DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Date: April 1, 2011

To: Antiviral Products Advisory Committee Members and Guests

From: Telaprevir Review Team

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

Re: Advisory Committee Briefing Document for NDA 201-917
Telaprevir 375 mg tablets

I. Summary of Regulatory Issues and Purpose of Meeting

This memorandum serves as an introduction to the FDA presentation at the upcoming April 28, 2011, meeting of the Antiviral Products' Advisory Committee (AVAC). At this meeting we will ask you to consider the results of Vertex Pharmaceutical's development program for telaprevir for the treatment of genotype 1 chronic hepatitis C virus (HCV) infection in adults as submitted in their New Drug Application (NDA).

The background materials from FDA represent the findings and opinions of the primary reviewers of each discipline, based on their reviews of the respective submissions from Vertex. It must be emphasized that this document represents the review team's preliminary findings, and that no regulatory decision has been made on the status of the application. Indeed, the advice the AVAC provides will be critical in our regulatory decision making.

The NDA for telaprevir provides for a new therapeutic approach to treatment of adults with genotype 1 HCV infection. The NDA contains data from adequate and well-controlled trials supporting thrice-daily administration of telaprevir, a linear peptidomimetic inhibitor of the viral NS3/4A protease, in combination with pegylated interferon-alfa (PegIFN) and ribavirin (RBV) in both treatment naïve and experienced subjects.

The current standard of care therapy for adults with genotype 1 chronic HCV infection is 48 weeks of PegIFN plus RBV. Under the Food, Drug and Cosmetics Act (FD&C Act), the FDA approves drugs based on "substantial evidence" of safety and effectiveness. A recommendation for approval by the committee must consider the

FD&C Act's evidentiary standard and the overall risk/benefit assessment for the drug in question. In the case of telaprevir, the risk/benefit assessment must include the proposed duration of treatment and the use of response guided therapy in certain populations, the adequacy of efficacy data in some subgroups (Blacks/African Americans and patients with cirrhosis), and the impact of significant telaprevir-related toxicities such as rash and anemia.

Beyond the overall examination of the safety and efficacy data for telaprevir, some critical issues to consider as you read the Agency's review summary and the Applicant's background materials include whether the available efficacy results, the resistance profile, and the overall safety support approval. We look forward to a very interesting meeting and thank you in advance for your time and efforts in this important meeting.

II. Overview of Clinical Pharmacology

General: Telaprevir exhibits greater than dose proportional increases in exposure within the therapeutic dose range; it has time-dependent pharmacokinetics (PK), accumulating 2-fold at steady-state. Following multiple-dose administration of telaprevir in HCV-infected patients, pyrazinoic acid, VRT-127394 (R-diastereomer of telaprevir), and VRT-0922061 are the predominant metabolites, present at >10% of total drug-related material at steady-state. However, no metabolite demonstrates comparable antiviral activity to the parent drug. Approximately 82% of a telaprevir dose is excreted through feces (as both unchanged drug and metabolites), with minimal renal elimination.

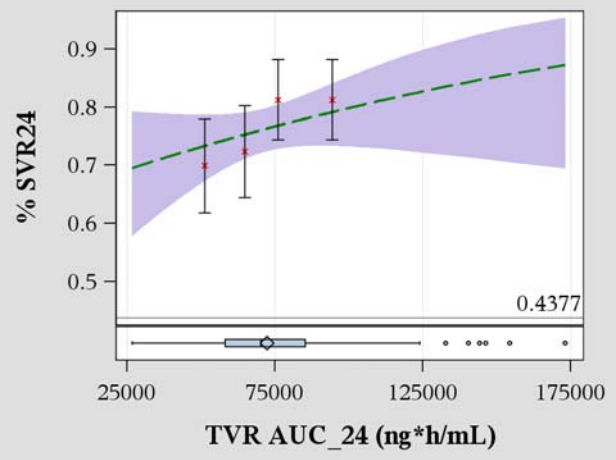
To achieve optimal exposure, telaprevir must be taken with food.

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, midazolam, and digoxin. In addition, the effects of potent CYP3A induction (rifampin) and inhibition (ketoconazole) on telaprevir PK were assessed in vivo. The results from these studies are described in the Applicant's briefing document. 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.

Exposure-Response: An exposure-response analysis for efficacy was performed using PK data from the treatment-naïve population receiving 12 weeks of telaprevir treatment combined with PegIFN/RBV in Studies 108 and 111 (n=461). The relationships between telaprevir exposure (AUC) and all efficacy endpoints were shallow, and not statistically significant. As shown in Figure 1, higher telaprevir exposure was weakly associated with

increased sustained virologic response 24 weeks after the end of planned treatment (SVR24).

Figure 1: Proportion of Treatment Naïve Subjects with SVR24 According to Telaprevir (TVR) Exposure[a]



[a]Exposure-SVR analysis was conducted in the pooled naïve patients receiving T12/PR (RGT or 48 WK). Vertical bars represent SVR in each quartile of AUC. The horizontal bar along the AUC axis represents the distribution of AUC (5-95%, 1st to 3rd quartile, mean, median).

Hepatic Impairment: Two hepatic impairment studies were conducted in non-HCV infected subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) impairment. Hepatic impairment decreased telaprevir exposures in subjects with Child-Pugh Class A and Child-Pugh Class B liver disease by 15% and 53%, respectively, compared to healthy control subjects. Because of reduced exposure to telaprevir in subjects with Child-Pugh Class B, subjects with Child-Pugh Class C have not been evaluated. Based on these data, we agree with the Applicant's assessment that telaprevir should not be administered to patients with moderate to severe hepatic impairment. This is also consistent with approved labeling for PegIFN and RBV, which are indicated for patients with chronic HCV infection and compensated liver function.

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 patients 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. Based on the data from the single-dose study alone, we do not agree with the Applicant's conclusion. Additional analyses are underway to determine whether the

extent of accumulation in patients with severe renal impairment can be estimated based on the single-dose study results.

Thorough QT Study: The FDA Interdisciplinary Review Team for QT Studies determined telaprevir has no clinically relevant effects on the PR or QRS intervals at either therapeutic or supratherapeutic exposures.

