remains unclear.

**Table 7: Nadir Hemoglobin Measures by Treatment Group and Sex – Anemia Analysis Population (Studies 108 and C216)**

Hemoglobin	PR48		T/PR	
	Female	Male	Female	Male
Pooled Subjects for Placebo-controlled Trials				
≤10g/dL	83/194 (43%)	50/298 (17%)	306/460 (67%)	252/797 (32%)
≤8.5g/dL	13/194 (7%)	11/298 (4%)	104/460 (23%)	54/797 (7%)
Subjects with Baseline Hemoglobin ≥14 and ≤15g/dL				
≤10g/dL	24/71 (34%)	16/52 (31%)	105/175 (60%)	72/155 (47%)
≤8.5g/dL	4/71 (6%)	2/52 (4%)	28/175 (16%)	16/155 (10%)

Source: C. Cooper, Safety Consultation, NDA 201917.

Other adverse events that deserve mention include anorectal disorders and hyperuricemia or gout. Anorectal adverse events, reported as hemorrhoids, pruritus ani, proctalgia, anal discomfort, and other specific anal complaints, were recognized early in the telaprevir development process. In the Phase 3 clinical trials, anorectal disorders were reported in 29% of subjects receiving telaprevir compared to 7% of those receiving Peg-IFN/ribavirin. Less than 1% of these events were serious AEs, < 1% were Grade 3 or greater severity, and only 7 subjects discontinued telaprevir because of anorectal events, however, these events were noted to be quite noticeable and unpleasant to subjects. Most of these events were managed with local/topical therapies. No visible signs of inflammation were noted at the time of subjects' medical assessments and the mechanism of anorectal adverse events is not known. Hyperuricemia was reported in the clinical trials, more frequently among subjects receiving telaprevir (see discussion under Laboratory Abnormalities). Among these subjects, 11 receiving telaprevir and 2 receiving Peg-IFN/ribavirin experienced events reported as gout or gouty arthritis. One subject had a history of gout. However, four of the episodes in telaprevir subjects occurred after the telaprevir dosing period was completed. None of the gout-related events were considered serious and none led to discontinuation.

- **Laboratory abnormalities**

The most notable hematologic laboratory abnormalities were those related to decreases in red blood cell parameters as described above in the discussion of anemia. Other hematologic parameters were less consistently affected by telaprevir use. Total white blood cell toxicity Grade 3 or higher (< 1499/mm<sup>3</sup>) was documented in 8% of subjects receiving telaprevir compared to 5% of those receiving Peg-IFN/ribavirin. Grade 3 or higher lymphopenia (< 499/mm<sup>3</sup>) was more frequent in the telaprevir group (18%) than in the Peg-IFN/ribavirin group (6%). Neutropenia and thrombocytopenia were documented at similar frequencies in subjects receiving telaprevir or not.

Biochemical laboratory monitoring identified elevations in uric acid and total bilirubin more frequently among subjects receiving telaprevir. Increased uric acid (any Grade toxicity) was documented in 73% of subjects receiving telaprevir compared to 29% of those receiving Peg-IFN/ribavirin. Elevated uric acid levels have been described with

ribavirin in association with hemolytic anemia and this is the presumed mechanism for telaprevir associated increases. A similar trend was noted with total bilirubin measurements. Any Grade elevation of total bilirubin occurred in 40% of telaprevir subjects compared to 28% of Peg-IFN/ribavirin subjects. Grade 3 or higher bilirubin was documented in 4% of telaprevir subjects and 2% of Peg-IFN/ribavirin subjects. Both of these laboratory parameters appeared to trend up with decreasing Hgb, suggesting that hemolysis of red blood cells may be the common etiology.

- ***Other notable issues (resolved or outstanding)***

The safety/toxicity profile of telaprevir has been well-characterized during the clinical development program. Serious skin reactions and anemia associated with telaprevir may be severe and may result in discontinuation of telaprevir and, more rarely, the entire treatment regimen. However, these events appear to be monitorable and manageable with good prescriber and patient education. Rash/serious skin reactions and anemia will be described in the Warnings and Precautions section of the product label and the Advisory Committee will be asked to discuss these events in the context of the risk/benefit assessment. Serious and life-threatening events may occur in the postmarketing period and both the Applicant and the FDA will be vigilant in tracking these events and assessing the need for additional education and labeling.

