CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201917Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	201-917
Priority or Standard	Priority
Submit Date(s)	November 22, 2010
Received Date(s)	November 22, 2010
PDUFA Goal Date	May 23, 2011
Division / Office	DAVP/OAP
Reviewer Name	Russell Fleischer, PA-C, MPH
Review Completion Date	April 22, 2011
Established Name	Telaprevir
(Proposed) Trade Name	(INCIVEK)
Therapeutic Class	Protease inhibitor
Applicant	Vertex Pharmaceuticals
Formulation(s)	Tablet
Dosing Regimen	750 mg Q8H for 12 weeks in combination with up to 48 weeks of pegylated interferon alfa-2a or 2b and ribavirin
Indication(s)	Treatment of Chronic Hepatitis C virus infection in treatment naïve and experienced patients
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA provides for a new therapeutic approach to treatment of Chronic Hepatitis C (CHC) virus infection in adults; the addition of a novel small molecule to the current standard of care (SOC) of pegylated interferon plus ribavirin (Peg-IFN/RBV, PR). The NDA provides data from adequate and well-controlled trials that support thrice-daily administration of telaprevir, a NS3/4A protease inhibitor, in combination with PR in treatment naïve and experienced adults with CHC genotype 1 virus infection.

The available data on antiviral efficacy and safety discussed in this draft review support a recommendation that this application be approved.

1.2 Risk Benefit Assessment

Telaprevir administered for 12 weeks in combination with Peg-IFN/RBV administered for 24 or 48 weeks resulted in significantly increased response rates in a broad range of treatment naïve and experienced subjects with genotype 1 CHC compared to treatment or re-treatment with Peg-IFN/RBV alone.

The current approach to treating genotype 1 CHC naïve subjects is to administer Peg-IFN/RBV for 48 weeks and then assess for sustained virologic response (SVR) 24 weeks after completion of therapy. This strategy results in between 40-50% of subjects achieving a favorable response. Re-treatment with Peg-IFN/RBV in subjects who failed to respond to a prior course of Peg-IFN/RBV is associated with very low response rates: 3% for prior null responders to ~30% for prior relapsers.

The proposed dosing regimen for telaprevir is 750 mg given three times daily for 12 weeks (T12) in combination with Peg-IFN/RBV for 24 weeks (T12/PR24) or 48 (T12/PR48) weeks, depending on treatment response. The data support a shorter duration of treatment in naïve subjects who achieve an extended virologic response (eRVR), defined as undetectable HCV RNA at Weeks 4 and 12. Treatment-naïve subjects who fail to achieve eRVR (no eRVR) and patients with null or partial response to prior treatment should receive the T12/PR48 regimen.

Cross-study clinical and virologic modeling data in prior relapse subjects suggests a similar approach may be reasonable, but the final decision on this approach will be made once the issue and data have been discussed with the Antiviral Products Advisory Committee.

In clinical trials of treatment naïve subjects, 75% of subjects treated with a telaprevir-containing regimen achieved a SVR compared to 46% of subjects treated with a regimen of placebo plus PR for 48 weeks (Pbo/PR48).

A regimen of a shortened duration of telaprevir (T8) was evaluated; this regimen was associated with lower SVR and higher virologic failure and relapse rates compared to the T12 regimen. As such, this duration of telaprevir should not be recommended as the primary regimen.

The plan to administer a shortened 24 week duration of PR treatment (T12/PR24) in eRVR subjects was called "response guided therapy" (RGT) and represented an evolution in HCV treatment. In the trials, 60% of subjects treated with telaprevir achieved eRVR, and of those 90% achieved a SVR with either T12/PR24 or T12/PR48. These data demonstrate that in many subjects treatment can be truncated. Peg-IFN/RBV induce a multitude of toxicities, and many are treatment limiting. Therefore, the ability to truncate therapy in many subjects represents a major step forward in the progress of CHC treatment resulting in high virologic cure rates.

For no eRVR subjects, treatment with T12/PR48 also led to higher SVR rates compared to treatment with Peg-IFN/RBV alone, demonstrating the added benefit of telaprevir to a population of subjects that are less likely to achieve a SVR with current SOC.

In treatment experienced subjects, the RGT approach was not used and all subjects received T12/PR48 with telaprevir being initiated immediately or after a 4-week PR lead in. The FDA statistical analyses found no relevant differences in response rates between these two approaches. The resultant SVR rates ranged from 35% (prior null responders) to 84% (prior relapsers) compared to 3% and 45%, respectively, with re-treatment with PR alone.

Based on cross-study comparisons and viral dynamic modeling, RGT may be an acceptable approach in prior relapse subjects who achieve an eRVR.

The significant increase in SVR for T12/PR48 compared to retreatment with PR alone in prior null responders is noteworthy, although lower than the SVR rate in prior partial responders and prior relapsers. However, there are no other available treatments that provide greater chance for response, and prior null responders are unlikely or, more likely, unwilling to wait until better therapies are made available. It was expected that prior relapsers would likely have robust responses as they have previously demonstrated interferon sensitivity.

In addition, the inclusion of telaprevir decreased the frequency of subjects who failed to achieve SVR by decreasing on-treatment virologic failure, virologic failure during PR dosing and relapse relative to the current SOC.

Although the number of subjects in some categories was small, increases in efficacy were observed in subjects who traditionally have had lower response rates to SOC treatment: Blacks/African Americans, Hispanics/Latinos, subjects with cirrhosis, those with high baseline HCV RNA (>800,000 IU/mL), and prior null and partial responders and prior relapsers

previously treated with Peg-IFN/RBV. Further discussion about the strength of data to support a full recommendation for treatment for some of these subgroups will occur during the Advisory Committee meeting.

Two key telaprevir-related safety issues emerged: rash/pruritis and anemia. These events occurred frequently, and were in some cases severe and treatment limiting. A brief discussion of other noteworthy adverse reactions follows.

Rash/pruritis: Telaprevir-related rash affects ~55% of subjects. Clinically and histologically, the rash is similar to the rash associated with Peg-IFN and RBV; but the frequency and severity appear increased with the addition of telaprevir.

The rash is typically maculopapular or papular-lichenoid, may have an excematous component, and in many cases accompanied by pruritis. Histologically, the rash appears as spongiform dermatitis, with predominantly lymphocytic or eosinophilic perivascular infiltration. In general telaprevir associated rash appears similar to rash associated with PR, but can be more severe. In the majority of subjects, the rash was mild to moderate in severity, but serious in 1% and led to discontinuation of telaprevir in 6% of subjects. The telaprevir-related rash occurred early (time to onset 16-20 days), and persisted for up to several weeks once telaprevir dosing was withdrawn or completed. Many subjects in the clinical trials required treatment with topical or systemic corticosteroids. The frequency of Severe Cutaneous Adverse Reactions (SCAR), such as Stevens Johnson Syndrome (SJS) and Drug Related Eruption with Systemic Symptoms (DRESS) were reported; no deaths were reported. However, the Applicant's Dermatology Expert Panel EP review may have been biased towards characterizing only the more severe events given their definitions. As such, labeling will need to clearly describe the risks of severe rash, SCAR events, and how these events should be managed. The mechanism of telaprevir-related rash has not been fully elucidated, and efforts to determine the mechanism are ongoing.

Anemia: Anemia is a well known RBV-related toxicity that also appears exacerbated by the addition of telaprevir. In preclinical studies, telaprevir demonstrated an effect on the hematopoietic system (decreased erythrocytic parameters and anemia accompanied by reticulocyte/bone marrow response). Subjects receiving telaprevir had a higher frequency of anemia (33% versus 15%), a higher frequency of $\geq$Grade 3 (<8.9 g/dL or >4.5 g/dL from baseline) hemoglobin reductions (55% versus 27%), more anemia-related SAEs (2% versus <1%), and a higher frequency of anemia-related discontinuations (3% versus <1%). Absolute hemoglobin decreases to <10 g/dL occurred in 45% of telaprevir subjects compared to 27% in Pbo/PR48 subjects, and decreases to <8.5 g/dL occurred in 25% and 14%, respectively. Hemoglobin values decreased steeply through Weeks 4-8, were generally stable between Weeks 8 and Week 12, and by Week 16-18 had risen to levels similar or higher compared to those of subjects in Pbo/PR48 groups.

Anorectal Events: Anorectal events (hemorrhoids, pruritis ani, proctalgia, anal inflammation, perianal erythema, and anal discomfort) were reported by ~20% (range 15-26%) of T-treated

subjects. These events appeared to be a bothersome (mild to moderate severity), but rarely serious, and resulted in 1 case of study discontinuation.

Eye Disorders: In Phase 2 trials a possible signal for excess eye disorders with telaprevir was observed. In Phase 3 trials, the frequency of eye disorders was 4% higher among subjects who received telaprevir (17% compared to 13%). The most frequently reported events in subjects treated with telaprevir were blurred vision, dry eyes, photophobia, eye pain, and retina-related events. Peginterferon is labeled for these ophthalmologic disorders, most resolved following completion of telaprevir dosing, and as such it is not clear that these events represent a clinically relevant signal for telaprevir.

Renal Disorders: All grade increases in creatinine levels were higher among subjects treated with T/PR: 6% compared to 1% for Pbo/PR, and creatinine elevations to ≥Grade 3 levels were <1% compared to 0%. All elevations were reversible upon cessation of telaprevir dosing. Renal failure occurred in <1% of telaprevir and Pbo/PR subjects in the Phase 3 program. Again, since most clinical events were mild and creatinine abnormalities were reversible upon cessation of telaprevir, it is not clear they represent a major safety signal for telaprevir.

General Adverse Events: The most frequent AEs (>20%) observed during T/Pbo dosing were fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, and pyrexia. Of these, AEs that were observed with at a frequency ≥5% higher in the T/PR groups compared to the Pbo/PR48 groups were: pruritus, fatigue, nausea, rash, anemia, diarrhea, hemorrhoids, dysgeusia, and anorectal discomfort. There were no clinically relevant differences between the adverse event profile of treatment naïve and treatment experience subjects.

Other Hematologic Abnormalities and Events: More telaprevir-treated subjects than Pbo/PR subjects had severe decreases in lymphocyte (≤499/mm^3) (15% compared to 6%) and platelet (≤49,999/mm^3) (3% compared to 1%) counts. No significant opportunistic infections in subjects with lymphopenia occurred.

Severe decreases in total white blood cells (≤1499/mm^3) were comparable (6% compared to 5%). Conversely, the frequency of severe decreases in absolute neutrophil counts (≤499/mm^3) were higher in subjects receiving Pbo/PR48 (15% compared to 12%). Five events of pancytopenia were reported in telaprevir subjects; none were fatal. Colony stimulating formula use to support white cell production was used in ~1% of telaprevir and PR-treated subjects.

Severe reductions in platelet counts (≤49,999/mm^3) occurred in 2% of T/PR compared to 1% of Pbo/PR subjects. Two percent of T/PR subjects had a clinical event of thrombocytopenia compared to 1% of Pbo/PR subjects. Epistaxis was the most common bleeding event reported: 4% (T/PR) compared to 3% (Pbo/PR).

Clinical Chemistry Abnormalities and Events: Elevations of bilirubin and uric acid were frequently observed and may be related to the excess breakdown of red blood cells in telaprevir-treated subjects with anemia. During the T/Pbo dosing period substantially more telaprevir-

treated subjects than Pbo/PR48 subjects had elevated uric acid levels (73% compared to 29%). Shifts from baseline to Grade 3 or higher uric acid levels were also more frequent among subjects treated with telaprevir (7%) compared to Pbo/PR48 (2%). Also, more subjects treated with telaprevir experienced gout/gouty arthritis.

Bilirubin elevations occurred in 40% of telaprevir-treated subjects compared to 28% of Pbo/PR48 subjects, and 4% and 2%, respectively, had Grade 3 or higher (>2.6 x ULN) elevations. Bilirubin levels increased most steeply during the first 1-2 weeks of telaprevir dosing, stabilized and by Weeks 12 to 16 were similar to baseline levels.

In summary, the risk:benefit assessment is in favor of an approval recommendation as it is clear that telaprevir substantially increases SVR rates (viral cure) with a decreased duration of therapy in a large proportion of treatment naïve subjects. The increased SVR rates in prior null and partial responders represent a major advance for subjects with very limited treatment options. The efficacy of telaprevir in some subgroups (e.g., Blacks/African Americans, null responders with cirrhosis) in which enrollment was limited raises questions about the strength of conclusions. The significant telaprevir-related toxicities of severe rash/pruritis and anemia are well known, easily recognized, and can be serious and treatment limiting; however, with labeling guidance they should be manageable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Telaprevir will have a Medication Guide only REMS and the Applicant will issue a Dear Health Care Profession letter to convey the risks of severe rash and anemia, how to assess and manage severe rash and anemia, and the importance of counseling and communicating with patients about these risks.

1.4 Recommendations for Postmarket Requirements and Commitments

Recommendations for PostMarket Requirements and Commitments will be made following a discussion of this application with the Antiviral Products Advisory Committee.

2 Introduction and Regulatory Background

2.1 Product Information

Telaprevir is a HCV NS3/4A protease inhibitor and represents one of the first of a new class of small molecules that targets steps in the hepatitis C virus (HCV) life cycle.

2.2 Currently Available Treatments for Proposed Indications

Over 170 million individuals are infected with HCV worldwide (about 3% of the world population). HCV infection presents a significant global health problem. Only 20–30% of HCV-infected individuals recover spontaneously, with the remaining 70–80% going on to develop chronic infection, with a significant risk for progressive liver fibrosis and subsequent cirrhosis and hepatocellular carcinoma. HCV-related end-stage liver disease has become the most common cause for liver transplantation in the Western world, with numbers steadily increasing. More importantly, liver transplantation of patients with HCV-related liver cirrhosis is associated with a high risk of HCV recurrence and rapidly progressive liver fibrosis post-transplantation. Thus, successful treatment of chronic HCV infection is crucial in reducing the morbidity and mortality of patients with chronic infection. While therapy for this condition has improved considerably, the currently available treatment regimens are not optimal.

The goal of anti-CHC therapy is to eradicate viremia. Treatment response is assessed by sustained virologic response (SVR), which is defined as undetectable HCV RNA 24 weeks following a course of interferon-based therapy. Attainment of an SVR is associated with a substantial decrease in long-term progression of liver disease, the occurrence of liver cancer, and the need for liver transplantation.

The current standard of care (SOC) therapy for chronic hepatitis C virus infection (CHC) is 48 (genotype 1) or 24 (genotype 2 and 3) weeks of pegylated interferon (Peg-IFN) plus ribavirin (RBV). Currently approved interferon products include Peg-Intron® (pegylated interferon alfa-2b, Schering) and Pegasys® (pegylated interferon alfa-2a, Roche). Ribavirin is approved as Rebetol®, Copegus®, ZyGeneric®, and Ribasphere®.

In patients infected with genotype 2 or 3 virus (the most treatment-responsive genotypes), treatment results in a SVR in about 80% of cases. In patients infected with genotypes 1a or 1b, which are the most common genotypes in North America and Europe, approximately 50% will achieve a SVR with 48 weeks of Peg-IFN and RBV.

Male sex, higher body weight, higher baseline viral load levels, African American race and Hispanic ethnicity, and HCV genotypes 1 and 4 are known to be associated with poorer responses to IFN/RBV-based therapies. There is no approved direct anti-viral agent directed against HCV and no vaccine for prevention of HCV infection. For all patients who are at a high risk of progressing to liver cirrhosis (liver biopsy with portal or bridging fibrosis and at least moderate inflammation and necrosis), particularly aggressive therapy is recommended.

Both Peg-IFN and RBV are associated with considerable toxicity. Adverse side effects associated with therapy, such as severe flu-like symptoms, depression, psychoses, and anemia, result in approximately 20% of patients discontinuing therapy.

Blacks and African Americans have a high prevalence of genotype 1 chronic HCV infection, they respond poorly to therapy with interferon alfa-based regimens, and they have been

underrepresented in clinical trials. Large racial disparities in the prevalence of HCV infection exist in the United States. Antibodies to HCV are 2 to 3 times more common among Blacks/African Americans than among Caucasian Americans, as is hepatocellular carcinoma. In addition, the distribution of HCV genotypes differs among racial groups, with genotype 1 virus responsible for approximately 90% of HCV infections in Blacks/African Americnas, compared with only 67% in Caucasians. Clinical trial data have demonstrated that SVR rates in Blacks/African Americans are generally lower than in Caucasians by ~20%.

Patients who have been treated with prior IFN-based regimens and failed to respond is a growing population, and one in need of effective therapies. In mid-2009, the results of a large trial of re-treatment of prior non-responders with Peg-IFN alfa 2b/RBV became available and demonstrated that re-treatment with Peg-IFN/RBV resulted in low overall response rates (range 10-20%) (Poynard T. et al: Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology, 2009 May; 136(5): 1618-28). Therefore, there remains a great need for therapies targeting this group of patients.

Thus, there is a clear unmet need for effective anti-HCV compounds which, when added to current standard of care, can decrease the duration of Peg-IFN/RBV-based therapy, decrease the associated morbidity, increase the likelihood of success in treatment of genotype 1-infected patients, and can offer some hope to subjects who have failed to respond to prior interferon-based therapies for which no adequate re-treatment strategies exist. To meet this need, there has been an increased interest in the development of small molecules with direct antiviral activity against specific stages of the HCV life cycle.

2.3 Availability of Proposed Active Ingredient in the United States

The drug substance is readily available in the US. Telaprevir is not approved but is expected to be marketed in the US by Vertex Pharmaceuticals.

2.4 Important Safety Issues With Consideration to Related Drugs

Telaprevir represents one of the first drugs in a new class of HCV NS3/4A serine protease inhibitors. At the time of this NDA review, there were no other approved NS3/4A protease inhibitors available for a direct comparison.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The IND for telaprevir (#71,832) was submitted in October 2005, and has been active since. The Applicant has conducted a panoply of clinical studies to support the development of telaprevir. Multiple meetings (telecons and face-to-face) have been held over the lifecycle.

In January 2008, an End-of-Phase 2 (EOP2) meeting was held to discuss the amount and type of data that would be required to support submission of a marketing application. At the time of the

EOP2 meeting, the Applicant proposed to conduct (b) (4) . The Applicant was advised to:

- Conduct more than one adequate and well-controlled Phase 3 studies to support registration in a single population. The Phase 2 trials could serve as supporting data
- Confirm whether a difference in SVR rates exist between a regimen of T12/PR24 and T12/PR48; a difference was noted in one small Phase 2 study
- Ensure the population(s) studied were representative of the US population with CHC
- Provide some data on HCV/HIV co-infected subjects in a marketing application
- Provide a pediatric development plan
- Provide a plan for evaluation of telaprevir in treatment-experienced subjects

Approximately 6 months later, the Applicant approached the Division with a proposal for an indication in treatment experienced subjects. The proposal included conduct of a Phase 3 trial and use of supportive data from two Phase 2 trials (Studies 106 and 107). The trial design was reviewed and commented on and subsequently initiated (Study C216).

A Pre-NDA meeting was held September 28, 2010. Important issues discussed included:

- Whether the telaprevir NDA would qualify for a Priority Review
- The proposed dose and regimen for marketing for treatment naïve and experienced subjects, and the amount and adequacy of the data to support approval
- The amount of resistance and IL28B data to be submitted in the NDA
- The amount of data and timing of the safety update
- The timing of an Advisory Committee meeting
- The requirement for REMS and/or Medication Guide
- Safety related issues, specifically rash and pruritis, anorectal toxicities, anemia, and cardiovascular safety

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was reviewable. All bookmarks and hyperlinks functioned normally. All required components were included.

3.2 Compliance with Good Clinical Practices

The trials appear to have been conducted in compliance with Good Clinical Practices (GCP). The Applicant attested that no investigators were found to be out of compliance with GCP, and no investigator was removed for non-compliance from any trial. The pivotal efficacy trials were conducted at sites both within and outside the US using the same design, same patients, and same control regimens with similar outcomes.

An audit of 4 clinical sites (2 for Study 108 and 2 for Study C216) that participated in the pivotal Phase 3 trials was conducted by the Division of Scientific Investigations (DSI). Thus far, one site in Vienna, Austria (Study 108) was issued a 483 due to issues related to trial conduct. Two subjects at that site were retrospectively granted protocol exemptions (not confirmed to have genotype 1 with detectable HCV RNA at baseline); both subjects were randomized to the T8 group and both failed to respond (no SVR).

A second site in Dallas, Texas (Study 108) had no deficiencies identified.

Reviewer Comment: The retrospectively granted protocol waivers had no impact on the outcomes of Study 108 individually, or the assessment of overall telaprevir efficacy. Inspection results from two sites for Study C216, and DSI's final assessment and recommendation are pending.

3.3 Financial Disclosures

Reportable trials for the purpose of financial disclosure are Studies 108, 111 and C216. The Applicant submitted Form 3455 identifying 11 investigators ((b) (6)) who received "any significant payments" as defined under 21 CFR Part 54. Payments were reported to be for such things as advisory board participation, manuscript and media preparation. The Applicant attested that steps were taken to minimize bias because these were controlled trials in which independent data monitoring committees were used.

The number of subjects enrolled at of these investigator's sites in each study was low (≤10), suggesting that individually, none of these investigators could have impacted the study results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

- Telaprevir is metabolized in the liver primarily by cytochrome CYP3A4, and is also a CYP3A inhibitor. As such, there are a substantial number of potential drug-drug interactions. There is an extensive list of medications with which telaprevir should not be co-administered with or that should be co-administered with caution (see Sections 4.4.3 and 7.6)

- Resistance to telaprevir can occur quickly, within 1-3 days of monotherapy, and for that reason must be administered in combination with Peg-IFN/RBV. Further, some mutations that confer resistance to telaprevir may persist for upwards of 3 years (see Section 4.2).
- Based on the results of two thorough QTc studies, telaprevir unlikely causes QT prolongation (see Section 4.2).
- Telaprevir will be classified as Pregnancy Category B. However, telaprevir must be co-administered with RBV which is category X. As such the label will recommend use of at least 2 acceptable non-hormonal forms of birth control be used during the telaprevir dosing period (see Section 4.3).
- In preclinical studies, telaprevir had an effect on the hematopoietic system (decreased erythrocytic parameters and anemia accompanied by reticulocyte/bone marrow response), which could be a partial explanation for the increase frequency of anemia observed in clinical trials (see Section 4.3).

All disciplines recommend approval of telaprevir.

4.1 Chemistry Manufacturing and Controls

Telaprevir will be supplied as immediate release 375 mg purple capsule shaped tablets. The proposed shelf life is 24 months at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) based on 24 months real time data at 25°C.

(b) (4)

The manufacturing process is extremely complicated, but was adequately described. Excipient levels have been held to minimal and acceptable levels in multiple batches. Site inspections yielded no major deficiencies.

4.2 Clinical Microbiology

Telaprevir is a peptidomimetic inhibitor of the HCV NS3/4A serine protease.

HCV is a positive-sense single-stranded RNA virus of the *Flaviviridae* family. There are six major genotypes and at least 50 subtypes. The HCV genome consists of 9600 nucleotides in a single open reading frame encoding a polyprotein of approximately 3000 amino acids. This viral polyprotein is processed by cellular and HCV-encoded proteases into three structural proteins (core, which forms the viral nucleocapsid, and the envelope glycoproteins E1 and E2) and seven nonstructural proteins that have essential functions in viral replication. NS3/4A has emerged as an attractive target for new antiviral agents since it contains protease, RNA helicase, and nucleoside triphosphatase activities, all of which are essential to viral replication.

The NS3/4A serine protease has key functions. It is responsible for cleavage at four downstream sites in the HCV polyprotein, to generate the N-termini of NS4A, NS4B, NS5A, and NS5B. It also has an important role in blunting the host antiviral interferon alfa response through inhibition of IFN-α regulatory factor-3, and by cleavage and inactivation of the host proteins Trif and Cardif, with resultant inhibition of toll-like receptor 3 and retinoic acid-inducible gene 1. Hence, NS3/4A represents a dual therapeutic target, the inhibition of which may block viral replication and restore control of HCV infection by interferon alfa-mediated pathways.

When telaprevir is administered, a stable enzyme-inhibitor (EI*) complex is formed, which has an enzymatic half-life of about 1 hour. The inhibition constant for formation of the EI* complex (Ki*) is 7 nM. The main metabolite, VRT-127394, is approximately 30-fold less potent than telaprevir at short reaction times, and significant potency was only reached after several hours of incubation. Data from *in vitro* studies indicate that T is active against the protease from HCV genotypes 1, 2, 3, and 4.

Single and double mutations at positions V36, T54, R155, and A156, confer low- to medium-level resistance (4-20-fold), whereas V36/R155 double mutants and A156V/T mutants confer high level resistance (>60-fold). The majority of other protease inhibitors currently in development are rendered inactive by the emergence of the same mutations. As such, subjects who virologically fail telaprevir may have persistent mutations that convey cross-resistance and may reduce responses to other agents in this class. Data suggests that many mutations persist and revert to wild-type over 1-2 years; the R155K mutation may persist for up to 3 years.

In vitro synergy was demonstrated when telaprevir was co-administered with interferon and ribavirin, and all variants that convey resistance to telaprevir remained fully sensitive to interferon-alfa and ribavirin in *in vitro* replicon assays.

4.3 Preclinical Pharmacology/Toxicology

Results from preclinical safety pharmacology studies evaluating telaprevir performed in repeat-dose toxicity studies suggest that telaprevir had no effects on vital function.

Toxicology

The Pharmacology/Toxicology review yielded that:

- Telaprevir affects the hematopoietic system (decreased erythrocytic parameters and anemia accompanied by reticulocyte/bone marrow response).
- Telaprevir and its epimere, VRT-127394, are non-genotoxic and non-mutagenic or teratogenic.
- Macroscopic and microcytic testicular toxicity was noted with a correlating decrease in organ weight. Decreased organ weight accompanied by microscopic changes was also detected in the epididymis. A decrease in the % of motile sperm as well as an increase in nonmotile sperm count also occurred. These male reproductive effects likely contributed

increased % preimplantation loss, % of dams with nonviable embryos, and % nonviable conceptuses/litter. In general, effects on male reproductive system appear reversible. The NOAEL for reproductive organ toxicity occurred at exposures 0.17-fold the human exposures at the recommended clinical dose. The sperm evaluation was conducted at a single dose level with an exposure 0.30-fold the clinical exposure.

- Chronic active vasculitis in the epididymis was observed in a single dog after 9 months of treatment. This lesion occurred in multiple organs in the 9 month dog study.
- Peri- and post-natal evaluations suggest that telaprevir has no effects on natural delivery in rats but may have adverse effects on the growth of offspring as evidenced by body weight effects pre- and post-weaning. However, no effects on development, behavior, and Caesarian-sectioning or litter parameters were noted in offspring.

The total duration of administration of telaprevir is 12 weeks. Since telaprevir and its metabolites are not genotoxic, long-term carcinogenicity studies were not required.

Telaprevir will be labeled as Pregnancy Category B based on nonclinical findings.

Reviewer Comment: Testing for levels of serum inhibin B, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were included in three Phase 2 studies (Studies 104, 104EU, and 106). Changes from baseline were similar between the telaprevir and placebo treatment. As such, the testicular finding in rats appears to be species specific and not relevant to clinical use of telaprevir.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Telaprevir is a selective and specific inhibitor of the HCV NS3•4A protease (see Section 4.2 above).

4.4.2 Pharmacodynamics

The proposed dose for marketing is 750 mg (administered as 2-375 mg tablets) q8h with food for 12 weeks. The results of multiple Phase 1, 2 and 3 clinical trials support the safety and efficacy of this regimen.

Phase 1 single and multiple dose pharmacodynamic studies demonstrated that telaprevir administered as monotherapy in doses between 450 mg and 1250 mg resulted in marked and rapid inhibition of HCV, with >3 $\log_{10}$ HCV RNA decline within 24 hours of the first dose and average reduction in plasma HCV RNA levels of >4 $\log_{10}$ IU/mL. Some subjects in the monotherapy trials experienced rapid viral breakthrough (by day 3), with viral sequence analysis revealing resistance-associated mutations in the catalytic domain of the NS3 protease. Fourteen and 28-day studies in which telaprevir was co-administered with Peg-IFN with and without RBV

demonstrated increased viral inhibition between -5 to -6 $\log_{10}$ IU/mL, and decreased the emergence of resistant strains.

QT/QTc: No clinically relevant QTcF prolongation effects of telaprevir (750 mg and 1875 mg) were detected in a TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between telaprevir (750 mg and 1875 mg) and placebo were 7.0 ms and 9.9 ms in QTcF. In addition, no significant concentration-QT relationship (P = 0.35) was established from the study. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms.