III. Overview of Efficacy

The Applicant proposes telaprevir, in combination with PegIFN and RBV, is indicated for the treatment of genotype 1 chronic HCV infection 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. The proposed dosing regimen for telaprevir is 750 mg given three times daily for 12 weeks (T12) in combination with PegIFN/RBV for 24 weeks (T12/PR24) or 48 (T12/PR48) weeks, depending on treatment response. In addition, the Applicant proposes treatment naïve patients and patients with relapse after prior treatment who achieve an extended virologic response (eRVR), defined as undetectable HCV RNA at Weeks 4 and 12, will receive the T12/PR24 regimen. Treatment-naïve subjects who fail to achieve eRVR and patients with null response and partial response to prior treatment will receive the T12/PR48 regimen. The Applicant's plan to administer a shortened duration of PegIFN/RBV treatment in subjects who achieve undetectable HCV RNA at Weeks 4 and 12, known as "response guided therapy" (RGT), represents an evolution in HCV treatment.

To support the proposed indication, the Applicant conducted three Phase 3 trials: Studies 108 and 111 in treatment-naïve subjects and Study C216 in treatment-experienced subjects. The primary efficacy endpoint in all clinical trials was the proportion of subjects achieving SVR24 (sustained virologic response 24 weeks after the end of planned treatment). The FDA efficacy analysis allowed data from the Week 12 follow-up visit to be carried forward to the Week 24 off-treatment follow-up visit if an HCV RNA value of < 25 IU/mL was documented at the Week 12 follow-up visit.

In Study 108 subjects were randomized to an initial regimen of either 8 or 12 weeks of telaprevir (T8 or T12) in combination with PegIFN/RBV or a control regimen of telaprevir-placebo plus PegIFN/RBV (PR48). Subjects who achieved eRVR were assigned to stop treatment after 24 weeks; subjects without eRVR received 48 weeks of treatment. The T8 arm was included to explore whether shorter treatment duration might change the risk/benefit assessment by improving tolerability, particularly by reducing the frequency of severe rash, while not sacrificing efficacy.

In Study 111, all subjects initiated treatment with T12 in combination with PegIFN/RBV. Using a RGT approach, subjects who achieved eRVR were randomized to either 24 or 48 weeks of total PegIFN/RBV treatment. This study design was intended to confirm the utility of RGT by determining whether subjects who achieved an early response derived

additional benefit from extending dosing with PegIFN/RBV to 48 weeks. Subjects who failed to achieve an eRVR were assigned to 48 weeks of PegIFN/RBV treatment.

In Study C216, the RGT approach was not used. All subjects were randomized to a regimen of immediately starting treatment (T12/PR48) or to delayed start of the telaprevir component for 4 weeks (T12(DS)/PR48) or to PR48. The rationale for inclusion of the 4 week lead-in with PegIFN/RBV was to assess the effect of a short initial course of treatment with PegIFN/RBV on the frequency of emergence of resistant strains during telaprevir exposure and on overall treatment efficacy. In Study C216, subjects were classified and stratified at entry based on their response to a prior course of PegIFN/RBV therapy as:

- Prior null responder: Achieved <2 log drop in HCV RNA at Week 12 of prior therapy
- Prior partial responder: Achieved ≥2 log drop in HCV RNA at Week 12 of prior therapy but never achieved undetectable HCV RNA while on treatment
- Prior relapser: Achieved undetectable HCV RNA at end of treatment (EOT), but failed to achieve SVR

Overall, the FDA review team's independent analyses confirmed the Applicant's primary efficacy findings and many secondary endpoint analyses for all pivotal clinical trials. The following points summarize the key findings of the FDA's clinical and statistical reviewers.

In Study 108, the FDA review confirmed the overall SVR rates of 73% for T8/PR and 79% for T12/PR compared to 46% for the PR48 control arm. Compared to the T8/PR regimen, the T12/PR regimen produced slightly higher overall SVR rates, and higher SVR rates among subjects with demographic or disease characteristics associated with poorer response: genotype 1a, high baseline viral load (≥800,000 IU/mL) and cirrhosis; T12/PR resulted in lower virologic failure rates compared to T8 (5% versus 10%). However, between Weeks 8 and 12 additional events of anemia and rash occurred in the T12 group.

Using the RGT approach, 58% of naïve subjects achieved eRVR, and 90% of those achieved SVR. Only 8% (29/361) of PR48 subjects achieved eRVR but this subgroup had a high success rate with 28/29 (97%) achieving SVR. For subjects without eRVR, extending the duration of PegIFN/RBV treatment to 48 weeks (T12/PR48) resulted in a higher SVR rate (61%) than the corresponding subgroup in the control arm receiving treatment with PegIFN/RBV alone (42%).

In Study 111, our review 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 PegIFN/RBV treatment. Approximately 60% of subjects achieved eRVR and were randomized to 24 or 48 weeks of PegIFN/RBV, and 90% of those receiving either

treatment duration achieved SVR. Of the 40% of subjects not achieving eRVR and assigned to receive T12/PR48, about 64% achieved SVR.

FDA analyses confirmed the primary efficacy conclusions of Study C216. In general, no differences were observed in SVR, virologic failure, virologic breakthrough, or relapse rates between the immediate and delayed start telaprevir regimens, so the data from these groups were pooled. The SVR rates for the pooled T12/PR48 groups were significantly higher than for re-treatment with PegIFN/RBV alone, 65% and 17%, respectively, and SVR rates varied according to prior treatment response: prior null responders 31% and 3%, prior partial responders 57% and 15%, and prior relapsers 84% and 24%, respectively.

Several of the review conclusions are applicable to both naïve and treatment-experienced subjects. Overall, the addition of 12 weeks of telaprevir to a PR regimen decreased the relapse rate from 26% (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.

The addition of T12 to PegIFN/RBV for 24 or 48 weeks increased SVR rates 30-40% compared to PR48 across a broad spectrum of demographic and disease characteristic subgroups including subgroups associated with poorer response to PR (i.e, older age, males, minorities, subjects with higher BMI, subjects with high baseline viral load, and genotype 1a). For some subgroups, the numbers of subjects enrolled in the clinical trials were relatively low, but the treatment benefit of adding telaprevir to PR appeared to be consistent.

As in earlier studies of HCV treatment, Blacks/African Americans had SVR rates approximately 20% lower than Caucasians. Enrollment of this subgroup was relatively low; Blacks/African Americans comprised 9% (158/1797) of telaprevir subjects and 8% (39/493) of PR48 subjects. However, treatment with telaprevir combined with PegIFN/RBV significantly improved response rates among Black/African Americans compared to those treated with PR48: SVR in 65% (range; 50% to 94%) among those receiving T/PR compared to 31% (range; 29% to 36%) among those receiving PR48. Similarly, Latino/Hispanic subjects comprised 10% (185/1797) of telaprevir subjects and 12% (58/493) of PR48 subjects. SVR rates for Latino/Hispanic subjects were also significantly improved; 79% (range; 70% to 94%) in subjects receiving T/PR and 31% (range; 10% to 42%) for PR48.