## **9. Advisory Committee Meeting**

An Advisory Committee meeting was convened on April 28, 2011 to discuss the merits of this NDA and the risk/benefit assessment for telaprevir in combination with Peg-IFN/ribavirin as treatment for chronic HCV infection. After hearing presentations by both the Applicant and the FDA review team, the Advisory Committee was asked to discuss the following questions. A summary of the Committee's key discussion points and recommendations are included below.

1. Rash associated with telaprevir use was common and sometimes severe and treatment-limiting and anemia was more frequent and more severe in patients treated with telaprevir. Please comment on the safety profile of telaprevir, focusing on the increased frequency and severity of rash and anemia when telaprevir is added to pegylated interferon and ribavirin. Do these adverse events affect your risk/benefit assessment and, if so, how?

*Committee members uniformly expressed concern regarding the increased incidence of both rash and anemia but felt strongly that the marked improvement in response as measured by SVR outweighed the risk of these events. They noted that although serious skin reactions occurred at a higher rate than generally expected, the Applicant's rash management plan in the clinical trials appeared effective in reducing the number of subjects who discontinued all treatment and identified subjects in a timely manner to optimize treatment of the rash. They also noted that although there were no deaths associated with serious skin reactions in the clinical trials, it is very likely that deaths may occur when the drug is used in a larger and less closely monitored population after approval. Similarly, the Committee members expressed a level of comfort with managing*

*anemia in patients who will receive telaprevir because most hepatologists have learned to manage the anemia associated with ribavirin use. The Committee members recommended several strategies to help mitigate the risks of rash and anemia including: having a patient hotline for adverse events, having strong educational materials for both health care providers and patients, providing clear guidance on recommended management of rash and anemia in labeling, providing access to expert consultation, and even potentially having a registry of patients who develop rash to try to identify predictors of serious skin reactions.*

2. Considering the overall risks and benefits, do the available data support approval of telaprevir for treatment of treatment-naïve and treatment-experienced patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin?

**VOTE: Yes/No/Abstain**

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

*The Committee members voted unanimously to recommend approval; 18 yes votes and 0 no/abstain. The development of telaprevir was characterized as a “stunning achievement” in the treatment of chronic HCV. The consensus was that the benefit of telaprevir as part of a treatment regimen greatly outweighed the risk associated with adverse events and the risks appear to be manageable.*

3. Please comment on the strength of evidence to support response-guided therapy with telaprevir in combination with pegylated interferon and ribavirin for the following patient groups?

- a. Treatment-naïve
- b. Prior relapsers

*The Committee agreed that the evidence to support RGT in treatment naïve patients was strong and well-supported by Studies 108 and 111, although some members expressed reservations about the use of RGT in treatment naïve patients with cirrhosis. The Committee members considered the evidence less strong to support RGT in prior relapsers. In general, they considered the Pharmacometrics discussion an “interesting argument” but not persuasive. However, most believed the limited clinical data from the Phase 2 trials was adequate to support RGT in this population. Some suggested a more nuanced approach to labeling that would provide clinicians enough information to make more individualized treatment decisions for relapsers with poor baseline prognostic factors or naïve cirrhotic patients who might benefit from longer treatment. Additionally, some Committee members stated that they agreed with the position that prior relapsers behave similarly to naïve patients (i.e., “the concept of past performance as a predictor of future performance”) and suggested it was “extreme” to subject prior relapsers to 48 weeks of Peg-IFN/ribavirin in light of the available, albeit limited, clinical data. Although the Committee did not reach consensus on the adequacy of data to support approval of RGT in prior relapsers, they appeared to be permissive of this approach.*

4. Please comment on the strength of evidence to support a recommendation for use in specific populations, including but not limited to Blacks/African Americans and patients with cirrhosis. What, if any, additional efficacy or safety data are needed for specific populations?

*Several Committee members expressed dissatisfaction at the low numbers of Blacks/African Americans enrolled in the Phase 3 clinical trials. Committee members wondered if IL28B genotyping might allow selection of Blacks/African Americans more likely to respond to treatment. Because the numbers were small, some Committee members were uncertain that the optimal duration of treatment for naïve subjects with cirrhosis has been identified and were concerned that RGT might not be appropriate for cirrhotic patients. Because patients with cirrhosis may be less able to wait for more potent therapy than telaprevir, the Committee thought it was important to get additional data to clarify whether this subgroup might benefit from a longer course of Peg-IFN/ribavirin. In addition, some Committee members expressed concern that prior null responders with cirrhosis appear to derive little benefit from telaprevir added to Peg-IFN/ribavirin but are very likely to develop resistance. They acknowledged that the number of null responder cirrhotics was also small. The Committee also recommended additional study of patients 65 years of age and older.*

5. Are there any other post marketing studies you would like to see conducted to further define risks or optimal use of telaprevir?