Dose Frequency Study: (b) (4) the Applicant conducted a Phase 2 Study VX-950-Q8hP-C208**.** In this trial, subjects were randomized to T 1125 mg q12h or 750 mg q8h for 12 weeks in combination with either Peg-IFN alfa 2a or 2b plus RBV. Pharmacokinetic data suggest that exposures to telaprevir, both Peg-IFNs and RBV were comparable across the treatment groups. However, the numbers of subjects in each treatment group was sparse (≤40), there was an under-representation of Blacks (91% Caucasian), subjects who received 1125 q12h experienced more gastrointestinal events. (b) (4) this study is currently ongoing (see Section 5.3 for more discussion of Study C208).

4.4.3 Pharmacokinetics

Absorption, Metabolism, and Excretion: Relevant Clinical Pharmacology findings include:

- Telaprevir is partially (about 30-40%) converted into VRT-127394 (its *R*-diastereomer).
- Telaprevir is orally available, most likely absorbed in the small intestine. There is no evidence of absorption in the colon. Telaprevir absorption is characterized by an initial slow phase followed by a second rapid phase, absorption being preceded by an average lag time of 0.21 hours.
- Telaprevir Cmax and AUC increase after multiple doses and steady state is reached after 3-7 days. The terminal half life following a single dose is ~4 hours. At steady-state, the half life of telaprevir is about 9-11 hours, suggesting that telaprevir is completely removed from the system within 3-4 days.
- Elimination in the feces was the predominant route of excretion for telaprevir and its metabolites.
- Exposures and elimination half lifes were similar in healthy volunteers and HCV infected subjects.
- When telaprevir was administered with food, telaprevir exposures were increased 2.6-fold to 5.1-fold and intra-subject variability was decreased. As such it is recommended that T be taken with food.
- At concentrations from 0.1 to 20 μM, 14C-telaprevir was moderately bound to plasma

proteins from all species evaluated and ranged from 63% to 71% in mouse, 82% to 86% in rat, 62% to 67% in dog, and 59% to 76% in human plasma.

- There were no differences in the pharmacokinetics of telaprevir or its metabolites between healthy and infected subjects.
- There was minimal impact of weight on the variability in telaprevir pharmacokinetics.

Drug-Drug Interactions: Telaprevir is metabolized primarily by cytochrome P450 CYP3A4; it is a strong inhibitor of CYP3A4 and it is a substrate of P-gp. As such, a substantial number of drug-drug interactions were anticipated. The Applicant conducted multiple drug interaction studies characterizing telaprevir's effect on various CYP3A4 substrates and commonly used medications in patients with chronic HCV infection, including methadone, escitalopram, a combined oral contraceptive, digoxin, HIV antiretrovirals, immunosuppresants, atorvastatin, and midazolam. In addition, the effects of potent CYP3A induction (rifampin) and inhibition (ketoconazole) on telaprevir PK were assessed in vivo.

In an oral contraceptive study, telaprevir decreased exposure to ethinyl estradiol by ~30%; with no effect on norethindrone.

Reviewer Comment: Telaprevir's drug interaction profile has been adequately characterized; results from the completed studies are sufficient for providing recommendations for the safe use of telaprevir with potentially interacting and commonly used drugs. It is likely the labeling will carry a recommendation that female subjects use two non-hormonal forms of birth control during telaprevir dosing.

Drug-Disease Interaction (Hepatic Impairment): Two studies were conducted in non-HCV infected subjects with mild and moderate hepatic impairment. Hepatic impairment decreased telaprevir exposures in subjects with mild (Child-Pugh Class A [CPA]) and moderate hepatic impairment (Child-Pugh Class B [CPB]) by 15% and 53%, respectively, compared to healthy subjects. Additionally, because of reduced exposure to telaprevir in CPB subjects, subjects with Child-Pugh Class C (CPC) have not been evaluated.

Reviewer Comment: The labeling should recommend that subjects with CPA can receive telaprevir without dose adjustment, but until further data are available, administration of telaprevir to subjects with CPB or CPC cannot be recommended. The inability to determine appropriate dose modifications for use in subjects with more advanced synthetic dysfunction will likely negatively impact the product's utility in such subjects as this population often includes subjects with decompensated cirrhosis and those waiting for a liver transplant.

Drug-Disease Interaction (Renal Impairment): A single dose study of telaprevir in subjects with severe renal impairment demonstrated a 10% higher C_{max} and 21% higher AUC compared to healthy control subjects. Based on these data, the Applicant has proposed that a dose adjustment of telaprevir is not needed for subjects with CrCl <30 ml/min. However, due to telaprevir's non-linear and time-dependent pharmacokinetics, exposure to telaprevir may be

greater in renally impaired patients following multiple-dosing. A multiple-dose study would have more accurately characterized the impact of renal impairment on telaprevir PK.

Additional discussions are underway to determine whether the extent of accumulation in subjects with severe renal impairment can be estimated based on the single-dose study results.

Reviewer Comment: Telaprevir must be co-administered with Peg-IFN and RBV. There are no approved dosing recommendations for administration of RBV in patients with a CrCl <50 ml/min. By extension, no dosing recommendations can be made for telaprevir in subjects with CrCl <50 ml/min. A multiple dose study or a model to simulate multiple dose pharmacokinetics from single dose data is under discussion.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant submitted the final study reports for several controlled and uncontrolled Phase 2 and 3 trials to support the approval of telaprevir (see Table 1). The Phase 2 trials considered most relevant to support approval of telaprevir included Study 104, 104EU, 106 and 107.

Two pivotal Phase 3 trials were conducted; one in treatment naïve (Study 108) and one in treatment experienced (Study C216) subjects. A supportive trial (Study 111) was conducted in order to answer questions about the appropriate duration of therapy among subjects who achieved an extended virologic response (eRVR).

Table 1 Phase 2 and 3 pivotal and supportive trials

Study title	Design	Population	Study treatments	Subjects
Phase 2 Trials				
VX05-950-104(PROVE 1)	Randomized Placebo controlled, Double-blind	Treatment naïve genotype 1	T12/PR12 T12/PR24 T12/PR48 Pbo/PR48	T regimen: 175 Pbo/PR48: 75
VX05-950-104EU (PROVE 2)	Randomized, Partially Placebo controlled, Partially double-blind	Treatment naïve genotype 1	T12/P12 T12/PR12 T12/PR24 Pbo/PR48	T regimen: 241 Pbo/PR48: 82
VX06-950-106 (PROVE 3)	Randomized, Partially Placebo controlled, Partially double-blind	Prior non-responders genotype 1	T24/PR48 T24/P24 T24/PR24 Pbo/PR48	T regimen: 339 Pbo/PR48: 114
VX06-950-107	Nonrandomized, Open-label, Multiple dose	Prior non-responders genotype 1 who were enrolled in the control arm of Studies 106, 104, or 104EU and discontinued due to an inadequate response	Subjects with prior null response: T12/PR48 Subjects with prior partial response, relapse, and viral breakthrough: T/PR24 or 48	T regimen: 117
Phase 3 Trials				
VX07-950-108: (ADVANCE) **Pivotal Trial**	Randomized Placebo controlled, Double-blind	Treatment-naïve genotype 1	T8/PR24-48 T12/PR24-48 Pbo/PR48	T8: 364 T12: 363 Pbo/PR48: 361
VX08-950-111 (ILLUMINATE) **Supportive Trial**	Open-label, Randomized based on on-treatment response	Treatment-naïve genotype 1	T12/PR24-48 (dependant on TW4 and 12 response)	T12: 540
VX-950-C216 (REALIZE) **Pivotal Trial**	Randomized Placebo controlled, Double-blind	Prior non-responders genotype 1	T12/PR48 Pbo/PR48	T12: 530 Pbo/PR48: 132

5.2 Review Strategy

Section 5.3 provides a summary of the design and results of salient Phase 1 and Phase 2 trials, other ongoing important trials at the time of NDA submission, and descriptions of the designs of the pivotal Phase 3 trials. The clinical efficacy results from the Phase 3 trials are presented in Section 6.1 and safety results are presented in Section 7.

There are a number of ongoing clinical trials in which subjects are receiving telaprevir, some of which are being conducted by the Applicant, and others being conducted by various marketing partners. Since these trials were ongoing at the time of NDA submission, no efficacy data were available. Where data was available, the salient efficacy data is presented in Section 5.3 and safety is included in Section 7 of this review.

5.3 Discussion of Individual Studies/Clinical Trials

The development of telaprevir involved a substantial number of single and multiple dose Phase 1 and 2 PK/PD studies. Data from these studies demonstrated that after 3, 14 and 28 days either as monotherapy or in combination with Peg-IFN with and without RBV, telaprevir achieved exposures expected to suppress HCV, produced robust antiviral efficacy, and had a generally acceptable safety profile. Subsequently, the Applicant conducted four main Phase 2 studies: two in treatment naïve and two in treatment experienced subjects. These trials were followed by one pivotal Phase 3 trial in each population of treatment naïve and experienced subjects, with an additional supportive trial in treatment naïve subjects. A review of the Phase 2 trials follows.

Integrated Summary of Supportive Phase 2 Studies

The results of the two Phase 2 trials conducted in treatment naïve subjects provided supportive evidence for the continued development of telaprevir by demonstrating:

- The addition of 12 weeks of telaprevir co-administered with Peg-IFN/RBV for 24 or 48 weeks led to substantially higher SVR rates with lower virologic failure, breakthrough and relapse rates compared to the current SOC.

- The regimen of T12/PR24 produced consistently higher SVR and lower relapse rates, and suggested this regimen may be beneficial and warranted further evaluation.

- Treatment with a T12/PR48 regimen resulted in comparable SVR rates to a T12/PR24 regimen, but only in one trial. Therefore, it could not be determined if this represented a true difference. The Applicant was asked to further evaluate different PR durations in Phase 3.

- The lower SVR and higher relapse rates withT12/PR12 suggested that longer duration PR would be required so this regimen was not further evaluated.

- A RBV-sparing regimen (T12/P12) failed to produce comparable SVR rates to SOC and resulted in higher rates of on-treatment virologic breakthrough and post-treatment relapses. As such, this strategy was also abandoned.

In treatment experienced subjects, the trials demonstrated:

- Re-treatment with a regimen of T/PR significantly increased response rates compared to re-treatment with PR alone across all categories of prior non-responders evaluated. Extending the duration of therapy for 48 weeks (T12/PR48) was associated with robust SVR rates compared to shorter duration regimens and historical response rates.

- The regimen of T12/PR48 appeared to be the most beneficial for further evaluation as the regimen of T24/PR48 was not associated with improved efficacy.

- The robust response and low virologic failure, breakthrough and relapse rates for subjects with prior relapse in the T12/PR24 arm suggested there may be an opportunity to shorten the duration of therapy.

- The increased SVR rates among prior null responders in both trials were very encouraging. However, the definitions of null response were different between the trials and therefore could not be integrated into a single analysis. Further, the results raise the question of the optimal duration of therapy for re-treatment of these subjects. In Study 106 the additional 24 weeks of PR (48 weeks total) did not increase the SVR rate among prior null responders while in Study 107 there appeared to be a benefit for this longer duration of therapy. A uniform definition of prior null response was developed for evaluation in Phase 3 trials.

- There were very few prior breakthrough and prior partial responder subjects. Positive response trends were noted, but it was not possible to be confident of which duration regimen would be most beneficial for these populations.

- Many subjects with negative predictive factors, such as prior null response, high baseline viral load, and genotype subtype 1a, and cirrhosis were able to mount a response providing them a reasonable chance to achieve a favorable long-term outcome.

- Although, there appeared to be trends toward increased response with the T/PR regimens among Blacks/African American subjects, the overall number was very low. The Applicant was advised to increase the participation of Blacks/African American subjects in the Phase 3 program.

Phase 2 Trials: Treatment-Naïve Subjects

The Applicant conducted two placebo controlled trials in treatment naïve subjects to evaluate different regimens of telaprevir/PR: Studies VX05-950-104 (PROVE 1) and VX05-950-104EU (PROVE 2). Study 104 was conducted in the US and Study 104EU was conducted in the European Union. The trials were conducted in parallel between 2006 and 2008.

Investigational Plan: The trials were similarly designed but not exactly the same. In Study 104, 190 subjects were randomized 1:1:1:1 to one of the following treatment groups:

- Placebo q8h/Peg-IFN/RBV for 48 weeks (Pbo/PR48)
- T/Peg-IFN/RBV for 12 weeks, Peg-IFN/RBV for 36 weeks (T12/PR48)
- T/Peg-IFN/RBV for 12 weeks, Peg-IFN/RBV for 12 weeks (T12/PR24)
- T/Peg-IFN for 12 weeks (T12/PR12)

In Study 104EU, 323 subjects were randomized 1:1:1:1 to one of the following treatment groups:

- Placebo q8h/Peg-IFN/RBV for 48 weeks (Pbo/PR48)
- T/Peg-IFN/RBV for 12 weeks (T12/PR12)
- T/Peg-IFN/RBV for 12 weeks, Peg-IFN/RBV for 12 weeks (T12/PR24)
- T/Peg-IFN for 12 weeks (T12/P12)

Subjects in the T12/PR12 and T12/P12 groups who had undetectable HCV RNA from Week 4 through Week 10 were considered to meet "RVR criterion" and stopped all therapy at Week 12. Subjects who did not meet the RVR criterion were to receive an additional 36 weeks of PR (total duration 48 weeks).

Subjects in the T12/PR24 group who met "RVR criterion" were to stop study drug treatment at Week 24, and if "RVR criterion" was not met, they also were to continue treatment with PR for a total duration of up to 48 weeks.

Study Subjects: A total of 573 subjects were enrolled, randomized, and received at least one dose of medication in Studies 104 and 104EU combined; 416 to T-containing regimens and 157 to Pbo/PR48.
The demographics and disease characteristics of enrollees were generally comparable across treatment arms and for the most part across studies, except for a few notable parameters where there are known differences between US and European subjects. In the US-based Study 104, there were fewer Caucasians (77% versus 93%), more had subtype 1a (64% versus 33%), more had bridging fibrosis (20% versus 8%), and subjects were heavier (81 kg versus 71 kg). Consistent across the trials, study subjects were 61% male with a mean age of 46 years. Mean baseline HCV RNA was 6.5 $\log_{10}$, 86% had HCV RNA >800,000 IU/mL, and <1% had cirrhosis.

- **Primary Efficacy Outcome**

The primary endpoint in both trials was SVR rate (see Table 2) defined as undetectable HCV RNA using the Roche COBAS TaqMan® HCV/HPS assay (Version 1.0). The lower limit of quantitation (LLOQ) for the assay was 30 IU/mL and the limit of detection (LOD) was 10 IU/mL.

Table 2 SVR Rates in Studies 104 and 104EU

	SVR Rate
Combined Common Regimens	
T12/PR12 (n=99)	55 (55%)
T12/PR24 (n=160)	104 (65%)
Pbo/PR48 (n=157)	69 (44%)
Individual Regimens Study 104 (PROVE 1)	
T12/PR12 (n=17)	6 (35%)
T12/PR24 (n=79)	48 (61%)
T12/PR48 (n=79)	53 (67%)
Pbo/PR48 (n=75)	31 (41%)
Individual Regimens Study 104EU (PROVE 2)	
T12/PR12 (n=82)	49 (60%)
T12/PR24 (n=81)	56 (69%)
T12/P12 (n=78)	28 (36%)
Pbo/PR48 (n=82)	38 (46%)

- **Other Efficacy Outcomes**

The following reflect other salient outcomes of the two treatment naïve trials.

- Regimens that included T/PR caused greater decreases in viral load levels from baseline by ~1 $\log_{10}$ more than Pbo through the first 12 weeks of treatment: mean (SD) maximum $\log_{10}$ decrease -5.7 (0.8) $\log_{10}$ for telaprevir compared to -4.3 (1.9) $\log_{10}$ for Pbo/PR48.

- The short duration regimen of T12/PR12 appeared beneficial in Study 104EU (SVR 60%) but the SVR rate could not be replicated in Study 104 (SVR 35%). No specific reason for this difference was identified, but the Applicant hypothesized this may have been due to the differences in demographic characteristics, or to chance. The results of this regimen suggested that longer duration PR (at least 24 weeks) might be necessary.

- The T12/PR48 regimen suggested a possible increase SVR rate in Study 104 over the T12/PR24 regimen; however, this regimen was not included in Study 104EU so it was not possible to determine if there was a difference between the regimens.

- Approximately 77% (260/338) of T/PR-treated subjects met the "RVR criterion" compared to 12% in the control group; of these, 73% of telaprevir and 84% of PR subjects achieved a SVR, respectively. Only 50% of T12/PR subjects achieved a RVR, and 56% of them achieved a SVR.

- The virologic breakthrough rate during the T/Pbo dosing period was 5% (17/338) compared to 2% in the combined Pbo/PR groups. Approximately 80% of breakthroughs occurred during the first four weeks of treatment, and 88% (15/17) failed to reach undetectable HCV RNA prior to breakthrough. In the T12/P12 group in Study 104EU, the incidence of viral breakthrough through Week 12 was 24% (19/78), with 47% (9/19)

occurring in the first 4 weeks of treatment. The majority (84%, 16/19) also did not reach undetectable levels of HCV RNA before breakthrough.

- The relapse rate was decreased from 23% for Pbo/PR48 to 11% for the combined T/PR groups. By regimen, the relapse rates were lowest in the T12/PR24 and T12/PR48 groups; 8% and 6%, respectively, and highest in the T12/PR12 (33%) and T12/P12 group 48%.

- Eighty-six percent of subjects had high (>800,000 IU/mL) levels of HCV RNA at baseline, a negative predictive factor. The SVR rates for the T12/PR24 and T12/PR48 groups were again higher (~60%) compared to 43% (T12/PR12), 27% (T12/P12), and 40% (Pbo/PR48). SVR rates for subjects with low baseline viral load levels were between 70-80% and comparable across treatment groups.

- Genotype 1 is further parsed into subtypes 1a and 1b, with subtype 1a being more difficult to treat and having a lower genetic barrier to selecting treatment-resistant variants. Subjects with subtype 1a responded best with the regimens of T12/PR24 and T12/PR48 (60% in both). Subtype 1a subjects responded less well to T12/PR12 (34%), T12/P12 (34%) or Pbo/PR (45%). Similarly, SVR rates for subjects with subtype 1b were lowest in the T12/PR12, T12/P12, and Pbo/PR groups (38-58%) compared to the T12/PR24 and T12/PR48 groups (70-80%).

- SVR rates among telaprevir-treated Caucasian subjects were 63%, 52% for Blacks/African Americans, 45% for Hispanics, 83% for Asians, and 66% for other race/ethnic subgroups. These subgroups' outcomes were 47%, 9%, 33%, 50% and 100%, respectively. Caution should be used in interpreting these results because >80% of study subjects were Caucasian and only ~10% were Black/African American.

- Subjects with cirrhosis were excluded. Among T/PR-treated subjects, SVR rates were 58% for subjects with no or minimal fibrosis, 55% for subjects with portal fibrosis and 70% for those with bridging fibrosis. In the combined Pbo/PR48 groups, the SVR rate was ~40% among subjects with no or minimal fibrosis, ~45% for subjects with portal fibrosis and 30% for those with bridging fibrosis.

- The majority of subjects had improvements in ALT levels regardless of treatment regimen received.

Phase 2 Trials: Treatment-Experienced Subjects

Two trials in treatment experienced subjects were conducted. The trials were not similarly designed and used different definitions of prior null response. The data were integrated to the extent possible.

Study VX05-950-106 (PROVE 3) was a phase 2, randomized, partially blinded, parallel group study and Study VX06-950-107 was a non-comparative open-label Phase 2 rollover protocol that provided T in combination with Peg-IFN/RBV in control arm subjects from Studies VX06-950-106, VX05-950-104 and VX05-950-104EU who had met a virologic stopping rule.

Investigational plans: In Study 106, 465 subjects were enrolled and randomized 1:1:1:1 to one of four treatment groups:

- Placebo q8h/Peg-IFN/RBV for 48 weeks (Pbo/PR48)
- Telaprevir for 12 weeks/Peg-IFN/RBV for 24 weeks (T12/PR24)
- Telaprevir for 24 weeks/Peg-IFN for 24 weeks (T24/P24)
- T/Peg-IFN/RBV for 24 weeks then Peg-IFN/RBV for 24 weeks (T24/PR48)

In Study 107, all subjects (N=117) were to receive open-label telaprevir 750 mg q8h for 12 weeks in combination with PR. The duration of PR was then based on the on-treatment responses in the parent trial. Subjects with prior null response were to receive 48 weeks of therapy (T12/PR48). Subjects with a prior partial response, prior viral breakthrough, or prior relapse were to receive 12 additional weeks of Peg-IFN/RBV (T12/PR24) if they achieved an eRVR. If they did not achieve an eRVR, they were to receive 36 additional weeks of Peg-IFN/RBV (T12/PR48).

Study Subjects: Across the trials, some groups of subjects were classified similarly:

- Partial responder: $\geq$2-log$_{10}$ decrease at week-12, detectable at week-24
- Relapse: HCV RNA undetectable at completion of prior treatment, but failed to achieve SVR
- Breakthrough: undetectable HCV RNA during prior treatment, but HCV RNA became detectable before end of prior treatment

The definition of prior non-response was different. In Study 106 the definition was never have achieved undetectable HCV RNA during or at the end of prior treatment, and in Study 107 it was achieving a < 1-log$_{10}$ HCV RNA decrease at week-4 or <2-log$_{10}$ decrease at week-12.

Almost 600 subjects were enrolled and treated. The majority of subjects in the combined trials were male (69%) and Caucasians (90%) with a mean age of 51 years, mean weight of 86 kg (range: 50; 147), and a mean BMI of 28 kg/m$_2$ (range: 18; 57). Eighty-seven percent had baseline HCV RNA $\geq$800,000 IU/mL, 59% had subtype 1a, ~20% had cirrhosis, and nine subjects (8%) were Blacks/African Americans. Approximately 51% of subjects had a prior non-response, ~30% had a prior partial response, ~30% had a prior relapse, and 7% had a prior viral breakthrough.

- **Primary Efficacy Outcome**

The primary endpoint was SVR (See Table 3).

Table 3 SVR rates by regimen and prior response status, Study 106 and 107

n/N, (%)	T12/PR24	T12/PR48	T24/PR48	T24/P24	Pbo/PR48
Overall SVR					
Prior NR	30/90 (33)	15/27 (56)	24/64 (38)	7/62 (11)	6/68 (9)
Prior Partial	16/29 (55)	15/25 (60)	-	-	-
Prior B'through	10/15 (67)	0/1 (0)	5/8 (62)	4/11 (36)	2/5 (40)
Prior Relapse	53/67 (79)	3/3 (100)	31/41 (76)	16/38 (42)	8/41 (20)
SVR by eRVR					
Prior NR					
eRVR	34/90 (38)	14/27 (52)	19/64 (30)	17/62 (27)	0/68
SVR	23/34 (68)	10/14 (71)	13/19 (68)	6/17 (35)	-
Prior Partial					
eRVR	22/29 (76)	0/3	NA	NA	NA
SVR	15/22 (68)	-			
Prior B'through					
eRVR	11/15 (73)	0/1	6/8 (75)	5/11 (45)	0/5
SVR	10/11 (91)	-	5/6 (83)	4/5 (80)	-
Prior Relapse					
eRVR	52/67 (78)	0/3	23/41 (56)	26/38 (68)	0/41
SVR	49/52 (94)	-	21/23 (91)	14/26 (54)	-

For each cohort, comparisons of the telaprevir-containing regimens to the Pbo/PR48 regimen reached statistical significance. Overall, the T12/PR24, T12/PR48 and T24/PR48 regimens demonstrated comparable response rates. However, the SVR rate for the other regimens was lower among prior non-responders than the SVR rate for T12/PR48. The number of prior breakthrough and partial response subjects was very low, and these small numbers make interpretation difficult.

Prior relapse subjects achieved the highest SVR rates with all regimens evaluated. This finding was generally expected since they had previously demonstrated interferon sensitivity and they tend to respond better to re-treatment with PR. Comparable overall SVR rates were observed for the T12/PR24 and T12/PR48 arms; however, it was not possible to compare SVR rates by eRVR status because of the low number of subjects in the T12/PR48 group of whom none achieved eRVR.

The overall SVR rate for the T24/PR24 arm was statistically significantly greater than the Pbo/PR48 arm, but for more difficult to treat subjects, there was no difference in outcomes.

- **Other Efficacy Outcomes**

The following reflect other salient outcomes of the two treatment experienced trials.

- Approximately 22% of subjects had on-treatment virologic failure, 40% of prior null responders, 20% of prior partial responders, and 25% of prior viral breakthrough subjects. No subjects with prior relapse had on-treatment virologic failure.

- The rates of viral breakthrough were 13%, 13%, 12%, 32% and 3% in the T12/PR24, T12/PR48, T24/PR48, T12/P24, and Pbo/PR48 arms, respectively. Most breakthroughs occurred prior to week 12. Viral breakthrough was higher among subjects who were prior non-responders (~25%), with subtype 1a (24%), generally associated with the presence of mutations known to convey high-level resistance to T (A156T or V36M+R155K), and was more common in the arm that did not include RBV. No prior relapse subjects had viral breakthrough.

- Relapse rates were substantially reduced from 53% in Pbo/PR48 and RBV-sparing groups to 30% (T12/PR24), and 13% (T12/PR48). By prior response, relapse rates were 12% (all), 19% (prior null), 23% (prior partial) and 0% (prior breakthrough and prior relapse). Additionally, relapse was more common in subjects with subtype 1a.

- Across regimens, 68% (101/149) of prior relapse subjects achieved eRVR and 83% of them achieved a SVR. It was not possible, however, to determine the appropriate duration of therapy because of the low number of subjects in the T12/PR48 group (n=3) of whom 0/3 achieved an eRVR.

- Prior null responders with high baseline HCV RNA (≥800,000 IU/mL) responded better with the regimen of T12/PR48: 56% compared to 17% for T12/PR24, suggesting longer duration therapy for these subjects would be necessary. There were too few enrolled prior partial responders or breakthrough subjects to make comparisons of longer to shorter duration.

- Subjects with Genotype subtype 1b responded better than subjects with Genotype subtype 1a (68% compared to 55%). Prior non-responders with subtype 1a responded better with longer duration therapy: 17% T12/PR24, 50% T12/PR48. More than 90% of prior relapsers with either subtype responded. The number of prior partial responders and prior breakthroughs that received T12/PR48 was again too small to reach any conclusions for that duration of therapy.

- Overall, subjects with cirrhosis did not respond as well as those without cirrhosis across all prior non-response categories: 39% compared to 50%. A couple of trends were noted: prior null responders with cirrhosis seemed to respond better with the regimen ofT12/PR48: 56% compared to 27% (T12/PR24) and 27% (T24/PR24). Prior relapsers with and without cirrhosis appeared to respond similarly regardless of duration.

- The majority of subjects had improvements in ALT levels regardless of treatment regimen received.

- Blacks/African Americans subjects responded similarly as Caucasians treated with T/PR regimen: ~55% for each compared to 10% for those treated with Pbo/PR48. Again, Blacks/African Americans represented only 7% of study subjects.

OTHER COMPLETED AND ONGOING TRIALS

The applicant submitted summaries of additional completed and ongoing trials; most were ongoing at the time of NDA submission. To the extent that summary data was available, it is briefly reviewed below. None of these trials support labeling claims at this time, but may once the trials are completed.

Change in Dosing Frequency

As discussed in Section 4.4.2, (b) (4) Study C208 was a Phase 2 study in which 170 treatment-naïve subjects with chronic genotype 1 HCV infection were administered either telaprevir 1125 mg q12h or 750 mg q8h in combination with Peg-IFN-alfa-2a (Pegasys®) and RBV (Copegus®) or Peg-IFN-alfa-2b, (PegIntron®) and RBV (Rebetol®). Approximately 40 subjects were enrolled into each of the four treatment groups. The dosing regimen for all arms was telaprevir for 12 weeks combined with PR for 24 weeks. Subjects who did not achieve virologic suppression at either Weeks 4, 8 or 12 were treated with an additional 36 weeks of Peg-IFN/RBV (total 48 weeks).

The subjects in the trial represented the general population of chronic HCV infected subjects, except again for the underrepresentation of Blacks (<10%). In total, 128/172 (80%) subjects completed treatment. More subjects in the combined T12(q8h)/PR groups, and the T12(q12h)/P(2a)R group completed treatment (80-85%) than in the T12(q12h)/P(2b)R group (72%). Main reasons for premature discontinuation of all study medication were the occurrence of an adverse event (in 13 [8%] subjects), reaching a virologic failure endpoint (in 10 [6%] subjects), and noncompliance (in seven [4%] subjects).

Efficacy Outcomes: The primary endpoint was SVR. SVR was achieved by most of the subjects who were initially assigned to 24 weeks of treatment: 97% in the T12(q8h)/P(2a)R group, 93% in the T12(q8h)/P(2b)R group, 100% in the T12(q12h)/P(2a)R group, and 95% in the T12(q12h)/P(2b)R group. Most subjects who were assigned to 48 weeks of treatment and those who completed treatment achieved an SVR (4/4 [100%], 5/6 [83%], 2/3 [67%], and 6/6 [100%] subjects, respectively).