Among telaprevir-treated subjects, 8% (108/1267) of naïve and 25% (134/530) of treatment-experienced subjects had cirrhosis at baseline, compared to 6% (21/361) of naïve and 23% (30/132) of experienced PR48 subjects. Positive trends were noted for increased SVR rates among cirrhotic subjects treated with telaprevir: 50% (range; 33% to 92%) among those receiving T/PR compared to 24% (range; 13% to 33%) among those treated with PR48.

Across the Phase 3 clinical trials, only 2% (31/1797) of telaprevir and 2% (8/493) of PR48 subjects were older than 65 years of age. Among telaprevir subjects, 21/31 (68%) achieved SVR and among PR48 subjects the SVR rate was 25% (2/8).

Response Guided Therapy in Patients Who Relapsed after Prior PegIFN/RBV

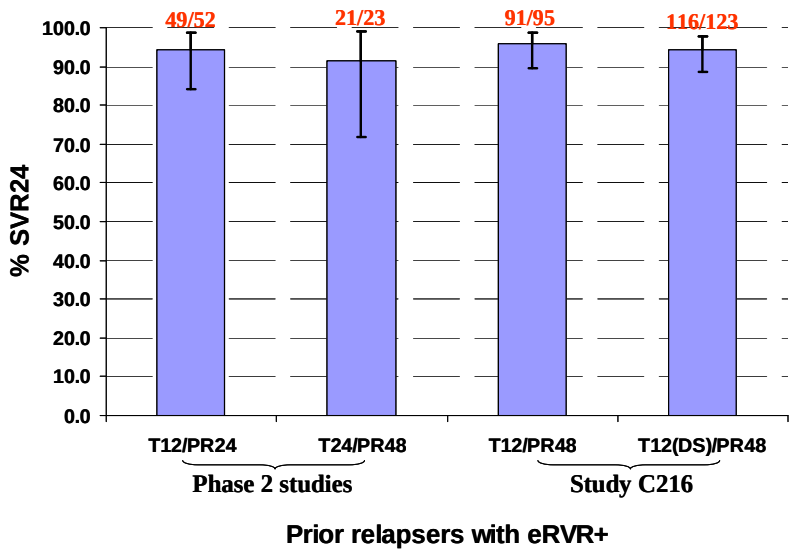
Although the RGT approach was not prospectively utilized or evaluated in any subgroup in Study C216, the Applicant has proposed dose recommendations to allow subjects who relapsed following completion of prior PR to receive a regimen of T12/PR24 if they achieve eRVR. They hypothesized that these interferon sensitive subjects could be re-treated with a shorter course of therapy. Because there are not adequate randomized, controlled trial data, we will ask the Advisory Committee to consider the evidence supporting effectiveness in this subgroup.

To support the proposed labeling recommendation, the Applicant conducted a retrospective viral dynamic simulation analysis of prior relapsers who achieved eRVR. The bases for the analysis were the results of two Phase 2 studies; in one RGT was used and prior relapse subjects who achieved an eRVR received 24 weeks of therapy. Seventy-eight percent (52/67) of prior relapsers who received T12/PR24 achieved eRVR and of those 94% (49/52) achieved 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 those, 95% (207/218) achieved SVR.

FDA pharmacometrics reviewers confirmed the outcomes of the viral dynamic simulation analysis by conducting a series of analyses to determine the likely efficacy of RGT in prior relapsers. The first step in this assessment compiled the available clinical data in prior relapser subjects receiving telaprevir combined with PR24 and those receiving telaprevir combined with PR48 in Phase 2 and 3 trials. In one of the Phase 2 trials, RGT was tested, assigning subjects to shorter or longer duration based on achieving eRVR. In addition, a non-RGT T12/PR24 regimen and a longer duration telaprevir regimen (T24/PR24) were also tested in another Phase 2 trial. Data from Study C216 were used to gain insights into SVR rates among prior relapse patients receiving the longer PR48 regimen.

Figure 2 displays SVR rates in subjects receiving different telaprevir/PR regimens who achieved eRVR. Of note, the SVR rates were high in all subsets of prior relapsers (~90%), regardless of duration of either telaprevir (12 or 24 weeks) or PegIFN/RBV (24 or 48 weeks) suggesting that achieving eRVR was the critical factor.

Figure 2: SVR Rates Among Cohorts of Prior Relapse Subjects Achieving eRVR in Phase 2 and Phase 3 Telaprevir Trials



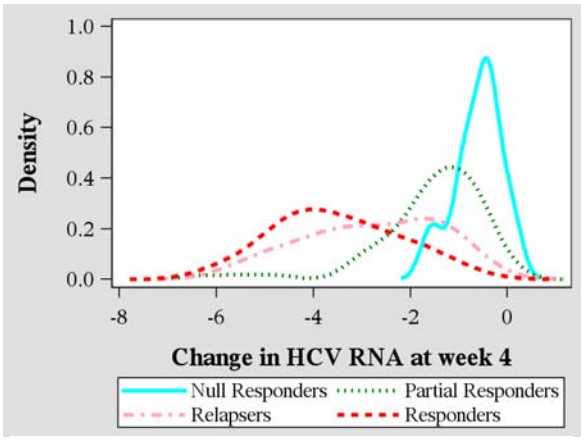
T12(DS)/PR48 is the treatment with 4-week delayed start of telaprevir. The Y-error bars are the 95% Fisher Exact Confidence Limits for each treatment group.

Although the clinical data were limited, the high rates (>90%) of SVR in prior relapse subjects who achieved eRVR suggested a strong response to the triple regimen in this subgroup. Therefore, prior relapsers respond very much like similar patients in the treatment naïve population. This result might be expected mechanistically based on the presumed lack of virologic resistance to PegIFN/RBV and emerging genetic evidence that response to PegIFN is dependent, in large part, on host factors (eg. *IL28B*) and not on the virus.

To further support the lack of virologic resistance to pegIFN/RBV, the FDA reviewers compared the distribution of mean change in HCV RNA at Week 4 of treatment in the control PR48 arm of Study 108 (treatment naïve subjects) according to their ultimate treatment outcome to a similar Week 4 HCV RNA measurement in subjects in the PR48 and the delayed start T12/PR48 arms of Study C216 (treatment experienced). Figure 3a shows the distribution of Week 4 HCV RNA change by end of treatment status for treatment-naïve patients in the PR48 arm. Figure 3b shows the same distribution of Week 4 HCV RNA change for treatment-experienced patients by response to prior treatment. The Week 4 response to PegIFN/RBV within each subgroup is similar suggesting that the previous exposure to PegIFN/RBV has not changed the patient's responsiveness to PegIFN/RBV.