*The Committee suggested a number of topics they considered appropriate for further study. These included:*

- *Additional study on the evolution of resistance substitutions and the implications for retreatment with telaprevir or other direct-acting antiviral drugs*
- *Further exploration of the optimal treatment regimen for prior null responders and patients with cirrhosis*
- *Further studies on optimal management of rash and anemia*
- *Evaluation of treatment in patients with bleeding disorders*
- *Study with larger numbers of Blacks/African Americans and patients over 65 years of age*
- *Study exploring the potential for IL28B genotype to select patients for shorter duration therapy*
- *Complete the evaluation of a twice daily regimen and evaluation of different formulations of Peg-IFN*
- *Complete the evaluation of treatment in patients with HIV/HCV co-infection*

## **10. Pediatrics**

The Applicant has submitted a pediatric development plan which has been discussed with the DAVP review team and revised over the last two years as data from clinical trials in adults became available. With submission of the NDA package, the Applicant requested a waiver from studying pediatric patients < 3 years of age and a deferral for submitting studies in pediatric patients 3 to < 18 years of age. The requests for waiver and deferral were discussed

at a meeting between the DAVP review team and the FDA Pediatric Review Committee (PeRC) on February 9, 2011. PeRC agreed with the review team's recommendation to defer studies in pediatric patients 3 years of age and older and waive studies in patients < 3 years.

Although we believe telaprevir represents a significant potential benefit to pediatric patients with chronic HCV, we agreed with the Applicant's assertion that studies in patients < 3 years of age would be impossible or highly impractical because the number of patients in this age group requiring treatment is small and is geographically dispersed. Severe manifestations or complications of HCV infection are unusual in infants and young children, and pediatric hepatologists acknowledge a lack of consensus regarding when to begin treatment in pediatric patients. Even with the advent of new direct-acting antiviral drugs like telaprevir, treatment of chronic HCV includes a regimen of subcutaneous injections of Peg-IFN and ribavirin for 6 to 12 months depending on subtype of HCV. At present, PegIntron/Rebetol is approved for use in pediatric patients 3 to 18 years of age but was also waived for study in patients < 3 years due to increased concern for toxicity in younger patients.

Studies in pediatric patients 3 years and older will be required under the Pediatric Research Equity Act (PREA) but will be deferred since the adult studies have been completed and the drug is ready for approval. The PREA deferred studies will be described in the approval letter.

## 11. Other Relevant Regulatory Issues

- ***Application Integrity Policy (AIP)***

This Applicant is not on the FDA Application Integrity Policy list.

- ***Exclusivity or patent issues of concern***

No issues related to patent or exclusivity were identified.

- ***Financial disclosures***

The Applicant reported a small number of investigators in the covered trials (Studies 108, 111, and C216) with financial interests. Collectively these investigators enrolled < 10% of subjects. Because the clinical trials were randomized, telaprevir treatment was blinded, and the trials were each overseen by an independent data monitoring committee, no issues of concern related to financial disclosure were identified.

- ***Other GCP issues***

No other issues related to GCP were identified.

- ***DSI audits***

Four clinical trials sites were audited by DSI, 2 domestic and 2 international, selected on the basis of enrolling a relatively large number of subjects and site-specific protocol violations. In addition, Vertex Pharmaceuticals, Cambridge, MA was also inspected. Although minor protocol and regulatory violations were identified at 3 of the 4 sites audited, the findings were not considered serious enough to affect data integrity. No deficiencies were identified at Vertex Pharmaceuticals.

- ***Other discipline consults***

The proposed proprietary name (Incivek) was reviewed by Walter Fava, R.Ph., Safety Evaluator, Division of Medication Error and Prevention Analysis (DMEPA). The name was determined to be acceptable; it did not resemble other known drug names, and was not unduly promotional. A previously proposed name (b)(4) was judged to be too similar visually to other drug names of products given on a similar schedule.