There were no differences in the frequency of viral breakthrough, relapse rates or response by genotype subtype between the two telaprevir doses or Peg-IFN products.
Reviewer Comment: The results of this pilot study suggested that a telaprevir dose of 1125 mg q12h co-administered with either Peg-IFN 2a or 2b plus RBV produced similar antiviral activity and pharmacokinetic exposures to the proposed for marketing dose of 750 mg q8h. However, there did appear to be some safety signals associated with administration of T q12h versus q8h (see below).

With the availability of data from other sources suggesting comparable outcomes independent of Peg-IFN administered, telaprevir can likely be dosed with either Peg-IFN product.

However, the numbers of subjects in each treatment group of Study C208 was overall sparse, there was an under-representation of Blacks, there were differences in safety outcomes, (b) (4)

[redacted]

HIV/HCV Co-Infected Subjects

Study VX08-950-110 is an ongoing 2-part, Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, multicenter study being conducted in HCV/HIV-1 co-infected subjects.

Investigative Plan: In Part A, 20 HCV-treatment naïve co-infected subjects who were not receiving HAART for HIV were to be randomized to one of two treatment groups: T for 12 week plus Peg-IFN/RBV for 36 additional weeks (T12/PR48) or Placebo for 12 weeks with PegIFN/RBV for 48 weeks (Pbo/PR48).

After all subjects in Part A finish 12 weeks of dosing (or discontinue prematurely) and an Independent Data Monitoring Committee (IDMC) conducted a planned review of safety data, if deemed appropriate, Part B was to start enrolling up to 40 subjects receiving one of the HAART regimens specified in the protocol (see below).

Study Subjects: General enrollment criteria were: males and females, 18 to 65 years of age, inclusive, with chronic, genotype 1, Hepatitis C with detectable HCV RNA, who had not received any previous treatment with an approved or investigational drug or drug regimen, HIV-1 infection for >6 months before the screening visit, and a liver biopsy within 1 year before the screening visit, or the subject must agree to have a biopsy performed within the screening period with evidence of inflammation and/or fibrosis. If a biopsy more than 1 year prior to screening has already demonstrated histological cirrhosis, the biopsy did not need to be repeated if the biopsy report could be provided.

Specific enrollment criteria for Part A subjects included a CD4 count of ≥500 cells/mm^3 within 30 days before Day 1 and an HIV-1 viral load ≤100,000 copies/mL within 30 days before Day 1. Part B subjects were to have had a CD4 count ≥300 cells/mm^3 within 30 days before Day 1, and an HIV-1 viral load <50 copies/mL within 30 days before Day 1, and been on a permissible HAART regimen as first- or second-line therapy for >12 weeks before Day 1. Permissible HAART regimens included Atripla® (fixed-dose combination of tenofovir, emtricitabine and efavirenz, Regimen 1) or ritonavir-boosted atazanavir and tenofovir disoproxil fumarate plus either emtricitabine or lamivudine (Regimen 2).

Outcome Measures: The primary endpoints for Part A and B are safety (adverse events, physical examination findings, clinical laboratory results, and vital sign assessments), and change in plasma HCV RNA levels during the first 29 days of dosing.

Secondary endpoints for Part A and B include:

- Plasma concentrations of telaprevir, VRT-127394, Peg-IFN, and RBV
- Proportion of subjects with undetectable HCV RNA at Week 4, Week 12, and end of treatment (EOT; Week 48 or last dose of study drug if subject prematurely discontinues study treatment), and 24 weeks after last dose of study drug (SVR24)
- Amino acid sequence of the HCV NS3•4A protease

An additional objective for Part B is assessment of plasma concentrations of tenofovir, atazanavir, and ritonavir.

Study Status: As of the cut-off date for the NDA submission (July 16, 2010), this trial was ongoing. Eight subjects (5 T/PR and 3 Pbo/PR) had been enrolled into Part A and 13 had been enrolled into Part B (9 T/PR and 4 Pbo/PR).

Study Outcomes: Among the 5 subjects randomized to T12/PR48 in Part A, three achieved an RVR and two achieved an eRVR, compared to 0 subjects in the Pbo/PR48 arm. In Part B, 4/7 and 2/7 subjects receiving Regimen 1 plus telaprevir achieved RVR and eRVR, respectively. Two subjects received Regimen 2 plus telaprevir and both achieved RVR and eRVR. None of the four Pbo/PR48 subjects achieved either a RVR or eRVR. No subjects had reached the SVR time point. One subject who received Regimen 1 had viral breakthrough. No clinically relevant changes in HIV RNA levels or CD4 cell counts have yet been reported.

Reviewer Comment: The preliminary data from this study suggests that telaprevir may improve the activity of PR in HIV/HCV co-infected subjects. (b) (4)

Efficacy in Other Genotypes

Data from *in vitro* studies indicate that telaprevir is active against the HCV protease from HCV genotypes 1, 2, 3, and 4. The majority of subjects with CHC are infected with genotype 1 (~70%). Approximately 25% of subjects are infected with genotype 2 and 3, and they respond well to treatment with Peg-IFN/RBV for 24 weeks with SVR rates that range from 80-90%. Genotype 4 represents approximately 5% of infections, but response to treatment is similar to Genotype 1. The Applicant conducted two pilot trials (VX-950-TiDP24-C209 in genotypes 2 and 3 and VX-950-TiDP-C210 in genotype 4). The results led the Applicant to conclude that telaprevir had inadequate clinical activity to support additional larger trials.

Study VX-950-TiDP24-C209 was conducted to assess the effects of telaprevir on Genotype 2 and 3 HCV early viral kinetics, safety, tolerability, and resistance patterns. A total of 49 treatment naïve subjects with either HCV genotype 2 (n=23) or 3 (n=26) were enrolled and randomized to one of three treatment groups: telaprevir for 2 weeks followed by PR for 24 weeks T2&PR24), telaprevir for 2 weeks with PR for 24 weeks (T2/PR24), or Pbo/PR24. The primary

endpoint was early viral kinetics by plasma HCV RNA quantification (Week 2). Secondary efficacy endpoints included virologic response, viral breakthrough, SVR, and relapse. The following tables showing the primary and efficacy analyses by genotype were reproduced from the Clinical Study Report.

Tables 4 and 5 Outcomes of Study C209

Antiviral Activity – Genotype 2	T2&PR24		T2/PR24		Pbo/PR24	
	N	Value	N	Value	N	Value
Log_{10} HCV RNA (IU/mL), median (range)						
Baseline actual value	9	6.61 (4.4; 7.3)	5	6.21 (5.3; 7.3)	9	6.15 (5.5; 7.4)
Change from baseline to Day 15	9	-3.66 (-5.4; -0.9)	5	-5.51 (-6.0; -4.6)	9	-4.83 (-6.0; -0.2)
Change from baseline to Week 24/26	7	-5.91 (-6.6; -3.7)	5	-5.51 (-6.6; -4.6)	9	-5.45 (-6.7; 0.7)
Virologic Response (HCV RNA < 10 IU/mL), n (%)						
by Day 15	9	0	5	2 (40.0)	9	2 (22.2)
by EOT	9	8 (88.9)	5	5 (100)	9	8 (88.9)
Median Time to Virologic Response (HCV RNA < 10 IU/mL), days	9	31.0	5	12.0	9	43.0
Cumulative Viral Breakthrough, n (%)						
by Day 15	9	6 (66.7)[a]	5	0	9	0
by Week 24/26	9	6 (66.7)[a]	5	0	9	1 (11.1)
Sustained Virologic Response, n (%)						
SVR12	9	6 (66.7)	5	5 (100)	9	8 (88.9)
SVR24	9	5 (55.6)[b]	5	5 (100)	9	8 (88.9)
Relapse, n (%)						
by FU Week 24	8	1 (12.5)	5	0	8	0

N = number of subjects with data; SVR12/24 = sustained virologic response 12 or 24 weeks after last actual dose
[a] Including 4 subjects with unconfirmed viral breakthrough during the investigational treatment phase
[b] One subject (CRF ID 209-0023) was undetectable at FU Week 12 but was lost to follow-up by FU Week 24.

Antiviral Activity – Genotype 3	T2&PR24		T2/PR24		Pbo/PR24	
	N	Value	N	Value	N	Value
Log_{10} HCV RNA (IU/mL), median (range)						
Baseline actual value	8	6.65 (5.8; 7.1)	9	6.79 (5.4; 7.4)	9	6.92 (3.9; 7.3)
Change from baseline to Day 15	8	-0.54 (-1.0; -0.1)	9	-4.85 (-6.1; -2.3)	9	-4.72 (-6.1; -3.2)
Change from baseline to Week 24/26	8	-5.71 (-6.4; -0.9)	7	-5.50 (-6.7; -4.7)	9	-6.22 (-6.6; -3.2)
Virologic Response (HCV RNA < 10 IU/mL), n (%)						
by Day 15	8	0	9	2 (22.2)	9	1 (11.1)
by EOT	8	6 (75.0)	9	9 (100)	9	9 (100)
Median Time to Virologic Response (HCV RNA < 10 IU/mL), days	8	99.0	9	43.0	9	29.0
Cumulative Viral Breakthrough, n (%)						
by Day 15	8	3 (37.5)[a]	9	0	9	0
by Week 24/26	8	3 (37.5)[a]	9	0	9	0
Sustained Virologic Response, n (%)						
SVR12	8	4 (50.0)	9	6 (66.7)	9	4 (44.4)[b]
SVR24	8	4 (50.0)	9	6 (66.7)	9	4 (44.4)[b]
Relapse, n (%)						
by FU Week 24	6	2 (33.3)	9	3 (33.3)	9	2 (22.2)[c]

N = number of subjects with data; SVR12/24 = sustained virologic response 12 or 24 weeks after last actual dose
[a] Including 2 subjects with unconfirmed viral breakthrough during the investigational treatment phase
[b] Note that 2 additional subjects in the Pbo/PR24 group were undetectable at EOT and at at least 1 of the FU visits but were lost to follow-up by FU Week 12.
[c] Note that 1 additional subject in the Pbo/PR24 group was undetectable at EOT but had no HCV RNA measurements during follow-up due to being lost to follow-up.

Reviewer Comment: In genotype 2 subjects, the delayed start strategy (T2&PR24) resulted in a longer time to virologic response, a lower SVR rate, and a higher breakthrough rate compared to immediate start with all three agents. Comparing T2/PR24 to Pbo/PR24, the time to virologic response was faster in the telaprevir arm, but on-treatment virologic response rates and SVR rates were comparable. In the subjects with genotype 3, again the T2&PR24 regimen underperformed compared to the other regimens. Time to virologic response was longer for the T2/PR24 regimen, but both the relapse and SVR rates were a bit higher than Pbo/PR. Of note, there were no important differences in safety between the regimens or genotypes.

The number of subjects in this pilot trial was extremely small. The results suggest that the addition of telaprevir may be of limited benefit in subjects with genotype 3 and of no benefit in subjects with genotype 2.

Study VX-950-TiDP24-C210 was conducted to assess the effects of telaprevir on genotype 4 HCV early viral kinetics, safety, tolerability, and resistance patterns. Subjects were randomized to T2&PR48, T2/PR48, or Pbo/PR48 Twenty-four treatment naïve subjects with genotype 4 were enrolled and randomized to one of three treatment groups: T2 followed by PR48, T2/PR48, or Pbo/PR48. Again, the important outcomes are shown in the following table that was reproduced from the Clinical Study Report.

Table 6 Outcomes of Study C210

Antiviral Activity	T2&PR48		T2/PR48		Pbo/PR48	
	N	Value	N	Value	N	Value
Log_{10} HCV RNA (log_{10} IU/mL), median (range)						
Baseline value	8	5.83 (5.2; 6.5)	8	6.16 (5.4; 6.8)	8	5.88 (5.0; 6.8)
Change from baseline at Day 15	7	-0.77 (-2.9; 0.3)	8	-4.32 (-5.2; 0.0)	8	-1.58 (-4.0; -0.8)
Viral response (undetectable HCV RNA), n (%)						
by Day 15	7	0	8	1 (12.5)	8	0
by EOT	8	7 (87.5)	8	6 (75.0)	8	6 (75.0)
Time to first viral response (undetectable HCV RNA), median (days)	8	93	8	86	8	128
Cumulative viral breakthrough, n (%)						
by Day 15 (i.e., end of the telaprevir/placebo treatment phase)	8	5 (62.5)	8	0	8	0
by EOT	8	5 (62.5)	8	2 (25.0)	8	1 (12.5)
Sustained viral response (SVR), n (%)						
SVR12	8	6 (75.0)	8	4 (50.0)	8	5 (62.5)
SVR24	8	5 (62.5)[a]	8	4 (50.0)	8	5 (62.5)
Relapse, n (%)	7	1 (14.3)	6	2 (33.3)	6	1 (16.7)

N: number of subjects with data or, in case of relapse, number of subjects with undetectable HCV RNA at EOT;
n: number of subjects with that observation
[a] SVR24 was achieved by all the subjects who achieved SVR12, except for 1 (12.5%) subject in the T2&PR48 group who was considered as failure for SVR24. This subject (CRF ID 210-0019) was undetectable at Follow-up Week 12 but was lost to follow-up afterwards and therefore not a candidate for SVR24.

Reviewer Comment: EOT and SVR rates were comparable across the three treatment regimens suggesting that telaprevir does not produce a clinically relevant added benefit.

Phase 3 Trial Design: Treatment-Naïve Subjects

Two Phase 3 trials in treatment naïve subjects were conducted to support approval of telaprevir: Studies VX07-950-108 (Study 108) and VX07-950-111 (Study 111). Both used a response guided therapy (RGT) approach to evaluate various durations of therapy in early responders and non-responders.

Study VX07-950-108 was the pivotal Phase 3 treatment-naïve trial. The title of the trial was A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination with Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C. It was given the moniker **ADVANCE** which stands for A New Direction in HCV Care: A study of Treatment Naïve Hepatitis C Patients with TelaprEvir.

Investigational Plan: Study 108 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in treatment-naïve subjects with genotype 1, CHC. The trial was conducted worldwide between mid-2008 and mid-2010.

Planned enrollment was 1050 subjects who were to be randomized to 1 of 3 treatment groups. Two of the groups received a regimen containing telaprevir, Peg-IFN-alfa-2a, and RBV. The third group (the control) received a regimen of telaprevir-matching placebo, Peg-IFN-alfa-2a, and RBV. Subjects were randomized in a 1:1:1 ratio stratified by 1 subtype (1a or 1b) and baseline viral load (<800,000 IU/mL or ≥800,000 IU/mL) as follows:

- Telaprevir for 8 weeks followed by placebo for 4 weeks combined with Peg-IFN/RBV for 24 weeks (T8/PR24)
- Telaprevir for 12 weeks combined with Peg-IFN/RBV for 24 weeks (T12/PR24)
- Placebo for 12 weeks combined with Peg-IFN/RB for 48 weeks (Pbo/PR48)

Telaprevir was administered as 2-375 mg tablets or as matching placebo q8h in the fed state. Peg-IFN was administered as a standard dose of 180 μg by SQ once weekly and RBV was administered in standard doses of 1000 mg/day for subjects weighing <75 kg and 1200 mg/day for those weighing ≥75 kg.

For the two telaprevir arms, subjects were to be treated for a total of 24 weeks. Subjects who achieved an extended rapid viral response (eRVR, defined as undetectable HCV RNA at Weeks 4 and 12) were to stop all therapy at Week 24 and enter off-therapy follow-up. Subjects who did not achieve eRVR were to continue Peg-IFN/RBV for a total of 48 weeks. Subjects in the control group had planned treatment duration of 48 weeks. All subjects were to remain on study through Week 72, regardless of treatment duration and HCV RNA status.

Reviewer Comment: DAVP requested the inclusion of the T8 regimen based on the hypothesis that a shorter treatment duration might change the risk:benefit assessment by improving tolerability, particularly by reducing the frequency of Grade 3 rash, and not sacrificing efficacy.

Subjects were managed based on their virologic response as follows:

Subjects who achieved an RVR (HCV RNA undetectable at TW4) were to continue dosing with all three study drugs.

Subjects who did not achieve RVR and HCV RNA was >10 to <1000 IU/mL:

- Telaprevir and PR dosing continue as planned, and at Week 24, investigators were notified that dosing should be extended to Week 48 (pending the outcomes of the Week 12 eRVR, Week 24, Week 28, and Week 36 viral response assessments)

If a subject did not achieve RVR and HCV RNA was >1000 IU/mL:

- Telaprevir dosing was to be discontinued, and replaced with telaprevir matching placebo from Week 6 through Week 12, and

- PR dosing was to continue as planned, and at Week 24, investigators were notified that dosing should be extended to Week 48 (pending the outcomes of the Week 12 EVR, Week 24, Week 28, and Week 36 viral response assessments.

- For T12/PR48 subjects, telaprevir dosing would be discontinued, and replaced with telaprevir-matching placebo from Week 10 through Week 12.

- For T8/PR48 and T12/PR48 subjects, Peg-IFN/RBV dosing would continue as planned, and at Week 24, investigators would be notified that dosing should be extended to Week 48 (pending the outcomes of the Week 12 EVR, Week 24, Week 28, and Week 36 viral response assessments).

Patients with undetectable HCV RNA at Week 72 were invited to participate in a rollover protocol to collect long-term follow-up data (Study VX08-950-112).

Study VX08-950-111 (**ILLUMINATE**; ILLUstrating the Effects of CoMbINAtion Therapy with TElaprevir) was a study of up to 48-weeks of treatment with a telaprevir based regimen in treatment-naïve subjects with genotype 1 CHC.

The rationale for this trial was to determine if there would be any increased efficacy associated with longer duration therapy for subjects who achieved an early response. As noted previously, in Study 104, a small numeric difference in SVR rates was observed between the T12/PR24 and T12/PR48 regimens. DAVP was concerned that there may be a difference in response rates if the number of subjects were to be increased, and requested that both durations, 24 and 48 weeks, be evaluated in Phase 3 to determine the optimal duration of therapy. For the purposes of this NDA, Study 111 is considered an uncontrolled supportive trial.

Study 111 was conducted in parallel to Study 108 between October 2008 and July 2010. The trial was conducted in the United States, Belgium and The Netherlands.

Investigational Plan: Five hundred forty subjects were enrolled and initiated treatment with T/PR. Subjects who achieved an eRVR were randomized at Week 20 to either stop all therapy at Week 24 or continue PR for 24 additional weeks (48 weeks total) and then stop. No eRVR subjects were to continue PR for an additional 24 weeks (48 weeks total treatment). All subjects were followed off-therapy for 24 weeks for assessment of SVR.

Telaprevir 750 mg (2-375 mg tablets) or matching placebo was administered q8h in the fed state. Peg-IFN was administered as 180 μg by SQ once weekly and RBV was administered in standard doses of 1000 mg/day for subjects weighing <75 kg and 1200 mg/day for those weighing ≥75 kg.

On-treatment virologic response management for subjects in Study 111 was:

- Subjects in the T12/PR48 arm with HCV RNA ≤1000 IU/mL at Week 4 continued their planned regimen. Subjects with HCV RNA >1000 IU/mL discontinued telaprevir but continued PR.

- At Week 12 (EVR) any subjects with a <2-log10 decrease in HCV RNA compared to baseline were to discontinue all study treatment and be followed to Week 72. A sample for HCV RNA and viral sequencing was to be collected 24 weeks after Week 12 visit (i.e., Week 36).

- At Week 12, T12/PR48 subjects who had HCV RNA ≤1000 IU/mL at Week 4 and Week 12 were to continue study drug dosing as planned. Subjects with HCV RNA ≤1000 IU/mL at Week 4, but HCV RNA >1000 IU/mL at Week 12 (Viral Breakthrough/Virologic Failure) were to continue PR dosing.

- Between Weeks 24 and 36 all subjects with HCV RNA <10 IU/mL were to continue study drug dosing as planned. Subjects with HCV RNA >10 IU/mL discontinued all study drugs and were followed until SVR assessment (Week 72). A sample for HCV RNA and viral sequencing was to be collected 24 weeks after Week 24 visit (i.e., Week 48).

Study Subjects: The inclusion criteria for both trials were the same: males and females, 18 to 70 years of age, with genotype 1, detectable HCV RNA, and a liver biopsy showing evidence of hepatitis (demonstrated by inflammation and/or fibrosis) within 1 year of screening with the following screening laboratory values: Hepatitis B surface antigen (HBsAg) negative, HlV-1 and 2 negative, ANC >1500/mm^3, platelet count >90,000 mm^3, with normal hemoglobin and uric acid levels.

Subjects were to be treatment naïve without contraindications to receiving Peg-IFN or RBV (based on product labeling), not have hepatic decompensation, significant mental illness, history

of organ transplant, with the exception of corneal transplants and skin grafts, history of hemophilia, history of acute or chronic pancreatitis, evidence of hepatocellular carcinoma, or alcohol abuse or excessive use in the two months prior to study entry.

For sites in the European Union females of childbearing potential agreed to use two effective barrier methods of contraception, if heterosexually active, from Screening until four months after the last dose of RBV. Non-vasectomized male subjects who had a female partner of childbearing potential were to use two effective methods of contraception if hetoersexually active, from Screening until seven months after the last dose of RBV.

For sites in non-European Union countries (including the US), female subjects of childbearing potential were to use two effective barrier methods of contraception, if heterosexually active, from Screening until six months after the last dose of RBV. Non-vasectomized heterosexually active male subjects with a female partner of childbearing potential also had to agree to use two effective methods of contraception from Screening until six months after the last dose of RBV.

For all sites, the use of birth control methods did not apply if the male partner had undergone a vasectomy or if the female partner had a bilateral oophrectomy, or a total hysterectomy, or if she was postmenopausal for at least two years prior to enrollment.

Endpoints and Outcome Measures: The primary endpoint for both trials was the proportion of subjects achieving SVR, again defined as undetectable HCV RNA 24 weeks after last planned dose of study treatment using a sensitive assay (Roche TaqMan assay, LOQ <25 IU/mL, LLOD 10 IU/mL).

Several on-treatment and off-treatment virologic assessments and changes in transaminase levels were evaluated as secondary outcome measures. Additionally, the Applicant evaluated Total Fatigue Score and other Patient Reported Outcomes.

Phase 3 Trial Design: Treatment-Experienced Subjects

Study VX-950-TiDP24-C216 (**REALIZE**; Re-treatment of Patients with Telaprevir-Based Regimen to Optimize Outcomes) was the pivotal Phase 3 trials in treatment-experienced subjects. This was a randomized, double-blind, placebo-controlled, Phase 3 trial of two regimens of telaprevir (with and without a 4 week delayed start) combined with Peg-IFN-alfa-2a (Pegasys®) and RBV (Copegus®) in subjects with chronic genotype 1 hepatitis C infection who failed prior Peg-IFN/RBV treatment.

In this trial 650 subjects (350 relapsers and 300 prior non-responders) were to be randomized in a 2:2:1 ratio to one of three treatment groups:

- T12/PR48 (260 subjects: 140 relapsers and 120 non-responders)
- T12(DS)/PR48 (delayed start) (260 subjects: 140 relapsers and 120 non-responders)
- Pbo/PR48 (130 subjects: 70 relapsers and 60 non-responders)

The rationale for inclusion of T12/PR48 with a 4 week lead-in with PR (T12(DS)) was to allow an assessment of the effect of a short course of treatment with PR on the frequency of emergence of resistant strains during telaprevir exposure, and to determine whether this strategy had an impact on overall treatment efficacy.

Randomization was stratified based on screening HCV RNA value (<800,000 IU/mL vs. ≥800,000 IU/mL) and on prior response (relapse vs. non-response). For the stratum of prior non-responders, an additional stratification was conducted for type of prior non-response: partial (≥2 log drop in HCV RNA at Week 12 of prior therapy but never achieved undetectable HCV RNA while on treatment) and null (<2 log drop in HCV RNA at Week 12 of prior therapy) response. Enrollment was limited so that subjects with prior partial or null response represented no more than 55% of the total study population.

Subjects in the two telaprevir treatment groups were assessed for virologic response at Weeks 4, 6, and 8. Subjects with HCV RNA >100 IU/mL at Week 8 discontinued telaprevir, but could continue PR for up to an additional 40 weeks.

Subjects in the control group (Pbo/PR48) were expected to have a slower viral decay than the telaprevir groups. Applying the same stopping rules at Weeks 4, 6, and 8 for the control group could have resulted in stopping this arm prematurely in a majority of subjects, of which some might have responded with longer duration therapy, and could have potentially un-blinded control subjects.

All subjects were monitored for early virologic response (EVR), defined as ≥ 2-log decrease from baseline in HCV RNA 12 weeks after the start of T or placebo. Subjects who did not achieve an EVR discontinued all study medication. Also, any subjects who continued to receive treatment at or beyond Week 24 were assessed for virologic response; those with detectable HCV RNA (≥10 IU/mL) at Week 24 or Week 36 also discontinued all study medication.

Reviewer Comment: This trial was not prospectively designed to answer the question whether some or all categories of prior non-responders could benefit from a RGT approach as all subgroups were planned to receive the same duration of treatment.

Study Subjects: To be eligible for enrollment, subjects were to be male or female, 18 to 70 years of age, inclusive, with CHC genotype 1 with HCV RNA level ≥1000 IU/mL, who had failed at least one prior course of PR therapy defined as:

- Undetectable HCV RNA level at the end of a prior course of PR therapy but did not achieve SVR (viral relapsers), or
- Never had an undetectable HCV RNA level during or at the end of a prior course of PR therapy (non-responders).

In addition, subjects were to have received 80% or more of the intended dose of PR, received their last dose of PR at least 12 weeks before screening, and had a liver biopsy within 18 months

prior to the screening visit. If a biopsy more than 18 months prior to screening had demonstrated histological cirrhosis (Metavir F4; Ishak score ≥5), the biopsy did not need to be repeated if the biopsy report could be provided. Patients with cirrhosis were to have serum alpha-fetoprotein (AFP) ≤50 ng/mL and normal abdominal ultrasound. If AFP was >50 ng/mL or an ultrasound was abnormal, a CT or MRI scan was required to exclude hepatocellular carcinoma. Breakthrough subjects were excluded since this population represented a small proportion of prior non-responders and in some cases it is difficult to determine the reason(s) for failure (i.e., lack of compliance).

6 Review of Efficacy

The results of the Phase 3 trials demonstrate that the regimen of T12 co-administered with 24 or 48 weeks of Peg-IFN/RBV in subjects with Genotype 1 CHC substantially increases SVR rates compared to treatment with the current standard of care of Peg-IFN/RBV for 48 weeks. This should translate into a greater number of subjects achieving cure of their hepatitis C virus infection.

In treatment naïve subjects:

- The regimen of T12/PR24 produced statistically significantly higher proportions of subjects achieving eRVR and SVR, lower virologic failure, breakthrough and relapse rates with a shorter duration of treatment compared to current SOC.

- Although the data could not be formally pooled, in both studies ~72% of all subjects treated with a telaprevir-containing regimen achieved a SVR.

- Using the RGT approach, the proportion of subjects who achieved eRVR was 58% in Study 108 and 65% in Study 111, and the SVR rates for those subjects were similar at 90% with the T12/PR24 regimen. These data support the RGT approach and the truncation of the total duration of therapy from 48 to 24 weeks in subjects who achieve an eRVR.

- In no eRVR subjects, continuing treatment for an additional 24 weeks produced an added benefit compared to continued treatment with the control regimen (SVR: 58% for combined telaprevir subjects compared to 40% for Pbo/PR48), and should be recommended for subjects who can tolerate continued PR.

- In Study 111, there was no significant difference in the SVR rate between eRVR subjects who received 24 (T12/PR24) or 48 weeks (T12/PR48) supporting the conclusion that subjects who achieve an eRVR can have their therapy truncated without necessarily jeopardizing SVR rates.
- Compared to T8/PR regimen, the T12/PR regimen produced higher overall SVR rates, and higher SVR rates among subjects with typical negative predictive characteristics:

subtype 1a, high (≥800,000 IU/mL) baseline viral load, cirrhosis, with lower virologic failure rates. These data demonstrate that the additional 4 weeks of telaprevir provided additional benefit; perhaps by suppressing potential mutations that confer resistance to telaprevir. However, there were additional events of rash and anemia during the additional 4 week telaprevir dosing period.

- Response rates were increased by 30-40% compared to re-treatment with PR48 alone across a broad spectrum of demographic and disease covariates. Of note, there was a suggestion that subjects with cirrhosis who achieve an eRVR may benefit from an additional 24 weeks of PR (48 weeks total).

In treatment experienced subjects:

- The regimen of T12/PR48 significantly increased SVR rates in most categories of prior non-responders to prior PR therapy.

- There were no differences in SVR, virologic failure or relapse rates between immediate and delayed start telaprevir.

- A viral dynamic analysis suggested that in prior relapse subjects who achieve an eRVR, the duration of therapy might be truncated to 24 weeks without negatively jeopardizing efficacy. However, there are no prospective data to confirm this analysis so a decision cannot be reached at this time. This issue will be discussed during the Antiviral AC meeting, with a formal decision on the label worthiness of this recommendation being made following the meeting.