Figure 3: Distribution of Change in HCV RNA at Week 4 in Cohorts receiving PegIFN/RBV

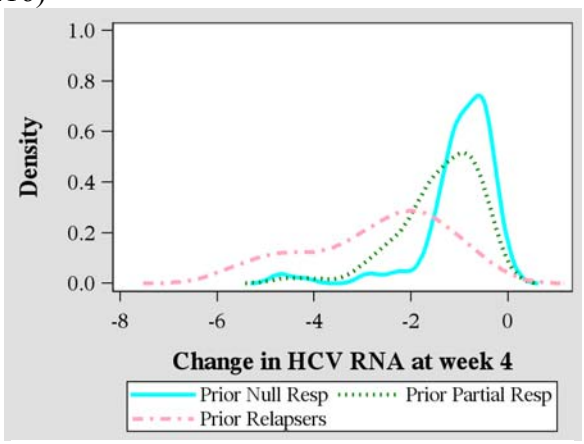
a. Treatment-naïve subjects receiving PR48 according to final treatment outcome (Study 108)



Log change in HCV RNA at week 4

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

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



Log change in HCV RNA at week 4

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

Consider that any treatment-naïve population can be theoretically divided into potential responder, relapser, partial responder, and null responder subgroups, although this response is not known at the time treatment is initiated. The FDA's analyses suggested that prior relapser subjects can be considered a subset of treatment-naïve subjects. In Study 108, potential relapsers were present in the overall treatment-naïve population treated with PegIFN/RBV. Reviewers conducted additional analyses to bridge information from the treatment-naïve population to the treatment-experienced population. In this extrapolation exercise, the predicted SVR rate calculated for treatment-naïve patients using data from treatment-experienced patients matched closely the overall actual SVR rate observed for the T/PR arms in Study 108.

In summary, the final treatment response to PegIFN/RBV in a naïve population (relapser, partial responder, and null responder subgroups) and response to a second course of PegIFN/RBV in treatment-experienced patients (relapser, partial responder, and null responder subgroups to prior PegIFN/RBV) identify similar sets of patients. Overall, the analyses suggest that prior relapse patients should respond to an RGT approach to treatment similarly to treatment-naïve patients.

Post hoc Analysis of *IL28B* Genotyping

A genetic polymorphism, rs12979860, near the *IL28B* gene (encoding interferon-lambda 3; hereafter referred to as "*IL28B* genotype") has been shown to be a strong predictor of SVR in patients receiving therapy with standard of care PegIFN/RBV. Previous studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype. Genotyping for rs12979860 was performed in subsets of two Phase 2 trials (60% of Study 104 [naïve], 52% of Study 106 [experienced]) and two Phase 3 trials (42% of Study 108 [naïve], 80% of Study C216 [experienced]). The total number of subjects included in the analysis was 1374: 610 treatment-naïve and 764 treatment-experienced subjects. These investigations were not performed prospectively and the cohort of subjects consenting to genetic testing may not be representative of the full study population. Specifically, the substudy population included very few Blacks/African American subjects.

Response rates and treatment effects were similar between the pharmacogenomic substudy and the overall trial populations for Studies 108 and C216. The Applicant's *IL28B* genetic substudy confirms previous reports of *IL28B* genotype effects on PegIFN/RBV responses in that C/T and T/T subjects had significantly lower SVR rates in the PR48 control arms. A similar genetic effect was apparent in the telaprevir-containing arms, although less pronounced than in PR48. In both trials, subjects with the C/T and T/T genotypes had higher SVR rates with telaprevir-containing regimens than PegIFN/RBV alone. Treatment-naïve C/C subjects responded favorably to PegIFN/RBV alone, although SVR rates were higher for all of the telaprevir-containing regimens in this subgroup. Table 1 summarizes the response rates by *IL28B* genotype in Studies 108 and C216. Statistical heterogeneity in telaprevir treatment effects was not apparent across the *IL28B* genotype strata (genotype x treatment interaction P>0.15). These results should be interpreted with caution because the sample size of some subgroups was small and the cohort may not fully represent the study population, however, the results are consistent with other studies evaluating the role of *IL28B* in treatment response.

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

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

Trial	Treatment	SVR, % (n/N)				
		Overall	**Substudy**	**IL28B C/C**	**IL28B C/T**	**IL28B T/T**
	T12 (DS)/PR48	66% (175/264)	54% (114/210)	83% (29/35)	58% (76/132)	65% (28/43)

Specific Populations

Some important populations with specific treatment needs are not included in sufficient numbers in this NDA to formally assess treatment effectiveness and safety of telaprevir in the population. Specific populations for which the Applicant has limited or no data include:

Decompensated Liver Function: There are no clinical trial data in subjects with decompensated liver function, and DAVP has not reviewed any proposed plans for trials in this population. At this time, telaprevir is administered in combination with PegIFN/RBV, which is contraindicated in patients with decompensated liver function. In addition, the hepatic impairment studies suggest there may be difficulty in dosing subjects with moderate or severe hepatic impairment.

HIV/HCV co-infection: The Applicant is conducting a 2-part pilot study to evaluate a regimen of T12/PR48 compared to PR48 in co-infected subjects who are receiving or not receiving concomitant antiretroviral therapy. The results of this trial, if successful, may support the conduct of an additional larger trial.

Other Populations: A methadone-telaprevir interaction study showed that concentrations of R-methadone were reduced when co-administered with telaprevir. With this in mind, subjects who had a history of use of illicit drugs or alcohol with no incidents of abuse within the 2 years prior to the screening visit or subjects with a history of abuse of narcotics or other controlled substances known by the investigative site and considered good candidates could be enrolled in the clinical trials. Very limited data in this patient population are available. A total of 11 illicit drug users were enrolled in the Phase 3 trials (9 to telaprevir-containing regimens and 2 to PR48). One PR48 (50%) and three (33%) telaprevir subjects achieved SVR.

Pediatrics: The Applicant has submitted a pediatric development plan to evaluate telaprevir in both treatment-naïve and experienced children 3 to 18 years of age. Formulation and clinical pharmacology studies have begun, but pediatric clinical trials have not been initiated at this time.

IV. Clinical Virology of Phase 3 Studies 108, 111 and C216

For the clinical virology analysis, the applicant submitted extensive genotypic data of the entire NS3/4A coding region and response outcome data from 2,260 baseline subject

isolates and comprehensive post-baseline and follow-up samples from 628 subjects who did not achieve SVR in the Phase 3 Studies 108, 111, and C216.