Dr. Carolyn Yancey, Risk Management Analyst, Division of Risk Management (DRISK), reviewed the Applicant's proposal for a Risk Evaluation and Mitigation Strategy (REMS). After discussion with the DAVP review team she agreed a REMS would not be required to ensure that the benefits of telaprevir use outweigh the risks of severe rash and anemia based on analysis of clinical safety data in the NDA. She also agreed that a Medication Guide would be an appropriate part of the labeling for telaprevir.

- ***Any other outstanding regulatory issues.***

There are no outstanding regulatory issues.

## 12. Labeling

Detailed discussion of labeling can not be provided in this CDTL Review because the review team is in the process of completing labeling negotiations with the Applicant. Some key issues are addressed briefly below.

- ***Proprietary name***

As noted above, the proprietary name (Incivek) was reviewed by DMEPA and was considered acceptable.

- ***Important issues raised by DDMAC and OSE***

At this time, no specific issues have been raised by DDMAC and OSE. A pre-approval safety meeting is scheduled.

- ***Physician labeling***

The language for the package insert is being developed by the multi-disciplinary review team but is not yet complete. The review team is likely to propose significant changes in many sections of the label.

In general, the review team agrees with the proposed indication for telaprevir. Caveats describing the limited data available in patients with cirrhosis and the high proportion of prior null responders who fail telaprevir treatment with resulting resistance substitutions may be added to the Indications and Usage section as "Points to consider."

The results of three Phase 3 clinical trials will be described in the Clinical Studies section with additional information regarding the adverse event profile included in the Adverse Reactions section. Both serious skin reactions and anemia merit specific Warnings and Precautions subsections and the risks of harm to a pregnant woman and fetus from

ribavirin use will also be included. Prescribers and patients will be instructed to read the package inserts for both Peg-IFN and ribavirin.

The emergence of telaprevir-associated resistance substitutions will be described in the Microbiology section, as will the potential for cross-resistance among other HCV protease inhibitors. The persistence of resistance substitutions after telaprevir treatment failure and the lack of certainty regarding implications for retreatment with telaprevir or another HCV protease inhibitor will be acknowledged. In addition, the results of the post hoc analysis of *IL28B* genotype will be described in a new Pharmacogenomics section (12.5).

- ***Carton and immediate container labels (if problems are noted)***  
The Safety Evaluator, DMEPA has also reviewed the carton and immediate container labels. The proposed packaging includes 2 tablets (a single dose) packaged within a single blister, with 3 blisters included on a strip (a daily dose). Seven strips are packaged into a carton and 4 cartons are included in a box. Each box, therefore, contains a 28-day supply of telaprevir for an adult patient. A conference call between DMEPA staff and the Applicant was held on April 19, 2011, during which the Safety Evaluator requested additional data regarding the Applicant's testing of the telaprevir packaging configuration. At the time of this CDTL, the final review of the packaging is not available.
- ***Patient labeling/Medication guide (if considered or required)***  
Telaprevir labeling will include a Medication Guide. Among the key patient labeling issues will be patient-appropriate descriptions of major drug-associated adverse events such as serious skin reactions, anemia, and anorectal disorders. Patients will be reminded that telaprevir must not be used alone but must be used in combination with Peg-IFN and ribavirin. In addition, patients will be warned about the potential teratogenic effects of ribavirin and the need to use 2 non-hormonal methods of birth control due to a possible drug interaction between telaprevir and estrogen-containing contraceptives. Exact language for the Medication Guide is being developed in collaboration with staff in the DRISK but has not been completed at this time.

## 13. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action***  
I concur with the conclusions of the review team and recommend this NDA for telaprevir be approved for the treatment of chronic HCV infection in combination with Peg-IFN and ribavirin. I also recommend approval of a response-guided therapy approach to the treatment of patients who have not received previous treatment and for those who have relapsed after prior treatment with a Peg-IFN/ribavirin regimen.
- ***Risk Benefit Assessment***  
After review of this NDA for telaprevir as part of a treatment regimen for chronic HCV infection, the multi-disciplinary team agrees that the potential benefit of telaprevir far outweighs the potential risks. Treatment with telaprevir for 12 weeks in combination with either 24 or 48 weeks of Peg-IFN/ribavirin provided significantly better treatment outcome

than Peg-IFN/ribavirin alone as measured by SVR. Telaprevir both increased virologic response at the end of treatment and also decreased the proportion of patients relapsing after completing treatment. The magnitude of the increase in SVR rates was about 30% greater than previous standard therapy in treatment naïve subjects and about 50% greater in subjects who had failed a previous course of Peg-IFN/ribavirin. Prior relapsers derived the greatest improvement in outcomes with over 85% of prior relapsers receiving telaprevir achieving SVR in Study C216 compared to only 22% of those receiving Peg-IFN/ribavirin. Improved SVR rates were observed in all demographic and disease characteristic subgroups including those known to be more difficult to treat, although some subgroups were under-represented in the clinical trials.