- As in treatment naïve subjects, the response rates were increased by 30-40% compared to re-treatment with PR48 alone across a broad spectrum of demographic and disease covariates. However, there appeared to be minimal benefit in prior null responders with cirrhosis.

Results applicable to both naïve and treatment experienced subjects:

- Achievement of an early response was associated with decreases in virologic failure, virologic breakthrough and relapse rates.

- The virologic failure data suggest that subjects who are going to fail telaprevir generally do so early, are usually genotype 1a and have high-level resistant variants. In treatment naïve subjects, the additional 4 weeks of telaprevir in Study 108 suggested that the longer duration exposure was associated with lower on-treatment failure rates. In experienced subjects, the delayed initiation of telaprevir did not have an impact on very early failures, but may have had a roll in decreasing failures after the initial 4 weeks of dosing.

- The addition of T12 to PR for 24 or 48 weeks substantially increased SVR rates across a broad spectrum of demographic and disease covariate 30-40% compared to Pbo/PR48; this finding was consistent across the treatment naïve trials.

- Positive trends were observed for improved response rates among Blacks/African Americans, Latinos/Hispanics, and subjects with cirrhosis. However, these subjects made up a minority of study subjects.

- Overall, 90% of relapses occurred between EOT and FU Week 12. Most subjects who relapsed did so with low-level resistant variants or wild-type virus.

- In a retrospective sub-group analysis, treatment naïve subjects, the addition of telaprevir resulted in higher response rates than SOC in C/T and T/T patients, and a smaller (but significant) effect in C/C subjects. In the same sub-study treatment experienced subjects, telaprevir appeared to benefit patients of all genotypes and may be supportive of treatment initiation irrespective of IL28B genotype. T12 appeared to increase response rates relative to T8, and there did not appear to be a difference between the immediate and delayed start of telaprevir in treatment experienced subjects. These data should be prospectively confirmed in subjects who are more representative of the general population with CHC.

- The PRO results were generally consistent with established patterns observed with PR therapy: subjects feel worse and are less productive on therapy, once therapy is completed, subjects begin to feel better, and subjects who achieve a SVR have more improvement because they have had a successful response to therapy. Here too, knowledge of response may have biased the results. It does appear; however, the addition of telaprevir increased fatigue and led to additional health care utilization suggesting there is an added burden when telaprevir is added to the regimen. None of these findings are clinically relevant or important enough to include in labeling.

Efficacy Summary

6.1 Indication

The proposed indication is: 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.

6.1.1 Methods

The primary efficacy review is based on the results from the three Phase 3 trials (studies 108, 111 and C216).

For the two naïve trials, Study 108 and 111, it was not possible to completely pool the efficacy results because the trials had different designs, one had a blinded, placebo controlled superiority design and subjects were randomized at enrollment (Study 108). The other trial was open label and not placebo controlled, and subjects were randomized based on on-treatment responses (Study 111).

Further, it was not possible to pool the results of the treatment naïve and experienced trials because they were of different designs, enrolled different populations, and used different treatment regimens.

The primary efficacy analysis compared the percentage of subjects with an SVR on the various telaprevir-containing regimens, with active control where used. The primary analysis assessed the superiority of telaprevir-containing regimens to control regimens when they were included in the trial design.

6.1.2 Demographics

Reviewer Comment: Blacks/African Americans and Latinos represent a large proportion of people infected with CHC. Despite strong recommendations to increase enrollment, enrollment of these subgroups was low.

Treatment Naive: Demographic and disease characteristics for subjects enrolled in the two naïve trials (Studies 108 and 111) are shown in Table 7. In this case, the characteristics for the population of subjects who received a T12-containing regimen were pooled because there were no differences in subject characteristics between treatment arms in the two trials.

Treatment naïve subjects were primarily middle aged (47 years old), Caucasian (88%), males (60%) who were moderately heavy (62% BMI >25), from North America (60%) with subtype 1a (60%), and high viral load levels (79%). Approximately 8% of subjects had cirrhosis on their pre-study biopsy, and 6% had a history of diabetes at enrollment. Blacks/African Americans and Latinos/Hispanic subjects accounted for 11% and 10% of study subjects, respectively.

Table 7 Demographic and disease characteristics, Studies 108 and 111 combined

N, (%)	**T8/PR (N=364)**	**T12/PR (N=903)**	**Pbo/PR48 (N=361)**
Mean Age Range	47 19-68	48 19-70	47 18-69
Age ≤45 >45-≤65 >65	 139 (38) 221 (61) 3 (1)	 277 (31) 611 (68) 15 (1)	 143 (40) 216 (60) 2 (1)
Sex Male Female	 211 (58) 153 (42)	 539 (60) 364 (40)	 211 (58) 150 (42)
Race Caucasian	 315 (87)	 752 (83)	 318 (88)

Black	40 (11)	99 (11)	28 (8)
Asian	5 (1)	14 (1.5)	10 (3)
Other	4 (1)	18 (2)	5 (1)
Ethnicity			
Latino/Hispanic	44 (12)	89 (10)	38 (10.5)
Geographic location			
North America	227 (62)	723 (80)	214 (59)
Europe	100 (28)	135 (15)	106 (29)
Other	37 (10)	45 (5)	41 (11)
BMI, kg/m^2			
<25	145 (40)	332 (37)	130 (36)
>25-<30	131 (36)	317 (35)	144 (40)
≥30	86 (24)	251 (28)	87 (24)
Genotype (Lipa 5'UTR)			
1a	210 (58)	600 (66)	208 (58)
1b	151 (41)	296 (33)	151 (42)
Unknown/untypeable	3 (<1)	7 (<1)	2 (<1)
Liver histology			
No to minimal fibrosis	128 (35)	281 (31)	147 (41)
Portal fibrosis	151 (41)	400 (44)	141 (39)
Bridging fibrosis	59 (16)	140 (15.5)	52 (14)
Cirrhosis	26 (7)	82 (9)	21 (6)
Median baseline RNA	6.4 log_{10} IU/mL	6.4 log_{10} IU/mL	6.4 log_{10} IU/mL
Range	4-8	2-8	3-8
Baseline RNA, IU/mL			
<800,000	85 (23)	177 (20)	82 (23)
≥800,000	279 (77)	726 (80)	279 (77)
Diabetes	23 (6)	33(4)	21 (6)

Treatment Experienced: Subjects in Study C216 were enrolled based on their response to prior treatment. Subjects were primarily male (70%) Caucasians (93%) with a mean age of 51 years (range: 21-70). A total of 180 (27%) subjects were from the US, and 20 (3%) were from Canada. The median baseline log_{10} HCV RNA level (IU/mL) was 6.64 (range: 3.0, 7.8). The majority (89%) of subjects had high baseline HCV RNA levels (≥800,000 IU/mL), 48% had bridging fibrosis or cirrhosis (26%), and 54% had subtype 1a.

Subject demography and baseline disease characteristics were generally well-balanced between treatment arms and prior response status. Of note, more prior non-responders had cirrhosis compared to prior relapsers: 31.5% versus 20%, respectively.

Table 8 Demographic and disease characteristics, Study C216

	T12/PR48 (n=266)	**T12(DS)/PR48 (n=264)**	**Pbo/PR48 (n=132)**
Prior response category			
Prior Null	72 (27)	75 (28)	37 (28)
Prior Partial	49 (18)	48 (18)	27 (20)
Prior Relapse	145 (54)	141 (53)	68 (49)
Age			
≤45	64 (24)	55 (21)	40 (30)
>45-≤65	197 (74)	201 (76)	85 (64)

>65	5 (2)	8 (3)	7 (5)
Sex			
Male	183 (69)	189 (72)	88 (67)
Female	83 (31)	75 (28)	44 (33)
Race			
Caucasian	246 (93)	252 (95)	117 (89)
Black	11 (4)	8 (3)	11 (8)
Asian/Oriental	6 (2)	2 (1)	3 (2)
Other	3 (1)	2 (1)	1 (1)
Ethnicity			
Latino/Hispanic	25 (9)	27 (10)	20 (15)
Geographic location			
North America	89 (33)	72 (27)	39 (29)
Europe	127 (48)	139 (53)	74 (56)
Rest of World	50 (19)	52 (20)	20 (15)
Weight			
Mean kg (SD)	82 (16.8)	82 (15.8)	82 (16.6)
BMI, kg/m^2			
<25	85 (32)	89 (34)	42 (32)
≥25-<30	108 (41)	112 (43)	53 (40)
≥30	73 (27)	62 (24)	27 (28)
Genotype (5'NC-T)			
1	27 (10)	28 (11)	13 (10)
1a	118 (44)	120 (46)	59 (45)
1b	121 (46)	115 (44)	59 (45)
1c	0	0	1 (<1)
Liver histology			
No to minimal fibrosis	51 (19)	68 (26)	35 (26)
Portal fibrosis	83 (31)	71 (27)	38 (29)
Bridging fibrosis	60 (22)	58 (22)	29 (22)
Cirrhosis	72 (27)	67 (25)	30 (23)
Median baseline RNA	6.6 $\log_{10}$ IU/mL	6.6 $\log_{10}$ IU/mL	6.6 $\log_{10}$ IU/mL
Range	4-8	2-7	3-8
Baseline RNA, IU/mL			
<800,000	28 (10)	30 (11)	18 (14)
≥800,000	238 (90)	234 (89)	114 (86)
Years since diagnosis			
Mean (SD)	10 (7)	9 (6)	9 (7)
HOMA IR <2	93 (37)	89 (35)	35 (28)
HOMA IR ≥2	161 (63)	164 (65)	89 (72)

6.1.3 Subject Disposition

Well over 90% of subjects treated with T/PR48 completed their assigned dosing. As the duration of treatment extended, so too did the proportion of subjects who discontinued, usually due to virologic failure or adverse events associated with prolonged exposure to PR.

Treatment Naïve: Across the two trials, 1632 subjects were randomized and 1628 received at least one dose of study medication: 365 (T8), 903 (T12) and 361 (Pbo/PR48). See Tables 9 and

10 for the number of subjects who completed and discontinued treatment, and the reasons for discontinuation.

Completion rates were highest among subjects who achieved an eRVR and were assigned to 24 weeks of total therapy. Failure to achieve an eRVR and receiving longer duration PR therapy was associated with higher rates of discontinuation due to adverse events and virologic failure. In Study 111, a separate category of subjects called "Other" was established to define subjects who discontinued treatment prior to the Week 20 randomization point.

Table 9 Subject disposition, Study 108

N (%)	T8/PR		T12/PR		Pbo/PR
	24 weeks N=207	48 weeks N=157	24 weeks N=210	48 weeks N=153	48 weeks N=361
Completed T/Pbo dosing	191 (92)	69 (44)	195 (93)	73 (48)	202 (56)
Discontinued dosing	16 (8)	88 (56)	15 (7)	80 (52)	159 (44)
Adverse event	10 (63)	27 (31)	9 (60)	27 (34)	26 (16)
Virologic failure	0	40 (45)	1 (7)	38 (47)	118 (74)
Lost to follow-up	1 (6)	2 (2)	0	4 (5)	4 (3)
Withdrew consent	0	1 (1)	0	0	2 (1)
Other[1]	5 (31)	18 (20)	5 (33)	12 (15)	8 (5)
Death	0	0	0	0	1 (<1)

1. Other included such reasons as non-compliance, use of a prohibited medication, withdrawal of consent, pregnancy.

Table 10 Subject disposition, Study 111

N (%)	T12/PR24 eRVR n=162	T12/PR48 eRVR n=160	T12/PR48 no eRVR n=118	Other N=100
Completed telaprevir	**161 (99)**	**119 (74)**	**79 (67)**	**0**
Discontinued telaprevir	1 (<1)	41 (26)	39 (33)	100 (100)
Virologic failure	0	6 (15)	18 (46)	12 (12)
Adverse events	1 (100)	20 (49)	12 (31)	62 (62)
Lost to follow-up	0	2 (5)	2 (5)	5 (5)
Non-compliance	0	0	0	2 (2)
Withdrawal of consent	0	1 (2)	1 (2.5)	4 (4)
Prohibited medication	0	0	1 (2.5)	3 (3)
Refused further treatment	0	11 (27)	5 (13)	8 (8)
Other	0	1 (2)	0	4 (4)

Treatment Experienced: In Study C216, 663 subjects were randomized of whom 662 were treated (266 in the T12/PR48 group, 264 in the T12(DS)/PR48 group, and 132 subjects in the Pbo/PR48 group). By prior non-response category, 354 were prior relapsers and 308 were prior non-responders. Among the prior non-responders, 184 (60%) were prior null and 124 (40%) were prior partial responders. The by-regimen distribution was T12/PR48 (266 subjects: 145 prior relapsers and 121 prior non-responders), T12(DS)/PR48 (264 subjects: 145 prior relapsers and 119 prior non-responders) and Pbo/PR48 (132 subjects: 71 prior relapsers and 61 prior non-responders).

Across the three arms, 74% of subjects completed T/Pbo dosing; more subjects discontinued telaprevir due to adverse events (primarily rash and anemia) while more subjects discontinued Pbo/PR due to meeting a pre-defined virologic stopping rule. Comparing prior relapsers to prior non-responders: 83% of prior relapsers completed the telaprevir dosing period compared to 70% of prior non-responders, 26 prior non-responders discontinued dosing due to adverse events compared to 42 prior relapsers, and 40 prior non-responders met a virologic stopping rule compared to only 2 prior relapsers.

Discontinuations from the T12 and T12(DS) groups due to adverse events and meeting a virologic stopping rule were comparable.

Table 11 Subject disposition, Study C216

N (%)	T12/PR48 N=266	T12(DS)/PR48 N=264	Pbo/PR48 N=132
Completed T/Pbo dosing	191 (72)	212 (80)	88 (67)
Discontinued T/Pbo	75 (28)	52 (20)	44 (33)
Virologic failure	26 (35)	16 (31)	35 (79)
Adverse events	39 (52)	29 (56)	4 (9)
Non-compliance	1 (1)	2 (4)	2 (4)
Other	9 (12)	5 (10)	3 (7)

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for all Phase 3 trials was SVR, which was assessed at 24 weeks following the last planned dose of study medication (SVR24). The assay used by the Applicant in all three Phase 3 trials was the Roche COBAS TaqMan® HCV test (LOQ 25 IU/mL, LOD 10 IU/mL). HCV RNA values below 25 IU/mL cannot be quantified by this assay. Values below LOQ were reported as <25 IU/mL HCV RNA "detected" or "undetected." In the Applicant's statistical evaluations, values reported as <25 IU/mL HCV RNA "detected" or "undetected" were substituted with the values of 17.5 IU/mL and 5 IU/mL respectively.

The Applicant's definition of undetectable HCV RNA for the purpose of assessing SVR was:

- <25 IU/mL not detected HCV RNA, or
- One value of <25 IU/mL detected HCV RNA if preceded and followed by 1 value of <25 IU/mL not detected HCV RNA, or
- 2 consecutive values of <25 IU/mL detected HCV RNA if preceded and followed by 2 consecutive values of <25 IU/mL not detected HCV RNA.

If the last available value was reported as <25 IU/mL "detected," it was considered detectable if no confirmatory value within a pre-defined window was available.

FDA used a less restrictive algorithm to assess SVR: (1) subjects who had HCV RNA <25 IU/mL at FU Week 24 were considered to have achieved a SVR, and (2) subjects with undetectable HCV RNA at EOT, FU Weeks 4 and 12, but who were missing a value at FU Week

24 were also considered as having a SVR. Using this less restrictive approach typically increased SVR rates by 1-4%.

Treatment Naïve: In Study 108 the Applicant's SVR rate for the pooled telaprevir treatment arms was 72% compared to 44% for the control group. RVR rates (HCV RNA undetectable at Week 4) were: 67% (242/364) in the T8 group, 68% (246/363) in the T12 group and 9% (34/361) in the Pbo/PR group.

Using the RGT approach, 57% and 59% of subjects in the T8 and T12 groups achieved eRVR and with 24 weeks of total treatment, the SVR rates were 83% and 89%, respectively. Among no eRVR subjects assigned to receive an additional 24 weeks of PR (48 weeks total); the SVR rates were 50% (T8), 54% (T12), and 40% for the control group.

The FDA overall SVR rate was 75% for telaprevir (73% for T8 and 79% for T12) compared to 46% for Pbo/PR48 (see Table 12). FDA agreed that 57% and 59% of subjects in the T8 and T12 groups, respectively, achieved eRVR, but using the less restrictive algorithm determined that the SVR rates were 92% for the T12 group and 87% for the T8 group. For no eRVR subjects, SVR rates were 55% (T8), 62% (T8) and 42% (Pbo/PR48).

Subjects in the control group were not included in the RGT approach; however, retrospectively 8% (29/361) achieved an eRVR and 97% (28/29) achieved a SVR. The FDA analysis also classified an additional 2% of Pbo/PR48 subjects as achieving SVR.

All comparisons between telaprevir-containing regimens and Pbo/PR48 reached statistical significance. The T12 regimen produced higher SVR rates compared to the T8 regimen in both eRVR and no eRVR subjects; these comparisons did not meet statistical significance.

Table 12 FDA analysis of SVR24 by eRVR status and regimen, Study 108

%	T8			T12			Pbo/PR48
	All (n=364)	eRVR (24 wks) (n=207)	No eRVR(48 wks) (n=157)	All (n=363)	eRVR (24 wks) (n=213)	No eRVR(48 wks) (n=150)	(n=361)
SVR Rate	73	87	55	79	92	62	46

In Study 111, the overall RVR rate was 82%. Sixty-five percent (322/540) of subjects achieved eRVR and were randomized to either 24 (n=162) or 48 (n=160) weeks of treatment. One-hundred eighteen subjects did not achieve eRVR and were assigned to 48 weeks of treatment.

A separate category called "Other" was established for subjects who discontinued the trial prior to the Week 20 randomization point. If these "Other" subjects were excluded, then 73% (322/440) of subjects would have been considered eRVR.

The Applicant's overall SVR rate was 72% (388/540); with SVR rates of 92% and 88% for eRVR subjects randomized to 24 or 48 weeks of treatment, respectively. The SVR rate for no

eRVR subjects was 88% and of the 100 subjects in the "Other" category, 27 (27%) achieved a SVR.

The FDA confirmed the overall SVR rate of all study participants was 72%. No differences in SVR rates were identified between subjects achieving eRVR who were randomized to receive either 24 weeks (T12/PR24) or 48 weeks (T12/PR48) of PR treatment; 60% of subjects achieved eRVR and 90% of those achieved SVR. Of the subjects not achieving eRVR and assigned to receive T12/PR48, 70% achieved SVR (see Table 13).

The results demonstrate no differences between SVR rates for eRVR subjects treated with either a 24 or 48 week regimen.

Table 13 FDA analysis of SVR24 by eRVR status and duration of therapy, Study 111

%	All[1] (N=540)	T12 eRVR (24 Weeks) (N=162)	T12 eRVR (48 Weeks) (N=160)	T12 no eRVR (48 Weeks) (N=118)
SVR rate	72	93	92	70

1. Includes subjects in the Other category.

Treatment Experienced: All subjects in Study C216 were assigned 48 weeks of treatment. Again, the FDA analyses confirmed the primary efficacy conclusions of Study C216. Also, no important differences were observed in SVR rates between the immediate and delayed start telaprevir regimens. Comparisons between the SVR rates for the T-containing regimens compared to the Pbo/PR48 regimen were all highly statistically significant (see Table 14).

Table 14 FDA analysis of SVR24 by regimen and prior response status, Study C216

%	SVR rate
All T combined	
All	66
Prior Null	32
Prior Partial	59
Prior Relapse	86
T12/PR48	
All	65
Prior Null	30
Prior Partial	61
Prior Relapse	84
T12(DS)/PR48	
All	67
Prior Null	33
Prior Partial	56
Prior Relapse	88
Pbo/PR48	
All	16
Prior Null	5
Prior Partial	15
Prior Relapse	22

The RGT approach was not utilized nor evaluated in Study C216. (b) (4) The interest here was to determine if these interferon sensitive subjects could be re-treated with a shorter course of therapy. (b) (4) The bases for this analysis were data from Phase 2 Study 107 in prior relapsers who received 24 or 48 weeks of treatment based on achievement of eRVR. In that trial, 78% (52/67) achieved eRVR, and 94% (49/52) achieved a SVR. In the viral dynamic analysis of Study C216, the Applicant determined that 76% (218/286) of prior relapsers in the pooled telaprevir groups achieved eRVR, and of these, 207/218 (95%) achieved a SVR.

Reviewer Comment: The Phase 2 data in combination with viral dynamic modeling from Phase 3 data suggest that RGT for prior relapsers may be a viable approach. However, there are no prospective data available to validate this assumption. This question will be raised to the Antiviral Products Advisory Committee.

6.1.5 Analysis of Secondary Endpoints(s)

Subjects who failed to achieve SVR (No SVR) were evaluated for virologic reasons for failure, such as on-treatment virologic failure, failure during PR dosing, and relapse.

In the Phase 3 trials, the rates of virologic failure, failure during PR dosing and relapse were substantially reduced among subjects treated with a telaprevir-containing regimen compared to Pbo/PR48.

On-Treatment Virologic Failure

On-treatment virologic failure was defined as a <2-log10 decrease in HCV RNA levels compared to baseline or HCV RNA levels >1000 IU/mL at Week 12.

Treatment Naïve: During the T/Pbo dosing period, the on-treatment virologic failure rate in Study 108 for the combined telaprevir groups was 3% compared to 12% for the Pbo/PR48 group. There was no difference in virologic failure rates between the T8 and T12 groups during the telaprevir dosing period.

In Study 111, only 12 subjects in the "Other" category met a virologic failure stopping rule during the telaprevir dosing period.

Almost all of the subjects who failed on T/PR by Week 12 had treatment-emergent substitutions. The substitutions V36M and R155K and combination of both emerged most frequently in subtype 1a failures and V36A, T54A or S and A156T emerged most frequently in subtype 1b failures.

Treatment Experienced: The virologic failure rate during the T/Pbo dosing period was 12% among T-treated subjects compared to 27% for Pbo/PR48 subjects. Virologic failure rates were slightly lower among delayed start subjects compared to immediate start: 9% compared to 6%. Again, the majority of subjects who failed did so within the first 4-weeks of telaprevir dosing (74%) and were more likely to be prior null responders (86%) with subtype 1a (81%). The V36M and R155K substitutions and the combination of both emerged most frequently in subtype 1a treatment failures. The V36A, T54S or A and A156T, S or V emerged most frequently in subtype 1b failures.

Virologic failure during PR dosing (Breakthrough)

Viral breakthrough was defined as an increase in on-treatment HCV RNA of >1-$\log_{10}$ compared to the lowest recorded on-treatment value or an on-treatment HCV RNA level of >100 IU/mL in a subject who had undetectable HCV RNA at a prior time point.

Treatment Naïve: In Study 108 the virologic breakthrough rate was higher in the T8 arm (16%) compared to 10% in the T12 arm; both were lower than in the Pbo/PR48 arm (24%).
In Study 111 after Week 12, breakthrough was low among eRVR subjects whether they received 24 (2%) or 48 (4%) weeks of treatment. The rate of failure in no eRVR subjects was 18%. In the "Other" group, 41% of subjects failed after telaprevir dosing was completed.

In Study 108 60% and in Study 111 90% of isolates from subjects who failed after Week 12 on PR had treatment-emergent substitutions. The substitutions V36M and R155K and combination of both emerged most frequently in subtype 1a failures and V36A, T54A or S and A156T emerged most frequently in subtype 1b failures.

Experienced Subjects: Fourteen percent of telaprevir subjects experienced virologic breakthrough compared to 33% in the Pbo/PR48 group. The majority of breakthroughs were in prior null-responders, and most subjects had subtype 1a. Consistent with the treatment naïve data, the V36M and R155K substitutions and the combination of both emerged most frequently in subtype 1a treatment failures, and the V36A, T54S or A and A156T, S or V emerged most frequently in subtype 1b failures.

Virologic Relapse

Relapse was defined as a confirmed undetectable HCV RNA at the end-of-treatment (EOT) visit and a confirmed detectable HCV RNA before or at the SVR24 time point. For this analysis, the denominator was based on the number of subjects in each treatment group who achieved an EOT response.

The addition of 12 weeks of telaprevir to a PR24 or 48 week regimen decreased the relapse rate from 26% (Pbo/PR48) to 5% in treatment-naïve subjects and from 57% to 10% in experienced subjects. Nearly 90% of relapses occurred between EOT and follow-up Week 12; more subjects with subtype 1a relapsed.

Treatment Naïve: In Study 108, the FDA analysis determined that the overall relapse rate was 6% for the pooled T/PR groups compared to 26% for Pbo/PR48. The relapse rate was slightly higher in the T8 group compared to the T12 group: 7% compared to 5%, respectively. For telaprevir-treated no eRVR subjects, relapse rates were higher (11%) than in eRVR subjects (5%) with no difference between the T8 and T12 groups. The 28% relapse rate in the Pbo/PR48 arm was consistent with other previously conducted trials.

In the combined telaprevir groups, 90% of relapses occurred by FU Week 12. After FU Week 12, 5 T8 subjects relapsed compared to 1 T12.

In Study 111, the relapse rates among randomized eRVR subjects were 6% (T12/PR24) and 1% (T12/PR48). In the no eRVR group, the relapse rate was 11%. For these three groups, 92% of relapses occurred by FU Week 12; one subject in the T12/PR24 group had late relapse (>Week 24). In the "Other" category, 59/100 subjects had achieved an EOT response, and of these 13 (22%) relapsed; all relapses in this group occurred by FU Week 4. Across all treatment groups, the majority of subjects who relapsed had subtype 1a.

Treatment Experienced: The overall relapse rate for combined T-treated subjects was 10% (38/379) compared to 58% (29/50) in the Pbo/PR48 group. Relapse rates were higher in prior null and partial responders compared to prior relapsers. Eighty-six percent of T-treated subjects relapsed by FU Week 12.

6.1.6 Other Endpoints

Assessment of SVR12

Traditionally, SVR has been assessed 24 weeks following completion of a course of therapy. In prior Peg-IFN/RBV studies it has become evident that the vast majority of relapses occur within the first 12 weeks of off-therapy follow-up. Previous reports suggest that between FU Week 12 and 24, an additional 0-10% of subjects relapse. SVR-24 is highly correlated to long term virologic suppression. Therefore, there is interest in comparing shorter to longer durations of follow-up with newer anti-HCV therapies.

Across the Phase 3 trials, ~90% of relapses occurred by FU Week 12. Further, there was ~98% concordance between SVR rates at FU Weeks 12 and 24.

Assessment of SVR72

SVR assessed 72 weeks after initiation of therapy (SVR72) was evaluated in Study 108 and Study 111 as this provided a common time point to assess the durability of the antiviral response. In Study C216, SVR was evaluated at week 72 of a planned 48 week treatment period.

The SVR72 rates in Studies 108 and 111 were significantly higher in the T/PR groups than in the Pbo/PR48 group. The SVR72 rate for the T8/PR group was 68%, 78% for the combined T12/PR groups, and 44% for the Pbo/PR48 group.

In total, 22 subjects with SVR24 did not have SVR72, of which 5 subjects relapsed, 7 subjects did not complete the study and, therefore, did not have an HCV RNA assessment at Week 72, and 10 subjects completed the study but was missing the Week 72 HCV RNA assessment.

ALT and AST Normalization

Mean baseline ALT and AST levels were elevated for most subjects. ALT and AST levels decreased (improved) by Week 1 and continued through the remainder of the study. At the Safety Follow-up visit mean ALT and AST levels were at or below their respective upper limit of normal.

IL28B Genotype as a Predictor of Virologic Response

In 2009, numerous publications described a novel association between single nucleotide polymorphisms (SNPs) near the interleukin (IL) 28B gene locus and response to treatment in subjects with CHC. Using a GWAS to investigate 300,000 to 900,000 SNPs in each sample, the investigators identified a particular SNP (rs12979860) strongly determined the outcome of HCV therapy. Three genotypes were identified: C/C, C/T and T/T.

The discovery of the IL28B SNPs occurred after the Phase 3 trials had been fully enrolled and mostly completed. As such, it was not possible for the Applicant to stratify subjects at enrollment based on the IL28B genotype.

Specific consent for genotyping for rs12979860 was obtained in subsets of two Phase 2 trials and two Phase 3 trials. A substudy was conducted on samples from participants of the Phase 3 trials.

The following was excerpted from Dr. Sashi Amur's Pharmacogenomics (PG) Review:
Response rates and treatment effects were similar between the PG substudy and the overall trial populations for the Phase 3 trials. The Applicant's IL28B genetic substudy confirms previous reports of IL28B genotype effects on PR responses in that C/T and T/T subjects had significantly lower SVR rates in the Pbo/PR48 arms. A similar genetic effect was apparent in the telaprevir-containing arms, although less pronounced than in Pbo/PR48. In both treatment-naïve and treatment-failure trials, subjects with the C/T and T/T genotypes had substantially higher SVR rates with telaprevir-containing regimens than PR alone. Statistical heterogeneity in telaprevir treatment effects was not apparent across the IL28B genotype strata (genotype x treatment interaction P>0.15) (see Table 15).