Telaprevir Treatment-Emergent Substitutions

In a pooled analysis of subjects who did not achieve SVR from the Phase 3 studies, NS3 amino acid substitutions V36M, A or L, T54A or S, R155K or T, A156S, T or V and D168N were determined to emerge frequently on telaprevir treatment. In replicon-based and enzymatic phenotypic assays using site-directed mutants, the V36M/A, T54A or S, R155K or T, A156S amino acid substitutions have been shown to confer 4- to 20-fold reduced susceptibility to telaprevir and substitutions V36M+R155K, A156T, or A156V have been shown to confer >60-fold reduced susceptibility to telaprevir. Variants at position D168, known to confer decreased susceptibility to the macrocyclic NS3/4A protease inhibitors, had not been previously reported to be associated with telaprevir resistance.

Telaprevir-associated resistance substitutions (substitutions at positions V36, T54, R155, A156 or D168) were present at baseline in 5% (117/2239) of the subjects in the combined Phase 3 Studies. Given the small number of subjects with baseline telaprevir resistance substitutions, it is hard to make conclusions on response outcomes when these specific substitutions are present at baseline. However, the limited data indicate that the presence of telaprevir resistance-associated substitutions at baseline do not preclude achieving SVR on treatment with a T/PR regimen.

Study 108: Treatment-Naïve
Overall, the proportion of telaprevir resistance substitutions that emerged on treatment was comparable between the T8/PR and T12/PR arms with more substitutions emerging in subtype 1a than 1b treatment failures. Almost all of the treatment failures who failed on T/PR at Week 12 or earlier had treatment-emergent substitutions and 60% of isolates from subjects who failed after Week 12 on PR or who relapsed 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.

Study 111: Treatment-Naïve
In Study 111, a high percentage of telaprevir treatment failures had treatment-emergent substitutions. Of the treatment failures who failed after Week 12 on PR or relapsed on T12-containing regimens, 90% (46/51) had treatment-emergent substitutions. As in Study 108, V36M and R155K and the combination of both emerged most frequently in 50-60% of Subtype 1a failures. In the subtype 1b failures, T54A emerged most frequently.

Study C216: Treatment-Experienced
Overall, the number of subjects who did not achieve SVR was similar in the T12/PR48 (36%) and lead-in arm T12(DS)/PR48 (34%). Overall, 70% of subject failing to achieve SVR had treatment-emergent substitutions when they experienced failure on treatment or

relapsed. The proportion of treatment-emergent substitutions was also similar between the two arms. Over half the treatment-failure subjects in Study 216 were prior null responders. Consistent with these data, the prior null responders also had the most treatment-emergent substitutions. 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.

Table 2: Treatment Emergent Substitutions in Pooled Phase 3 Studies: Subjects Not Achieving SVR24 in T/PR Arms (n=525)

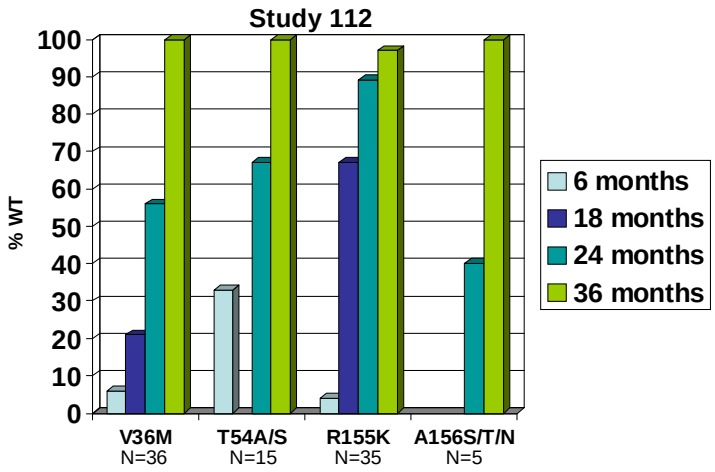
Emerging Substitutions in NS3	% of No SVR T/PR Subjects n=525	% Subtype 1a No SVR Subjects N=356	% Subtype 1b No SVR Subjects N=169
Any substitution at V36, T54, R155, V156 or D168	324 (62%)	247 (69%)	77 (46%)
R155K	193 (37%)	192 (54%)	1 (0.6%)
V36M	175 (33%)	170 (48%)	5 (3%)
V36M + R155K	142 (27%)	142 (40%)	-
V36A	40 (8%)	17 (5%)	23 (14%)
T54A	30 (6%)	5 (1%)	25 (15%)
T54S	25 (5%)	14 (4%)	11 (7%)
A156T	37 (7%)	23 (6%)	14 (8%)
A156S	16 (3%)	6 (2%)	10 (6%)
A156V/F/N	8 (2%)	1 (0.3)	7 (4%)
R155T	16 (3%)	16 (4%)	-
D168N	5 (1%)	5 (1%)	-
V36L/G/I or R155M/G	<1%	-	-

Persistence of Telaprevir Resistant Variants/Follow-up Analysis

Study 112 is an on-going, 3-year, virology follow-up study in subjects previously treated with telaprevir from Phase 2 clinical trials. In this study, changes in telaprevir resistance-associated HCV variants over time are evaluated in subjects who did not achieve an SVR24 and had developed one or more telaprevir resistance-associated substitutions. In this interim analysis, follow-up periods in Study 112 range from 5 - 40 months with a median of 25 months. A total of 56 subjects were used for the analysis of persistence of resistant variants V36A/M/L, T54S/A, R155T/K/I, and A156S/T in the absence of telaprevir selection. Figure 4 shows the percentage of variants (V36M, T54A and S, R155K, and A156S or T or N) that were no longer detectable by population nucleotide sequencing at 6, 18, 24 and 36 months with the caveat that the follow-up data were limited and incomplete. Variants expressing one or more telaprevir substitutions remained detectable (i.e., present at >25% of the viral population) in some subjects at 24 months. By 36 months, V36M, T54S or A, and A156S/T/N variants had fallen below the

level of detection in all subjects. Three percent of the subject isolates that had the R155K variant still had detectable R155K variants by population sequencing at 36 months. Lack of detection of a substitution based on a population-based assay does not necessarily indicate that viral populations carrying that substitution have declined to a background level that may have existed prior to treatment.