The telaprevir development program confirmed response-guided therapy as a successful approach to HCV treatment. Not only are more patients likely to achieve SVR with the addition of telaprevir to the Peg-IFN/ribavirin regimen but about 60% of patients are likely to receive a 24-week course of Peg-IFN/ribavirin rather than the current 48-week course. The prospect of a shortened course of the poorly tolerated Peg-IFN/ribavirin regimen is welcome to both health care providers and patients. In addition, use of the eRVR milestones, undetectable HCV RNA at both Weeks 4 and 12, provide patients with a highly predictive marker of successful treatment since those achieving eRVR have a 90% probability of achieving SVR. Over 60% of treatment-naïve patients who do not achieve eRVR still achieve SVR but those with HCV RNA > 1000 IU/mL at Week 4 or 12 are highly unlikely to achieve SVR and can discontinue treatment and consequently limit potential toxicity.

This improvement in treatment outcome comes with a cost. Across the Phase 3 clinical trials, adverse events led to discontinuation of telaprevir or placebo in about 17% of subjects receiving telaprevir compared to about 4% of those receiving placebo. Adverse events leading to discontinuation of all study drugs occurred in about 7% of subjects receiving telaprevir compared to about 3% of those in the comparator arms. Both serious skin reactions and anemia occurred more frequently and were more severe among clinical trials subjects receiving telaprevir and were the most likely adverse events to result in discontinuation of telaprevir. Although a great majority of rash events were mild or moderate in severity and did not progress, serious cases of Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) were reported during the clinical trials. Anemia with Hgb < 8.5 g/dL, the value at which ribavirin dosing should be discontinued, occurred in about 10% of subjects receiving telaprevir compared to about 3% of those receiving Peg-IFN/ribavirin. The use of ESAs was not permitted in the Phase 3 telaprevir trials and 6% of subjects on telaprevir received a blood transfusion compared to 1% of those on Peg-IFN/ribavirin. These events will require careful monitoring in the postmarketing period.

Overall, I agree with the conclusions of the Advisory Committee that the benefits of telaprevir treatment far outweigh the risks of adverse events. With good health care provider training, patient education materials, and appropriate drug labeling the risks of telaprevir appear to be manageable. This risk/benefit assessment incorporates the advice received from the Advisory Committee.

- ***Recommendation for Postmarketing Risk Evaluation and Management Strategies***

At this time, no formal REMS is recommended. A Medication Guide will be required to ensure that patients have access to important safety information and instructions for use of telaprevir in patient-friendly language.

- ***Recommendation for other Postmarketing Requirements and Commitments***

Postmarketing studies/trials are still under discussion by the review team, taking into consideration the recommendations of the Advisory Committee. More thorough discussion regarding postmarketing commitments and requirements will be included in the Division Director's Memo.

Vertex will be required to complete clinical trials of telaprevir in pediatric patients with chronic HCV infection as a PREA PMR.

The following clinical virology PMCs and PMRs have been requested by Dr. Naeger to more fully characterize resistance to telaprevir:

1. 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)
2. Conduct a study using the HCV replicon system to assess phenotypic susceptibility of baseline and treatment-failure isolates from a subset of telaprevir-treated subjects in Phase 3 studies who did not achieve SVR with representative genotypic resistance patterns. Isolates from some telaprevir-treated subjects without known telaprevir substitutions and baseline samples from subjects who achieved SVR should also be included in these assessments for comparison.
3. 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.

The Pharmacogenomics team suggested conducting a genome-wide association study (GWAS) to identify factor(s) associated with severe skin reactions to telaprevir in combination with Peg-IFN/ribavirin using cases from existing DNA substudies and appropriately selected controls. At the time of this CDTL Review, this proposed PMC is still under discussion but may not be feasible.

- ***Recommended Comments to Applicant***

No additional comments need to be communicated to the Applicant.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LINDA L LEWIS  
05/02/2011