Table 15 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
Treatment-naïve						
108	Pbo/PR48	44% (158/361)	38% (61/161)	64% (35/55)	25% (20/80)	23% (6/26)
	T8/PR	69% (250/364)	67% (102/153)	84% (38/45)	57% (43/76)	59% (19/32)
	T12/PR	75% (271/363)	78% (109/140)	90% (45/50)	71% (48/68)	73% (16/22)
Treatment-experienced						
C216	Pbo/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)/PR	66% (175/264)	54% (114/210)	83% (29/35)	58% (76/132)	65% (28/43)

Treatment naïve C/C subjects appeared to respond favorably to PR alone, although SVR rates were higher for all of the telaprevir-containing regimens in this subgroup. C/T carriers had lower response rates than C/C carriers in all treatment arms. The addition of 12 weeks of telaprevir appeared to substantially increase SVR rates among subjects with C/T and T/T genotypes compared to Pbo/PR48, and improved by ~13% responses compared to similar subjects in the T8 group.

In treatment experienced subjects, telaprevir appeared to benefit subjects of all genotypes by increasing SVR rates by 50-60% for each genotype compared to Pbo/PR. In C/T and T/T carriers, there was no difference between the immediate delayed start regimens.

Reviewer Comment: The above data must be interpreted with caution because: (1) the data were not collected and analyzed prospectively, (2) the sample size of some subgroups was small, and (3) less than 4% of samples were from Blacks/African Americans who are known to more likely have the C/T and T/T genotypes.

6.1.7 Subpopulations

Negative predictive characteristics for response to Peg-IFN/RBV include: male, age >45 years, high body weight, subtype 1a, high baseline viral load (>800,000 IU/mL), and Black/African American race or Hispanic/Latino ethnicity.

The overall SVR data demonstrate that the addition of T12 to PR for 24 or 48 weeks substantially increased response rates across a broad spectrum of demographic and disease covariate. Consistent across the three trials, SVR rates for many covariates associated with a negative response to PR were increased 25-40% with the addition of telaprevir. The demographic and disease characteristics of certain subgroups of telaprevir treated subjects who achieved eRVR in the two treatment naïve trials were evaluated in more detail.

- Males and females and heavier and lighter subjects responded similarly to telaprevir-based treatment.

- Blacks/African Americans had SVR rates approximately 20% lower than Caucasians, which was consistent with prior trials of interferon-based therapies. A positive trend was observed for improved response rates among Black/African Americans treated with telaprevir compared to those treated with Pbo/PR48: 65% (range; 50% to 94%) SVR compared to 31% (range; 29% to 36%). However, Black/African Americans comprised only 9% (158/1797) of telaprevir subjects and 8% (39/493) of Pbo/PR48 subjects.

- Among telaprevir-treated subjects, 8% (108/1267) of naïve and 26% (139/530) of treatment experienced subjects had cirrhosis at baseline, compared to 6% (21/361) of naïve and 23% (30/132) of experienced Pbo/PR48 subjects. Positive trends were noted for increased SVR rates among subjects treated with T/PR compared to Pbo/PR. Of note, it appears that T12 was better than T8 in treatment naïve subjects with cirrhosis, and that subjects with who achieve an eRVR may benefit from 48 weeks of treatment compared to 24 weeks; however, the number of subjects was small.

Table 16 SVR by presence of cirrhosis, naïve subjects

	eRVR	eRVR SVR	no eRVR	no eRVR SVR
Study 108				
T8/PR	11/26 (42)	7/11 (64)	15/26 (58)	4/15 (27)
T12/PR	9/21 (43)	7/9 (78)	12/21 (57)	9/12 (75)
Study 111				
T12/PR24	18/30 (60)	12/18 (67)	N/A	N/A
T12/PR48	12/30 (40)	11/12 (92)	N/A	N/A
T12/PR48	N/A	N/A	12/31 (40)	4/12 (33)

In treatment experienced subjects, there was a substantial benefit in favor of treatment with telaprevir among prior relapsers with cirrhosis: 84% SVR compared to 13% with Pbo/PR, a moderate benefit for prior partial responders (34% compared to 20%), and a minimal benefit for prior null responders (14% compared to 10%).

- Latino/Hispanic subjects comprised 10% (185/1797) of telaprevir subjects and 12% (58/493) of Pbo/PR48 subjects. SVR rates for Latino/Hispanic subjects were 79% (range; 70% to 94%) for telaprevir and 31% (range; 10% to 42%) for Pbo/PR48.

- Younger subjects, <45 years of age, responded better than older subjects. Only 2% (31/1797) of telaprevir and 2% (8/493) of Pbo/PR48 subjects were >65 years of age. Among telaprevir subjects, 21/31 (68%) achieved SVR and among Pbo/PR48 subjects the SVR rate was 25% (2/8). As such, these data must be interpreted cautiously.

Table 17 SVR by all demographic and disease characteristics, Study 108

n/N (%)	T8/PR (N=364)	T12/PR (N=363)	Pbo/PR48 (N=361)
Age			
≤45	114/139 (82)	125/142 (88)	80/143 (56)
>45	153/225 (68)	168/221 (73)	87/218 (40)
Sex			
Male	160/211 (76)	167/214 (78)	98/211 (46)
Female	107/153 (70)	120/149 (81)	69/150 (46)
Race			
Caucasian	234/315 (74)	260/325 (80)	154/318 (48)
Black/African Am	25/40 (63)	16/26 (62)	8/28 (29)
Other	8/9 (89)	11/12 (92)	5/15 (33)
Ethnicity			
Latino/Hispanic	31/44 (70)	27/35 (77)	16/38 (42)
Non-Hispanic	236/320 (74)	260/326 (79)	151/323 (47)
Geographic locality			
North America	158/227 (70)	162/214 (75)	92/214 (43)
Europe	82/100 (82)	87/104 (84)	53/106 (50)
Rest of World	27/37 (73)	40/45 (89)	22/41 (54)
BMI, kg/m^2			
≤25	109/145 (75)	134/155 (86)	60/130 (46)
>25-<30	97/131 (74)	96/129 (74)	69/144 (46)
≥30	60/86 (70)	56/77 (73)	35/87 (44)
Liver histology			
No to min fibrosis	107/128 (84)	115/134 (86)	71/147 (48)
Portal fibrosis	113/151 (75)	123/156 (79)	70/141 (50)
Bridging fibrosis	36/59 (61)	33/52 (63)	18/52 (35)
Cirrhosis	11/26 (42)	16/21 (76)	8/21 (38)
Genotype subtype			
1a	150/210 (71)	163/217 (75)	91/210 (43)
1b	116/151 (77)	120/142 (85)	76/149 (51)
Baseline HCV RNA			
<800,000 IU/mL	75/92 (82)	77/88 (88)	64/92 (70)
≥800,000 IU/mL	192/272 (71)	210/275 (76)	103/269 (38)
Diabetes	13/23 (57)	16/21 (76)	7/21 (33)
No Diabetes	254/341 (74)	271/342 (79)	160/340 (47)

Table 18 SVR by demographic and disease characteristics, Study 111

n/N (%)	eRVR T12/PR24 N=162	eRVR T12/PR48 N=160	no eRVR T12/PR48 N=118
Age			
≤45	43/44 (98)	41/44 (93)	18/26 (69)
>45	105/118 (89)	106/115 (92)	58/92 (63)
Sex			
Male	95/104 (91)	88/96 (92)	40/75 (64)
Female	55/58 (95)	59/63 (94)	38/41 (65)
Race			
Caucasian	127/135 (94)	119/130 (92)	56/86 (65)
Black/African Am	15/17 (88)	16/17 (94)	19/30 (63)
Ethnicity			
Latino/Hispanic	17/18 (94)	10/11 (91)	6/8 (75)
Non-Hispanic	130/140 (93)	134/145 (92)	67/105 (64)
Geographic locality			
North America	143/154 (93)	139/150 (93)	67/106 (63)
Europe	7/8 (88)	8/9 (89)	9/12 (75)
BMI, kg/m^2			
<25	42/44 (95)	57/60 (95)	10/38 (26)
≥25-<30	52/56 (93)	47/50 (94)	6/32 (19)
≥30	55/61 (90)	42/49 (88)	7/30 (23)
Liver histology			
No to min fibrosis	45/46 (98)	43/47 (91)	18/27 (67)
Portal fibrosis	74/78 (95)	75/79 (95)	35/49 (71)
Bridging fibrosis	19/20 (95)	18/21 (86)	19/30 (65)
Cirrhosis	12/18 (67)	11/12 (92)	4/12 (33)
Genotype subtype			
1a	103/114 (90)	107/115 (93)	49/84 (58)
1b	44/45 (98)	38/42 (93)	26/33 (79)
Untypeable	3/3 (100)	1/2 (50)	1/1 (100)
Diabetes	7/8 (88)	4/5 (80)	4/8 (50)
No Diabetes	143/154 (93)	143/154 (93)	72/110 (65)

Table 19 SVR rates by disease and demographic characteristics, Study C216

n/N (%)	T12/PR48 (N=266)	T12(DS)/PR48 (N=264)	Pbo/PR48 (N=132)
Age			
<45	39/55 (71)	33/47 (70)	5/34 (15)
≥45	135/211 (64)	143/217 (66)	17/99 (17)
Sex			
Male	120/183 (66)	127/189 (67)	13/89 (15)
Female	54/83 (65)	49/75 (65)	9/44 (20)
Race			
Caucasian	158/246 (64)	170/257 (67)	18/118 (15)
Black	8/11 (73)	4/8 (50)	4/11 (36)
Ethnicity			
Latino/Hispanic	18/25 (72)	19/27 (70)	2/20 (10)
Non-Hispanic	156/241 (65)	157/237 (66)	20/113 (18)
Geographic locality			
North America	52/89 (58)	45/72 (63)	5/39 (13)
Europe	87/127 (69)	91/139 (65)	16/74 (22)
Rest of World	35/50 (70)	40/52 (75)	1/20 (5)
BMI, kg/m^2			
<25	54/85 (64)	60/89 (67)	7/42 (17)
≥25-<30	79/108 (73)	77/112 (69)	7/53 (13)
≥30	41/73 (56)	38/62 (61)	8/37 (22)
Liver histology			
No to min fibrosis	37/51 (73)	55/68 (81)	7/35 (20)
Portal fibrosis	59/83 (71)	54/71 (76)	9/39 (23)
Bridging fibrosis	44/60 (73)	35/68 (60)	2/29 (7)
Cirrhosis	34/72 (47)	32/67 (48)	4/30 (13)
Subtype (5'NC-T)			
1	18/27 (67)	18/28 (64)	1/13 (8)
1a	67/118 (57)	74/120 (62)	14/59 (24)
1b	89/121 (74)	83/115 (72)	7/59 (12)
Baseline HCV RNA			
<800,000 IU/mL	28/34 (82)	27/34 (79)	6/18 (33)
≥800,000 IU/mL	146/232 (63)	149/230 (65)	16/115 (14)
HOMA IR <2	69/93 (72)	66/89 (74)	10/35 (29)
HOMA IR ≥2	99/161 (61)	102/164 (62)	10/89 (11)

Illicit Drug Users: A methadone-telaprevir interaction study showed that concentrations of R methadone were reduced when co-administered with telaprevir. Subjects abusing illicit drugs (narcotics or other controlled substances) or alcohol, or who had a history of illicit substance or alcohol abuse within 2 years prior to the screening visit were to be excluded. However, subjects who had a history of abuse of illicit drugs or alcohol and incidents of abuse within the 2 years prior to the screening visit or subjects who had a history of abuse of narcotics or other controlled substances known by the investigative site and considered to be a good candidate for clinical research could be included. Also, subjects being treated with methadone were to have been on a stable methadone program for at least 6 months prior to screening.

A total of 11 illicit drug users were enrolled in the Phase 3 trials (9 to telaprevir-containing regimens and 2 to Pbo/PR48). One Pbo/PR48 (50%) and three (33%) telaprevir-treated subject achieved a SVR.

The data support the T12/PR24 regimen for the majority of naïve subjects by demonstrating that the T12 regimen generally outperformed the T8 regimen in Study 108 and there were no differences in SVR rates between the T12/PR24 and T12/PR48 regimens in Study 111 across demographic or disease characteristics. In experienced subjects, there were no differences in SVR rates between immediate and delayed initiation of telaprevir.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see Section 4.3 above for a more detailed discussion of the evolution of the selection of the 750 mg q8h for 12 weeks dosing of telaprevir. The T8 regimen produced slightly more favorable safety outcomes, but was associated with lower SVR and higher virologic failure and relapse rates compared to 12 weeks of telaprevir dosing. Therefore, the recommended dose for marketing is telaprevir 750 mg q8h (administered with food) for 12 weeks.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of Efficacy: Achievement of SVR is considered to equate to cure of HCV infection; but the long term consequences of progression of liver disease are not completely understood. Several longitudinal studies have demonstrated very low virologic relapse rates and decreases in liver-related morbidity and mortality (development of cirrhosis and hepatocellular carcinoma).

To evaluate long-term outcomes of subjects treated with telaprevir, the Applicant is conducting Study VX08-950-112**,** which is a nonrandomized, 3-year follow-up of subjects who either did achieve or did not achieve SVR in Studies 104, 104EU, 106, 107, 108, 111, or C216. Cohort A is to include approximately 150 subjects who achieved an SVR and Cohort B includes ~250 who did not. The objectives for Cohort A are to assess the durability of virologic response, evaluate HCV variants in subjects with late relapse, and evaluate the incidence of clinical outcomes related to severe liver disease. Cohort B subjects will be evaluated for changes in HCV variants over time and the incidence of clinical outcomes related to liver disease. No treatment is being administered in this follow-up study.

Preliminary data from an interim analysis included data for 202 subjects that were enrolled in the study at the time of the NDA data cut-off (01 March 2010): 123 subjects in Cohort A and 79 subjects in Cohort B. Thus far, only subjects from Phase 2 trials have been enrolled. Of the 79 subjects in Cohort B, 56 had paired HCV sequencing data and were included in an analysis of changes in HCV sequencing. As of the NDA cut-off, 1 subject in the SVR cohort relapsed. Virologic data suggests that it could take up to three years for reversion of some mutations (V36M, T54A/S, R155K, A156/S/T/N) to wild-type.

Persistence of Tolerance: At steady-state, the terminal half life of telaprevir is 9-11 hours, suggesting that shortly after cessation of dosing telaprevir is out of the system. Telaprevir-related toxicities, as described in Section 7, occurred most frequently during the first 12 weeks of therapy which correlated with the duration of telaprevir dosing. In most cases, telaprevir-related adverse clinical events, such as rash and anemia, and laboratory abnormalities resolved within 4-8 weeks following cessation of telaprevir dosing. As such, there was no indication that telaprevir-related toxicities persist.

6.1.10 Additional Efficacy Issues/Analyses

Patient Reported Outcomes

Patient reported outcomes (PRO) were assessed in Studies 111 and C216. Three questionnaires (fatigue severity scale [FSS], EQ-5D, and work productivity questionnaire [WPQ]) were self-administered by subjects at baseline and at Weeks 2 (FSS only), 4, 12, 24, 48, and 72. In addition, healthcare utilization assessments (recording of any visits to healthcare providers other than site staff since the previous visit) were conducted.

The FSS is a 9-item questionnaire. Each item is scored between 1 and 7, in which higher scores indicate a higher degree of fatigue. The 9-item responses are combined into 1 total score (FSS total score). The EQ-5D questionnaire consists of a descriptive system and a visual analogue scale (VAS) to score subjects' health state in 5 health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 3 possible response levels (no problems, some problems, and extreme problems). Results for each dimension were tabulated per time point. The WPQ consists of 5 questions regarding the influence of hepatitis C and its treatment on the subjects' ability to work. Descriptive statistics or tabulations per time point were generated for these questions (as applicable).

Fatigue and other health-related dimensions worsened during therapy in all treatment groups, which was consistent with results of previous trials of PR therapy. Further, during the telaprevir dosing period, PRO results were generally similar or worse compared to the Pbo/PR48 group. After discontinuation of telaprevir, PRO results showed improvement by Week 24 and then stabilized up to Week 48. Between Weeks 24 and 48, PRO results in the Pbo/PR48 group were stable or slightly worsened, likely due to continued exposure to PR. The improvement in the T/PR groups may have been due to the shorter duration of telaprevir treatment but may also have been related to the higher proportion of subjects in these groups who respond to treatment. After the end of therapy, fatigue and other health-related dimensions returned to baseline in all treatment groups. Also, subjects in the T/PR groups rated their health status and work productivity slightly better than at baseline. Healthcare utilization was higher in the T/PR groups than in the Pbo/PR48 group, both for the number of subjects visiting healthcare providers outside this study and the median number of visits.

Subjects were aware of their end of study HCV RNA results. There were no differences between prior relapsers and prior non-responders or between subjects from Europe, North America, and other regions.

7 Review of Safety

The key telaprevir-related toxicities are skin disorders (rash and pruritis) and anemia. Both rash and anemia are known adverse drug reactions with PR but occurred with substantially greater frequency and severity when telaprevir was added to the regimen. Each of these toxicities should be in the *WARNINGS and PRECAUTIONS* section of the label. Other clinical adverse events at least possibly related to telaprevir, or where a potential safety signal was identified, include: anorectal disorders, eye disorders, renal disorders, elevated bilirubin levels, and hyperuricemia/gout.

Rash/pruritis: Rash/pruritis were reported in ~55% of subjects treated with telaprevir in clinical trials compared to ~30% of Pbo/PR recipients. The majority of rash and prutitis events were mild to moderate in severity. However, more subjects treated with telaprevir had ≥Grade 3 rash events (3% versus 1%), SAEs (1% versus <1%), and had treatment limiting events (5% versus <1%) compared to those treated with Pbo/PR48. Telaprevir-related rash occurred early (median time to onset 16-20 days) and was often pruritic. The rash appeared eczematous, maculopapular, and papular-lichenoid, with spongiform dermatitis, predominantly lymphocytic or eosinophilic perivascular infiltration on histopathology. Less than 1% of subjects experienced suspected SJS or DRESS. However, not all occurred during treatment with telaprevir, none were life-threatening type 1 hypersensitivity/anaphylactic reactions, and the rash did not appear to be drug induced hypersensitivity. A number of subjects received topical or systemic corticosteroids; however, it was not possible to determine if these interventions either decreased the severity of duration of rash.

Anemia: Anemia is a Peg-INF/RBV-related toxicity that is exacerbated by the addition of telaprevir, which may be due to its effect on the hematopoietic system (decreased erythrocytic parameters and anemia accompanied by reticulocyte/bone marrow response).

Subjects receiving telaprevir had a higher frequency of anemia (36% versus 17%), a higher frequency of ≥Grade 3 hemoglobin reductions (55% versus 27%), more anemia-related SAEs (2% versus <1%), and a higher frequency of anemia-related discontinuations (3% versus <1%). Time to onset of anemia was ~43 days. Among subjects treated with telaprevir, hemoglobin values decreased steeply through Week 4, were generally stable between Weeks 8 and Week 12, and by Week 16-18 had risen to levels similar or higher compared to those of subjects in Pbo/PR48 groups. Overall, telaprevir increased the decline in hemoglobin levels ~1.0-1.5 g/dL greater compared to Pbo/PR-treated subjects.

Anorectal Events: Anorectal events (hemorrhoids, pruritis ani, proctalgia, anal inflammation, perianal erythema, and anal discomfort) were reported by ~20% (range 15-26%) of T-treated

subjects. These events appeared to be a bothersome (mild to moderate severity), but rarely serious, and resulted in 1 case of study discontinuation.

Eye Disorders: In Phase 2 trials a possible signal for excess eye disorders with telaprevir was observed. In Phase 3 trials, the frequency of eye disorders was 4% higher among subjects who received telaprevir, with more retina-related events. As such these retina-related events may represent a safety signal. However, subjects were also receiving Peg-IFN at the same time which is labeled for numerous significant eye disorders. Also, there were no eye-related findings in nonclinical animal studies. The incidence of SAEs and discontinuations were comparable at <1% in each group.

Renal Disorders: All grade increases in creatinine levels were higher among subjects treated with T/PR: 6% compared to 1% for Pbo/PR, and creatinine elevations to ≥Grade 3 levels were <1% compared to 0%. Less than 1% of subjects experienced renal failure in the Phase 3 trials. All creatinine elevations were reversible upon cessation of telaprevir dosing.

General Adverse Events: Telaprevir will be required to be co-administered with Peg-IFN/RBV. The currently approved Peg-IFNs are immunomodulators with very well characterized safety profiles; all are associated with a panoply of toxicities affecting almost every organ system. Known adverse events that are the most concerning, and often limit continued treatment include: fatigue, flu-like symptoms (fever, chills, arthralgias/myalgias), depression, impaired memory and concentration, suicidal ideation/attempt, homicidal ideation/attempt, and bone marrow suppression.

General Adverse Events: The most frequent AEs (>20%) observed during the T/Pbo dosing period were fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, and pyrexia. AEs that were observed with at frequency ≥5% higher in the T/PR groups compared to the Pbo/PR48 groups were: pruritus, nausea, rash, anemia, diarrhea, hemorrhoids, dysgeusia, and anorectal discomfort.

There were no clinically relevant differences between the adverse event profile of treatment naïve and treatment experienced subjects. Also, the general safety profile of the T8/PR regimen evaluated in Study 108 was similar to that of the T12/PR regimen, with the exception of more cases of rash and anemia occurring between Weeks 8 and 12.

Other Hematologic Abnormalities and Events: Overall, the frequency of severe (Grade 3 or higher) hematologic abnormalities was low in the clinical trials. More telaprevir-treated subjects than Pbo/PR subjects had severe decreases in lymphocyte counts. Severe decreases in total white blood cells were comparable, but the frequency of severe decreases in absolute neutrophil counts was higher in subjects receiving Pbo/PR48. The incidence of ≥Grade 3 reductions in platelet counts were comparable.

Clinical Chemistry Abnormalities and Events: Elevations of bilirubin and uric acid were frequently observed and may be related to the excess breakdown of red blood cells in telaprevir-

treated subjects with anemia. During the T/Pbo dosing period substantially more telaprevir-treated subjects than Pbo/PR48 subjects had elevated uric acid levels (73% compared to 29%). Shifts from baseline to Grade 3 or higher uric acid levels were also more frequent among subjects treated with telaprevir (7%) compared to Pbo/PR48 (2%), and there were more cases of gout/gouty arthritis among T/PR subjects. Bilirubin elevations occurred in 40% of telaprevir-treated subjects compared to 28% of Pbo/PR48 subjects, and 4% and 2%, respectively, had Grade 3 or higher (>2.6 x ULN) elevations.

Other Safety Issues: All the approved interferon products carry a Pregnancy Category rating of C. The most common and concerning adverse effects related to RBV are hemolytic anemia and rash. RBV is classified as Pregnancy Category X. Based on preclinical studies, telaprevir will be labeled at Pregnancy Category B, but will carry the same Pregnancy warnings as Peg-IFN/RBV.

7.1 Methods

The primary safety data was derived from the Phase 2 and 3 trials in which telaprevir was co-administered with Peg-IFN/RBV. The focus of the review is on safety findings during the period of T/Pbo administration (up to 12 weeks in Studies 108 and 111, and up to Week 16 in Study C216 to account for the delayed start of T) to ~30 days after the last dose of T/Pbo. Where appropriate and important, adverse events that occurred beyond the T/Pbo dosing period will be presented and discussed.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary NDA safety review is based on Studies 104, 104EU, 106, 107, 108, 111, and C216.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the MeDRA adverse event dictionary (Version 11.0) and the Division of AIDS Table for Grading the Severity of Adult Adverse Events and Laboratory Abnormalities of the National Institutes of Health. Both systems are well established and acceptable as means for defining adverse clinical and laboratory events. Data on deaths, life-threatening events, and ESIs were provided in the Council for International Organizations of Medical Sciences (CIOMS) forms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Approximately 2800 subjects have received the proposed dose (750 mg q8h) and regimens (T12/PR24 for naïve and T12/PR48 for treatment experienced) for marketing in clinical trials; of these, 1433 received these regimens in Phase 3 trials. An additional 364 subjects received a shorter duration of telaprevir for 8 weeks. There did not appear to be substantial differences between the safety profile for naïve and experienced subjects. Therefore, the overall safety data was pooled and where applicable, compared to control data.

7.2 Adequacy of Safety Assessments

As noted above, a substantial number of HCV-infected adults have received the proposed dose and duration of telaprevir for marketing. As such, the number of subjects exposed to telaprevir is adequate to determine the most relevant toxicities related to its proposed use.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The NDA safety database contains data from ~3800 subjects who received at least one dose of telaprevir in single and multiple dose Phase 1, 2 and 3 trials.

In the Phase 3 trials, 1797 subjects were enrolled and received at least one dose of telaprevir; 1433 subjects received the proposed dose of telaprevir (750 mg q8h) for the proposed duration (12 weeks) for marketing in combination with PR for 24 or 48 weeks, and 364 subjects received a shorter duration of telaprevir (8 weeks). The overall mean duration of exposure to telaprevir was ~12.5 weeks (SD 3.75).

7.2.2 Explorations for Dose Response

Multiple Phase 1 and 2 trials in healthy volunteers and subjects with CHC were conducted to select the 750 mg q8h with food dose of telaprevir further evaluation and confirmation in Phase 3 trials (See Section 4.6.6).

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in vitro studies were needed or conducted.

7.2.4 Routine Clinical Testing

Routine clinical testing for adverse clinical and laboratory events was comprehensive. Adverse events, serious and non-serious, were collected beginning after the informed consent form was signed through the Safety follow-up assessment. Adverse events were recorded regardless of the suspected cause of the event. Study visits occurred at Weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 36, and 48 (end of longest duration of dosing) and at FU Weeks 4, 12 and 24. Unscheduled visits were conducted as needed to assess progression and/or resolution of events.

Safety evaluations included clinical laboratory assessments, clinical evaluation of vital signs, physical examinations, ECGs, and the subjective reporting of adverse events. For each adverse event, the following information was collected: description, classification of “serious” or “not serious,” date of first occurrence and date of resolution (if applicable), severity, causal relationship, action taken, outcome, and concomitant or other treatment given. Similar requirements were in place for laboratory abnormalities as adverse events. Events were graded as mild (Grade 1) Awareness of the event; may cause minimal interference with the subject’s daily

life; moderate (Grade 2) Discomfort enough to cause a noticeable impact on the subject's daily life; or, severe (Grade 3) Incapacitation or significant impact on the subject's daily life. Although not graded, some life-threatening events were reported.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Metabolic, Clearance and Interaction workups were adequate. Please see Sections 4.4 above and 7.5.5 below for additional details. Most importantly, in vitro studies demonstrate that telaprevir is metabolized in the liver primarily by cytochrome P450 (CYP) 3A4 and is a CYP3A inhibitor indicating the potential for telaprevir to cause drug-drug interactions. Additionally, in vitro studies indicated telaprevir is a mild inducer of CYP1A activity. Telaprevir does not have clinically relevant QTcF prolongation potential.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There are no other currently approved HCV NS3/4A protease inhibitors available for comparison. The primary toxicities associated with another experimental NS3/4A protease inhibitor that is currently in late-stage development are anemia and dysguesia (bad taste). Because of overlapping mechanism of action and cross resistance potential, these two protease inhibitors would not be co-administered.

7.3 Major Safety Results

7.3.1 Deaths

The safety database (including the safety update) contained information on 12 deaths; 8 in telaprevir and 4 in Pbo subjects. Narratives were reviewed. Six of the 8 deaths in telaprevir subjects occurred >100 days following the last dose of telaprevir, and due to events that were unlikely related to telaprevir. One subject who died in a non-IND trial, and one subject included in the safety database are described in more detail below (see Table 20).