Figure 4: Persistence of Telaprevir Resistance-Associated Substitutions in Study 112: Percentage Wild-type (Months after Post Nadir Visit)



In addition, the viral populations of subjects failing a telaprevir-containing regimen in Studies 108, 111, and 216 were assessed at multiple time points after treatment-failure by population nucleotide sequencing to determine if the telaprevir-resistant variants initially present at the post-nadir visit were detectable in the viral population by the end of study (EOS) visit. Of the combined subjects from Phase 3 studies with a total of 443 resistant variants, 176 (40%) had detectable resistant variants by population sequencing by EOS (follow-up range 5-71 weeks, median 45 weeks) and results for loss of variants were similar across the three studies. In the combined studies, 50% of these substitutions in subtype 1a and 20% of the substitutions in subtype 1b were still detected by the EOS.

V. Overview of Safety

The safety profile of telaprevir was well characterized during the development program. The focus of the safety review was on the period of telaprevir or telaprevir-placebo dosing (12 weeks in Study 108 and 111 and up to Week 16 in Study C216 to account for the delayed start of telaprevir).

Specifically, the risks of telaprevir use are associated with two key toxicities: skin reactions (rash and pruritus) and anemia, events that were common, sometimes severe, and in some cases treatment-limiting. Other events of interest include ano-rectal disorders and hyperuricemia.

Rash/Pruritus: Characteristics of telaprevir-associated rash/pruritus include:

- Rash/pruritus reported in 56% (range; 51% to 60%) of subjects receiving telaprevir compared to 32% of PR48 subjects
- Rash is typically eczematous, maculopapular, and papular-lichenoid, and in many cases accompanied by pruritus.
- Histologically, the rash appeared as spongiform dermatitis, with predominantly lymphocytic or eosinophilic perivascular infiltration.
- In most subjects, the rash was mild to moderate in severity, but was severe in 1% and resulted in discontinuing telaprevir in about 6% of subjects.
- Telaprevir-associated rash occurred early, usually within the first 16 to 20 days of treatment.
- Fewer than 1% of subjects experienced Stevens Johnson Syndrome (SJS) or Drug Related Eruption with Systemic Symptoms (DRESS); no subjects died of rash-related complications.
- Many subjects received treatment with oral antihistamines, topical steroids and/or systemic corticosteroids; no data are available to assess effectiveness of these interventions.

The Applicant devised an Event of Special Interest (ESI) category to capture clinically significant rash events. All skin reactions involving rash or rash-like events that occurred during the clinical trials and met any of the following three criteria were considered to be ESIs:

- Grade 1 and 2 rash (including multiple MedDRA search terms or "special search categories" [SSC]) that led to discontinuation of at least 1 study drug
- Grade 3 (severe) rash (including multiple SSC)
- Rash SSC events which met the criteria of a serious adverse event (SAE)

The frequency of rash ESI was 7% for combined telaprevir groups compared to <1% for combined PR48 groups.

The incidence of pruritus SSC events among telaprevir-treated naïve subjects was ~40% compared to 34% in combined PR48 groups. Among telaprevir subjects, 11 had a Grade 3 or higher pruritus SSC event, one was an SAE, 10 discontinued telaprevir, and 3 discontinued the entire treatment regimen. One subject in the PR48 group had a pruritus SSC event that led to discontinuation of all study drugs. During the telaprevir dosing period, the median time to onset of a pruritus SSC event was 21 days (range: 1 to 86 days) in the telaprevir groups, and 16 days (range: 1 to 85 days) in the PR48 group.

Among subjects treated with T/PR, rash was managed by discontinuation of telaprevir (6%), discontinuation of the entire regimen (1%), and/or use of oral antihistamines (9%), topical steroids (10%) or systemic corticosteroids (3%). One subject in the combined PR48 groups discontinued due to rash, <1% were treated with oral antihistamines or systemic steroids, and 3% were treated with topical steroids.

In Study 108, the incidence of Rash SSC and ESI was balanced between the T8 and T12 groups during the first 8 weeks of dosing. Between Weeks 8 and 12, the incidence of Grade 3 rash was higher in the T12 group (7 additional events compared to 1 additional event in T8 arm), likely due to the additional 4 weeks of exposure to telaprevir.

In treatment-naïve subjects, no trends were noted for the incidence of rash events by demographic or disease characteristics. In treatment-experienced subjects, rash 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%).

The Applicant convened a Dermatology Expert Panel (DEP) to review rash cases. In Study 108, subjects with rash ESI were more systematically evaluated with a dermatologist consultation, photographs of the rash, biopsy of the rash, and specific laboratory monitoring; this study provided most of the histologic and photographic data reviewed by the DEP. All rash ESI in Study 108 and other clinical trials were reviewed by the DEP, although the DEP focused primarily on severe cutaneous adverse reactions (SCAR), severe rashes such as SJS and DRESS thought to be drug-induced. The DEP concluded that the histology showed that most rashes had a spongiotic pattern with lymphocytic perivascular infiltration which correlated with the eczematous appearance, rash ESI were similar clinically and histologically to those reported with PegIFN/RBV, and most evaluable rash ESI involved $\leq$ 30% body surface area. This histologic and clinical pattern differs from other commonly seen drug rashes. In addition, the DEP identified subjects with suspected SCAR not identified by study investigators.

The mechanism of 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 case-control study of rash to explore a potential association of *HLA* alleles in subjects treated with T/PR. A total of 187 telaprevir-treated subjects were included from pooled treatment-naïve trials: 114 had developed a rash during telaprevir treatment (59 severe cases) and 73 tolerated telaprevir treatment for 12 weeks without rash. The sponsor tested 143 *HLA* alleles (HLA-A, HLA-B, HLA-CW, HLA-DRB1, and HLADQB1). For rash of any severity, seven alleles were nominally significant at $P<0.05$, although none were significant after correcting for multiple comparisons. HLA-DQB1*0202 was the top-ranking allele, with an odds ratio of 3.42 (95% confidence interval 1.53-7.61, unadjusted $P=0.0026$). This does not represent a strong association and the clinical importance of the association is not clear.

- The telaprevir metabolites VRT-126032 and VRT-841125 were evaluated and were positive for skin sensitizing potential in animal studies. However, the relationship of the metabolites to incidence of rash remains unclear based on the low circulating levels observed in humans.

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

- Pyrazinoic acid (PZA) is a major metabolite of telaprevir and may have the potential to contribute to rash and pruritus. PZA is a structural analog of niacin which has also been associated with rash/pruritus 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. The relationship between levels of the pyrazinoic acid metabolite and rash or pruritus is being further explored.

Anemia: Anemia is a known RBV-related toxicity exacerbated by the addition of telaprevir. Telaprevir's effect on hemoglobin may be due to broader effects on the hematopoietic system demonstrated in preclinical studies (decreased erythrocytic parameters and anemia accompanied by reticulocyte/bone marrow response).

Subjects treated with telaprevir had:

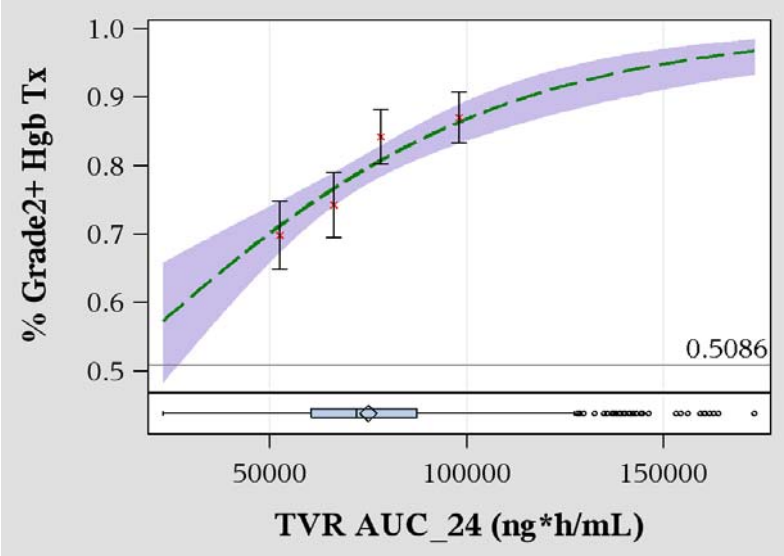
- A higher frequency of anemia (36% versus 15%)
- A higher frequency of hemoglobin reductions to Grade 3 or higher toxicity (7.0 to <8.9 g/dL or any decrease $\geq$ 4.5 m/dL) levels (55% versus 25%)
- A higher frequency of any hemoglobin level <10 g/dL (45% versus 27%) and <8.5 g/dL (14% versus 5%)
- More anemia-related SAEs (2.5% versus <1%)
- A higher frequency of anemia-related discontinuations (3% versus <1%)

The clinical trials allowed telaprevir's contribution to anemia to be characterized. The time to onset of anemia was ~43 days. In most subjects treated with telaprevir, hemoglobin values decreased steeply through Weeks 4 to 8, were generally stable between Weeks 8 and 16, and had began to return toward baseline by Weeks 16 to 18 to levels similar to or higher than those of subjects in PR48 groups. Telaprevir increased the decline in hemoglobin levels by ~1.0-1.5 g/dL greater compared to PR48. Anemia occurred somewhat more often in females, subjects older than 45 years of age, subjects with BMI <30 kg/m^2, and subjects with cirrhosis.

FDA reviewers conducted exposure-response analyses for the relationship between telaprevir and occurrence of anemia. Higher telaprevir exposure was significantly associated with increased risk of anemia and Grade 2 or higher hemoglobin toxicity, defined as hemoglobin <10 g/dL or any decrease from baseline > 3.5 g/dL (see Figure 5). This exposure-response analysis for safety was performed using the pooled population (both treatment-naïve and prior experienced) receiving 12-weeks of telaprevir treatment combined with PegIFN/RBV in Phase 2 and Phase 3 studies (n=1127). From a multivariate logistic analysis, the odds ratio of hemoglobin toxicity associated with doubling of telaprevir exposure is 2.4 (95% CI: 1.6, 3.6), after adjusting for PegIFN and RBV exposure. As shown in Figure 6, the exposure-response relationship between hemoglobin toxicity and RBV exposure was steeper than the relationship of telaprevir or

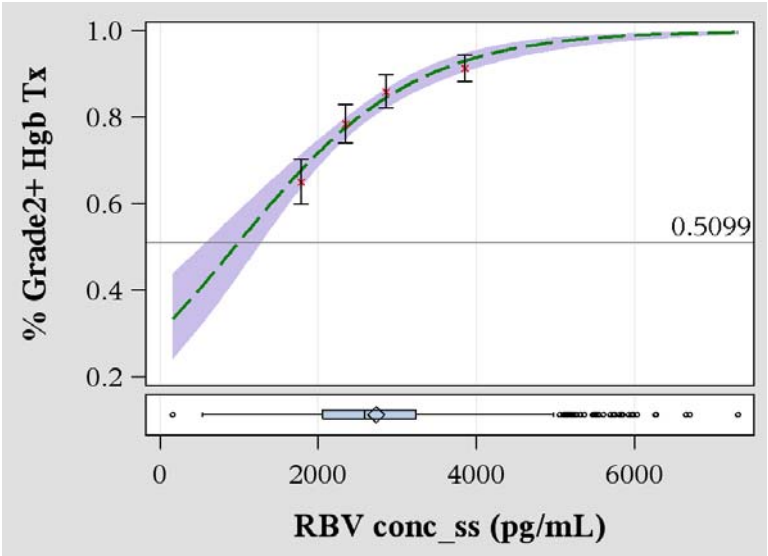
PegIFN exposure, with the odds ratio associated with doubling of RBV exposure as 5.2 (95% CI: 3.6, 7.5).

Figure 5: Effect of Telaprevir (TVR) Exposure on Hemoglobin Toxicity[a]



[a] Hemoglobin toxicity of Grade 2+ (Grade 2+ Hgb Tx) was defined as Hgb < 10 g/dL or any decrease from baseline > 3.5 g/dL.
Vertical bars represent rates of Hgb toxicity in each quartile of AUC.
The horizontal bar along the AUC axis represents the distribution of AUC (5-95%, 1st to 3rd quartile, mean, median).

Figure 6: Effect of Ribavirin (RBV) Exposure on Hemoglobin Toxicity[a]



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

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

Management of anemia in the clinical trials involved RBV dose reductions in accordance with the product labeling. If RBV had to be permanently discontinued for the management of anemia, telaprevir was also discontinued. Telaprevir dose reductions were prohibited and once telaprevir was discontinued for the management of anemia or other telaprevir-related safety reasons, it could not be restarted. The use of erythropoietin stimulating agents (ESAs) was generally prohibited during the Phase 3 trials. Table 3 summarizes the interventions used in the Phase 3 clinical trials to manage anemia. Of the subjects who received blood transfusions for anemia, 59% (62/105) achieved SVR. Of the 24 subjects who received an ESA for anemia, 14 (58%) achieved SVR.