Table 20 Deaths

Study #/PT ID	Demographics	Regimen	Cause	Study Day
Initial 12 weeks: T/Pbo dosing period				
216-0431	56 year old female	Pbo/PR48	Coma and sepsis	Found comatose on Day 40; died on Day 43
After Week 12				
104-010003	51 year old female	T12/PR	Trauma due to car accident	323 days after completing T, 22 days after completing PR
106-128006	52 year old male	Pbo24/PR48	Small cell lung cancer	Diagnosed day 39; subject died ~day 350 (261 days after therapy stopped due

				to non-response)
108-143005	56 year old male	Pbo/PR48	Suicide (self-inflicted GSW)	96 days after completing Pbo while on PR
108-140006	49 year old female	T12/PR	Suicide (self-inflicted GSW)	396 days after completing T
108-160002	57 year old male	T8/PR	Unknown-being treated with oseltamivir for flu at time of death	403 days after discontinuing T for rash and PR for anemia
108-311009	37 year old female	T12/PR	Progressive liver failure, possible pneumonia	295 days after completing T
111-132010	30 year old male	T12/PR24 (eRVR)	Head trauma	277 days after completing T
216-0803	59 year old male	T(DS)/PR48	Bronchopulmonary carcinoma (60-80 pack-years of tobacco smoking)	138 days after completing T
216-0631	48 year old female	Pbo/PR48	Acute respiratory distress syndrome, cholecystitis	During follow-up; 324 days after completing Pbo and 108 days after completing PR
Mitsubishi non-IND study	62 year old male	T12/PR	Sepsis, delirium, pulmonary embolism	9 days after completing T; Study day 82

Non-IND Study: This was 62-year-old male, prior relapser, treated with T/PR. On day 8 day the subject experienced a serious rash. On day 72 day he had anemia, severe malaise, chills and impaired appetite; telaprevir was discontinued. He was also being treated for urinary sepsis during this time. The subject recovered and 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. He was forcibly paced in bed and treated with diazepam and haloperidol; PR were discontinued. On day 82, the subject had chest pain and dyspnea and went into cardiopulmonary arrest and was resuscitated. A thoracoabdominal CT scan with contrast revealed clots in the right main pulmonary artery and the left superior pulmonary artery. An inferior vena cava filter was placed, and the clots were crushed and aspirated. However, the subject's blood pressure severely decreased and he died.

Safety Update: A safety update covering the period from 17 July 2010 through 31 October 2010 reported 1 additional death that occurred in a 69 year old male subject with a history of hypertension. The subject experienced a myocardial infarct secondary to LAD disease 5 days after last dose of telaprevir, and he died 42 days after the last dose of telaprevir.

Reviewer Comment: No causal relationship could be made for 7/8 deaths in telaprevir recipients. It is unclear if the death due to pulmonary embolism could be attributable to telaprevir.

7.3.2 Nonfatal Serious Adverse Events

Across the Phase 2 and 3 trials, ~11% of telaprevir-treated subjects experienced nonfatal SAEs. Skin disorders, such as rash and pruritis, and anemia were the most frequent SAEs observed during the telaprevir dosing periods. There were no differences in frequency or type of SAEs observed between treatment naïve and experienced subjects.

- **Phase 2**

In Phase 2 trials 11% (95/872) of subjects treated with a telaprevir-containing regimen reported SAEs compared to 8% (21/271) in control regimens. Among telaprevir recipients, the majority of SAEs were reported within the telaprevir dosing period. The most frequently reported SAEs regardless of relatedness to telaprevir were: skin disorders (19%) anemia (19%), pancreatitis (5%), and eye disorders (3%).

Other events occurred in no more than 1-2 subjects. SAEs for which a causal relationship could not be determined, but telaprevir may have been a contributing factor, included mostly gastrointestinal events such as erosive gastritis, cholecystitis, acute diverticulitis, and acute bowel obstruction. There was also one case of necrotizing fasciitis, and one case of renal failure possibly due to multiple recurrent urinary tract infections.

Narratives for four cases of acute pancreatitis were reviewed. Three subjects were receiving telaprevir at the time of the event. In one case, the triglyceride levels had increased to >1900 while in another two only amylase and lipase levels were significantly increased. Two subjects had concurrent cholelithiasis. All subjects recovered.

In Study 107, there was one SAE of drug rash with eosinophilia and systemic symptoms (DRESS) that was reported with onset 3 days after the final dose of telaprevir; however the onset of preceding adverse events of rash and pruritus were reported as 2 and 12 days before the final dose of telaprevir, respectively. The investigator reported this event as related to treatment with telaprevir, and not related to PR.

Events occurring well beyond the telaprevir dosing period or where a conclusion could be reached that the event was not related to telaprevir included (subjects were receiving PR only): B-cell lymphoma, ruptured cerebral aneurysm, alcohol abuse, suicidal ideation, bursitis and costochondritis, headache, angina, and hypertension, gastroenteritis, adrenal disorder, bronchitis, ischemic colitis, non-cardiac chest pain, depression, furuncle, lumbar radiculopathy, and an incisional hernia.

In Pbo/PR48 subjects SAEs included, headache, syncope, sinusitis, back pain, pneumonia, dehydration with renal tubular acidosis, anemia with acute renal failure, lung cancer, decubitus ulcer, depression, dehydration, and a hand hematoma, anxiety, anemia, lymphadenitis/pancytopenia, pneumonia, and deafness.

Reviewer Comment: Pancreatitis associated with peginterferon use is typically due to increased triglyceride levels is a known and labeled toxicity of peginterferon, so it was not possible to determine the contribution of telaprevir to these events. Further, confounding co-morbidities such as dehydration and gall stones appeared to be contributing factors.

- **Phase 3**

In the Phase 3 trials, 10% (180/1797) of subjects who received telaprevir experienced SAEs compared to 6% (28/493) of those treated with Pbo/PR48. Of these, 62% (111/180) of T subjects and 11 (39%) of Pbo/PR subjects had SAEs during the T/Pbo dosing periods. The most frequently reported SAEs during the telaprevir dosing period were anemia (35%, 39/111) and skin disorders (15%, 17/111).

Skin disorders included all types of rash with and without pruritis, toxic skin eruption, erythema multiforme, and Stevens Johnson Syndrome.

In Study 108, 86% of SAEs occurred between baseline and Week 8 and were balanced between the two telaprevir regimens. Between Weeks 8-12 there were an additional 3 SAEs of anemia in the T12 group; likely due to the extended duration of telaprevir.

Other SAEs for which a causal relationship to telaprevir could not be completely ruled out included events of: eye disorders (retinopathy, retinal hemorrhage and papilloedema), acute pancreatitis, acute renal failure, lymphopenia, dehydration secondary to nausea and vomiting, viral and non-viral gastroenteritis, nausea, pneumonia, hypotension, vertigo, pancytopenia, pericarditis, non-cardiac chest pain, syncope, eczema, and dyspnea. Each event occurred in no more than 4 subjects.

Based on review of the events, it was possible that the events of eye disorders, acute renal failure, pancytopenia, and pancreatitis may have some attribution to telaprevir, but there were multiple confounding factors that preclude a straightforward causality assessment. For example, all subjects were also receiving PR at the time the events were reported, and all of these events are known (labeled) to be related to PR.

Other SAEs not likely related to telaprevir or that occurred beyond the telaprevir dosing period (while subject was receiving PR alone or during the off-therapy follow-up period) included individual cases of: throat cancer, gastric cancer, bronchial cancer, multiple drug overdose, other substance abuse, H pylori gastritis, animal scratch infection, acute alcohol poisoning, joint dislocation (hip), change in mental status, sinusitis, vertigo, common bile duct stone, gastroenteritis, acute myocardial infarction, non-cardiac chest pain, hyper-echoic liver lesion (possibly HCC), community acquired pneumonia, cryptogenic organizing pneumonia, and interstitial lung disease.

SAEs reported by Pbo/PR recipients during the Pbo dosing period were either unrelated to study medication or consistent with the known toxicity profiles of PR, and included such events as

anemia, acute renal failure, psychiatric events (amnesia, anxiety, insomnia, panic attack), blurred vision, convulsions, neutropenia, leucopenia, cryoglobulinemia, ischemic colitis, and diarrhea.

- **Safety Update**

The Safety Update included 6 subjects treated with telaprevir who experienced SAEs: myocardial infarction (also a death), three events of anemia, one event of MRSA with facial cellulitis, and one event of depression.

7.3.3 Dropouts and/or Discontinuations

Throughout the development program, discontinuations due to adverse events from regimens containing telaprevir occurred more frequently compared to regimens containing Peg-IFN/RBV alone. Between 8-14% of subjects treated in the Phase 2 and 3 trials with a telaprevir-containing regimen discontinued telaprevir due to adverse events compared to ~3% for Pbo/PR regimens. The most common events leading to discontinuation of telaprevir were rash, pruritis, anemia, and fatigue.

- **Phase 2**

Twelve percent of subjects discontinued a telaprevir-containing regimen in Phase 2 trials due to an adverse event compared to 5% from Pbo/PR48 arms. Most subjects who discontinued from a telaprevir-containing regimen did so within the first 12 weeks of dosing.

Adverse events of rash, pruritis, anemia and fatigue accounted for the majority of discontinuations during the 12 week T/Pbo dosing period. Most of the events leading to discontinuation were also reported as SAEs (60%). Other events leading to study drug discontinuation were generally comparable between the telaprevir-containing regimens, and could have been attributable to PR.

- **Phase 3**

Overall 14% (249/1797) of subjects discontinued telaprevir due to adverse events compared to 7/493 (1%) subjects who discontinued in Pbo/PR groups. Anemia (22%), skin disorders (20%), fatigue (6%), followed by nausea (4%) and vomiting (4%) were the most frequent events leading to discontinuation of telaprevir. Also, four subjects discontinued telaprevir due to ano-rectal events (proctalgia/anorectal discomfort, hemorrhoids, rectal bleeding).

Events leading to discontinuation in Pbo/PR included: rash, fatigue, nausea, myalgia, headache, neutropenia, coma, depressed mood, and attention disturbance. No subjects discontinued Pbo/PR due to anemia.

In Study 108, 75% of discontinuations of telaprevir occurred between baseline and Week 8. Between Weeks 8 and 12, 4 additional subjects discontinued from the T8 group compared to 15

from the T12 group. The additional events in the T12 group were skin disorders (10), anemia (4) and nausea (1); this difference was again likely due to exposure to the additional 4 weeks of telaprevir.

In Study 111, more subjects discontinued due to adverse events in the eRVR T12/PR48 (20, 12%) and no eRVR T12/PR48 (11, 9%) groups compared to the eRVR T12/PR24 group (1 subject, 0.6%); this appeared attributable to the longer duration of Peg-IFN/RBV exposure.

- **Safety Update**

One subject in Study 110 (HIV/HCV co-infected) discontinued telaprevir due to jaundice on study day 3. This was a 44 year old female who on day 1 of telaprevir dosing was found to have a total bilirubin of 50 μmol/L, indirect bilirubin 41 μmol/L and direct bilirubin of 9 μmol/L. Concomitant medications included peginterferon, ribavirin, ritonavir, emtricitabine, tenofovir, and atazanavir. On day 2, she presented with Grade 2 nausea and Grade 1 dizziness, malaise, and occasional vomiting. On day 3, she had Grade 3 jaundice. On day 8, total bilirubin was 182 μmol/L, direct bilirubin was 7 μmol/L, and indirect bilirubin was 175 μmol/L; AST and ALT were within normal limits. On day 9, the malaise resolved. On day 23 T/Pbo dosing was discontinued due to jaundice; no action was taken towards PR. Laboratory results showed that the ALT was 19 U/L, AST was 19 U/L, total bilirubin was 87 μmol/L, direct bilirubin level 7 μmol/L, and indirect bilirubin was 80 μmol/L. On day 25, dizziness, nausea, and occasional vomiting resolved. On day 30, the jaundice resolved. On day 31, laboratory results showed ALT was 29 U/L, AST was 29 U/L, total bilirubin was 68 μmol/L, direct bilirubin was 7 μmol/L, and indirect bilirubin was 61 μmol/L. On day 58, ALT was 26 U/L, AST was 30 U/L, total bilirubin 31 μmol/L, direct bilirubin was 7 μmol/L, and indirect bilirubin was 24 μmol/L.

Reviewer Comment: A causal relationship with telaprevir cannot be completely ruled out. However, this case is confounded by concomitant use of multiple drugs known to cause increases in bilirubin levels, malaise, dizziness, nausea, vomiting and clinical jaundice.

7.3.4 Significant Adverse Events

Life-Threatening Events: There were 12 life-threatening events reported; 10 occurred in telaprevir subjects. Of the events, it is possible that telaprevir contributed to one event of panctytopenia and one of thrombocytopenia.

Events in telaprevir subjects included:

- Squamous cell carcinoma of the cervix that was diagnosed 166 days after telaprevir dosing was completed
- An event of SJS 48 days after telaprevir dosing completed; subject was receiving PR at time of event.
- Splenic laceration secondary to a MVA during the telaprevir dosing period,

- Acute Myocardial Infarction 7 days after completion of telaprevir in a subject with history of hypertension and diabetes (subject did not have anemia).
- Supraventricular tachycardia and pulmonary embolism 280 days after completing telaprevir dosing.
- Pancytopenia with febrile neutropenia was reported on study day 29; all study medications were discontinued and the neutropenia resolved (see Section 7.4.2 below).
- On day 93 a subject presented with a pancreatic mass and was diagnosed with gastric carcinoma.
- A heroin overdose on day 6; the subject completed T/PR dosing per protocol and achieved a SVR.
- On day 85 a subject was diagnosed with bronchial carcinoma; the subject discontinued all study medications to start chemotherapy.
- On day 67 a subject was admitted to hospital with epistaxis, purpura, and hepatorrhagia; platelet count was 10,000/mm^3. All study medications were discontinued and the subject was lost to follow-up (see Section 7.4.2 below).

The 2 life-threatening events that occurred in Pbo/PR48 recipients included:

- Acute appendicitis 74 days after Pbo dosing was completed.
- Death due to coma and sepsis; on Day 40 the subject was found comatose with evidence of severe diarrhea; blood cultures were positive for Staphylococcus aureus, treatment was initiated but the subject died and no source of the infection was identified.

Dose Interruptions: Interruptions of telaprevir for more than 7 days were not allowed and these events were considered protocol violations. Dose interruptions were permitted only for PR.

The incidence of adverse events that led to interruption of telaprevir or Pbo in Studies 108 and 111 was 18/1267 (1%) in T/PR groups and 7/493 (2%) in the Pbo/PR48 groups. In Study C216, dose modifications of telaprevir were prohibited, so no data on telaprevir was collected. Peg-IFN was interrupted due to an adverse event in 10 (2%) of telaprevir-treated subjects compared to 0 in the Pbo/PR group; RBV was temporarily interrupted in 36 (7%) of telaprevir and 2 (1%) of Pbo subjects.

Anemia, gastrointestinal events (nausea, proctalgia, viral gastroenteritis, stomach discomfort), cough or fatigue were the adverse events that led to interruption of telaprevir. The most common reasons for dose interruptions of Peg-IFN were neutropenia or thrombocytopenia, and for RBV it was anemia.

Dose Reductions: Dose reductions of telaprevir were not allowed in the Phase 3 trials; however, 9 subjects had adverse events (gastrointestinal disorders; nausea and vomiting) that led to a reduction of telaprevir.

The incidence of adverse events that led to reduction of Peg-IFN was similar in the 3 treatment groups: 10% (179/1797) subjects in the T/PR groups and 48 (10%) subjects in the Pbo/PR48

groups. Neutropenia was the most common event, followed by anemia, thromobocytopenia, and fatigue were the most frequent reasons leading to a dose reduction of Peg-IFN.

Dose reductions of RBV were higher in T/PR groups than Pbo/PR48 groups: 525/1797 (30%) subjects in the T/PR groups and 63/493 (13%) subjects in the Pbo/PR48 groups. Anemia was the most frequently reported adverse event that led to dose reduction of RBV. Other reasons for RBV dose reductions included fatigue, and rash/pruritis.

7.3.5 Submission Specific Primary Safety Concerns

Through the course of development, skin disorders (rash/pruritis), anemia emerged as the two primary safety concerns related to telaprevir. These events were further analyzed with consideration of relevance to product labeling.

Skin Disorders

Skin disorders (primarily rash and/or pruritis) were reported in 56% of subjects treated with telaprevir compared to 32% of Pbo/PR recipients. The majority of rash and prutitis events were mild to moderate in severity. However, more subjects treated with telaprevir had ≥Grade 3 rash events (3% versus 1%), SAEs (1% versus <1%), and had treatment limiting events (6% versus <1%) compared to those treated with Pbo/PR48. Telaprevir-related rash occurred early (median time to onset 25 days) and was often pruritic. The rash appeared maculopapular and papular-lichenoid, with excematous components. Histologically, rashes appeared as spongiform dermatitis with predominantly lymphocytic or eosinophilic perivascular infiltration. Less than 1% of subjects experienced suspected Severe Cutaneous Adverse Reaction (SCAR)such as SJS or DRESS. However, not all occurred during treatment with telaprevir, none were life-threatening type 1 hypersensitivity/anaphylactic reactions, and the rash did not appear to be drug induced hypersensitivity. Five percent of subjects received treatment with oral antihistamines, 4% with topical and 3% with systemic corticosteroids.

- **Background**

Interferon/RBV are associated with various skin disorders including, but not limited to rash, dermatitis, and pruritis, with incidences reported to range from 13% to 23%. The frequency and severity of rash and pruritis were substantially increased with co-administration of T.

During the conduct of the major Phase 2 trials, the Applicant became aware of several reports of serious and non-serious rash events, some requiring treatment with corticosteroids and/or leading to study drug discontinuation. The Applicant, in conjunction with DAVP, developed a comprehensive rash monitoring and management plan for use in ongoing and future trials. Rash and pruritis have continued to occur throughout development with the frequency of and severity through the first 12 weeks of treatment being consistently higher among subjects receiving T compared to those receiving Pbo/PR.

Because some subjects experienced more than 1 type of rash event, and because investigators described rash using different verbatim terms at different times in the same subject, the Applicant undertook a comprehensive analysis of rash/pruritis events using a Special Search Category (SSC) to ensure that all events were tabulated and analyzed (see Appendix 9.4 for full list of terms).

Additionally, the Applicant devised an Event of Special Interest (ESI) category. This category captured clinical events for which the Applicant implemented special reporting procedures for surveillance, monitoring, and management purposes. All skin reactions involving rash or rash-like events that occurred during the study and met any of the following three criteria were considered to be ESIs:

- Grade 1 and 2 rash SSC that led to discontinuation of at least 1 study drug
- Grade 3 (severe) rash SSC[1]
- Rash SSC events which met the criteria of an SAE

Also, the Applicant convened a Dermatology Expert Panel (DEP) to evaluate ESI and other SAE and non-SAE rash events that occurred in T trials. The CVs of the panel members were reviewed and they were very qualified to conduct such an evaluation.

- **Phase 2**

Rash SSC events occurred in 55-70% of telaprevir-treated subjects, compared to 20-30% of Pbo/PR- treated subjects during the T/Pbo dosing periods. Also, 57% of telaprevir-treated subjects versus 23% of Pbo/PR-treated subjects experienced pruritis during the same time periods. The most common events included rash, pruritis, dry skin and alopecia.

The median time to onset of any rash event was ~10 days (range: 1-85 days) in the combined telaprevir groups compared to 26 days (range: 2-81 days) in the combined Pbo/PR48 groups. The median time from discontinuation due to rash SSC to resolution of rash SSC was 15 days (range: 3-57).

The majority of rash events were mild or moderate in severity, ~7% were graded as severe, ~1% were SAEs, and ~7% of subjects discontinued. Thirty four subjects received treatment with systemic steroidal medications for their rash. All events in the Pbo/PR groups were mild, and there were no SAEs or discontinuations due to rash.

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1 **Grade 3 (Severe)** Defined as generalized rash involving over 50% of the body surface; or rash presenting with any of the following characteristics: rash with vesicles or bullae, superficial ulceration of mucous membranes, epidermal detachment (full thickness epidermal necrosis and separation of epidermis from underlying dermis), atypical or typical target lesions, palpable purpura/non-blanching erythema, appearance of significant systemic signs or symptoms that were new and were considered related to the onset and/or progression of rash, any events of Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug-Related Eosinophilia with Systemic Symptoms (DRESS), or Erythema Multiforme (EM).

Of note, in the T24 arm of Study 106 the incidence or rash events was approximately 5% higher than in the T12 arm, likely due to the longer duration administration of T. Further, the frequency of skin disorders was lowest in the RBV-sparing arm.

Finally, one case of SJS was reported in the Phase 2 trials, but was not attributable to telaprevir because it occurred after telaprevir dosing had been completed. One case of DRESS was reported in a subject treated with telaprevir in Study 107 as a SAE (see Section 7.3.2).

- **Phase 3**

During the T/Pbo dosing period, the frequency of all grade Rash SSC events among all subjects treated with telaprevir was 56% compared to 32% in the combined PboPR48 groups. More subjects treated with telaprevir experienced severe rash, serious adverse events, and discontinuations compared to Pbo/PR; time to onset was also faster in the telaprevir-treated groups (median 25 versus 40 days). Rash and/or pruritis were concomitantly reported by 72% of subjects treated with telaprevir. Additionally, ~44% of telaprevir-treated subjects compared to 30% of Pbo/PR recipients had pruritis without rash.

Treatment Naïve: The frequency of Rash SSC, Rash ESI and Pruritis SSC are shown in Table 21. There were no differences between the T12 arms of studies 108 and 111, so those data were pooled.

The median time to onset of any rash was ~16 days for telaprevir compared to 29 days for Pbo/PR. In general the incidence of Rash SSC events was highest from baseline through Week 4 and then decreased gradually until Week 16. After Week 16, the prevalence of Rash SSC events was lower and comparable across T/PR and Pbo/PR treatment groups.

Specific to Study 108, however, the incidence of Rash SSC and ESI was balanced between the two telaprevir groups during the first 8 weeks of dosing. Between Weeks 8-12, the incidence of Grade 3 rash was increased in the T12 group (7 additional events compared to 1 additional event); all these events were also considered ESI. Also, from approximately Week 4 through Week 8, discontinuation due to rash SSC was higher in the T8/PR group than in the T12/PR group, but after Week 8, discontinuations were higher in the T12/PR group (n=6) than the T8/PR group (n=2) and continued through Week 12. Finally, the incidence of pruritis was approximately 5% higher in the T12 group compared to the T8 group: 51% compared to 46%. These differences were likely due to the additional 4 weeks of exposure to telaprevir.

Among telaprevir-treated subjects, 11 had a $\geq$Grade 3 Pruritus SSC event, 1 was an SAE, 10 discontinued telaprevir, and 3 discontinued the entire treatment regimen. One subject in the Pbo/PR48 group had a Pruritus SSC event that led to discontinuation of all study drugs. During the T/Pbo dosing period, the median time to onset of a Pruritus SSC event was 21 days (range: 1 to 86 days) for T/PR groups, and 16 days (range: 1 to 85 days) in the Pbo/PR48 group.

During the T/Pbo dosing period, the incidence of Rash and/or Pruritus SSC was 74% in the combined T/PR groups compared to 50% in the Pbo/PR48 group.

No trends were noted for the incidence of Rash SSC events, Rash ESI events or Pruritus SSC events by demographic or disease characteristics.

Table 21 Rash events during T/Pbo dosing period, treatment naïve subjects

	T8 N=364	**T12 N=903**	**Pbo/PR48 N=361**
Any Rash SSC event	193 (53)	544 (60)	132 (32)
≥Grade 3 Rash SSC	11 (3)	38 (4)	2 (<1)
≥1 Serious Adverse Event	4 (<1)	4 (<1)	0
Rash ESI	21 (6)	81 (9)	1 (<1)
Pruritis SSC Event	156 (46)	461 (51)	112 (31)

Treatment Experienced: The incidence of Rash SSC event was comparable between the two telaprevir-containing arms and between categories of prior response; so the data were pooled(see Table 22). Time to onset was ~22 days after the start of telaprevir.

In the combined telaprevir group, 53% (279/530) compared to 27% (36/132) of Pbo/PR subjects experienced a Pruritis SSC during the T/Pbo dosing period. In the telaprevir groups, 1 was an SAE, 7 were ≥Grade 3 in severity, and 4 subjects discontinued telaprevir. None of the events in the Pbo group was a SAE, ≥Grade 3 or led to discontinuation. Rash and/or Pruritus SSC events were reported in 72% of subjects in the pooled T/PR48 group and 47% of the subjects in the Pbo/PR48 group.

Rash SSC events occurred more frequently in telaprevir-treated subjects from North America than from Europe (56% versus 46%), subjects with cirrhosis compared to no cirrhosis (62% versus 48%), and Caucasians compared to Blacks/African Americans (52% versus 21%). Pruritus SSC events occurred more frequently in males than females (55% versus 48%), in subjects from Europe than North America (55% versus 42%) and Caucasians (53%) compared to Blacks/African Americans (42%).

Table 22 Rash events during T/Pbo dosing period, Study C216

N (%)	**Combined T/PR N=530**	**Pbo/PR48 N=132**
Any Rash SSC event	272 (51)	36 (27)
≥Grade 3 Rash SSC	17 (3)	0
≥1 Serious Adverse Event	5 (1)	0
Rash ESI	28 (5)	0
Pruritis SSC	279 (53)	36 (27)

Rash Management

Management of rash ESI was to follow generally accepted medical standards. Additionally, management involved discontinuation of telaprevir (dose reductions were not allowed), reductions of RBV, discontinuation of all study medications and use of oral antihistamines, topical steroids (limited to up to 2 weeks of continuous/regular use and limited to use on up to 50% of the body surface) or systemic corticosteroids (all study drugs were to be discontinued if a subject received systemic corticosteroids) (see Tables 23 and 24).

Table 23 Rash management, treatment naïve subjects

	T8 N=364	**T12 N=903**	**Pbo/PR48 N=361**
T/Pbo discontinuation	20 (6)	88 (10)	1 (<1)
Discontinuation of all study medications	2 (<1)	11 (1)	0
Systemic corticosteroids	2 (<1)	31 (3)	1 (<1)
Topical steroids	13 (4)	37 (4)	1 (<1)
Oral antihistamines	14 (4)	48 (5)	2 (<1)

Table 24 Rash management, treatment-experienced subjects

N (%)	**Combined T/PR N=530**	**Pbo/PR48 N=132**
T/Pbo discontinuation	22 (4)	0
Discontinuation of all study medications	2 (<1)	0
Systemic corticosteroids	14 (3)	4 (3)
Topical steroids	27 (5)	7 (5)
Oral antihistamines	25 (5)	7 (5)

Dermatology Expert Panel Assessment

A total of 221 rash cases were reviewed by the DEP. The majority (208 of 221; 94%) was reported from subjects receiving a telaprevir-based regimen; the remaining 13 (6%) cases were reported from subjects receiving a non-telaprevir-based regimen. The distribution of cases was: Phase 2 and 3 (n=171; 165 telaprevir, 6 non-telaprevir), Phase 1 (n=10), and non-IND studies (n=40).

- Of the 165 telaprevir-treated subjects who had photographs, the DEP was able to assess 87; rash morphology contained mostly eczematous, maculopapular, and papular-lichenoid components: 83 (95%), 23 (26%), 6 (7%), respectively.

- There were 83 cases in telaprevir recipients for which the DEP could assess body surface area (BSA) involvement. There was one Grade 1 case, 29 Grade 2 cases, and 53 Grade 3 cases. Seventy-two of the 83 cases (87%) had ≤30% BSA involvement, 9 had >30 to 50%, and 2 had >50%. This differed from the assessment of investigators who judged most rashes to have >50% BSA involvement.

- Histopathology showed spongiform dermatitis, predominantly lymphocytic or eosinophilic perivascular infiltration changes. There were no biopsies suggestive of vasculitis.

- The DEP identified 3 cases suggestive of SJS and 11 cases suggestive of DRESS. Investigators reported only 6 cases of severe cutaneous adverse reactions (SCAR). The DEP assessed 4 as suspect SCAR event, only 3 occurred during the telaprevir dosing period, and there were no deaths. The DEP identified 2 additional cases suggestive of SJS (1 probable and 1 possible) and 9 cases suggestive of DRESS (1 probable, 8 possible). The cases suggestive of DRESS predominantly had fever, rash and eosinophilia; seven required hospitalization. Of the 11 suspected DRESS cases, 9 did not have systemic organ involvement while organ involvement was unconfirmed in two.

- Pruritus as a symptom of rash was noted by the investigator in 136 (95%) cases, absent in 5 (3%) cases, and not reported in 2 (1%). Pruritis was present in the 3 rash cases in subjects receiving a non-telaprevir-based regimen.

- Ninety-six percent (137) of cases among telaprevir-treated subjects resolved. Of the remaining 6 cases, 5 subjects withdrew consent and 1 case was ongoing; therefore resolution information was not available. All 3 (100%) rash cases reported in subjects receiving a non-telaprevir based regimen resolved.

The DEP concluded that rashes were similar clinically and histologically to those reported with Peg-IFN/RBV, most involved <30% BSA, and were primarily pruritic and eczematous; though some had an additional maculopapular component. Histologic examination showed that most rashes had a spongiotic pattern with lymphocytic perivascular infiltration, which correlated with the eczematous appearance, but no common or dominant pattern could be identified. However, none of the biopsies were suggestive of vasculitis.

Mechanism Assessment

The mechanism of the telaprevir-related rash remains unknown. To further attempt to elucidate the mechanism of rash, the Applicant conducted a variety of nonclinical and clinical investigations. The results of these investigations are summarized:

- The Applicant conducted a study to explore a potential association of 143 *HLA* alleles with the occurrence of rash in subjects treated with T/PR. Although this was a relatively small sample, a trend for HLA-DQB1*0202 was observed. Strong associations for any *HLA* allele with mild, moderate or severe rash could not be identified (See Pharmacogenomics Review).