Table 3: Interventions Used in Management of Anemia, Phase 3 trials

N (%)	**Combined Telaprevir N=1797**	**Combined PR48 N=493**
Telaprevir/Placebo discontinuation	58 (3)	0
Reduction of RBV dose	318 (18)	48 (10)
Interruption of RBV	104 (6)	5 (1)
Discontinuation of RBV	39 (2)	2 (<1)
Blood transfusions	104 (6)	7 (1)
ESA use	24 (1)	4 (<1)

Ano-rectal Events: Ano-rectal events (hemorrhoids, pruritus ani, proctalgia, anal inflammation, perianal erythema, and anal discomfort) were reported by ~20% (range; 15% to 26%) of telaprevir-treated subjects compared to 5% of PR48 recipients. These events were primarily mild to moderate in severity, rarely serious, and resulted in only a few incidents of study discontinuation.

Hyperuricemia/Gout: Hyperuricemia was more frequently reported in subjects receiving telaprevir. Increases in uric acid have been associated with RBV-related hemolysis and a possible mechanism for the finding in telaprevir-treated subjects is that telparevir exacerbates the hemolysis due to anemia. A total of 13 subjects experienced clinical gout/gouty arthritis: 11 in telaprevir-treated subjects and 2 in PR-treated subjects (<1% for both regimens). Four events in the telaprevir group occurred after the telaprevir dosing period. Only one subject had a previous history of gout. Subjects were treated with colchicine, indomethacin, vicodin, sodium chloride, or ibuprofen. No events of hyperuricemia or gout were serious or led to discontinuation of trial drugs and all subjects recovered.

General Adverse Events: Adverse Drug Reactions (ADRs) occurred frequently in the clinical trials and were generally consistent with the types of events previously associated

with PegIFN/RBV treatment. There were no clinically relevant differences between the adverse event profile of treatment-naïve and treatment-experienced subjects.

The most frequent adverse events, observed in >20% of subjects, of all grades regardless of attribution, during the telaprevir dosing period were fatigue, pruritus, nausea, headache, influenza-like illness, rash, anemia, insomnia, diarrhea, and pyrexia. ADRs that were observed with a frequency ≥5% higher in the T/PR groups compared to the PR48 groups are shown in Table 4.

Table 4: Adverse Drug Reactions Occurring with ≥5% Higher Frequency in Subjects Treated with Telaprevir, Phase 3 Trials

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

Laboratory Abnormalities

Hematologic Abnormalities: Overall, the frequency of severe (Grade 3 or higher) hematologic abnormalities was low in the clinical trials. More telaprevir-treated subjects than 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. 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) was higher in subjects receiving PR48 (15% compared to 12%). Table 5 summarizes the hematologic laboratory abnormalities reported in the Phase 3 clinical trials.

Table 5: Hematologic Laboratory Abnormalities, Phase 3 Trials

	Combined Telaprevir N=1797	Combined PR48 N=493
Absolute Leukocytes		
All Grades	55%	50%
≥Grade 3 (<1,499/mm^3)	8%	5%
Absolute Lymphocytes		
All Grades	35%	14%
≥Grade 3 (<499/mm^3)	15%	5%

ANC		
All Grades	59%	64%
≥Grade 3 (<749/mm^3)	13%	15%
Platelets		
All Grades	47%	36%
≥Grade 3 (<49,999/mm^3)	2.5%	1%

Clinical Chemistry Abnormalities: The proportion of subjects with Grade 3 or higher clinical chemistry abnormalities during the telaprevir dosing period was low and balanced across all treatment groups. There were no differences between the T8 and T12 groups in Study 108 or between treatment-naïve and -experienced subjects; all telaprevir and PR subjects were pooled for the laboratory analysis.

During the blinded dosing period, no clinically relevant differences between telaprevir and PR groups were observed in severe increases in amylase, lipase, creatinine, BUN, potassium, sodium, glucose, decrease TSH, or triglyceride levels. Subjects treated with telaprevir more frequently had elevations of cholesterol and TSH levels, but no clinical 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 telaprevir dosing period substantially more telaprevir-treated subjects than PR48 subjects had elevated uric acid levels (73% compared to 29%). Shifts from baseline to Grade 3 or higher uric acid levels (>12.1 mg/dL) were also more frequent among subjects treated with telaprevir (7%) compared to PR48 (2%). The steepest increase in uric acid levels occurred during the first two weeks of treatment. Mean maximal uric acid increases in uric acid levels for all telaprevir treatment groups was +2.5 mg/dL compared to +0.6 mg/dL in the combined PR48 groups. Bilirubin elevations occurred in 40% of telaprevir-treated subjects compared to 28% of 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.

VI. Conclusions

The Applicant submitted an NDA dossier including substantial non-clinical toxicology, clinical pharmacology, clinical virology, and clinical trials data to support the approval of telaprevir as a component of a treatment regimen for chronic HCV infection in adult patients. The FDA review team has reviewed the submitted data and this document summarizes our reviews to date. We look forward to an interactive and productive discussion of the data.

VII. Draft Questions for the Committee

Question 1: Rash and anemia were more frequent and more severe in patients treated with telaprevir. Please comment on the increased frequency and severity of rash and anemia when telaprevir is added to pegylated interferon and ribavirin and how this affects your risk/benefit assessment.

Refer to Section V of this Briefing Document (Overview of Safety) for a discussion of the frequency and characteristics of rash events and anemia as toxicity of telaprevir.

Question 2: Considering the potential risks and benefits, do the available data support approval of telaprevir for treatment of treatment naive and treatment experienced patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin?

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

Refer to Section III of this Briefing Document (Overview of Efficacy) for a discussion of the treatment effect of telaprevir in combination with PegIFN/RBV in both treatment naïve and treatment experienced patients, including important subgroups. Discussion of the overall safety profile of telaprevir is included in Section V.

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

a) **Treatment naïve**
b) **Prior null responders**
c) **Prior partial responders**
d) **Prior relapsers**

Refer to Section III of the Briefing Document (Overview of Efficacy) for a discussion of the use of RGT in treatment naïve patients in Studies 108 and 111. Additional description of the Pharmacometrics team's analysis of RGT for prior relapse patients in the absence of comparative clinical trial data for this population is included (Overview of Efficacy, Response Guided Therapy in Patients who Relapsed after Prior PegIFN/RBV).

Question 4: Please comment on the strength of evidence to support a recommendation for use in specific populations. What, if any, additional efficacy or safety data are needed for specific populations?

Refer to Section III of the Briefing Document (Overview of Efficacy) for a discussion of the treatment effects of telaprevir in combination with PegIFN/RBV in key subpopulations.

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