- Telaprevir was evaluated in a murine local lymph node assay and concluded to be negative. VRT-126032 and VRT-841125 (metabolite M11) were evaluated and were

positive for skin sensitizing potential. However, the relationship of this metabolite to incidence of rash remains unlikely based on the relatively low circulating levels observed in humans and the nature of observed rash.

- No relationship was found between the occurrence and severity of rash and the exposure (AUC) to telaprevir or Peg-IFN/RBV concentrations.

- Pyrazinoic acid (PZA) is a major metabolite of telaprevir and may have the potential to contribute to rash and pruritis. PZA is a structural analog of niacin which also can cause these effects. In a small substudy of one Phase 2 trial, it appeared PZA was present at higher levels in subjects with severe rash than in subjects without rash, but the number of subjects was small and variation between subjects was high. However, PZA-associated rash typically appears differently, and it is usually detected in much higher concentrations in plasma following pyrazinamide administration compared with telaprevir administration. Thus, it is unlikely that this metabolite is a major causative contributor.

Division of Dermatologic and Dental Products Consult

A consult from the Division of Dermatologic and Dental Products was requested to assess the DEP's findings and conclusions. The Dermatology consultant raised the following issues:

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

- Most ESI (95%) had an eczematous *component* (emphasis added). However, it is not clear to the consultant that that necessarily translates to "typically" eczematous rash." Per the DEP review, 60% of subjects had at least 2 assessable morphological components to their rashes (47% of whom had 3 components assessable). The consultant also agrees that an eczematous reaction pattern was a common feature and that some eruptions had mixed morphologies. We do not believe that the cutaneous eruption(s) has been sufficiently characterized to have clinicians limit their focus and concern to "severe rash," described as "primarily eczematous, pruritic and involves more than 50% body surface area."

- Investigators estimated the extent of BSA to be greater than did the DEP. Thus, it is possible that some ESI categorized by investigators as Grade 3 (severe) may have been of lesser severity, if investigators overestimated the extent of BSA involvement to be > 50% and graded the event based solely on this criterion as was permitted by the protocol.

Thus, it is not clear that inclusion of a % BSA involvement would necessarily be useful to prescribers.

- A possible limitation of the DEP review is that it may have been biased towards characterizing only the more severe events (reflective of the definition of ESI which constituted the primary database). However, the extent to which the conclusions about the eruptions from the DEP review might apply to the broader population of telaprevir-reated subjects who experience cutaneous eruptions is unclear.

- When investigators suspected SCAR, the DEP concordance with those assessments was 67%. However, when the DEP suspected SCAR, investigators did not suspect the same in 69% of these subjects.

- Not all severe rashes met the criteria for SCAR events, as SCAR has implications for morbidity and mortality.

- **Anemia**

Subjects receiving telaprevir had a higher frequency of anemia (36% versus 15%), a higher frequency of hemoglobin reductions to ≥Grade 3 (<8.9 g/dL or >4.5 g/dL decrease from baseline) levels (55% versus 27%), had more anemia-related SAEs (2.5% versus <1%), and had a higher frequency of anemia-related discontinuations (3% versus <1%). Time to onset of any anemia was also faster among telaprevir-treated subjects (median 11 days versus median 29 days). In most subjects treated with telaprevir, hemoglobin values decreased steeply through Weeks 4-8, were generally stable between Week 8 and Week 20, and then began to rise to levels similar or higher to those of subjects in Pbo/PR48 groups.

Overall, telaprevir increased the decline in hemoglobin levels ~1.0-1.5 g/dL greater compared to Pbo/PR-treated subjects. Across Phase 3, 801/1797 (45%) of telaprevir and 134/493 (27%) of Pbo/PR subjects had hemoglobin levels ≤10 g/dL, and 14% (245/1797) and 5% (25/493) had levels ≤8.5 g/dL.

- **Background**

The most problematic side effect of RBV is reversible hemolytic anemia. While the etiology of anemia is multifactorial, the RBV dose–dependent hemolytic anemia is due to RBV accumulation in erythrocytes, where it is phosphorylated; depleting adenosine triphosphate (ATP) reserves, which ultimately leads to senescence and erythrophagocytic removal. RBV-induced hemolytic anemia typically appears within the first two to four weeks of dosing and is manifest by a 2-5 g/dL decrease in Hgb levels. The anemia can affect patients' quality of life, can lead to constitutional symptoms (fatigue), and can worsen underlying cardiac disease. Management is typically through dose reductions, temporary or permanent discontinuation, and sometimes use of growth factors such as erythropoeitin.

The addition of interferon also suppresses red blood cell (RBC) production, and the anemia seen with the combination of Peg-IFN and RBV therapy can lead to RBV dose reductions or discontinuations, which can result in a lower chance of SVR.

In preclinical studies, telaprevir demonstrated an effect on the hematopoietic system (decreased erythrocytic parameters and anemia accompanied by reticulocyte/bone marrow response). In clinical trials, lower reticulocyte counts combined with decreased hemoglobin levels observed in clinical studies suggests that telaprevir has an effect on blood cell production. A pharmacodynamic analysis suggested a relationship between the occurrence and severity of hemoglobin abnormalities during telaprevir dosing and three parameters: exposure (AUC) to telaprevir, Peg-IFN concentration at Week 4, and RBV concentration at Week 4.

- **Phase 2**

The frequency of anemia was approximately 30% in telaprevir-treated subjects; ~6% were classified as ≥Grade 3, ~10% had a shift in hemoglobin to <8.9 g/dL, and ~2% discontinued due to anemia. Overall, hemoglobin levels declined approximately ~1.0-1.5 g/dL greater in telaprevir-treated subjects compared to Pbo/PR-treated subjects.

The majority of anemia events occurred within the first 12 weeks of telaprevir dosing. In most subjects treated with telaprevir, hemoglobin values decreased most steeply through Week 4, were generally stable between Week 8 and Week 12, and by Weeks 16-18 had risen to levels similar or higher compared to those of subjects in Pbo/PR48 groups. The median time-to-onset of hemoglobin toxicity Grade ≥1 was ~41 days (range: 18; 86 days) compared to Pbo/PR48 ~64 days (range: 52; 85 days).

The frequency and severity of anemia was lowest (and comparable to control subjects) among subjects treated with RBV-sparing regimens.

- **Phase 3**

Across the Phase 3 trials, ~36% of telaprevir-treated subjects experienced an Anemia SSC event compared to 17% of Pbo/PR recipients. Treatment experienced subjects experienced a similar frequency of anemia SSC events, but more subjects had reductions in hemoglobin levels to ≥Grade 3 compared to naïve subjects.

In treatment naïve subjects, the greatest mean decrease from baseline occurred around Week 8 for the T8/PR group (-3 g/dL), Week 10 for the T12/PR groups (-4 g/dL), and Week 48 for the Pbo/PR48 groups (-3 g/dL). In treatment experienced subjects, the greatest mean decrease from baseline occurred later between Weeks 14-16 (-4.3 g/dL), for the combined telaprevir groups and Week 36 for Pbo/PR48 (-3.6 g/dL). In both populations, after completion of telaprevir dosing hemoglobin increased and by Week 20 (range; 16 to 24) the levels were comparable to those observed in the Pbo/PR48 group.

Forty-five percent (804/1797) of telaprevir- compared to 27% (134/493) of Pbo/PR48-treated subjects had absolute hemoglobin levels decrease to ≤10 g/dL during the trials. Corresponding proportions for subjects with hemoglobin levels ≤8.5 g/dL were 14% (247/1797) and 5% (23/493) for T/PR and Pbo/PR48, respectively.

Also, in Study 108, there were additional cases of anemia in the T12 group compared to the T8 group, but there was no difference in the severity of anemia. In experienced subjects, there were no clinically relevant differences between the two T12 regimens based on prior non-response categories.
Anemia occurred more often in:

- Females 52% compared to 28% in males
- Older subjects (>45 years of age) 40% compared to 23% for younger subjects
- Subjects with lower BMI (<30 kg/m^2) 35% compared to 31% for BMI ≥30 kg/m^2
- Subjects with cirrhosis 41% compared to 33% for those with less fibrosis

Tables 25 and 26 show the data for treatment naïve and experienced subjects for anemia-related events during the TPV/Pbo dosing period.

Table 25 Anemia events during T/Pbo dosing period, naïve subjects

	T8/PR N=364	**T12/PR N=903**	**Pbo/PR48 N=361**
Any Anemia SSC event	142 (39)	328 (36)	63 (18)
≥Grade 3 Anemia SSC event	25 (7)	46 (5)	2 (<1)
Serious Adverse Event	9 (3)	26 (3)	0
Hgb shift from baseline [1, 2,3]			
Shift to Grade 1	58 (16)	134 (15)	94 (26)
Shift to Grade 2	97 (27)	233 (26)	95 (26)
Shift to Grade 3	171 (47)	407 (45)	90 (25)
Shift to Grade 4	2 (<1)	13 (1)	0
Maximal ↑ reticulocyte	+2.4% (TW10)	+2.7% (TW4)	+3% (TW4)

1. DAIDS scale: Grade 1, 10.0–10.9 g/dL or any decrease of 2.5–3.4 g/dL; Grade 2, 9.0–9.9 g/dL or any decrease of 3.5-4.4 g/dL; Grade 3, 7.0–8.9 g/dL or any decrease ≥4.5 g/dL; and Grade 4, <7.0 g/dL.
2. Through Week 8 for T8 and Week 12 for T12 and Pbo/PR.
3. All subjects had normal Hgb levels (Grade 0) at baseline.

Table 26 Anemia events during T/Pbo dosing period, experienced subjects

	Pooled T/PR48 (n=530)	Pbo/PR48 (n=132)
Any Anemia SSC event	172 (32.5)	19 (14)
Anemia SSC events ≥Grade 3	34 (6)	1 (1)
Serious Adverse Events	10 (2)	1 (1)
Hgb shift from baseline[1,2,3]		
Shift to Grade 1	67 (13)	40 (30.5)
Shift to Grade 2	126 (24)	37 (28)
Shift to Grade 3	300 (57)	39 (30)
Shift to Grade 4	9 (2)	0
Maximal increase in reticulocytes	+1.64% (TW4)	+2.3% (TW6)

1. DAIDS scale: Grade 1, 10.0–10.9 g/dL or any decrease of 2.5–3.4 g/dL; Grade 2, 9.0–9.9 g/dL or any decrease of 3.5-4.4 g/dL; Grade 3, 7.0–8.9 g/dL or any decrease ≥4.5 g/dL; and Grade 4, <7.0 g/dL.
2. Through Week 12 for immediate start and Week 16 for delayed start.
3. All subjects had normal Hgb levels (Grade 0) at baseline.

- **Management of Anemia**

Management of anemia was to involve RBV dose reductions in accordance with the product labeling. If RBV had to be permanently discontinued for the management of anemia, T/Pbo were also to be discontinued. T/Pbo dose reductions were prohibited and once T/Pbo treatment was discontinued for the management of anemia or other telaprevir-related safety reason, it could not be restarted. The use of erythropoietin stimulating agents (ESAs) was generally prohibited during the Phase 3 trials.

Anemia was managed by discontinuation or modification of study drug(s), blood transfusions, ESAs, folic acid, iron oxide, other iron preparations, granulocyte stimulating factors, ondansetron hydrochloride, and methylprednisone sodium as concomitant medications.

Table 27 Management of Anemia, Phase 3 trials combined

	Combined TPV N=1797	Combined Pbo/PR N=493
TPV/Pbo discontinuation	76 (4)	2 (<1)
Reduction of RBV dose	420 (23)	49 (10)
Interruption of RBV	104 (6)	5 (1)
Discontinuation of RBV	39 (2)	2 (<1)
Discontinuation of all medications	24 (1)	2 (<1)
Blood transfusions	105 (6)	7 (1)
ESA use	24 (1)	4 (<1)

Among subjects who underwent a dose modification and/or interruption of RBV, 73% of naïve and 77% of experienced subjects achieved a SVR. RBV modifications, interruptions and discontinuations decreased SVR rates from ~75% to ~40% in treatment naïve and from ~65% to 20% in treatment experienced subjects. Of the subjects who received blood transfusions for anemia, 59% (62/105) achieved a SVR. Of the 24 subjects who received an ESA for anemia, 14 (58%) achieved a SVR.

- **Anemia-Associated Clinical Events**

The safety data base was reviewed for clinical events possibly associated with anemia, such as myocardial infarction, angina pectoris, dizziness, dyspnea, fatigue, and syncope.

- Three acute myocardial infarctions occurred, all in telaprevir-treated subjects. One subject was a 58 year old male who had an anterior myocardial infarction on study day 42; he did not have anemia, the event was not serious, no change was made to his study medications and he recovered and completed dosing. The second subject was a 52 year old male who on study day 38 complained of chest pain and was diagnosed with a myocardial infarction. At catheterization he was found to have 90% occlusion of this Right coronary artery and underwent a stenting procedure. He also did not have anemia at the time of the myocardial infarction. The event was considered serious, all study medications were discontinued, and he recovered without sequelae. The third case involved a 69 year old male subject with a history of hypertension. The subject experienced a myocardial infarct secondary to chronic LAD disease 5 days after last dose of telaprevir and he died 42 days after the last dose of telaprevir; this subject did not have anemia.

- Less than 1% of subjects had an event of angina (7 T/PR, 2 Pbo/PR). Of the telaprevir-treated subjects, all but one event occurred during the telaprevir dosing period, four subjects had anemia at the time of the angina event, one subject discontinued telaprevir, one subject discontinued all study medications due to anemia and neutropenia, and one underwent a RBV dose reduction for anemia. Of the Pbo/PR subjects, one had severe angina with moderate anemia on study day 26 and one had mild angina with mild anemia on study day 192 (this event was considered a SAE).

- Twenty-three (1%) subjects treated with T/PR compared to 3 (<1%) treated with Pbo/PR experienced an event of syncope; not all occurred during the telaprevir dosing period; most subjects did not have anemia at the time of the event.

- Approximately 10% of subjects in the pooled T/PR and Pbo/PR groups experienced dizziness. None were considered serious. Five subjects (4 T/PR and 1 Pbo/PR) discontinued due to dizziness; three of the telaprevir and the 1 Pbo/PR subject had dizziness and anemia at the same time.

- Dyspnea/exertional dyspnea was reported by 17% of T/PR and 16% of Pbo/PR-treated subjects. Only one event in a telaprevir subject was considered a SAE: dyspnea with orthostatic hypotension was reported on study day 59 (11 days prior to the onset of anemia); no change in study medication was made and the subject completed telaprevir dosing per protocol. In addition, 9 T/PR subjects compared to 1 Pbo/PR subject discontinued study medications due to dyspnea.

- Fatigue was reported somewhat more frequently in subjects treated with telaprevir: 55% (T/PR) compared to 50% (Pbo/PR). Thirty-two subjects discontinued due to fatigue: 30 from T/PR (2%) and 2 from Pbo/PR (<1%). There were no serious fatigue events.

Reviewer Comment: Not all events occurred in subjects with concomitant anemia. Overall there were no major differences between the incidence or severity of most of these events between telaprevir and PR.

AnoRectal Events

During the conduct of the Phase 2 trials, anorectal events were noted in greater frequencies than in Pbo/PR recipients. Telapevir and its metabolites are excreted nearly exclusively in the feces, and it was considered possible that one or more of these components were responsible for the reported anorectal symptoms. Since the Pbo tablets contain the same excipients as telaprevir tablets, it was unlikely that an excipient was responsible. To date, neither the risk factors nor the mechanism of these adverse events are known.

Again, the Applicant developed an Anorectal SSC that included the following terms: anal fissure, anal inflammation, anal pruritus, anorectal discomfort, hemorrhoids, painful defecation, perianal erythema, proctalgia, and rectal fissure.

- **Phase 2**

Across the Phase 2 studies, between 15-20% of subjects treated with telaprevir experienced an ano-rectal disorder, such as hemorrhoids, pruritis ani, proctalgia, anal inflammation, perianal erythema, or anal discomfort compared to 3% in Pbo/PR48 groups. Nearly all cases occurred during the telaprevir dosing period. The median time to onset of an Anorectal SSC was 11 days. Most events were mild or moderate and produced discomfort, but no SAEs were reported and no subjects discontinued treatment due to them.

- **Phase 3**

In the Phase 3 trials, 26% of subjects treated with telaprevir experienced Anorectal SSC events compared to 5% of Pbo/PR-treated subjects. The three most commonly reported Anorectal SSCs were hemorrhoids (12% telaprevir, 3% Pbo/PR), anorectal discomfort (11% telaprevir, 2% Pbo/PR) and anal pruritis (6% telaprevir, 1% Pbo/PR). Seventy-nine percent of events were considered possibly related to telaprevir, <0.1% were serious, <1% were ≥Grade 3, and <1% (7) discontinued telaprevir due to Anorectal SSC events (rectal hemorrhage, proctitis, anal fistula, and two cases each of anorectal discomfort and proctalgia).

Across T/PR groups, the incidence new Anorectal SSC events was the highest from baseline through Week 4 with a median time to onset of 9 days, and then decreased gradually until Week 16. The median duration was 57 days. Due to the delayed start of telaprevir in the T12(DS)/PR48 group of Study C216, the incidence from baseline through Week 4 was higher in the T12/PR48

group than in the T12(DS)/PR48 group and lower from Week 13 through Week 16 in the T12/PR48 group.

Eye Disorders

In Phase 2 trials a possible signal for excess eye disorders with telaprevir was observed. In Phase 3 trials, the frequency of eye disorders was 4% higher among subjects who received telaprevir, with more retina-related events. The frequency of SAEs and discontinuations were comparable at <1% in each group. It is not clear that eye disorders represent a significant safety signal for telaprevir: peginterferon is labeled for all the events that were reported, there were only small differences between telaprevir and PR, most cases were mild, and most resolved upon cessation of dosing.

- **Background**

Ophthalmologic disorders, including decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, and papilledema, may be induced or aggravated by interferon treatment, and are labeled events. The Peg-IFN labeling recommends that all patients receive an eye examination at baseline and those with preexisting ophthalmologic disorders should receive periodic ophthalmologic exams during treatment. Any patient who develops ocular symptoms should receive a prompt and complete eye examination. Peg-IFN treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.

- **Phase 2**

Between 17-32% of subjects treated with treated subjects experienced eye disorders during the T/Pbo dosing period compared to Pbo/PR48 (~18%). The most frequent eye disorders reported by telaprevir recipients were dry eye (15% versus 8%), blurred vision (5% versus 4%), photophobia (3% versus 1%) and asthenopia (4% T12/P12 group only). The majority of events occurred within the first 12 weeks of treatment, and >90% were considered mild or moderate in severity. Individual serious events included retinal hemorrhage, viitreous hemorrhage, scotoma and severe retinal infarction, and severe eye pain.

- **Phase 3**

Across the Phase 3 trials, the frequency of eye disorders was 314/1797 (17%) in telaprevir-treated compared to 63/493 (13%) in Pbo/PR-treated subjects. The most frequently reported events in telaprevir-treated and Pbo/PR-treated subjects, respectively, were blurred vision (6% vs. 5%), dry eye (2% vs. 2%), photophobia (2% vs. 1%), and eye pain (1% vs. 1%).

In addition, there were 40 events in 35 subjects involving the retina (e.g., retinopathy, retinal exudates, diabetic retinopathy, retinal hemorrhage, retinal edema, retinal degeneration, and retinal pallor): 33 (2%) subjects in T/PR and 2 (<1%) subjects in Pbo/PR subjects.

Four subjects had SAEs: 3 T/PR (retinal hemorrhage, retinopathy, and papilloedema) and 1 Pbo/PR (blurred vision). Less than 1% of subjects in each treatment group discontinued due to an eye disorder: 13 T/PR and 2 Pbo/PR subjects. The events leading to discontinuation from T/PR included: retinal exudates (4), diabetic retinopathy (1), photopsia (1), eye hemorrhage (1), hemorrhagic retinopathy (1), visual disturbance (1), retinopathy (1), blurred vision (2), and papilloedema (1). Asthenopia and retinal exudates were the two events in the Pbo/PR subjects.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse events reported in subjects treated with telaprevir (and possibly, probably or definitely related) included: anemia, skin disorders, anorectal disorders, eye disorders, fatigue and diarrhea.

INTEGRATED PHASE 1 AND 2

Adverse events that occurred with an incidence of ≥25% of telaprevir-treated subjects included fatigue (82%), nausea (65%), influenza-like illness (49%), headache (53%), pruritus (48%), insomnia (44%), diarrhea (42%), rash (41%), anemia (37%), injection site erythema (35%), and dizziness (28%). Of these, events that occurred at a ≥5% higher incidence in the T/PR groups than in the Pbo/PR groups were nausea (65% versus 29%), pruritus (48% versus 23%), diarrhea (42% versus 28%), rash (41% versus 27%), and anemia (37% versus 27%).
In Part A of Study 110 (HIV/HCV co-infection trial), one T12/PR48 subject had a severe adverse event of increased lipase and one Pbo/PR48 subject had a severe adverse event of neutropenia. One subject in the T12/PR48-Regimen 2 group experienced an SAE of anemia and chest pain that led to study drug discontinuation; the subject did not have a myocardial infarction and the events resolved shortly following discontinuation. Another subject in this group had an SAE of an unrelated groin infection on study day 31; he continued dosing with no change in study medications.

Nausea, dizziness, rash, pruritis, and anemia appeared to occur in more subjects who received telaprevir. Also, of note, 9/14 (64%) subjects who received telaprevir had a shift to ≥Grade 2 post-baseline uric acid level.

In study C208 (comparison of q8h versus q12h dosing) a difference in incidence between the pooled q8h and q12h groups was observed for nausea (39% versus 49%), vomiting (15% versus 24%), diarrhea (23% versus 32%) and decreased appetite (15% versus 27%). Further, telaprevir was permanently discontinued due an adverse event in 13% of subjects in the pooled q8h group and in 18% subjects in the pooled q12h group. The most frequently reported events leading to discontinuation of telaprevir were rash, pruritus, anemia, and vomiting. These data suggested that dosing with the higher dose and less frequent telaprevir regimen was associated with increased rates of adverse events; these findings will be further evaluated in Study C211 which is comparing 1125 mg q12h versus 750 mg q8h in a larger cohort of subjects.

PHASE 3

Adverse events occurring during the T/Pbo dosing period at a rate of ≥10% are listed in Table 28. In Study 108, adverse events were captured during the first 12 weeks and in Study C216 they were captured during the first 16 weeks to account for the T(DS) arm.

During the T/Pbo treatment period, adverse events that occurred at a ≥5% higher incidence in T/PR groups than in Pbo/PR48 groups were fatigue, rash, pruritus, anemia, nausea, diarrhea, vomiting, hemorrhoids, ano-rectal discomfort, and dysgeusia, and were probably related to telaprevir.

There were no clinically relevant differences in adverse events between T-containing arms, or between naïve and experienced subjects, so the data were pooled.

Table 28 Adverse events in ≥10%, all Grades, during T/Pbo dosing period regardless of attribution, Studies 108, 111 and C216 combined

N (%)	T/PR N=1797	Pbo/PR N=493
Rash	1009 (56)	158 (32)
Fatigue	998 (55)	245 (50)
Pruritis	840 (47)	137 (28)
Nausea	704 (39)	138 (28)
Headache	657 (37)	171 (35)
Anemia	590 (33)	66 (14)
Influenza-like illness	516 (29)	126 (26)
Diarrhea	458 (25)	86 (17)
Insomnia	458 (25)	116 (23)
Pyrexia	392 (22)	110 (22)
Chills	283 (16)	71 (14)
Cough	278 (15)	86 (17)
Myalgia	270 (15)	91 (18)
Irritability	260 (14)	75 (15)
Dyspnea	242 (13)	52 (11)
Vomiting	241 (13)	40 (8)
Dry skin	232 (13)	69 (14)
Asthenia	228 (13)	88 (18)
Depression	222 (12)	66 (13)
Hemorrhoids	220 (12)	9 (2)
Dizziness	198 (11)	46 (9)
Anorexia	196 (11)	52 (11)
Neutropenia	193 (11)	62 (13)
Ano-rectal discomfort	191 (11)	13 (3)
Arthralgia	181 (10)	78 (16)
Dysgeusia	178 (10)	15 (3)

The following table shows the adverse events reported by ≥5% more subjects treated with telaprevir. Of note, arthralgia and asthenia occurred with ≥5% frequency in Pbo/PR48 subjects compared to telaprevir subjects.

Table 29 Adverse events occurring with ≥5% frequency in subjects treated with telaprevir

N (%)	T/PR N=1797	Pbo/PR N=493
Rash	1009 (56)	158 (32)
Fatigue	998 (55)	245 (50)
Pruritis	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)

During the overall treatment period the types and frequency of adverse events were generally comparable to those observed during the T/Pbo dosing period. Additionally, for some events there was a small numeric increase in frequency in subjects who received 48 weeks compared to those who received 24 weeks of total treatment; these differences were observed while subjects were receiving Peg-IFN/RBV alone. None of the differences appeared to be clinically relevant, and could be attributable to the longer duration of exposure to Peg-IFN/RBV.

7.4.2 Laboratory Findings

Hematologic and clinical chemistry abnormalities were graded using the DAIDS Grading criteria.

- **Other Hematologic Parameters**

Overall, the frequency of severe (≥Grade 3) hematologic abnormalities was low in the clinical trials.

More telaprevir-treated subjects had severe decreases in lymphocyte (≤499/mm^3) (15% compared to 6%) counts and 10 T/PR subjects had a clinical event of lymphopenia; one was considered a SAE. The Phase 3 data base was searched for opportunistic infections possibly related to lymphopenia. Eight cases of oral candidiasis were identified: 7 in telaprevir subjects and 1 in a Pbo/PR subject. There were no cases of systemic fungal or other opportunistic infections reported in any clinical trials (including the ongoing HIV/HCV co-infection trial). Of the seven telaprevir cases,

- Two events occurred well beyond the telaprevir dosing period while the subjects were receiving PR alone, days 218 and 153, respectively. One subject had mild lymphopenia and the other had a normal lymphocyte count.
- One subject had oral thrush diagnosed on day 56; he had mild lymphopenia from day 1. Of note his oral thrush had resolved by day 84 when he was found to have severe lymphopenia.

- One subject had mild candidiasis diagnosed on day 89; he had mild lymphopenia.
- One subject had severe candidiasis diagnosed on day 28; lymphocyte count was normal. There was no change in study medications.
- One subject had moderate candidiasis diagnosed on day 60; this subject had moderate lymphopenia.
- One subject had mild candidiasis diagnosed on day 18 which lasted through day 145; moderate lymphopenia was noted from day 14 through day 200.

Most subjects were treated with oral nystatin; there were no SAEs, no subjects discontinued and all subjects recovered.

The single case in the Pbo/PR group was diagnosed with oral candidiasis on day 153; lymphocyte count was normal, treatment was oral nystatin.

Severe reductions in platelet counts ($\leq$49,999/mm^3) occurred in 2% of T/PR compared to 1% of Pbo/PR subjects. Forty-one T/PR subjects had a clinical event of thrombocytopenia compared to 7 Pbo/PR. Epistaxis was the most common bleeding event: 4% (T/PR) compared to 3% (Pbo/PR).

There was one life-threatening bleeding event probably related to T/PR: on day 67 a 53 year old female in the immediate start group of Study C216 presented with vaginal bleeding, epistaxis, thrombocytopenic purpura, and hepatorrhagia; platelet count was 10,000/mm^3. All study medications were discontinued and the subject was treated with prednisone and etamsilate. Approximately study day 87 she requested discharge from the hospital and did not return for follow-up visits.

No subjects in the Phase 3 trials received platelet transfusions for thrombocytopenia.

Severe decreases in total white cell ($\leq$1499/mm^3) were comparable: 6% (T/PR) compared to 5% (Pbo/PR).

The frequency of severe decreases in absolute neutrophil counts ($\leq$499/mm^3) was higher with Pbo/PR48 (15% compared to 12%). More events of neutropenia/decreased neutrophils were reported in subjects treated with Pbo/PR: 14% compared to 12%. Two subjects (1 T/PR and 1 Pbo/PR) had a SAE of neutropenia.

There were two events of febrile neutropenia in T/PR subjects. One subject had life-threatening pancytopenia with febrile neutropenia (no infection) on study day 29; all study medications were discontinued and the neutropenia and fever resolved. The other subject's case was considered mild, there were no changes to study medications, and the subject completed the study. No serious or severe infections related to low white cell counts were reported in any subjects. Twenty-four T/PR (1%) and 6 Pbo/PR (1%) received a colony stimulating formulation for neutropenia. Twenty two of the T/PR subjects were treatment experienced: 16 prior relapse, 4 prior null and 2 prior partial responders. Thirteen subjects had cirrhosis, 6 had portal fibrosis 2

had bridging fibrosis, and 1 had no or minimal fibrosis. Fifteen of the subjects received colony stimulating formulations during the telaprevir dosing period. There were two naïve subjects in the T/PR group who received a colony stimulating formulation: 1 was during telaprevir dosing and the other was well after telaprevir dosing had completed and while the subject was on PR alone.

Among treatment experienced subjects, in the Pbo/PR group three subjects who received a colony stimulating factor were treatment experienced (1 prior null and 2 prior relapse), two had bridging fibrosis and one had partial fibrosis. Two of the three naïve subjects had no to minimal fibrosis and one had partial fibrosis.

Five telaprevir recipients experienced pancytopenia:

- One T(DS) subject had mild pancytopenia diagnosed on day 56; the subject had discontinued telaprevir ~20 days earlier due to abdominal pain, but continued on PR. Pancytopenia had not resolved by end of the study.
- One T8 subject had moderate pancytopenia diagnosed on day 22; this event was considered a SAE and the subject discontinued all study medications and recovered.
- One T8 subject had pancytopenia with an onset at day 20; the severity was graded as moderate. The subject discontinued all study medications primarily due to severe anemia.
- One T12 subject was diagnosed on day 55 with mild pancytopenia. The dose of RBV was reduced, no changes to telaprevir or peginterferon doses were made; the pancytopenia resolved and the subject completed dosing.
- One subject had life-threatening pancytopenia with febrile neutropenia (no infection) on study day 29; all study medications were discontinued and the events resolved.

Reviewer Comment: Peginterferon is known to cause pancytopenia. Although there were no events among PR subjects, these cases do not necessarily represent a significant safety signal for telaprevir, but bear watching for in the post-marketing setting.

Comparing naïve to experienced subjects, experienced subjects had more severe reductions in leukocytes (10% versus 7%), lymphocytes (21% versus 11%) and platelet counts (4% versus 2%); severe reductions in ANC were comparable at 13% and 12%. Of note, there were more clinical events of neutropenia reported in subjects treated with Pbo/PR48.

Changes in hemoglobin levels are discussed in more detail in Section 7.3.5 above.

Table 30 Hematologic abnormalities during T/Pbo dosing period, naïve subjects

N (%)	T8/PR N=364	T12/PR N=903	Pbo/PR48 N=361
Total WBC Count			
All Grades	211 (58)	480 (53)	179 (50)
≥Grade 3 (<1,499/mm^3)	27 (7)	65 (7)	20 (5.5)
Absolute Lymphocytes			
All Grades	97 (27)	309 (34)	45 (12)
≥Grade 3 (<499/mm^3)	25 (7)	135 (15)	11 (3)
ANC			
All Grades	246 (68)	507 (56)	229 (63)
≥Grade 3 (<499/mm^3)	48 (13)	93 (10)	53 (15)
Platelets			
All Grades	153 (42)	382 (42)	122 (34)
≥Grade 3 (<49,999/mm^3)	5 (1)	18 (2)	2 (<1)

Table 31 Hematologic abnormalities during T/Pbo dosing period, experienced subjects

N (%)	T12/PR48 N=266	T12(DS)/PR48 N=264	Pooled T/PR48 N=530	Pbo/PR48 N=132
Total WBC count				
All Grades	146 (55)	154 (58)	300 (57)	67 (51)
≥Grade 3	27 (10)	25 (9)	52 (10)	5 (4)
Absolute Lymphs				
All Grades	100 (38)	118 (45)	218 (41)	25 (19)
≥Grade 3	55 (21)	57 (22)	112 (21)	12 (9)
ANC				
All Grades	157 (59)	149 (56)	306 (58)	85 (64)
≥Grade 3	37 (14)	31 (12)	68 (13)	19 (14)
Platelets				
All Grades	145 (54)	162 (61)	307 (58)	54 (41)
≥Grade 3	7 (3)	16 (6)	23 (4)	4 (3)

- **Clinical Chemistry Abnormalities**

The proportion of subjects with all grade and ≥Grade 3 clinical chemistry abnormalities during the T/Pbo dosing period are shown in Table 32. There were no differences between the T8 and T12 groups in Study 108 or between treatment naïve and experienced subjects, so all telaprevir and Pbo data were pooled. The denominator in each cell represents the number of subjects who had post-baseline values. All clinical laboratory abnormalities were graded according to the DAIDS Laboratory Grading Scale.

Following is a discussion of various clinical chemistries where differences between telaprevir and Pbo/PR were identified.

Uric Acid: During the T/Pbo dosing period uric acid elevations were reported by more subjects in telaprevir groups (73%) compared to Pbo/PR48 groups (29%); shifts to ≥Grade 3 elevations (≥12.1 mg/dL) from baseline in uric acid levels were also more frequent among subjects treated with telaprevir (7%) compared to Pbo/PR48 (2%).

The steepest increase in uric acid levels occurred during the first two weeks of treatment. The peak mean value typically occurred between Weeks 6-8 for T/PR groups and at Week 1 in the Pbo/PR48 groups. Uric acid levels remained stable and then decreased to levels similar to the Pbo/PR48 group by Week 10 for the T8/PR group in Study 108 and by Week 16 for the combined T12/PR groups in other trials. Mean maximal uric acid increases for all telaprevir treatment groups was +2.5 mg/dL compared to +0.6 mg/dL in the combined Pbo/PR48 groups.

A total of 13 subjects experienced clinical gout/gouty arthritis: 11 in telaprevir groups and 2 in Pbo groups (<1% for both regimens). Four events in the telaprevir groups occurred after the telaprevir dosing period. Only one subject had a previous history of gout. Subjects were treated with colchicine, indomethacin, oxycodone/acetaminophen, hydration, or ibuprofen. All subjects recovered and no subject discontinued due to clinical gout.

Bilirubin: Forty percent of telaprevir compared to 28% of Pbo/PR48 subjects had all grade elevations in total bilirubin levels, and 4% and 2% of subjects had ≥Grade 3 (≥2.6 x ULN) elevations, respectively.

Direct and indirect bilirubin values are non-graded abnormalities. During the T/Pbo treatment period, 60% of the pooled T/PR groups and 50% of the pooled Pbo/PR groups had shifts from baseline in indirect bilirubin levels. For shifts in direct bilirubin levels, the incidence was 51% (T/PR) compared to 16% (Pbo/PR). Further, in Study C216, a difference in incidence >10% between the T12/PR48 and T12(DS)/PR48 treatment groups was observed for indirect bilirubin above normal limits (28% compared to 14%).

Bilirubin levels increased most steeply during the first 1-2 weeks of telaprevir dosing, stabilized and between Weeks 12-16 were at similar to baseline levels. There were 18 telaprevir and 3 Pbo/PR48 subjects who had adverse events related to increased bilirubin levels. In the telaprevir groups, 14 subjects had events of elevated bilirubin/hyperbilirubinemia, 2 had ocular icterus (one discontinued), and 1 had jaundice (history of Gilbert's disease); all but one event of increased bilirubin occurred after the telaprevir dosing period. The three events in the Pbo/PR group were increased bilirubin (2) and increased bilirubin with jaundice (1).

Reviewer Comment: The mechanism of the uric acid and bilirubin abnormalities may be related to the excess breakdown of red blood cells in telaprevir-treated subjects with anemia.

ALT/AST: Overall, more subjects in the Pbo/PR groups had ≥Grade 3 ALT and/or AST levels (see Table 32). In Study C216, a difference in incidence >10% between the T12/PR48 and T12(DS)/PR48 treatment groups was observed for all grade increases in AST (13% versus 25%), but not for severe increases, during the T/Pbo dosing period.

AST and ALT increases were reported as AEs in <1% of subjects in the pooled T/PR48 groups during the T/Pbo dosing period. In Study 108, 1 T8 subject had an adverse event of ALT/AST increase and 1 had an elevated AST level. In Study C216, 3 subjects in the immediate start

T12/PR group had adverse events of increased ALT and one had an event of increased AST. No SAEs or discontinuations due to increased ALT or AST levels were reported.

Reviewer Comment: Significant increases in ALT and AST levels during telaprevir occurred less often than in subjects receiving PR alone. Lower AST and ALT levels were possibly due to telaprevir's greater efficacy in reducing viral load levels faster and subsequent impact on reducing inflammation caused by HCV.

Amylase/Lipase: Amylase and lipase levels were routinely evaluated only in Study C216. There were four events in pancreatitis in the Phase 2 and three events the Phase 3 trials. The Phase 2 cases were all SAEs and are discussed above. In the Phase 3 trials:

- A 47 year old male with abdominal pain, an amylase level of 2990 U/L and a lipase level of 4397 U/L on Day 40. All work-ups were negative for other causes. Trial medications were discontinued and the event resolved in approximately 14 days.

- A 69 year old female complained of left upper quadrant pain on study day 39; a diagnosis of pancreatitis secondary to multiple gall stones was made; all trial medications were discontinued and she recovered without sequelae.

- A 53 year old male with vomiting was with pancreatitis secondary to a biliary etiology (bile duct stone). All trial medications were discontinued and he recovered.

Reviewer Comment: All three subjects were receiving PR at the time pancreatitis was diagnosed, which is labeled for this event. Further, in two cases pancreatitis was confounded by other biliary etiologies. As such, it is possible that telaprevir contributed to these events, but a confirmatory causal relationship could not be made.

Creatinine and Renal Dysfunction: All grade increases in creatinine levels were higher among subjects treated with T/PR: 6% compared to 1% for Pbo/PR, and creatinine elevations to $\geq$Grade 3 levels were <1% compared to 0%. There were seven events of renal failure in the Phase 3 trials; five in T/PR and 2 in Pbo/PR subjects; of these 4 T/PR cases occurred during the telaprevir dosing period, and 1 while the subject was receiving PR alone. All creatinine elevations were reversible upon cessation of telaprevir dosing.

Reviewer Comment: Elevations in creatinine levels during telaprevir dosing represent a possible safety signal. Of note, there have been reports of increased creatinine levels, renal insufficiency and renal failure from a non-IND temporary authorization program in France (VX-950HEP3001); additional information on these cases is pending. These events bear further evaluation and may be relevant to the safe use of telaprevir.

TSH and Thyroid Dysfunction: More telaprevir treated subjects had TSH increases (see Table 32). However, clinical events of hypothyroidism were lower in telaprevir subjects (27; 1.5%) compared to PR subjects (14; 3%). Of the subjects on telaprevir, 17/27 (63%) events occurred

during the telaprevir dosing period; the majority were mild, and there were no SAEs or discontinuations.

Decreases in TSH were slightly higher in the PR groups (see Table 32), and events of hyperthyroidism were rare: 1 event in telaprevir and 7 in PR subjects. The sole event in a telaprevir subject occurred after the telaprevir dosing period while the subject was receiving PR alone.

Reviewer Comment: Peginterferon is known to cause both hyper and hypothyrodism. Although the incidence of increased TSH levels was greater in the telaprevir group, this did not translate into a higher frequency or severity of hypothyroidism. Hyperthyroid events were rare. These findings do not appear to be clinically relevant for the safe use of telaprevir.

Table 32 All Grade and Severe clinical laboratory abnormalities, all subjects

N (%)	T/PR N=1797	Pbo/PR48 N=493
ALT		
All Grades	177/1777 (10)	65/487 (13)
≥Grade 3 (≥5.1 x ULN)	29 (1)	14 (3)
AST		
All Grades	227/1777 (13)	82/487 (17)
≥Grade 3 (≥5.1 x ULN)	27 (1)	15 (3)
Total Bilirubin		
All Grades	709/1773 (40)	137/487 (28)
≥Grade 3 (>2.6 x ULN)	70 (4)	9 (2)
↑ Glucose		
All Grades	562/1674 (34)	145/480 (30)
≥Grade 3 (≥251 mg/dL)	13 (1)	4 (1)
Total Cholesterol		
All Grades	524/1622 (32)	34/474 (7)
≥Grade 3 (≥300 mg/dL)	16 (1)	0
Triglycerides		
All Grades	61/1113 (5)	21/474 (4)
≥Grade 3 (≥751 mg/dL)	6 (1)	4 (<1)
↑TSH*		
All Grades	172/1699 (10)	29/479 (4)
≥Grade 3	Not evaluated	Not evaluated
↓ TSH		
All Grades	28/1699 (2)	18/479 (4)
≥Grade 3	Not evaluated	Not evaluated
↑ Amylase		
All Grades	84/527 (16)	16/131 (12)
≥Grade 3	5 (1)	1 (1)
↑ Lipase		
All Grades	48/527 (9)	7/131 (5)
≥Grade 3	5 (1)	1 (1)

*DAIDS Laboratory Grading Scale does not include an evaluation for TSH.

7.4.3 Vital Signs

No clinically relevant pattern of changes in vital signs was observed between subjects who received telaprevir in combination with Peg-IFN/RBV and those who received only Peg-IFN/RBV.

Mean changes from baseline in pulse rate ranged from ~3 to 8 beats per minute (bpm) and mean changes in diastolic blood pressure (DBP) and systolic blood pressure (SBP) ranged from ~-3 to 0 mmHg. Similar changes were observed in the Pbo/PR groups.

7.4.4 Electrocardiograms (ECGs)

The Applicant conducted two studies to evaluate telaprevir's potential effect on prolongation of the QT/QTc interval. Based on the results of these trials, telaprevir has minimal risk to prolong the QTc interval. The incidences of treatment-emergent QTcF interval >500 ms and between 480 and 500 ms were low (~1%). No cases of sudden cardiac death or Torsades des Pointe were reported. Across the clinical trials, no patterns of changes in ECG parameters were identified.

7.4.5 Special Safety Studies/Clinical Trials

As described above, the applicant undertook an extensive program in an attempt to evaluate the etiology and mechanism of rash and pruritis; however, no specific mechanisms were identified.

7.4.6 Immunogenicity

Telaprevir is not immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no apparent dose dependency for any adverse events. Adverse events considered possibly, probably or definitely related to telaprevir (see Section 7.4.1) occurred at all dose levels.

7.5.2 Time Dependency for Adverse Events

There was a substantial increased frequency and severity of certain adverse events during the first 12 weeks of treatment, which corresponded to the duration of telaprevir dosing. As discussed in section 7.3.4, rashes and pruritis appeared to arise within 2-3 weeks of telaprevir treatment (median time to onset ~18 days). Also, in subjects treated with telaprevir, median hemoglobin values decreased most steeply through Week 4, were generally stable from Week 8 through Week 12 (completion of telaprevir dosing), and by Week 16 had risen to levels similar to those of subjects in Pbo/PR48 groups (see Section 7.3.4). Other events, such as anorectal

disorders, elevated uric acid and bilirubin levels, occurred more rapidly in telaprevir-treated subjects compared to Pbo/PR48 recipients and were most predominant during the telaprevir dosing period.

7.5.3 Drug-Demographic Interactions

There were no clinically relevant differences in the severity of adverse events between males and females, subjects >45 and <45 years of age, subjects with BMI $\leq$25 and $\geq$30 kg/m^2, subjects from North America and Europe, and those with more or less fibrosis, or Caucasians versus non-Caucasians. Approximately 90% of study subjects were Caucasian so caution should be exercised in interpreting any differences.

- Female subjects experienced more nausea, vomiting, fatigue, asthenia, headaches, abdominal pain and alopecia while males experienced more insomnia.
- Subjects $\geq$45 years of age experienced more diarrhea, chills, irritability, neutropenia, and anorexia.
- Subjects with BMI <25 kg/m^2 experienced more asthenia, nausea, dry mouth, dry skin and anorexia. Subjects with BMI $\geq$30 kg/m^2 experienced more fatigue.
- Subjects from North America experienced more fatigue, irritability, chills, pain, diarrhea, headaches, dizziness, insomnia, dyspnea and arthralgia while those from Europe had more asthenia, pyrexia, anorexia, dry skin and cough.
- Subjects with more advanced fibrosis experienced more dry mouth and cough and those with less fibrosis had more mylagia, dizziness and alopecia.

Discussion of disease-demographic interactions for rash and anemia are discussed above.

7.5.4 Drug-Disease Interactions

No drug-disease interactions were identified.

7.5.5 Drug-Drug Interactions

As discussed in Section 4.4 above, telaprevir is metabolized primarily by cytochrome P450 CYP3A4, it inhibits CYP3A4, and it is a substrate of P-gp. Telaprevir's drug interaction profile has been adequately characterized; results from the completed studies are sufficient for providing recommendations for the safe use of telaprevir with potentially interacting and commonly used drugs; these recommendations will be determined during labeling discussions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The total duration of telaprevir administration is 12 weeks. As such, no carcinogenicity studies were required or conducted.

7.6.2 Human Reproduction and Pregnancy Data

Overall 6% (38/675) of female subjects treated with telaprevir were using a hormone-based contraceptive during the Phase 3 trials. There were a total of 15 pregnancies included in the Safety data base, 10 of which occurred in a subject or a subject's partner who had received telaprevir. No pregnancies occurred during the telaprevir dosing period and there were no events related to telaprevir-related contraception failure.

Maternal exposure to telaprevir (3):

- Three female subjects who became pregnant 163-243 days after the last dose of telaprevir: one underwent an elective termination, one refused further follow-up, and one had a normal healthy newborn.

Paternal exposure to telaprevir (7):

- Two partner pregnancies prior to telaprevir administration: on day 1 of dosing (spontaneous abortion), and 22 days prior to day 1 of dosing (normal outcome).

- Five partner pregnancies 15, 17, 25, 41 and 193 days after the last dose of telaprevir: three elective terminations, one normal outcome and one lost to follow-up (outcome unknown).

Five pregnancies were reported in Pbo/PR subjects (2) or partners (3); 2 had normal outcomes, 1 had an elective abortion, and 2 were continuing at the end of the study period (outcome unknown).

Reviewer Comment: Telaprevir will be labeled as Pregnancy Category B based on the results of animal studies. Telaprevir is to be co-administered with Peg-IFN (Category D) and RBV (Category X); both of which are contraindicated during pregnancy. There is a potential interaction between telaprevir and estrogen-containing contraceptive. Therefore, the label should include precautionary language advising female patients to use at least 2 forms of non-hormonal containing contraception during telaprevir dosing.

7.6.3 Pediatrics and Assessment of Effects on Growth

To date, the Applicant has only initiated work to develop an age appropriate formulation. No clinical trials have been initiated or completed in pediatric subjects with chronic HCV infection. A pediatric plan was submitted with the NDA. The Applicant requested a Waiver for subjects <3 years of age and a deferral for subjects 3-18 years of age.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose data are available, and there is no specific antidote in case of overdose. The highest doses given were the supra-therapeutic regimen of a total daily dose of 5625 mg was given for 4 days (1875 mg q8h)**,** with an additional dose of 1875 mg on Day 5 in a Phase 1 thorough QTc study. Compared to the proposed therapeutic dose of 750 mg q8h (total daily dose of 2250 mg), subjects on the supra-therapeutic dose had higher incidences of nausea, headache, diarrhea, decreased appetite, dysgeusia, and vomiting.

Treatment of overdose with treatment likely consists of general supportive measures. Administration of activated charcoal may also be used to aid in the removal of unabsorbed active substance. It is not known whether telaprevir is dialyzable by peritoneal or hemodialysis; however, based on a plasma protein binding of 59% to 76%, dialysis may increase the clearance of telaprevir.

No abuse studies have been performed. The potential for illegal use is unlikely given that the target of telaprevir is virus specific, and it does not cause central nervous system effects.

It does not appear that acute discontinuation of telaprevir is associated with any direct safety concerns as most subjects in the clinical trials completed dosing after 12 weeks and then stopped telaprevir.

7.7 Additional Submissions / Safety Issues

There were no other safety issues identified that have not been addressed above.

8 Postmarket Experience

There is no Postmarket Experience as telaprevir is not currently marketed anywhere in the world.

9 Appendices

9.1 Literature Review/References

Telaprevir has been in clinical development for >5 years. Most every study conducted has been published or presented at meetings. Additionally, multiple editorials have been written describing clinical trials data and the potential role telaprevir will play in the anti-HCV therapeutic armamentarium. A search of the Medline data base found no publications that the Applicant was not aware of.

9.2 Labeling Recommendations

Telaprevir Review: The Applicant submitted INCIVEK™ as a proposed tradename. The Division of Medication Error Prevention and Analysis (DMEPA) has tentatively determined that this proposed name should be acceptable from a look-alike and sound-alike perspective, and has not identified other factors that would render the name unacceptable; however, a final decision is pending.

Labeling Recommendations: The labeling review and discussions with the Applicant are pending the outcome of the Antiviral Products Advisory Committee meeting.

9.3 Advisory Committee Meeting

The Antiviral Advisory Committee will be convened to review this application on April 28, 2011. The major issues identified for discussion include: overall efficacy outcomes, appropriate regimens for naïve and prior non-responders (including the potential for a shortened duration of therapy for prior relapsers based on achievement of eRVR), adequacy of data to support labeling in Blacks/African Americans, Latinos and subjects with cirrhosis, and monitoring and management of rash/pruritis and anemia. Additionally, the Advisory Committee will also be asked to comment on possible post-marketing trials that should be conducted.

9.4 MedDRA Terms Used for Identifying Rash SSC

Allergic rash, Eczema (rash) in the outer ear, Eczematous rash, Hemolytic type rash, Petechial rash, Purpuric rash, Rash acneiform, Rash ecchymotic, Rash gum, Rash haemorrhagic, Rash lips, Rash pemphigoid, Rash petechial, Rash purpuric, Sensitization rash, Acute generalized exanthematous pustulosis, Dermatitis, Dermatitis bullous, Dermatitis exfoliative, Dermatitis exfoliative generalized, Drug eruption, Drug rash with eosinophilia and systemic symptoms, Erythema multiforme, Exfoliative rash, Fixed eruption, Genital rash, Haemorrhagic urticaria, Idiopathic urticaria, Mucocutaneous rash, Oral mucosal eruption, Rash, Rash erythematous, Rash follicular, Rash generalized, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash popular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Septic rash, Stevens-Johnson syndrome, Tongue eruption, Toxic epidermal necrolysis, Toxic skin eruption, Urticaria, Urticaria generalized, Urticaria localized, Urticaria popular, and Vasculitic rash.

9.5 MedDRA Terms Used for Identifying Anemia SSC

Anemia, Anemia hemolytic autoimmune, Anemia Heinz body, Anemia macrocytic, Anemia megaloblastic, Anemia splenic, Aplasia pure red cell, Aplastic anemia, Bone marrow failure, Cold type hemolytic anemia, Coombs negative hemolytic anemia, Erythroidblast count decreased, Erythroid maturation arrest, Erythropenia, Evans syndrome, Febrile bone marrow aplasia, Hematocrit decreased, Hemoglobin decreased, Hemolytic anemia, Hemolytic icteroanemia, Hyperchromic anemia, Hypochromic anemia, Hypoplastic anemia,

Leukoerythroblastic anemia, Microangiopathic hemolytic anemia, Microcytic anemia, Normochromic normocytic anemia, Pancytopenia, Panmyelopathy, Proerythroblast count decreased, Red blood cell count decreased, Sideroblastic anemia, Spur cell anemia, and Warm type hemolytic anemia.

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/s/

RUSSELL D FLEISCHER
04/22/2011

LINDA L LEWIS
04/22/2011

Filing Meeting/Clinical Reviewer

NDA 201,917 (Telaprevir, (b) (4)) Filing Meeting: December 22, 2010

Telaprevir (VX-950) is a NS3/4A serine protease inhibitor that blocks viral replication.

Proposed Indication

(b) (4) (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.

Proposed Treatment Regimen

Telaprevir 750 mg q8h (with food) for 12 weeks in combination with Peg-IFN/RBV for 24-48 weeks.

Key Clinical Trials

Study title	Design	Population	Study treatments	Subjects
Phase 2 Trials				
VX05-950-104 (PROVE 1)	Randomized Placebo controlled, Double blind, Parallel group, Multiple dose	Treatment naïve with genotype 1	TVR12/PR12 TVR12/PR24 TVR12/PR48 Pbo/PR48	250
VX05-950-104EU (PROVE 2)	Randomized, Partially Placebo controlled, Partially double-blind, Parallel group, Multiple dose	Treatment naïve with genotype 1	TVR12/P12 TVR12/PR12 TVR12/PR24 Pbo/PR48	323
VX06-950-106 (PROVE 3)	Randomized, Partially Placebo controlled, Partially Double blind, Parallel group, Multiple dose	Genotype 1 non-responders to prior Peg-IFN/RBV	TVR24/PR48 TVR24/P24 TVR24/PR24 Pbo/PR48	453
VX06-950-107	Nonrandomized, Open-label, Multiple dose	Subjects enrolled in the control arm of Studies 106, 104, or 104EU and discontinued treatment due to an inadequate	Subjects with prior null response: TVR12/PR48 Subjects with prior partial response, relapse, and viral breakthrough: TVR/PR24 or 48	117

		response		
Phase 3 Trials				
VX07-950-108: (ADVANCE) **Pivotal Trial**	Randomized Placebo controlled, Double blind, Parallel group, Multiple dose	Treatment-naïve genotype 1	TVR8/PR24-48 TVR12/PR24-48 Pbo/PR48	1088
VX08-950-111 (ILLUMINATE) **Supportive Trial**	Open-label	Treatment-naïve genotype 1	TVR12/PR24-48 depending on eRVR status (TW4 and 12) eRVR+: 24 weeks eRVR-: 48 weeks	540
VX-950-C216 (REALIZE) **Pivotal Trial**	Randomized Placebo controlled, Double blind, Parallel group, Multiple dose	Treatment-failure genotype 1 (Null, prior partial, prior relapse)	TVR12/PR48 TVR12(DS)/PR48 Pbo/PR48	662

Topline Efficacy Results

- **Study 108 (Naïve)**

	TVR8			**TVR12**			**Pbo/PR48**
	All (n=364)	**eRVR+ (24 wks) (n=207)**	**eRVR- (48 wks) (n=157)**	**All (n=363)**	**eRVR+ (24 wks) (n=212)**	**eRVR- (48 wks) (n=151)**	**(n=361)**
SVR Rate	69%	83%	50%	75%	89%	54%	44%

- **Study 111 (Naïve)**

	All (n=540)	**TVR12 eRVR+ (24 Weeks) (n=162)**	**TVR12 eRVR+ (48 Weeks) (n=160)**	**TVR12 eRVR- (48 Weeks) (n=118)**	**Other (n=100)**
SVR Rate	72%	92%	88%	76%	23%

Other=subjects who discontinued prior to the Week 20 randomization point.

- ~59% of TVR12 subjects achieved eRVR and received 24 weeks of total treatment
- ~90% of eRVR subjects achieved SVR
- TVR12 probably better than TVR8: higher SVR, lower breakthrough and relapse. But if a subject discontinued between TW8-12, did have very good response.

- **Study C216 (Experienced)**

	SVR Rate
All TVR combined	
All	65% (346/530)
Prior Null	31% (46/84)
Prior Partial	57% (55/97)
Prior Relapse	86% (245/354)
TVR12/PR48	
All	64% (171/266)
Prior Null	29% (21/72)
Prior Partial	59% (29/49)
Prior Relapse	83% (121/145)
TVR12(DS)/PR48	
All	66% (175/264)
Prior Null	33% (25/75)
Prior Partial	54% (26/48)
Prior Relapse	88% (124/141)
Pbo/PR48	
All	17% (22/132)
Prior Null	5% (2/37)
Prior Partial	15% (4/27)
Prior Relapse	24% (16/68)

Prior partial (≥2 log drop in HCV RNA at Week 12 of prior therapy but never achieved undetectable HCV RNA while on treatment)
Null (<2 log drop in HCV RNA at Week 12 of prior therapy)
Enrollment was limited so that subjects with prior partial or null response represented no more than 55% of the total study population

- No apparent benefit from DS (but is a strategy that worked)
- ~25% increase in response for true prior Null responders
- No breakthrough subjects included (?)

Potential Safety Issues

- Rash/pruritis
  - Noted in Phase 2 (50-60% with 8% discontinuation)
  - Rash management plan instituted for Phase 3
  - In Phase 3 ~30% with ~6% discontinuation
  - A couple of SJS/DRESS (still looking at relatedness)
  - SSC and ESI
  - DEP (consistent with drug eruption; so far nothing else found to explain MOA)
  - Derm consult requested
- Anemia
  - TVR adds 0.5-1.0 g/dL decrease over RBV
  - Pre-clinical: decreased erythrocytic parameters and anemia accompanied by reticulocyte/bone marrow response
  - No EPO allowed
  -

- QT prolongation potential
    - 2 QTc studies
    - Few cardiac events; do not appear arrhythmia related
- Drug-Drug Interactions
    - Metabolized primarily by CYP 3A4
    - Lots of do not co-administer and co-administer with caution
- Ano-rectal events
    - Hemorrhoids in Phase 2
    - Anal pruritis in Phase 3
- Hyperuricemia
    - Noted in both Phase 2 and 3 studies

Clinical Reviewer's Filing Recommendation

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/s/

RUSSELL D FLEISCHER
05/04/2011